

#1.

SUMMER SCHOOL IN MEDICAL ONCOLOGY

Part 2 – Thursday (5.9.) & Friday (6.9.)

**LJUBLJANA
3-6. SEPTEMBER 2019**

Strokovni odbor:

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Uredniki zbornika:

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dr. Tanja Mesti, dr.med.

Organizator in izdajatelj (založnik):

Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Ljubljana, september 2019

AGENDA & INDEX

Thursday, September 5

Part 1	Moderator: dr. Borštnar	
8:30-10:00	<i>Early and locally advanced Breast cancer</i> (dr. Borštnar, dr. Ribnikar, dr. Bešlija)	
	Introduction (20-30 min) (Dr. Borštnar)	
	Case 1: HR+HER2- luminal A BC (dr. Geršak, dr. Borštnar)	
	Case 2: HR+HER2- luminal B BC (dr. Prepeluh, dr. Borštnar)	
	Case 3: Early TNBC (dr. Geršak, dr. Borštnar)	
	Case 4: First-line ribociclib in primary metastatic hormone receptor-positive breast cancer (dr. Rugelj, dr. Borštnar)	
10:00-10:15	Break	
10:15-11:45	<i>Metastatic breast cancer</i> (dr. Borštnar, dr. Ribnikar, dr. Bešlija)	
	Introduction (20-30 min) (Dr. Ribnikar)	
	Case 5: Metastatic HR+ BC with visceral crisis (dr. Dobovišek, dr. Borštnar)	
	Case 6: Primary metastatic HER2+, HR+ BC (dr. Dobovišek, dr. Borštnar)	
	Case 7: Metastatic TNBC (dr. Dobovišek, dr. Borštnar)	
11:45-12:00	Discussion	
12:00-12:30	Systemic treatment of sarcomas (dr. Unk)	
12:30-13:20	Lunch break	
Part 2	Moderators: dr. Kandolf Sekulović, dr. Ocirk	
13:20-14:00	Satellite symposium (MSD)	
14:00-14:30	Adjuvant treatment strategies for malignant melanoma (dr. Herceg)	
14:30-15:15	Melanoma 2020 Standards of care and unmet needs (dr. Kandolf Sekulović)	
15:15-15:30	Discussion	
15:30-15:40	Break	
15:40-16:10	Systemic treatment of non melanoma skin cancers (dr. Ocirk)	
16:10-17:10	Interesting cases from audience Case 1: Skin toxicity of immunotherapy (dr. Vermiglio, dr. Mesti)	
17:10-17:40	Satellite symposium	

Friday, September 6

	Moderators: dr. Reberšek, dr. Ebert Moltara	
8:30-9:30	Interesting cases from audience	
9:30-10:00	Systemic treatment of ovarian cancer (dr. Škof)	
10:00-11:00	How to manage patients with renal insufficiency (dr. Milanez)	
11:00-11:30	Side effects of immunotherapy and the management (dr. Hribernik, dr. Reberšek)	
11:30-11:40	Break	
11:40-12:30	Side effects of chemotherapy (including extravasation) and TKI and the management (dr. Ovčariček, dr. Bokal)	
12:30-13:00	Discussion and conclusions	



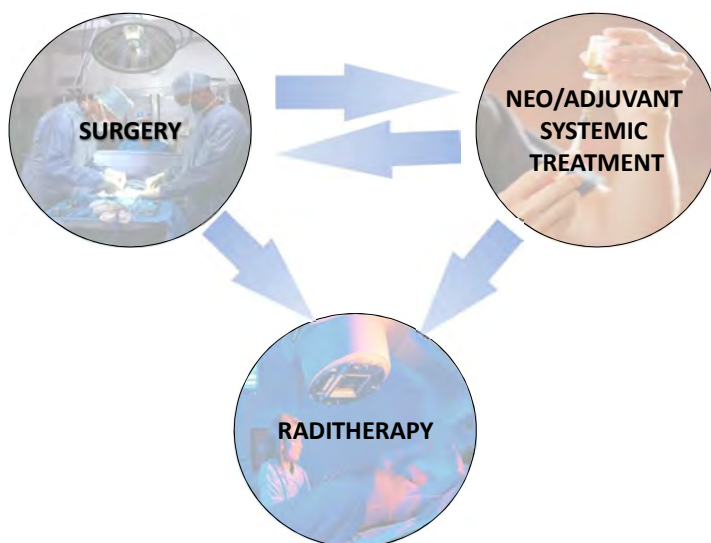
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Treatment of early and locally advanced breast cancer

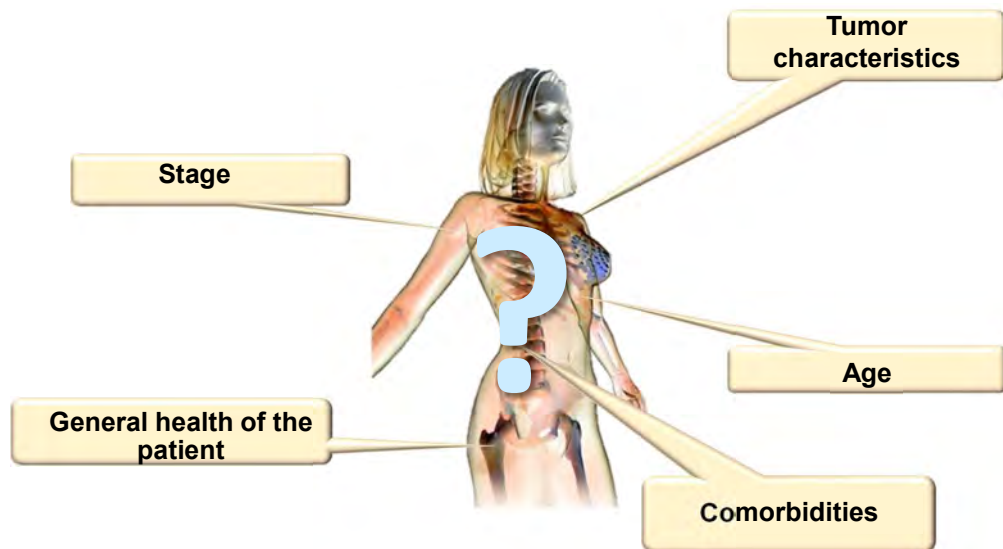
Simona Borštnar

*1st Summer School of Medical oncology,
September 2019, Ljubljana*

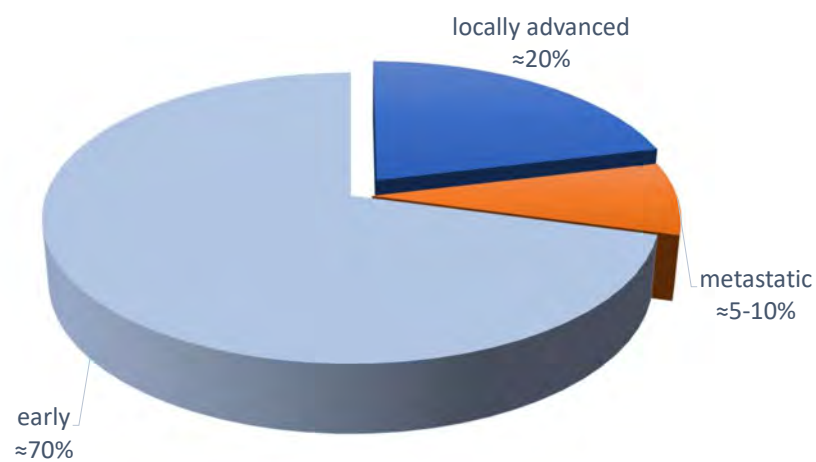
Multidisciplinary approach in treatment of breast cancer



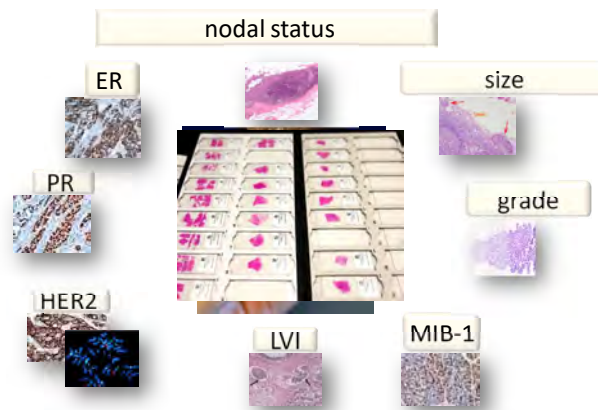
Features for selection of treatment



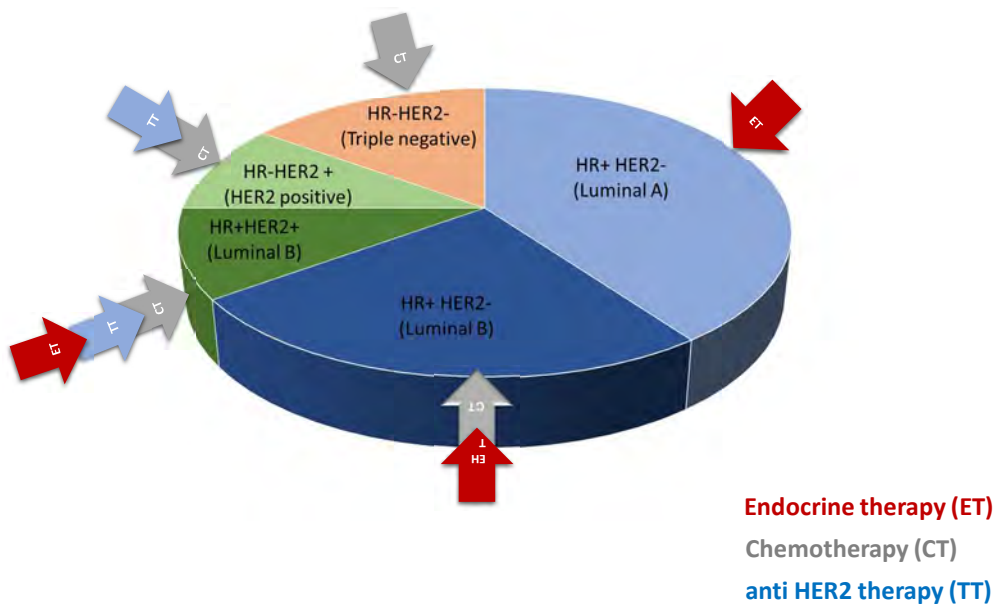
Distribution of patients by stage



Tumor characteristics



Division into subtypes and treatment decision



Gene signatures in ER+ subtype



HUMAN GENOM:
~25 000 genes

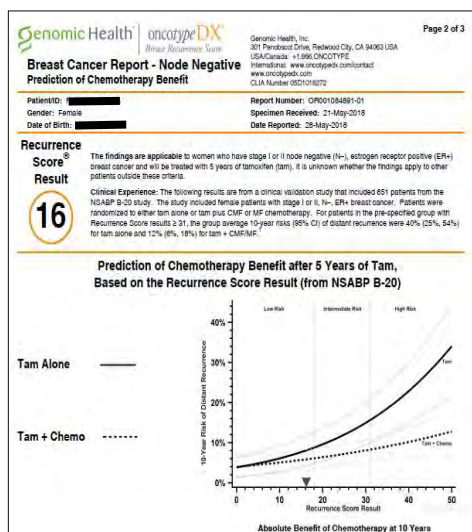


GENES RELATED TO
PROLIFERATION AND
INVASION OF BREAST
CANCER:
231 genes

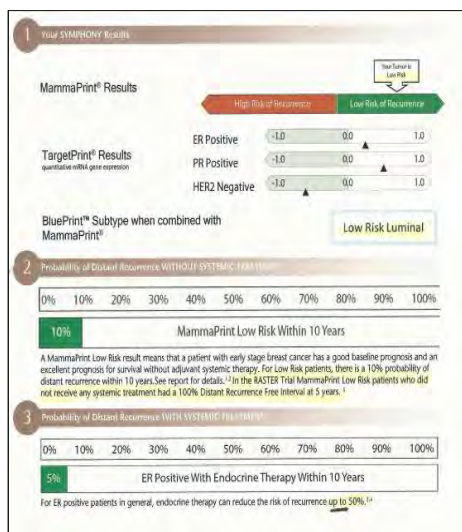
- ❖ MammaPrint (70 genes)
- ❖ Oncotype (21 genes)

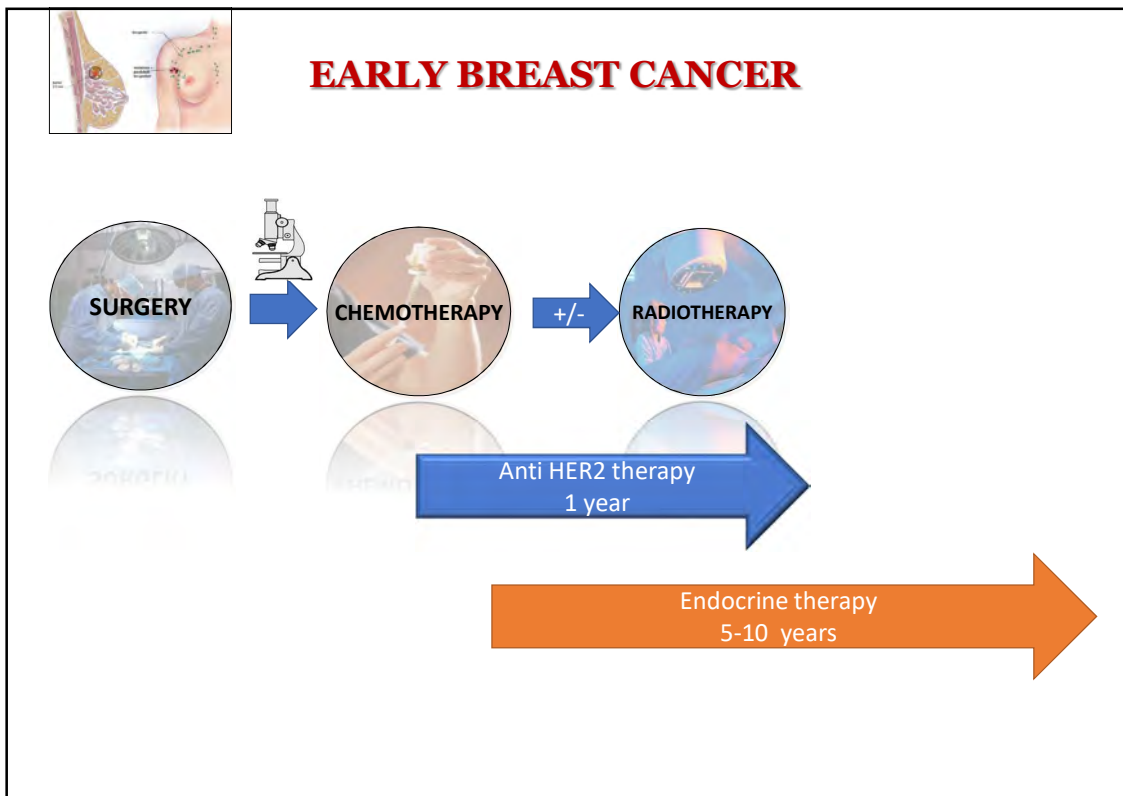
The 70-gene and the 21-gene signatures identify patients who may not require adjuvant chemotherapy.

Oncotype DX



Mammamprint





Adjuvant therapy of triple negative BC

- ❑ CT in all pts, except *ductal, T1aNo*
 - CT with anthracyclines and taxanes (dose dense AC followed by paclitaxel every 2 weeks, dose dense AC followed by weekly paclitaxel, TC, FEC followed by docetaxel etc.); TC, TAC, CMF
- ❑ In pts with Stage II in III neoadjuvant treatment is recommended

Adjuvant treatment of HER2+ breast cancer

CT +anti-HER2 therapy (+ ET in HR+)

- ❑ CT should contain anthracyclines and taxanes;
 - a possible but not preferred choice is a combination without anthracyclines TCH (docetaxel + carboplatin + trastuzumab)
 - For pT1b,c NO, paclitaxel weekly x 12 is sufficient
 - For stage II and III, neoadjuvant CT is recommended
- ❑ Anti-HER2 treatment
 - Trastuzumab +/- pertuzumab (addition of pertuzumab if positive lymphnodes or negative HR)
 - infusions or subcutaneous applications every 3 weeks;
→duration: 1 year
- ❑ In pts with HR+ tumors , ET after completion of CT, selection by age and menopausal status

Adjuvant therapy of HR+ (luminal) breast cancer

LUMINAL A

ET only

- ❑ *Premenopausal*: tamoxifen 5 years
- ❑ *Postmenopausal*: tamoxifen or aromatase inhibitors (AI), or both in sequence up to 5 years

LUMINAL B

CT followed by ET

- ❑ *Premenopausal*: CT and then AI+ OS or tamoxifen ± OS; prolongation of ET to 10 or 15 years depending on side effects
- ❑ *Postmenopausal*: CT and then AI ± bisphosphonates; prolongation of ET to 10 or 15 years based on side effects.

Adjuvant therapy in INTERMEDIATE (HR+) BC

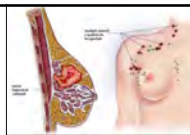
CT in majority of pts, ET in all pts

□ Premenopausal:

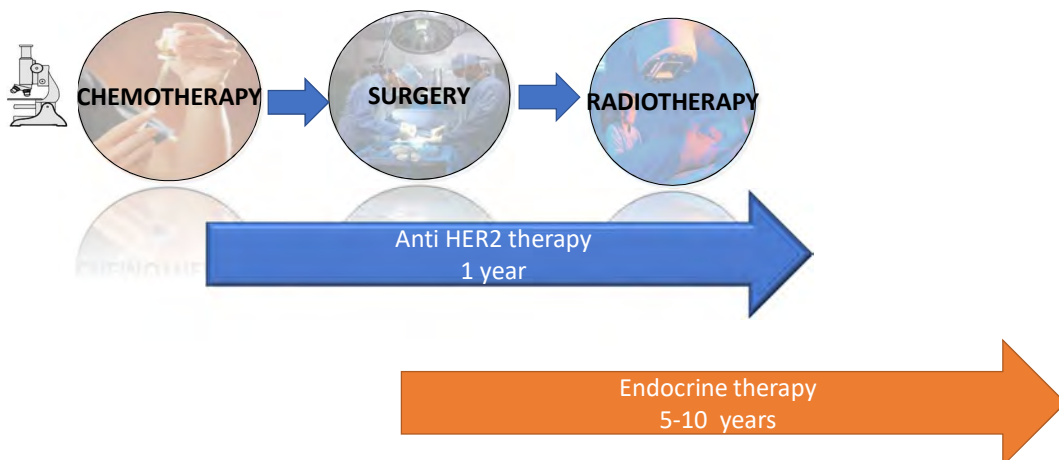
- Tamoxifen ± OS or AI + OS in No and intermediate characteristics (gradus, proliferation, gene signature)
- CT and then AI + OS or tamoxifen ± OS in N + and intermediate / poor characteristics (gradus, proliferation, gene signature); prolongation of HT to 10 or 15 years depending on side effects

□ Pomenopausal:

- AI in NO and intermediate characteristics (gradus, proliferation, gene signature) ± bisphosphonates
- CT and AI in N + and intermediate / poor characteristics (gradus, proliferation, gene signature) ± bisphosphonates; prolongation of HT to 10 or 15 years depending on side effects



LOCALLY ADVANCED OR TNBC/ HER2 positive, stage II or III BC



Indications for neoadjuvant CT

- ☐ Inflammatory breast cancer
- ☐ Triple-negative or HER2-positive stages II and III
- ☐ Luminal B with intention to deescalate surgical treatment

Diagnostic procedure before neoadjuvant CT

- ☐ Core biopsy is mandatory to determine tumor characteristics
- ☐ CT of the neck, chest and abdomen, bone scan
- ☐ Insertion of a marker clip into the tumor before the onset of neoadjuvant CT
- ☐ Breast MRI before and after neoadjuvant CT

Choice of neoadjuvant systemic therapy

- ☐ polychemotherapy: a combination of anthracyclines and taxanes is preferred (dose dense AC followed by paclitaxel every 2 weeks; dose dense AC followed by weekly paclitaxel, FEC followed by docetaxel)
- ☐ trastuzumab + pertuzumab in HER2 positive patients
- ☐ capecitabine (8 cycles) is recommended in patients with triple-negative cancer where a complete response is not obtained after neoadjuvant CT,
- ☐ ET in elderly patients with hormone-dependent cancer and / or contraindications for CT; 5-8 months or until the best response

Literature

- ❑ Cardoso F , Kyriakides S , Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S and Senkus E, on behalf of the ESMO Guidelines Committee. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2019;30: 1194–1220.
- ❑ Waks AG, Winer EP. Breast Cancer Treatment. : A Review. *JAMA* 2019;321(3):288-300.
- ❑ Burstein HJ et al: Estimating the Benefits of Therapy for Early Stage Breast Cancer The St Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer 2019. *Ann Oncol.* 2019 Aug 2. pii: mdz235. doi: 10.1093/annonc/mdz235. [Epub ahead of print]
- ❑ https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Version 2.2019; 07/02/2019



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Case 1:
Bilateral breast cancer
luminal A + luminal B (HER2+)

Author: Klara Geršak, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

NCCN Guidelines Version 1.2018
Genetic/Familial High-Risk Assessment: Breast and Ovarian

NCCN National Comprehensive Cancer Network®

Increased risk of BC

Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y (c,d)

Risk-reducing mastectomy: Evidence insufficient, manage based on family history

c May be modified based on family history (typically beginning screening 5–10 years earlier than the youngest diagnosis in the family but not later than stated in the table) or specific gene mutation.

d For women with mutations who are treated for breast cancer and have not had bilateral mastectomy, screening should continue as described

27.9.1967

Family history:
Mother **bilateral breast cancer** at age 50 and 52
Aunt (mother) **breast cancer** at age 39
Aunt (father) **breast cancer**

Medical history:
Healthy

Gynecological history:
Menarche at age 13
Menstrual periods not regular
No oral contraceptives
One child - at age 31

Year 2004 **37 years old**

Two suspicious breast lesions on mammography

↓

Core needle biopsy:
LCIS and atypical ductal hyperplasia

↓

ROLL bilateral

↓

Histology results: **fibroadenoma**

Year 2002 **35 years old**

High risk for developing breast cancer

↓

CHEK2 mutation

Regular follow ups
Mammography, breast US, MRI of the breast & visit at Medical oncologist every 6 months

Year 2014 **47 years old**

Right breast:
IDC 8mm (**T1 No Mo**)

↓

Mastectomy bilaterally & sentinel node biopsy bilaterally; with immediate reconstruction

↓

Histology results:
Right: IDC, grade III, 10mm, ER 100%, PR 100%, MIB-1 25%, HER2 +, N 0/8
Left: ILC, grade II, 6mm, ER 100%, PR 100%, MIB-1 5%, HER2 -

voting

Following treatment:

A ET + trastuzumab

B ChT + trastuzumab

C ChT + trastuzumab + ET

D ChT + trastuzumab + ET + RT

Right: IDC, grade III, 10mm, ER 100%, PR 100%, HER2 +, MIB-1 25%, N 0/8

Left: ILC, grade II, 6mm, ER 100%, PR 100%, HER2 -, MIB-1 5%

O

Year 2016

49 years old

Ovarian cyst → laparoscopic adnexectomy bilaterally

Side effects of hormonal therapy:

Muscle pain in arms and legs,
severe joint pain,
small foot joint stiffness,
ankle pain,
tiredness,
lower physical capacity,
hot flashes,
occasional headaches

O

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Which ChT:

A anthracyclines

B taxanes

C anthracyclines + taxanes

D capecitabine

Right: IDC, grade III, 10mm, ER 100%, PR 100%, HER2 +, MIB-1 25%, N 0/8

Left: ILC, grade II, 6mm, ER 100%, PR 100%, HER2 -, MIB-1 5%

O

voting

Extended Adjuvant Endocrine Therapy:

A YES

B NO

Right: IDC, grade III, 10mm, ER 100%, PR 100%, HER2 +, MIB-1 25%, N 0/8

Left: ILC, grade II, 6mm, ER 100%, PR 100%, HER2 -, MIB-1 5%

O

Year 2014

47 years old

3x **FEC-100** (5-fluorouracil, epirubicin, cyclophosphamide)

+ 3x **docetaxel**

+ **trastuzumab** (July 2014 - July 2015)

+ **tamoxifen** (from September 2014)

O

Year 2019

52 years old

END of adjuvant HT (start: september 2014)

Follow-ups once a year

Regular US of the heart

Lab tests repeatedly ok

Tumor marker (CA 15-3): negative

O

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Follow ups:

A LAB + tumor marker CA 15-3

B Mammography/breast US

C Clinical exam

D A+B+C



Case 2: HR+HER2+ luminal B breast cancer

Nina Prepeluh
Simona Borštnar, PhD., MD.
Institute of Oncology Ljubljana

1st Summer School in Medical Oncology
3–6. September 2019
LJUBLJANA

Clinical presentation

- 43- years old female
- history: lump in left breast for 6 months, otherwise healthy
- family history: cousin had uterine cancer
- gynecological history: regular menses, 4x partus, no use of contraceptive pills
- smoker (25 years, a pack a day)

Diagnostic work-up

- mammography (June 2018) – tumor formation in upper inner quadrant of left breast, 5 cm in diameter with microcalcinations; MRI- tumor formation 27x22 mm, one pathological lymph node
- core needle biopsy: IDC, grade 3, ER 100%, PgR 0%, Ki-67 15%, HER-2 positive (3+)
- staging: CT of the thorax & abdomen + bone scan – no metastases detected

TABLE 1

Criteria for staging breast tumors according to the American Joint Committee on Cancer's TNM classification¹

	Primary tumor (T)*	Regional lymph node status (N)	Distant metastasis (M)
Stage 0	Carcinoma in situ	No evidence of cancer in nearby nodes	No
Stage I	Tumor ≤ 2 cm [†]	No evidence of cancer in nearby nodes	No
Stage IIA	No evidence of primary tumor	Metastasis to 1–3 nodes	No
Stage IIB	Tumor ≤ 2 cm [†]	Metastasis to 1–3 nodes	No
Stage IIC	Tumor > 2 cm but ≤ 5 cm	No evidence of cancer in nearby nodes	No
Stage IIIA	Tumor > 2 cm but ≤ 5 cm	Metastasis to 1–3 nodes	No
Stage IIIB	Tumor > 5 cm	No evidence of cancer in nearby nodes	No
Stage IIIC	No evidence of primary tumor	Metastasis to 4–10 nodes	No
Stage IVA	Tumor ≤ 2 cm [†]	Metastasis to 4–10 nodes	No
Stage IVB	Tumor > 2 cm but ≤ 5 cm	Metastasis to 4–10 nodes	No
Stage IVC	Tumor > 5 cm	Metastasis to 4–10 nodes	No
Stage IIIC	Tumor of any size with direct extension to chest wall or skin	No evidence of cancer in nearby nodes	No
Stage IIIC	Tumor of any size with direct extension to chest wall or skin	Metastasis to 1–3 nodes	No
Stage IIIC	Tumor of any size with direct extension to chest wall or skin	Metastasis to 4–10 nodes	No
Stage IIIC	Any tumor designation	Metastasis to > 10 nodes	No
Stage IV	Any tumor designation	Any lymph node designation	Yes

Reference: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4995050/>

What treatment regimen would you recommend to start with?

- neoadjuvant chemotherapy (anthracyclines + taxanes) + neoadjuvant antiHER-2 therapy (trastuzumab)
- neoadjuvant chemotherapy (anthracyclines + taxanes) + dual neoadjuvant antiHER-2 therapy (trastuzumab+ pertuzumab)
- surgery followed by adjuvant chemotherapy + adjuvant antiHER-2 therapy
- surgery followed by adjuvant antiHER-2 therapy



Treatment timeline

June – November 2018
NACT (4x EC + 4x DOCE+
trastuzumab)

December 2018 –
breast conserving
surgery with
SLNB

January 2019 –
ALND

MRI breast
(November 2018):
- Tumor
formation of the
left breast 1 cm
- US of the axilla –
no suspect nodes

Pathological examination
after NACT:
- partial response – 10
mm residual tumor, Ro
resection
- 2/3 positive nodes; 3
mm and 6 mm

Pathological
examination
- regressive changes in
3/22 nodes

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Case 3: Early TNBC

Author: Klara Geršak, MD
Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
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Born: 4.11.1990

Family history of cancer:
Aunt - cancer of the **larynx** at age 67 (father's side)
Grandfather - **breast** cancer at age 60
Aunt - **breast** cancer at age 80

Hashimoto thyroiditis
Euthyrox 50 mcg/day

Menarche at age 12
Menstrual periods regular
Oral **contraceptive** use for 9 years
0 pregnancies, 0 abortions

Medical doctor (just started internship), lives with her family

Year 2018:

27 years old

LEFT breast

Self examination
Upper quadrants
Fine needle aspiration of the breast tumor (US 1.4x1 cm) and lymph node in the left axilla (US 7 mm)
Cytology results: adenocarcinoma and metastasis of the adenocarcinoma in the lymph node

Core needle biopsy 5.7.2018:
IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg.

Tumor size - clinically:
1.5 x 1 cm
Clinically no lymph node in the axilla.

VAP
Genetic counselling and testing

Year 2018:

27 years old

LEFT breast

Self examination
Upper quadrants
Fine needle aspiration of the breast tumor (US 1.4x1 cm) and lymph node in the left axilla (US 7 mm)
Cytology results: adenocarcinoma and metastasis of the adenocarcinoma in the lymph node

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IDC, poorly differentiated, high nuclear grade,
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Tumor size - clinically:
1.5 x 1 cm
Clinically no lymph node in the axilla.

VAP
Genetic counselling and testing

BRCA 2 mutation

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How to treat:

A NACT + surgery
B surgery + adjuvant ChT

US 1.4x1 cm
lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%,
HER-2 neg

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Which ChT:

A dose dense anthracyclines+taxanes (AC+PACLI)
B (F)EC+DOCE
C capecitabine

US 1.4x1 cm
lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade,
ER 0%, PR 0%, MIB-1 around 30%,
HER-2 neg

NEOADJUVANT SYSTEMIC THERAPY

4x AC (DOXORUBICIN+CYCLOPHOSPHAMIDE)

+

4x PAKLITAKSEL

+ pegfilgrastim

D
O
S
E

D
E
N
S
E

After 2. Cycles of the therapy: no tumor clinically

16.11.2018 OPERATION

27 years old

LEFT: Subcutaneous mastectomy with axillary lymph node dissection + immediate reconstruction

RIGHT: prophylactic mastectomy + immediate reconstruction

Pathohistological results:

Residual IDC and DCIS,
partial response to therapy - 10-50% residual tumor.
No vascular invasion. No perineural invasion. Surgical margins clear.
Nodal status 2/24 - 1mm & 5mm - without extracapsular growth.

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Following treatment:

A RT

B capecitabine

C RT + capecitabine

partial response to therapy

nodal status 2/24 - 1mm & 5mm - without extracapsular growth

US 14 x 10 mm

lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade, ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg

Adjuvant RADIATION therapy

28 years old

From 14.1.- 20.2.2019
(+ parasternal lymph nodes)

25.2.2019 adjuvant CHEMOTHERAPY

28 years old

Capecitabine 2150 mg/12 hours, 14 days

+ goserelin 3.6 mg sc

6th, 7th and 8th cycle 75% dose - because of hematotoxicity

Last visit: 16.8.2019

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Expected 10-year survival:

A More than 90%

B 80-89%

C 70-79%

US 14 x 10 mm

lymph node in the left axilla (US 7 mm)

IDC, poorly differentiated, high nuclear grade, ER 0%, PR 0%, MIB-1 around 30%, HER-2 neg

partial response to therapy

nodal status 2/24 - 1mm & 5mm - without extracapsular growth

Overall survival

This chart shows the percentage of women surviving 10 years after surgery.





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Case 4: First-line ribociclib in primary metastatic hormone receptor- positive breast cancer

Author: Urška Rugelj, MD

Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
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LJUBLJANA

Clinical case

- 43-year-old premenopausal woman
- No comorbidities
- Medication: antihistamines due to atopy
- Family history negative for malignancy
- First visit in June 2017
 - Patient presented with a lump 5x4cm lump in the upper inner quadrant of the left breast
 - No skin or areola abnormalities
 - No enlarged lymph nodes
 - ECOG: 0



Initial assessment

- Imaging:
 - Mammography – structural abnormality in the left breast
 - Magnetic resonance imaging of the left breast: tumor on the border of upper quadrants 50x35 mm, 2 other foci in the upper and lower inner quadrant 30 and 35 mm, pathological axillary lymph nodes with enlarged capsule – the largest 6 mm in diameter
 - Bone scan: no signs of osteoblastic lesions
 - Ultrasound of the abdomen: no signs of metastases
 - Chest X-ray: no signs of metastases
- Cytological puncture of the tumor: adenocarcinoma
- Ultrasound guided cytological puncture of the axillary lymph node: metastasis of the adenocarcinoma
- Diagnosis: adenocarcinoma of the left breast with positive ipsilateral axillary lymph nodes



Core needle biopsy – pathology report

- Biopsy
 - Core needle biopsy
 - Histopathology: ILC
- Biomarkers
 - HER2–, PgR 95%, ER 100%, Ki67 5–10%
- Gene signature
 - Not done



- Luminal A like disease



Initial treatment and final pathology

- Surgery:
 - Radical mastectomy and axillary lymph node dissection with immediate reconstruction with DIEP flap
- Definitive histology
 - Invasive lobular carcinoma, 50 mm in largest diameter, with foci of lobular carcinoma in situ, grade 2, mitosis 2, lymphovascular invasion present
 - 25/28 axillary lymph nodes positive, the largest metastasis measuring 18 mm with extension outside of the capsule and infiltrating the surrounding adipose tissue



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What additional treatment would you recomend?

- A. Adjuvant endocrine therapy
- A. Adjuvant endocrine therapy and radiotherapy
- A. Adjuvant chemotherapy and endocrine therapy
- A. Adjuvant chemotherapy, endocrine therapy and radiotherapy

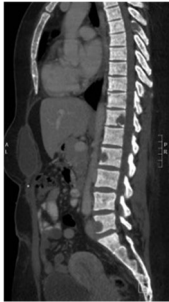


- Early breast cancer
- Invasive lobular carcinoma
- pT2N3aMx
- Stage IIIC
- HR positive, Her-2 negative, grade II, MIB1 10-15%



New symptoms

- Before chemotherapy was started new onset of pain with deterioration of performance status from 0 to 1 was observed
- Additional bone scan – September 2018
 - No changes from the preoperative scan in June 2018 – most likely degenerative changes in both shoulders and hips
- CT of the chest and abdomen – September 2018
 - Diffuse osteolytic bone metastases, no signs of metastases elsewhere



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What would you do now?

- A. Continue with the initial treatment plan (ChT, ET, RT)
- B. Ovarian function suppression and ET with AI
- C. Ovarian function suppression and ET with tamoxifen
- D. Ovarian function suppression and ET with AI and CD4/6 inh
- E. Ovarian function suppression and ET with tamoxifen and CD4/6 inh
- F. Chemotherapy



primary metastatic
HR+/HER2- breast
cancer, bone only



First line treatment

- Ribociclib 600 mg once daily (OD) for 21 days, then 7 days off
- Letrozole 2.5 mg OD continuously
- Goserelin 3.6 mg subcutaneously monthly
- Denosumab 120 mg subcutaneously monthly
- Monitoring strategy
 - Complete blood count (CBC), liver tests, electrolytes and electrocardiogram – every 14 days for the first 2 or 3 cycles
 - CBC, liver tests, electrolytes monthly
- Supportive treatment:
 - Analgesia with paracetamol/tramadol combination, later de-escalation to a non-steroidal anti-inflammatory drug
 - Calcium carbonate, vitamin D due to bone antiresorptive agent



Treatment - cont.

- Patient responded well to therapy, no major adverse effects were noted, no treatment delays, the pain improved
- Improvement in ECOG from 1 to 0 was noted
- Quality of life was improved
- The best response is stable disease. The duration of response is currently 20 months



Month 3



Month 6



Month 9



Conclusion

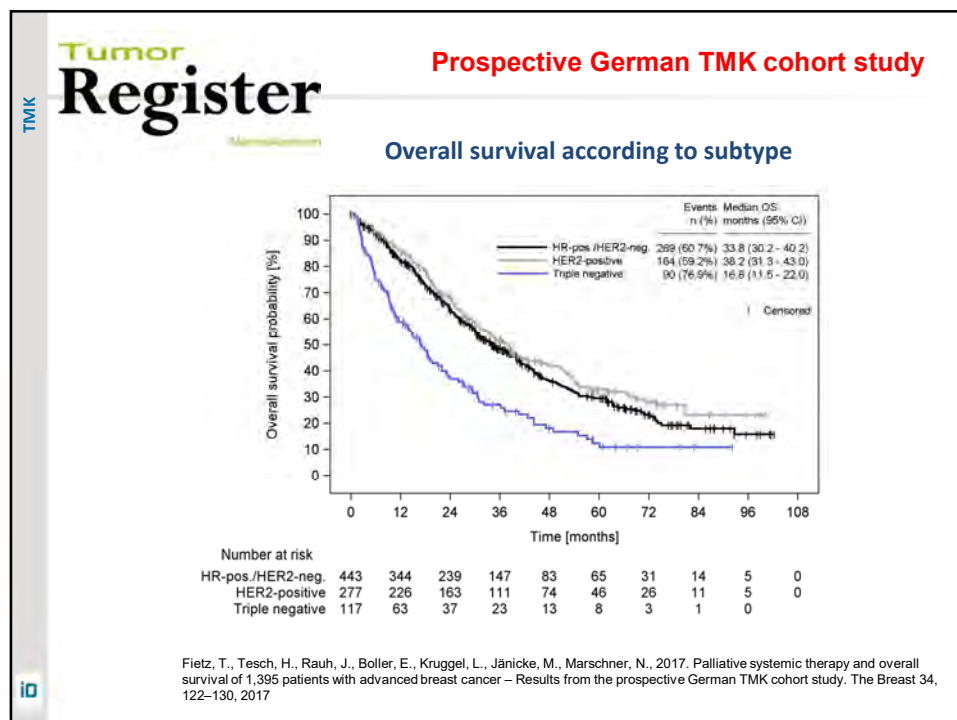
- Patient started her treatment of an early breast cancer
- Bone metastases were found after surgery when new symptoms were present
- Treatment plan was changed from adjuvant chemotherapy, followed by endocrinal therapy and radiotherapy to treatment of primary metastatic HR+/HER2- breast cancer with a combination of hormonal therapy and a CDK 4/6 inhibitor



Metastatic breast cancer

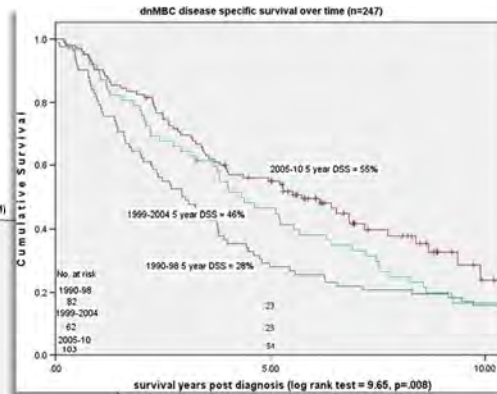
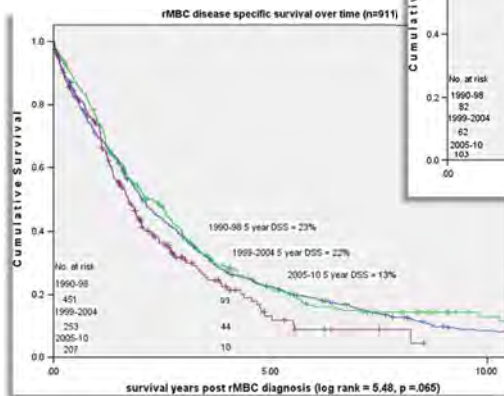
1st Summer School in medical oncology – Standards and open questions

Domen Ribnikar, MD, Medical Oncology staff
Institute of Oncology Ljubljana
Department of Medical Oncology
Ljubljana, September 5th 2019



Prognosis of de novo & recurrent MBC diverges over time

de novo MBC
mean survival = 5.03 yrs.

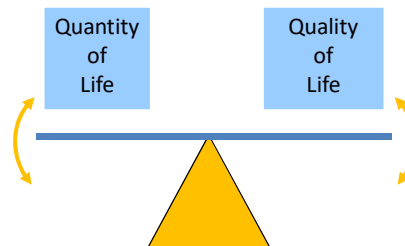


Recurrent MBC
mean survival = 2.81 yrs.

M. Mayer, ABC4

Goals of the Treatment in MBC

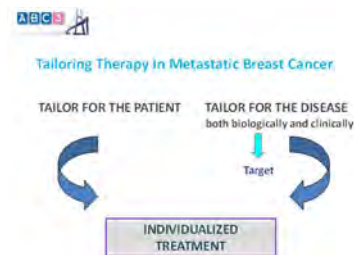
- Balancing treatment efficacy and toxicity is the main objective
- Goals of treatment:
 - Improve survival (*very few agents achieve it!*)
 - Delay disease progression
 - Prolong duration of response
 - Palliate symptoms
 - Improve or maintain quality of life
 - Transform into a chronic disease



TREATMENT TAILORING IN MBC

Treatment choice should take into account at least these factors:

HR & HER-2 status,
previous therapies and their toxicities, disease-free interval,
tumor burden (defined as number and site of metastases),
biological age, performance status, co-morbidities (including organ
dysfunctions),
menopausal status (for ET),
need for a rapid disease/symptom control,
socio-economic and psychological factors,
available therapies in the patient's country
and **patient preference!**



The management of MBC is complex and, therefore, involvement of all appropriate specialties in a **multidisciplinary team** (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial.

Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women

OPEN ACCESS

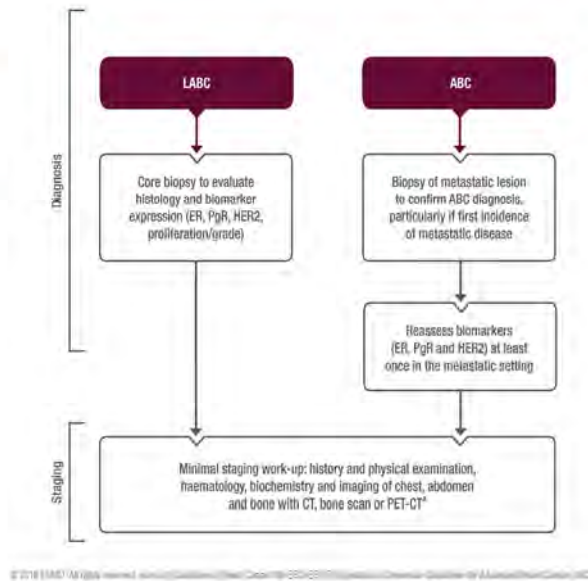
Eileen M Kesson *project manager*^{1,4}, Gwen M Allardice *statistician*^{1,4}, W David George *school of medicine honorary professor*², Harry J G Burns *chief medical officer for Scotland*³, David S Morrison *director*⁴

BMJ 2012;344:e2718 doi: 10.1136/bmj.e2718 (Published 26 April 2012)

CLINICAL PRACTICE GUIDELINES

ABC diagnostic work-up and staging

*Discuss indications. Brain MRI not indicated unless there are symptoms



LUMINAL TUMOURS = HETEROGENEOUS GROUP

- The principal characteristic of the luminal group is the **luminal expression signature**, composed of **ESR1, GATA3, FOXA1, XBP1, and cMYB**
 - the most frequent mutations in the **luminal A** subtype are **PIK3CA (45%)**, **MAP3K1 (13%)**, **GATA3 (13%)**, **TP53 (12%)**, and **CDH1 (9%)**
 - the most frequent mutations in **luminal B** tumors are **TP53 (29%)**, **PIK3CA (29%)**, **GATA3 (13%)**, and **TTN (12%)**
- In addition to **TP53** mutations, several other events may intervene in other steps of the same pathway, including **ATM** loss and **MDM2** amplification
- **ESR1** mutations (up to 19%) after **AI treatment => resistance**

Mechanisms of De Novo & Acquired Endocrine Resistance

De Novo ET Resistance

Acquired ET Resistance



- The **lost/inactivation of ER/ER pathway**
- **Activation of PI3K/AKT/mTOR pathway**
- **Activation of the growth factor or HER pathway activation**

1. Osborne CK, et al. *Ann Rev Med.* 2011;62:233-247; 2. Arpino G, et al. *Endocr Rev.* 2008;29:217-233; 3. Shou J, et al. *J Natl Cancer Inst.* 2004;96(12):926-935; 4. Chung YL, et al. *Int J Cancer.* 2002;97:306-312; 5. Meng S, et al. *Proc Natl Acad Sci USA.* 2004;101:9393-9398; 6. Nicholson RI, et al. *Endocr Relat Cancer.* 2004;11:623-641; 7. Gee JM, et al. *Endocrinology.* 2003;144:5105-5117; 8. Knowlden JM, et al. *Endocrinology.* 2005;146:4609-4618; 9. Miller W, et al. AARC Special Conference: Targeting PI3K/mTOR Signaling in Cancer; 2011. Abstract A09.

HOW TO TACKLE HETEROGENEITY OF LUMINAL-LIKE MBC? Are there ready-to-use (bio)markers to individualize treatment?

- **None ready for clinical practice yet!**
- **So, how do we choose?**

HOW TO TREAT ER+/HER-2 neg (LUMINAL) MBC:

MAIN QUESTIONS:

- 1. Do we need Chemotherapy (CT)?**
- 2. If Endocrine Therapy (ET) which agent?**
- 3. Is a targeted agent also necessary or is ET alone sufficient?**
- 4. If CT: combination vs. sequential monotherapy?**
- 5. If CT: which agent(s)?**



ER POSITIVE / HER-2 NEGATIVE MBC

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.

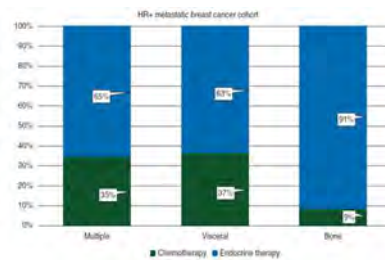
ALL guidelines are in agreement for this recommendation

In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium

D. J. A. Lobbezoo^{1,2}, R. J. W. van Kampen¹, A. C. Voogd^{1,3}, M. W. Dercksen², F. van den Berkmortel⁴, T. J. Smilde⁵, A. J. van de Woude⁶, F. P. J. Peters⁷, J. M. G. H. van Riel⁸, N. A. J. B. Peters⁹, M. de Boer¹, P. G. M. Peer¹⁰ & V. C. G. Tjan-Heijnen¹¹

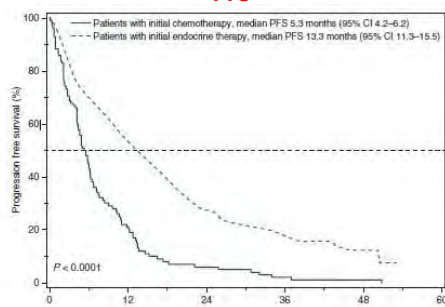
¹ Gronov - School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht; ² Department of Internal Medicine, Maastricht Medical Center, Maastricht; ³ Netherlands Comprehensive Cancer Organisation, Limburg; ⁴ Department of Internal Medicine, Alrijde-Catharina Hospital, Maastricht; ⁵ Department of Medical Oncology, Amc, Amsterdam; ⁶ Department of Internal Medicine, Streekl. Ziekenhuis, Groningen; ⁷ Department of Internal Medicine, Streekl. Ziekenhuis, Groningen; ⁸ Department of Internal Medicine, Streekl. Ziekenhuis, Groningen; ⁹ Department of Internal Medicine, Streekl. Ziekenhuis, Groningen; ¹⁰ Department of Internal Medicine, Streekl. Ziekenhuis, Groningen; ¹¹ Department for Health Economics, Radboud University Medical Center, Nijmegen, The Netherlands

Received 24 May 2015; revised 28 August 2015; accepted 14 October 2015; accepted 28 October 2015

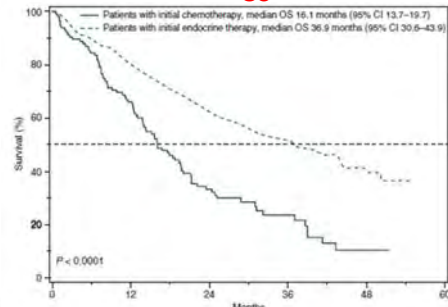


Starting with ET vs. Starting with CT

PFS

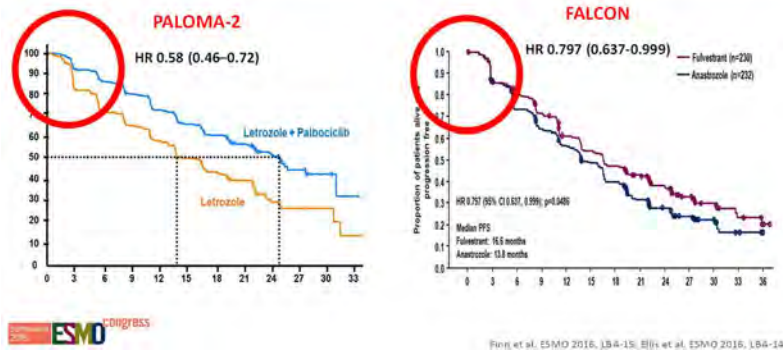


OS



MAIN CHALLENGE: Identify small percentage of “fast progressors”

First line endocrine therapy: FALCON or PALOMA-2?



Courtesy Peter Schmid, ESMO 2016, Discussant



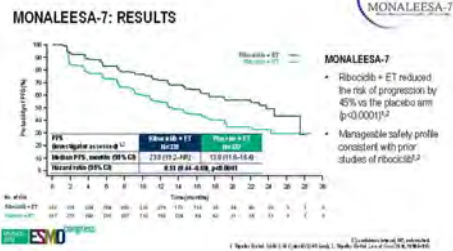
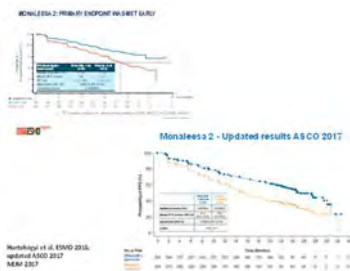
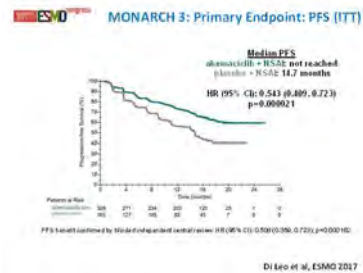
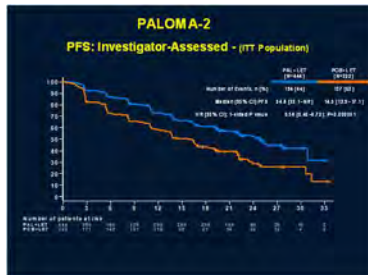
ER POSITIVE / HER-2 NEGATIVE MBC

The addition of a **CDK4/6 inhibitor to an aromatase inhibitor**, in patients **naïve or pre-exposed** to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore **one of the preferred treatment options***. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.

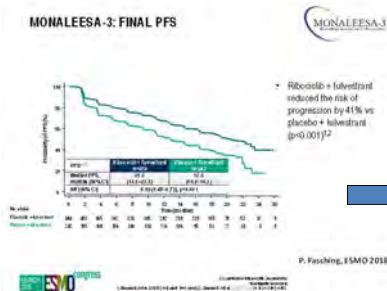
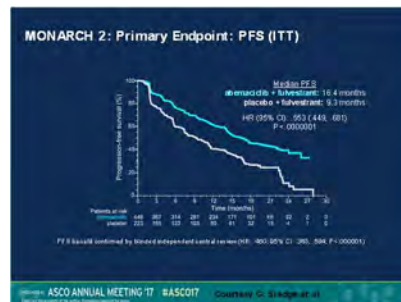
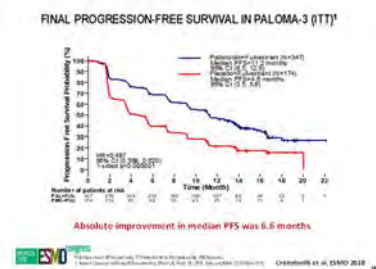
OS results are still awaited. QoL was comparable to that with ET alone.

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

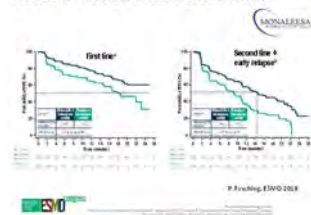
1st Line CDK 4/6 INHIBITORS: EFFICACY



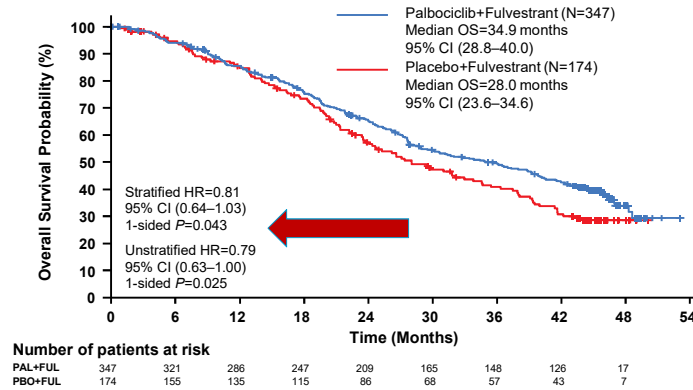
2nd Line CDK 4/6 INHIBITORS: EFFICACY



PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS



OVERALL SURVIVAL IN PALOMA-3 (ITT)



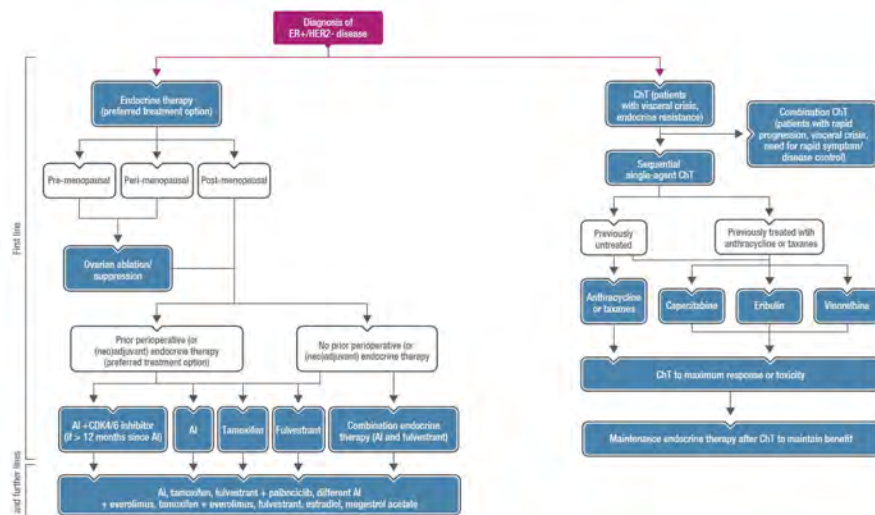
Absolute improvement in median OS was 6.9 months

BUT

NOT STATISTICALLY SIGNIFICANT

Cristofanilli et al, ESMO 2018

MANAGEMENT OF LUMINAL MBC



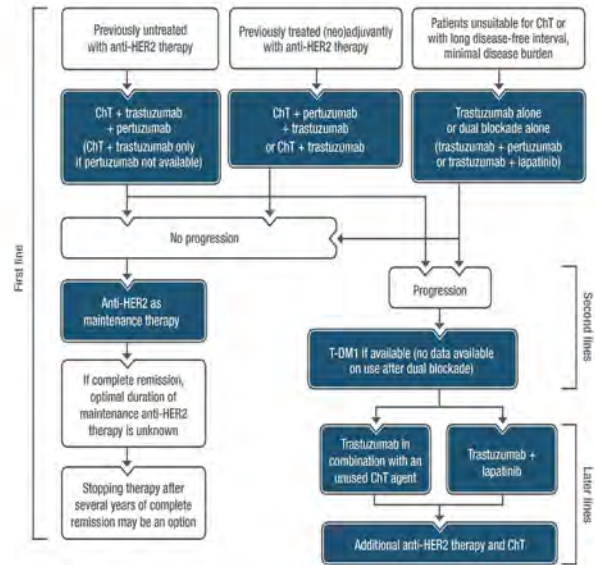
ABC, advanced breast cancer; AI, aromatase inhibitor; ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2

F Cardoso et al, Annals of Oncology 2018

CLINICAL PRACTICE GUIDELINES

Treatment of ER-negative / HER2-positive ABC

Note: Include in clinical trials when available

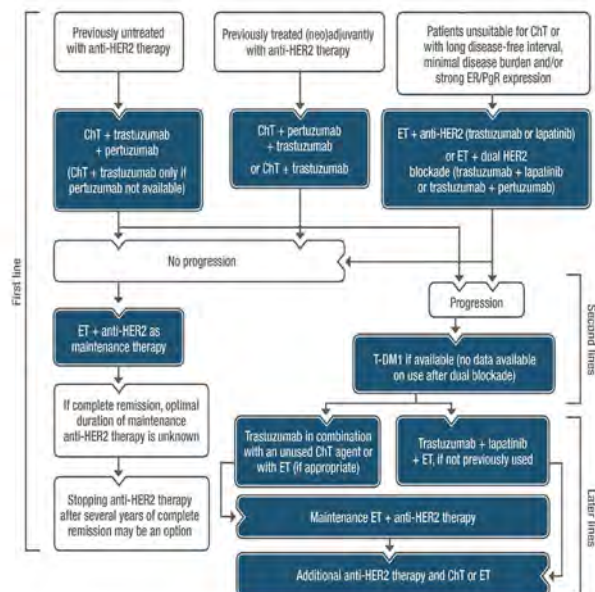


© 2018 ESMO. All rights reserved. esmo.org/Guidelines/BreastCancer46-ESO-ESMO-International-Conference-Guidelines-for-Adjuvant-Breast-Cancer-ABC-4

CLINICAL PRACTICE GUIDELINES

Treatment of ER-positive / HER2-positive ABC

Note: Include in clinical trials when available

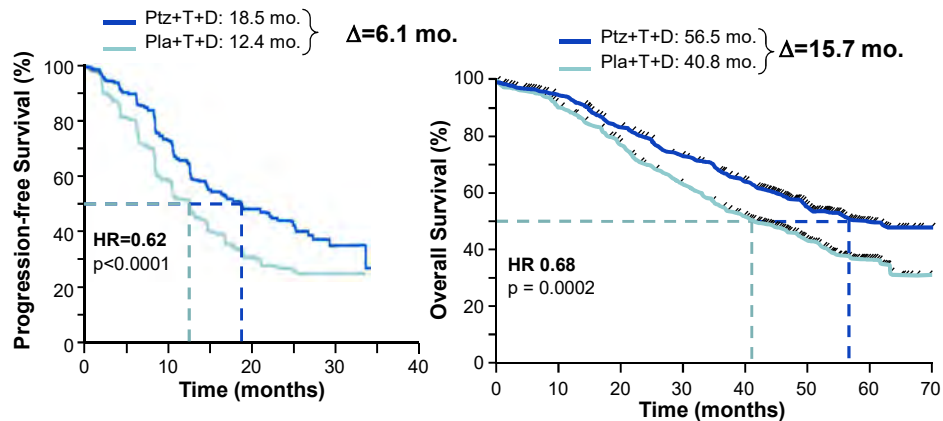


© 2018 ESMO. All rights reserved. esmo.org/Guidelines/BreastCancer46-ESO-ESMO-International-Conference-Guidelines-for-Adjuvant-Breast-Cancer-ABC-4

CLEOPATRA: Median PFS and OS

CAUTION!!!!

Only 21% -26% pts had previously received (neo)adjuvant trastuzumab



Baselga et al., NEJM 2012., Swain et al., NEJM, 2015.



HER-2 POSITIVE MBC: 2nd line and beyond

After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice).

T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, because it provides an OS benefit.



TNBC: CHEMOTHERAPY (general)

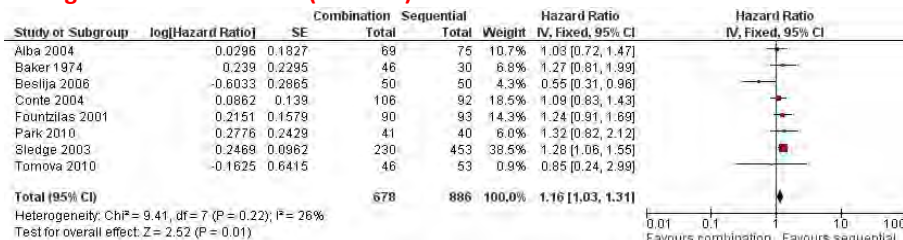
Both combination and sequential single agent CT are reasonable options. Based on the available data, **we recommend sequential monotherapy as the preferred choice for MBC.**

Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

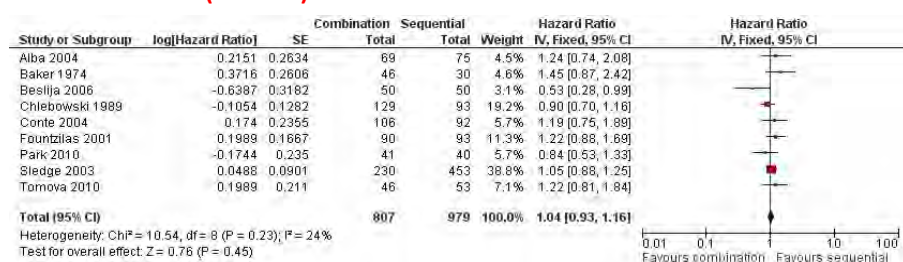
ALL guidelines are in agreement for this recommendation

Cochrane meta-analysis of Combination vs. Sequential monoCT for MBC

Progression-free survival (all trials)



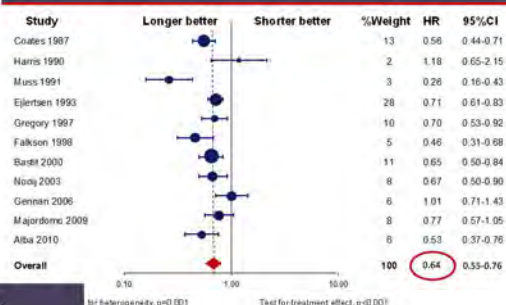
Overall survival (all trials)



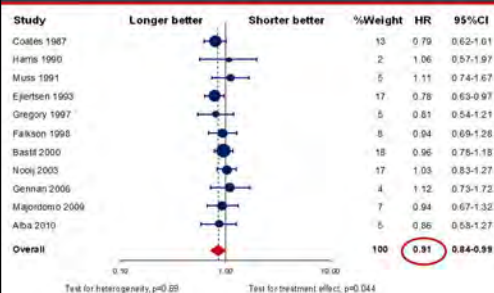
Optimal Duration of Chemotherapy?

- Longer CT duration associated with :
- significant improvement in PFS (HR 0.64; 95% CI 0.55 – 0.76)
- significant improvement in OS (HR 0.91; 95% CI 0.84-0.99)

Results: Progression Free Survival



Results: Overall Survival



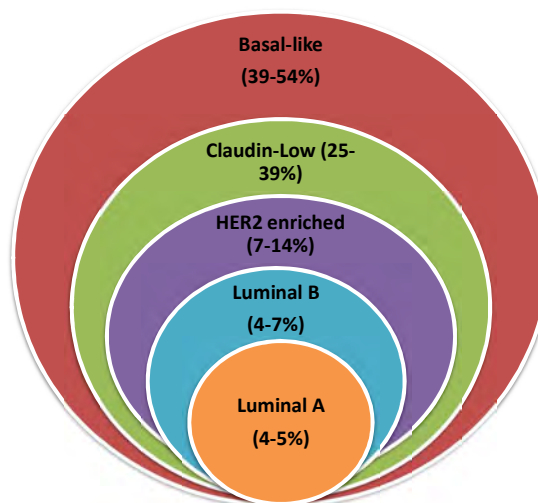
These results provide support to the clinical approach of prolonging 1st line CT in the absence of significant toxicity and disease progression (when CT is the only option...)

Role of biologics, HT, metronomic CT !?!

Gennari et al, J Clin Oncol 2011

Heterogeneity of TNBC:

Data from the UNC337, NKI1295, MDACC133 databases



Basal-like

- Up to 19% are ER+

Claudin-low

- Up to 33% are ER+

Pratt et al, Breast Cancer Res, 2010

Courtesy H. Rugo, ASCO 2011



ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Case 5: Metastatic HR+ BC with visceral crisis

*Authors: Luka Dobovišek, MD; Anja Kovač, MD
Mentor: Simona Borštnar, MD, PhD*

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

CLINICAL PRESENTATION

- 51-year old female (March 2017)
- 2 months history of dry cough, pleuritic and abdominal pain
- Other medical conditions: none
- Gynecological history: regular menses, 1x partus, 1x abortus
- PS 2, jaundice, palpable mass left breast (5 cm), enlarged liver (reaching the umbilical line)
- CT (thorax, abdomen): multiple confluating liver lesions, tumour left breast (35 mm), tumor in the left ovary



TUMOR BIOMARKERS AND STAGING

- Core needle biopsy (left breast): IDC, grade II, ER 100 %, PR 70 %, Ki67 5 %, Her2 negative
- Laboratory:
 - **AST 3.06** ukat/l (>5xULN),
 - **ALT 1.24** ukat/l (>2xULN),
 - **AF 11.03** ukat/l (>6xULN),
 - **GGT 30.79** ukat/l (>48xULN),
 - **bilirubin total 75** umol/l (>5xULN),
 - Ca 15-3 >3000 kU/l,
 - LDH 3,52 ukat/l.



voting

QUESTION 1: FIRST-LINE TREATMENT?

- A ENDOCRINE THERAPY
- B ENDOCRINE THERAPY + CDK 4/6 INHIBITOR
- C CHT



voting

QUESTION 2: WHAT KIND OF CHT WOULD YOU GIVE?

- A TAXANE
- B VINORELBINE
- C ERIBULIN
- D ANTHRACYCLINE
- E CAPECITABINE



FIRST-LINE TREATMENT

- March – June 2017 – 12 x weekly vinorelbine 25 mg/m²
- Clinically improvement in PS (now 1), pain well controlled on analgetics, liver border palpable 8 cm above umbilical line
 - Lab Jun 2017:
 - AST 1.33 ukat/l,
 - ALT 1.52 ukat/l,
 - AF 8.46 ukat/l,
 - yGT 33.27 ukat/l,
 - bilirubin total 16 umol/l,
 - Ca 15-3 >3000 kU/l,
 - LDH 3.07 ukat/l.
- CT (thorax, abdomen) Jun 2017: stable disease in liver



voting

QUESTION 3:

AFTER VISCERAL CRISIS IS OVER ... WHAT WOULD YOU GIVE NEXT?

- A TAMOXIFEN
- B TAMOXIFEN + CDK 4/6 INHIBITOR
- C TAMOXIFEN + LHRH ANALOG
- D AI + LHRH ANALOG
- E AI + LHRH ANALOG + CDK 4/6 INHIBITOR
- F METRONOMIC CHT



SECOND-LINE THERAPY

- July 2017 – COMPLEMENT-1:
 - Ribociclib 600 mg
 - Letrozol 2,5 mg
 - Goserelin 3,6 mg
- Patient returned to work, asymptomatic, no analgetics needed, tumour left breast 2 cm, liver border not palpable
- Lab Aug 2018:
 - AST 0.75 ukat/l,
 - ALT 0.96 ukat/l,
 - AF 4.32 ukat/l,
 - yGT 7.16 ukat/l,
 - bilirubin total 5 umol/l,
 - Ca 15-3 344 kU/l,
 - LDH 2.79 ukat/l



- CT Jul 2018: stable liver metastasis (target lesion regression from Oct 2017 22 in 13 mm to 9 and 11 mm in Apr 2018)

voting

QUESTION 4:

WHAT WOULD YOU GIVE AFTER PROGRESSION?

- A TAMOXIFEN
- B FULVESTRANT
- C FULVESTRANT + CDK 4/6 INHIBITOR
- D FULVESTRANT + ALPELISIB
- E EXEMESTANE + EVEROLIMUS
- F CHT



CONCLUSION

- CHT is the optimal choice for the treatment of visceral crisis in luminal subtype of BC
- Otherwise ET (+/- CDK 4/6 inhibitor) is the preferred option in endocrine-responsive BC



Case 6: Primary metastatic HER2+, HR+ BC

Author: *Luka Dobovišek, MD*

Mentor: *Simona Borštnar, MD, PhD*

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

CLINICAL PRESENTATION

- 49-year old female, nurse (april, 2019)
- 2 months history of cough
- Skin changes in the right breast (peau d'orange)
- Other medical conditions: none
- Gynecological history: regular menses, 1x partus
- Family history: grandmother on her mother side had BC



CLINICAL PRESENTATION

- Because of the cough hospitalized at the internal medicine department (pneumonia? pulmonary embolism?)
- Abnormal chest x-ray: effusion and pathological lesions
- Pleural puncture: atypical cells – malignant pleural effusion?



voting

QUESTION 1:

WHICH PROCEDURES WOULD YOU ORDER?

- A CT SCAN OF THE ABDOMEN AND THORAX
- B BONE SCAN
- C CORE NEEDLE BIOPSY (CNB)
- D PET-CT
- E A + B
- F A + B + C



IMAGING STUDIES

- Mammography with tomosynthesis (march, 2019):
 - 23x12 mm tumor formation in the lower two quadrants
 - Thickened skin in the lower quadrants
- Bone scan (april, 2019):
 - Many of the points of increased activity in practically whole axial skeleton – diffuse infiltration



IMAGING STUDIES

- CT (thorax, abdomen, neck):
 - Pronounced thickened skin of right breast
 - Signs of pulmonary lymphangitic carcinomatosis of the right lung with pleural effusion
 - Pericardial effusion
 - Diffuse osteoblastic infiltration of the skeleton



TUMOR BIOMARKERS AND STAGING

- PATHOLOGY:
- Core needle biopsy (17.4.2019):
- IDC, Grade 2, ER 100%, PR 15%, Ki67 25%, HER2+ (IHK 3+)
- LABORATORY:
 - Ca 15-3: 527
 - AF: 2.40
 - AST: 0.79
 - GGT: 0.65



voting

QUESTION 1: FIRST-LINE THERAPY?

- A CHT + ANTI-HER2 THERAPY
- B ET + ANTI-HER2 THERAPY
- C CHT
- D ET



voting

QUESTION 2: WHICH CHT WOULD YOU CHOOSE?

- A TAXANE
- B DOXORUBICIN + CYCLOPHOSPHAMIDE (AC)
- C GEMCITABINE + CISPLATIN
- D CMF



voting

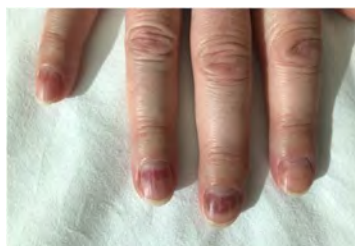
QUESTION 3: WHAT KIND OF ANTI-HER2 THERAPY?

- A TRASTUZUMAB
- B TRASTUZUMAB + PERTUZUMAB
- C NERATINIB
- D TRASTUZUMAB EMTANSINE (T-DM1)



FIRST-LINE TREATMENT

- Docetaxel + Trastuzumab + Pertuzumab
 - No major AE
 - Taxane induced paronychia, nail changes, fatigue
- Normalization of the tumor marker



voting

QUESTION 4: HOW LONG DO YOU CONTINUE CHT?

- A 2 MONTHS
- B 4 MONTHS
- C 6 MONTHS
- D UNTIL BEST RESPONSE
- E UNTIL MAJOR ADVERSE EVENTS



voting

QUESTION 5:

WHAT KIND OF TREATMENT WOULD YOU GIVE AFTER COMPLETION OF CHT?

- A TRASTUZUMAB + PERTUZUMAB
- B TRASTUZUMAB + PERTUZUMAB + ET
- C TRASTUZUMAB + ET
- D ET



voting

QUESTION 6:

WHAT KIND OF ENDOCRINE THERAPY WOULD YOU GIVE?

- A AROMATASE INHIBITOR
- B TAMOXIFEN
- C AROMATASE INHIBITOR + LHRH ANALOG
- D TAMOXIFEN + LHRH ANALOG



voting

QUESTION 7:

WHAT IS EXPECTED MEDIAN OVERALL SURVIVAL FOR THIS PATIENT?

- A 12 MONTHS
- B 24 MONTHS
- C 59 MONTHS



voting

QUESTION 8:

WHAT THERAPY WOULD YOU GIVE AFTER PROGRESSION?

- A CHT
- B TRASTUZUMAB EMTANSINE (T-DM1)
- C CHANGE THE ENDOCRINE THERAPY AND CONTINUE TRASTUZUMAB + PERTUZUMAB
- D NERATINIB



CONCLUSION

- There are many therapeutical options in „triple positive“ (ER+, PR+, HER2+) metastatic BC
- Anti-HER2 therapy is the backbone of HER2+ BC treatment
- Majority of patients with HER2+ disease have long OS



Case 7: Metastatic TNBC

Author: Luka Dobovišek, MD

Mentor: Simona Borštnar, MD, PhD

1st Summer School in Medical Oncology
3. - 6. September 2019
LJUBLJANA

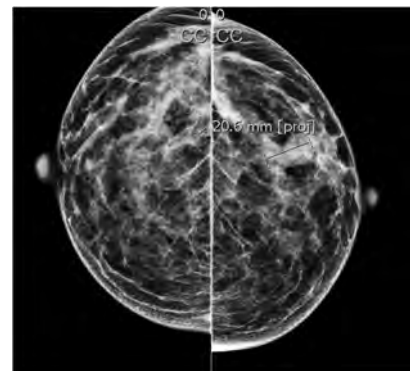
CLINICAL PRESENTATION

- 38-year old female (January, 2017)
- Lump in left breast
- Other medical conditions: none
- Gynecological history: regular menses, 2x partus, uses contraceptive pills
- Family history: aunt had a BC at similar age

IMAGING

- Mammography: 21 mm tumor formation in upper outer quadrant of the left breast
- US guided core needle biopsy with clip marking
- US of left axilla: one pathological lymph node
 - FNA: adenocarcinoma
- CT (thorax, abdomen): tumor formation in left breast, 3 pathological ipsilateral internal mammary nodes

MAMMOGRAPHY



TUMOR BIOMARKERS AND STAGING

- Core needle biopsy:
 - IDC
 - Grade 3
 - ER 0%
 - PR 0%
 - HER-2 neg.
 - Ki67 50%
- Germline BRCA 1/2 negative

NACT AND OPERATION

- 4x dd AC + 4x dd paclitaxel with growth factor support
- CT (thorax): partial response in the left breast, complete response in internal mammary nodes (May, 2017)
- Breast conserving surgery with SLNB and ALND (June, 2017)
- Pathological examination after NACT:
 - Partial response in the breast: 9 mm residual tumor
 - 1/27 positive nodes: 5 mm, focal extracapsular extension, lymphovascular invasion

ADJUVANT CHT AND RT

- RT (august - september, 2017)
 - 50 Gy in 28 fractions
- Capecitabine 8 cycles (september, 2017 - february, 2018)
- Lower back and hip pain (april, 2018)
- CT (thorax, abdomen):
 - pathological lymph nodes in mediastinum,
 - new lytic bone lesions (spine, ribs, right sacrum)



voting

QUESTION 1:

FIRST-LINE THERAPY FOR mTNBC BC?

- A GEMCITABINE - CISPLATIN
- B VINORELBINE
- C ERIBULIN
- D CAPECITABINE
- E TAXANE + IMMUNOTHERAPY (ATEZOLIZUMAB)
- F PALLIATIVE RADIATION THERAPY



METASTATIC DISEASE

- Palliative radiation to the sacroiliacal joint (12 Gy) and 10th rib (9 Gy)
- Gemcitabine-cisplatin /3 week (june - september, 2018)
 - AE: fatigue, neutropenia (+ pegfilgrastim)
- CT (thorax, abdomen): regression of nodal and skeletal metastases (september, 2018)
- After 4 cycles refuses further therapy



voting

QUESTION 2:

WHAT WOULD YOU DO NOW?

- A ERIBULIN
- B VINORELBINE
- C CAPECITABINE
- D METRONOMIC CM
- E WAIT UNTIL PROGRESSION



METASTATIC DISEASE

- NGS (Foundation One):
 - somatic mutation of BRCA1
 - FGFR2 amplification, TP53 mutation
 - MS-Stable
 - TMB-low (4 muts/Mb)
- Olaparib (PARPi) 2x 300 mg (november, 2018)
 - AE: nausea, diarrhea, loss of appetite, fatigue, depression
- She refuses further therapy after 2 weeks



DISEASE PROGRESSION

- Pain in thoracic spine (january, 2019)
 - CT (thorax, abdomen): progression of skeletal metastasis and pathological fracture of TH9 and L2.
- Confusion and headache (february, 2019)
 - CT (head): diffuse metastatic infiltration of the brain, intrametastatic hemorrhage, herniation in foramen ovale



voting

QUESTION 3:

TREATMENT FOR CNS METASTASIS?

- A RADIOTHERAPY
- B SYSTEMIC THERAPY
- C RADIOTHERAPY FOLLOWED BY SYSTEMIC THERAPY



PROGRESSION IN THE CNS

- RADIOTHERAPY:
 - Palliative radiation to the head (30 Gy)
 - Palliative radiation to the spine Th9-L2 (20 Gy)
- Hospitalized for symptomatic treatment and dies at the department (march, 2019)



CONCLUSION

- mTNBC is the subtype with the worst prognosis with mOS approximately 1 year
- TNBC remains a challenge in everyday clinical practice, new therapies are in active development
- New therapies are needed for CNS metastasis in all BC types



1st Summer School in Medical Oncology –
Standards and Open Questions

Systemic treatment in advanced soft tissue sarcoma (STS): what is standard, what is new

Mojca Unk, MD, MSc
Institute of Oncology Ljubljana
Department of Medical Oncology

3. - 6. September 2019

Audience....

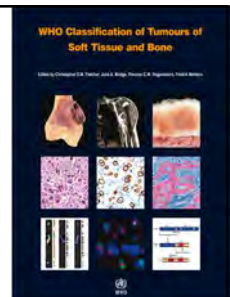


1st question

- How confident are you in systemic treatment of advanced STS?
- 1. very confident
- 2. somehow confident
- 3. not confident at all

Background

- Heterogeneous group of rare neoplasms with mesenchymal origin
- More than 70 different entities
- Strong tendency toward local recurrence (10 -30 %) and metastatic spreading (30 – 40 %)
- Lung: most common site of STS metastases
- Pulmonary metastasectomy - the standard treatment for selected patients with limited lung disease
- Chemotherapy - the most relevant role in the management of metastatic disease
- Outcome for M1 disease - very poor (mOS 14–17 months)



Prognostic factors

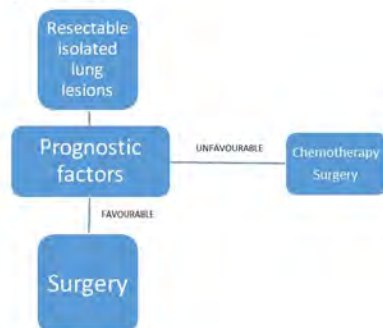
- Age (> 60 y)
- Size (> 5 cm)
- Grade (high)
- Mitotic count (high)
- Location (limb or torzo)
- Deep
- Lymph nodes positive
- Lung; most common site
 - liver; visceral STS
- Complex treatment (multidisciplinary decision); mostly systemic
- Poor prognosis: mOS $\begin{smallmatrix} x & x & x \\ x & & x \\ x & x & x \end{smallmatrix}$ 14 m

Pisters et al. JCO. 1996; Singer et al. Ann Surg. 1994; Van Glebbeke et al. JCO. 1999; Gustafson et al. Acta Orthop Scand. 1994; Lewis et al. Ann Surg. 1998; Trovik et al. Eur J Cancer. 2000; Erzen et al. J Surg Oncol. 2005. ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018

Pulmonary resection

surgery of isolated lung metastases

5-y OS 32 %



J Thorac Cardiovasc Surg. 1994 Feb;107(2):260-6

Analysis of prognostic factors in patients undergoing resection of pulmonary metastases from soft tissue sarcomas.

Eytan AJ, Roth JA, Gressler ME, Johnston MR, Rosenbers SA

- the tumour doubling time (20 days; mOS 22 vs 6 m)
- the number of metastases on preoperative CT (4 mets; mOS 23 vs 6 m)
- the disease-free interval (12 m; mOS 32 vs 10 m)

Blackmon et al. Ann Thorac Surg. 2009

STS – 1st line systemic treatment

Lancet Oncol 2014; 15: 415–23

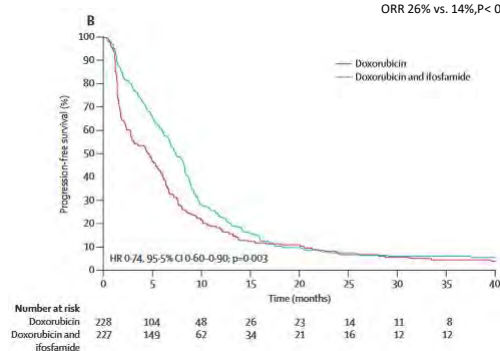
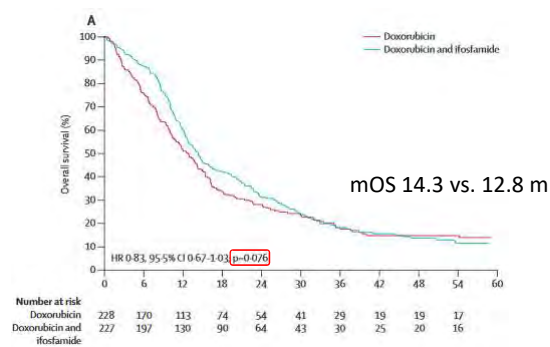
Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarski, Jeremy Whelan, Peter Höbinger, Anders Kjaer-Hansen, Thierry Akinci, Sandrine Marraud, Saskia Lilière, Catherine Hermans, Cynil Fisher, Pinaras C W Hogendoorn, A Paolo del Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group*

	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable	11 (5%)	16 (7%)

Data are n (%).

ORR 26% vs. 14%, $P < 0.0006$



Mono/polychemotherapy

author	chemotherapy	Pt (number)	response rate	survival
Muss (1985)	A/AC	104	NS	NS
Omura (1983)	A/AD	146	NS	NS
Borden (1987)	A/AD	186	AD 30% (p=.02)	NS
Lerner (1987)	A/AD	66	AD 40% (LMS)	NS
Santoro (1995)	A/AI/CYVADIC	449	NS	NS
Borden (1990)	A/AV	195	NS	NS
Edmonson (1993)	A/AI/APM	262	AI 34% (p=.03)	NS
Antman (1993)	AD/MAID	340	MAID 32 % (p=.02)	NS
Judson (2014)	A/AI	415	AI 26% (A 14%)	NS
Ryan (2013)	A/APal	447	APal 28% (A 19%)	NS

NO SURVIVAL BENEFIT; doxorubicin 75mg/m² is golden standard for more than 40 years!

A- doxorubicin; C- cyclofosfamid; D-dacarabazin; I- ifosfamid; CYVADIC- cyclofosfamid, vincristin, doxorubicin, dacarabazin;
MAID- mesna, doxorubicin, ifosfamid, dacarabazin; V-vincristin; APM-doxorubicin, cisplatin, mitomycin; Pal-palifosfamid

.... no convincing evidence of superiority as upfront treatment (prodrugs, novel drugs)

- Amrubicin (3rd gen)

- nonrandomised single arm phase II: similar results as doxo
- cardiac sparing alternative

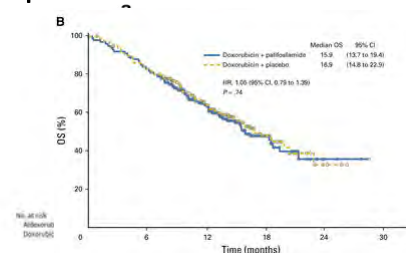
- Aldoxorubicin (prodrug of doxorubicin) with a pH-sensitive linker; activity in acidic tumour environment: enhancing activity and minimising toxicity

phase 2b: aldoxo vs doxo ↑ PFS (5.6 vs. 2.7 months; P= 0.02) ↑ ORR (25% vs. 0%)

on-going phase 1b: safety and activity of aldoxo + ifo

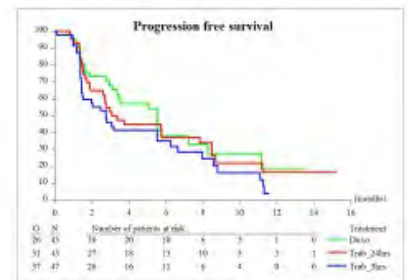
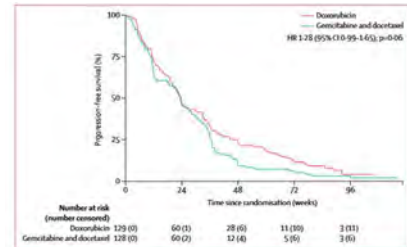
- Palifosfamide (active metabolite of ifosfamide)

- Neg PICASSO III (palif+doxo vs doxo)



.... no convincing evidence of superiority as upfront treatment (the upfront administration of compounds known to be active in further lines)

- GeDDiS: gem+doce vs doxo
 - no differential treatment effect by histological subtype ($p=0.24$)
 - superiority of single agent doxo: ORR (65.9% vs. 58.6%)
 - PFS(23 vs. 24 weeks)
- Trabectedin: 2 phase 2 trails
 - Trabectedin (3 or 24h inf.) vs doxo; neg
 - Trabectedin + doxo vs doxo; stopped for futility



Seddon et al. Lancet Oncol 2014; Bui-Nguyen et al. Eur J Cancer 2015; Martin-Brito et al. JCO 2016.

.... no convincing evidence of superiority as upfront treatment (monoclonal antibodies)

ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS).

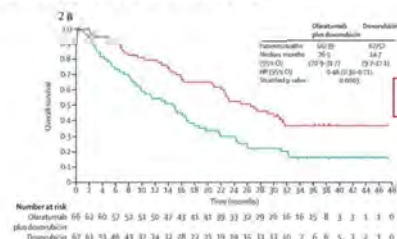
Tap et al. ASCO 2019.

ANNOUNCE did not confirm that olaratumab + doxorubicin, followed by olaratumab monotherapy, improves OS over doxorubicin in pts with advanced STS. Further analyses are warranted to explore the inconsistent outcomes between the Ph 3 and Ph 2 studies.

Lancet. 2016 July 30; 388(10043): 488–497. doi:10.1016/S0140-6736(16)30587-6.

Olaratumab and doxorubicin versus doxorubicin alone in soft tissue sarcoma

William D. Tap, MD¹, Robin L. Jones, MD^{2,a}, Brian A. Van Tine, MD³, Bartosz Chmielewski, MD⁴, Anthony D. Elias, MD⁵, Douglas Adkins, MD³, Mark Agulnik, MD⁶, Matthew M. Cooney, MD⁷, Michael B. Livingston, MD⁸, Gregory Pennock, MD⁹, Meera R. Hameed, MD¹⁰, Gaurav D. Shah, MD¹¹, Amy Qin, PhD¹², Ashwin Shahir, MD¹³, Damien M. Cronier, PhD¹³, Robert Ilaria Jr, MD¹⁴, Ilaria Conti, MD¹⁴, Jan Cosaert, MD^{12,b}, and Gary K. Schwartz, MD¹⁵



+ 12months!

Targeted therapy

- Dermatofibrosarcoma protuberans (DFSP) and imatinib
 - translocation COL1A1/PDGFB fusion gene → PDGFRB activation
 - metastatic potential- fibrosarcomatous (FS) component
 - imatinib mesylate: ORR 60–70%
 - FS-DFSP: translocation +, imatinib sensitivity + with RR ~ 80%, but shorter duration
- Alveolar soft part sarcoma (ASPS)
 - Chemo resistant, MET overexpression
 - Antiangiogenic drugs: sunitinib, pazopanib, cediranib
 - MET inhibitors: crizotinib
 - Immunotherapy (phase 2: atezo and tremi/durva)
- Solitary fibrous tumour (SFT)
 - NAB2-STAT6 fusion
 - Chemotherapy but also antiangiogenic drugs: sunitinib, sorafenib, pazopanib, axitinib

Simon et al. Nat. Genet. 1997; Greco et al. Oncogene 1998; Stacchiotti et al. Clin. Can. Res. 2016; Reichardt et al. EJC 2003; Stacchiotti et al. EJC 2013; Somala, discussant@CTOX2018; Schoffski et al. Ann. Oncol. 2017; Judson et al. Lancet Oncol. 2018.

Doxorubicin remains the standard of care, with or without ifosfamide!

STS – further line systemic treatment

Further lines

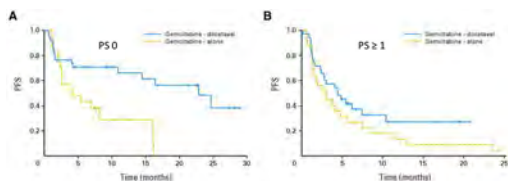
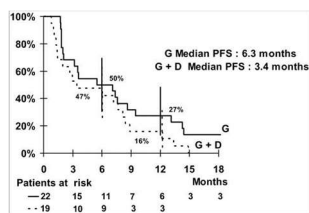


- Histology driven treatment:
 - Chemotherapy
 - TKI targeting angiogenesis
 - Other TKI
 - Immunotherapy
- Best supportive care

Chemotherapy

Gemcitabine (alone or in combination)

- LMS: gem+doce; conflicting results

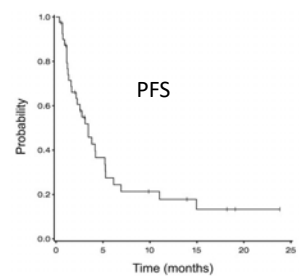


Pautier et al. Oncologist 2012; Maki et al, JCO 2007

- Gem+vinorelbin

clinical benefit rate 25%

Dileo et al, cancer 2008



- Gem+dacarbazine

mPFS 4.2 vs. 2 m, $P = 0.005$

mOS 16.8 vs. 8.2 m, $P = 0.014$

clinical benefit rate (49% vs. 25%, $P = 0.009$)

Garcia del Muro et al, JCO 2011

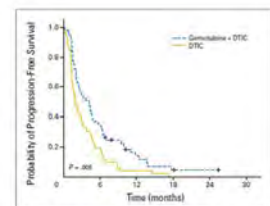
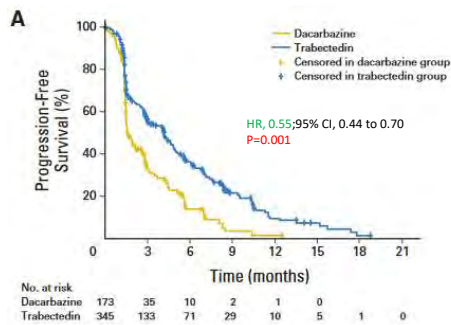


Fig 2. Kaplan-Meier curves for progression-free survival. DTIC, dacarbazine.

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

George D. Demetri, Margarete von Minckwitz, Robin L. Jones, Marlene L. Hensley, Scott M. Schacter, Arthur Stauden, Mohammed Milhem, Anthony Elias, Kristen Gajdos, Hsueh-Tsai, Brian A. Van Tine, Alexander Spin, Andrew Dearn, Naohisa Z. Kihara, Yoon Choi Park, Roland E. Kneiblich, Trish V. Parikh, Robert G. Maki, and Shreyaskumar R. Patel

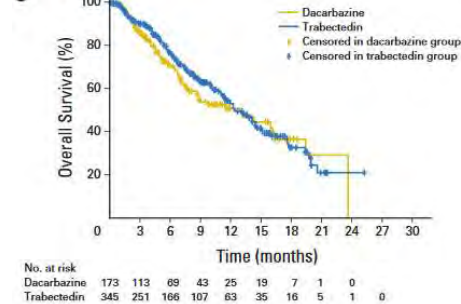
myxoid liposarcoma: t(12;16)(q13;p11)
additional 'targeted' mechanism of action
inactivation FUS-CHOP oncogene



B

Variable	Subgroup	Median (months)		HR	95% CI	Events/n	
		Dacarbazine	Trabectedin			Dacarbazine	Trabectedin
All	All	1.5	4.2	0.55	0.44 to 0.70	112/173	217/345
Lines of prior chemotherapy	1	2.7	4.9	0.49	0.23 to 1.04	11/22	24/38
	> 2	1.5	4.2	0.56	0.43 to 0.71	101/150	193/267
EDOG PS	0	1.5	4.7	0.51	0.38 to 0.71	52/86	104/171
	1	1.5	2.9	0.60	0.43 to 0.82	60/97	113/174
Histologic subtype	Leiomyosarcoma	1.8	4.3	0.55	0.42 to 0.73	85/126	154/252
	Nonleiomyosarcoma	1.6	4.9	0.58	0.37 to 0.92	28/48	70/118
	Uterine	1.5	4.0	0.58	0.41 to 0.81	57/78	84/134
	Liposarcoma	1.5	3.0	0.55	0.34 to 0.87	20/47	63/93
	Dedifferentiated	1.9	2.2	0.68	0.37 to 1.25	19/25	35/45
	Myxoid ± round cell	1.5	5.8	0.41	0.17 to 0.98	8/19	21/38
	Phenotypic	1.4	1.5	0.33	0.07 to 1.84	3/5	7/10
Age, years	< 65	1.8	4.1	0.60	0.46 to 0.78	87/139	173/264
	≥ 65	1.5	4.9	0.40	0.24 to 0.67	25/34	44/81
Sex	Female	1.6	4.2	0.56	0.43 to 0.74	81/116	141/238
	Male	1.5	4.1	0.53	0.34 to 0.82	31/47	76/107
Race	White	1.5	4.2	0.52	0.38 to 0.68	82/125	173/268
	Nonwhite	1.8	2.5	0.65	0.40 to 1.03	30/40	44/76
BMI, kg/m ²	< 30	1.5	4.0	0.56	0.41 to 0.75	72/112	128/203
	≥ 30	2	4.4	0.54	0.37 to 0.80	40/61	89/142

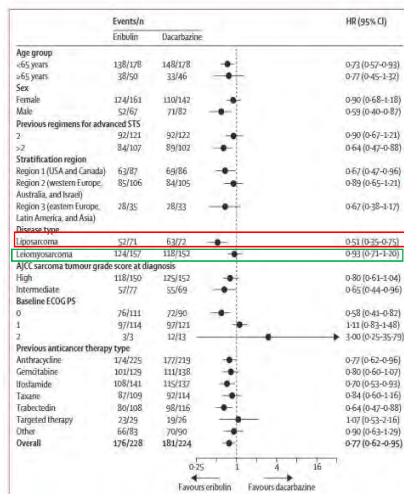
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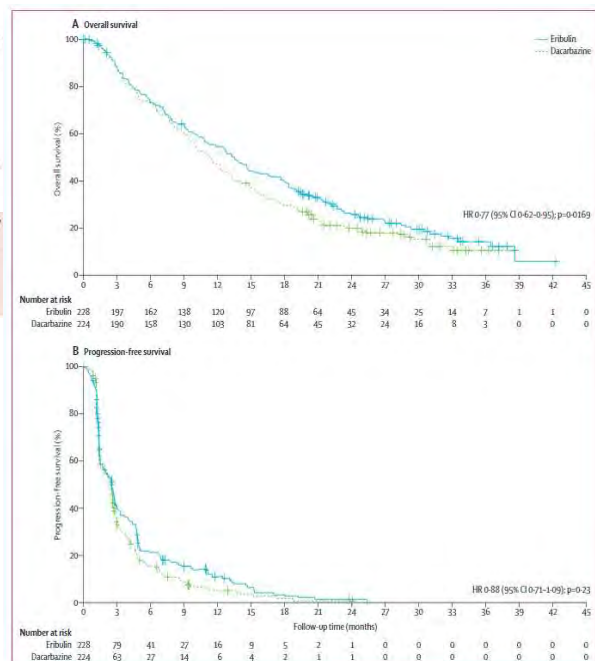
Lancet 2016; 387: 1629-37

Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial

Patrick Schöffski, Sant Chawla, Robert G Maki, Antoine Italiano, Hans Gelderblom, Edwin Choy, Giovanni Grignani, Veridiana Camargo, Sebastian Bauer, Sun Young Rho, Jean-Yves Blay, Peter Hohenberger, David D'Adamo, Matthew Guo, Bartosz Chmielowski, Axel Le Cesne, George D Demetri, Shreyaskumar R Patel



LPS: mOS 15.6 vs 8.4 m
LMS: mOS 12.7 vs 13.0 m



Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study

Nicolas Pendi, Binh Nguyen Bui, Jacques-Olivier Bay, Didier Capissol, Isabelle Ray-Coquard, Sophie Piperno-Neumann, Pierre Kerbrat, Charles Fournier, Sophie Taieb, Maria Jimenez, Nicolas Isambert, Frédéric Peyrache, Christine Chevreau, Emmanuelle Bompas, Etienne G.C. Brain, and Jean-Yves Blay

From the Département de Cancérologie Générale, Unité de Biostatistiques, and

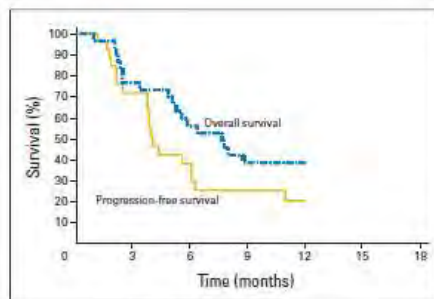


Fig 1. Overall and progression-free survival.

Disease Status	No. of Patients		
	At 2 Months	At 4 Months	At 6 Months
Assessable patients	27*	22	21
Progressive disease	7	12	16
Complete response	0	1	2†
Partial response	6	3	1
Stable disease	15	6	4
Overall response rate			
%	18	18	19
95% CI	4 to 33	2 to 34	3 to 35
Nonprogression rate			
%	71	45	24
95% CI	57 to 80	25 to 66	6 to 42

*Three patients of the 30 enrolled patients were not assessable because of the following reasons: death by unrelated stroke (one patient), severe toxicities with treatment cessation (two patients).

†Complete responses were obtained by surgery (table 4).

weekly paclitaxel seems to be an effective and well-tolerated treatment for patients with unresectable angiosarcoma

Histology driven approach

Histology	Cytotoxic compounds with selective activity
Leiomyosarcoma	Gemcitabine ± docetaxel, trabectedin, dacarbazine
Dedifferentiated liposarcoma	High-dose ifosfamide, trabectedin, eribulin
Myxoid liposarcoma	Trabectedin, eribulin
Synovial sarcoma	Ifosfamide, trabectedin
Epithelioid sarcoma	Gemcitabine
Angiosarcoma/intimal sarcoma	Gemcitabine, paclitaxel
Alveolar soft part sarcoma	
Solitary fibrous tumour	Dacarbazine
Clear cell sarcoma	
Extraskeletal myxoid chondrosarcoma	
Perivascular epithelioid cell tumor	Gemcitabine
Epithelioid hemangioendothelioma	
Inflammatory myofibroblastic tumour	
Undifferentiated pleomorphic sarcoma	High-dose ifosfamide, gemcitabine
Dermatofibrosarcoma protuberans	

TKI targeting angiogenesis

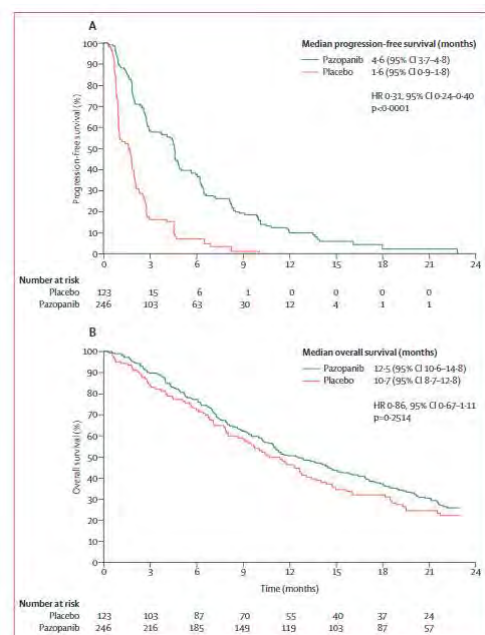
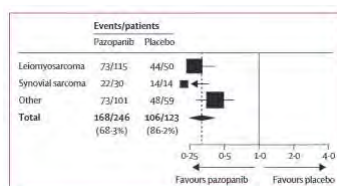
Lancet 2012; 379: 1879-86

Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Cornel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group

Excluded:

adipocytic sarcoma
embryonal rhabdomyosarcoma
bone sarcoma
PNET
GIST
dermatofibrosarcoma protuberans
inflammatory myofibroblastic sarcoma



Other TKI, targeting angiogenesis

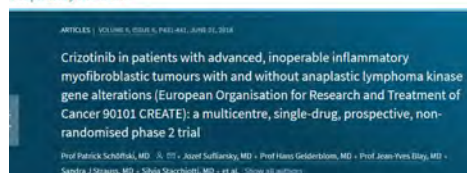
- Sorafenib
- Regorafenib
- Sunitinib
- Cediranib
- Tivozanitinib

Ray-Coquard et al, Oncologist. 2012; Mir et al, Lancet Oncol. 2016; Hindi et al, JCO 2015; Kumar et al, JCO 2013; Agulnik et al, Ann Oncol 2017

Other TKI

- crizotinib

THE LANCET
Respiratory Medicine



crizotinib for pts with locally advanced or metastatic ALK-positive IMFT

ESMO
ORIGINAL ARTICLE

Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE'

P. Schöffski^{1,2*}, A. Wozniak³, S. Stachurski⁴, P. Rutkowski⁵, J. Y. Blay⁶, L. H. Lindner⁷, S. Strauss⁸, A. Anthony⁹, J. Duffaud¹⁰, S. Richter¹¹, V. Grunewald¹², M. G. Leahy¹³, J. Reichardt¹⁴, J. Sallusti¹⁵, W. T. van der Graaf¹⁶, R. Soria¹⁷, M. Delbecq¹⁸, J. van Can¹⁹, S. Marechal²⁰, M. Liat²¹, T. Riekerink²², J. Collette²³ & S. Bauer²⁴

crizotinib provided clinical benefit to patients with locally advanced or metastatic MET+ CCSA

ESMO
ORIGINAL ARTICLE

Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of *TFE3*: European Organization for Research and Treatment of Cancer (EORTC) phase II trial 90101 'CREATE'

P. Schöffski^{1,2*}, A. Wozniak³, B. Kasper⁴, S. Aarndt⁵, M. G. Leahy⁶, P. Rutkowski⁷, S. Bauer⁸, H. Gelderblom⁹, A. Italiano¹⁰, L. H. Lindner¹¹, J. Henning¹², S. Strauss¹³, B. Zakaria¹⁴, A. Anthony¹⁵, L. Abago¹⁶, J. Y. Blay¹⁷, P. Reichardt¹⁸, J. Sallusti¹⁹, W. T. A. van der Graaf²⁰, M. Delbecq²¹, R. Soria²², T. Van Can²³, S. Marechal²⁴, T. Riekerink²⁵, J. Collette²⁶ & S. Stachurski²⁷

crizotinib has activity in TFE3 rearranged ASPS MET+ pts

Immunotherapy

Immunotherapy in STS

Study	Population	Study phase, status	Drug and schedule	Patients	Overall response rate (%)
Mackall et al., 2016 [88]	Synovial sarcoma	I/II, recruiting	NY-ESO-1c259 SPEAR T-cells Cohort 1 and 2: FL 30 mg/m ² /day, day 1–4; CTX 1800 mg/m ² /day day 1–2 Cohort 3: CTX 1800 mg/m ² /day day 1–2 Cohort 4: FL 30 mg/m ² /day, day 1–3; CTX 600 mg/m ² /day, day 1–3	Cohort 1: 15 Cohort 2: 2 Cohort 3: 2 Cohort 4: 0	Cohort 1: 50 Cohort 2: NA Cohort 3: NA Cohort 4: NA
Italiano et al., 2016 [90]	LMS (Arm A), UPS (Arm B), GIST (Arm C), OS (Arm D), other sarcomas (Arm E)	II, recruiting in arm B and D	Pembrolizumab 200 mg i.v. 3-weekly; CTX 50 mg BID 1 week on, 1 week off	Arm A: 15 Arm B: 0 Arm C: 10 Arm D: 0 Arm E: 16	No objective responses
Burgess et al., 2016 [89]	All-type STS (arm A) and BS (arm B)	II, completed	Pembrolizumab, 200mg i.v., 3-weekly	Arm A: 40 Arm B: 40	Arm A: 17.5 (UPS, LPS, SS) Arm B: 5 (OS, CS)
Paoluzzi et al., 2016 [91]	All-type STS and BS	Retrospective	Arm A: nivolumab 3 mg/kg i.v., 2-weekly Arm B: nivolumab 3 mg/kg i.v., 2-weekly + pazopanib 800 mg/day	Arm A: 10 Arm B: 18	Arm A: 10 (CS) Arm B: 11 (ES, OS)
George et al., 2016 [90]	Leiomyosarcoma	II	Nivolumab 3 mg/kg i.v., 2-weekly	12	No objective responses

BS bone sarcomas; CS chondrosarcoma; CTX cyclophosphamide; ES epithelioid sarcoma; FL fludarabine; GIST Gastrointestinal stromal tumors; LMS leiomyosarcoma; LPS liposarcoma; NA not available; OS osteosarcoma; SS synovial sarcoma; STS soft tissue sarcomas; UPS undifferentiated pleomorphic sarcoma

Conclusion

- Doxorubicin remains the standard in the treatment of advanced STS
- Combination with ifosfamide: fit patients, tumour response needed, histologies with selective sensitivity to alkylating agents
- Beyond the 1st line: histology driven treatment
- Newer strategies (drugs targeting epigenetic mechanisms and immunotherapies) are being developed to improve the outcome in this population.

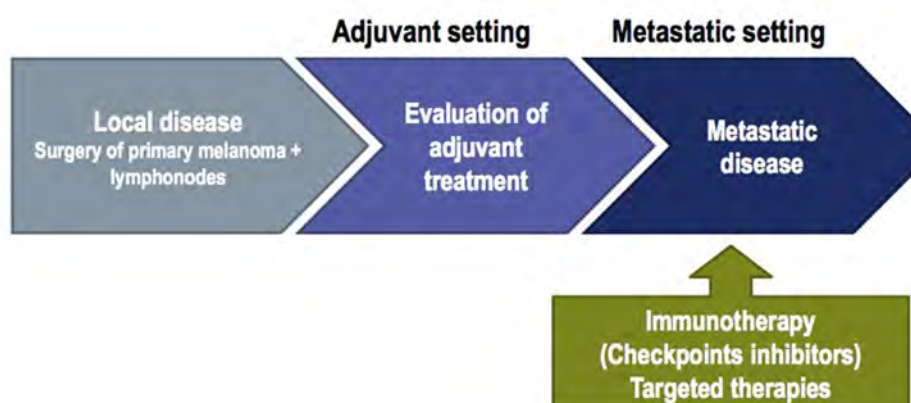
Thank you for your attention!

1st Summer School in medical oncology - Standards and open questions
Ljubljana 2019

Adjuvant treatment strategies for malignant melanoma

Davorin Herceg
University Hospital Zagreb

MELANOMA PATIENT HISTORY: RESEARCH AREAS



Drugs used in metastatic setting have been experimented in the adjuvant setting

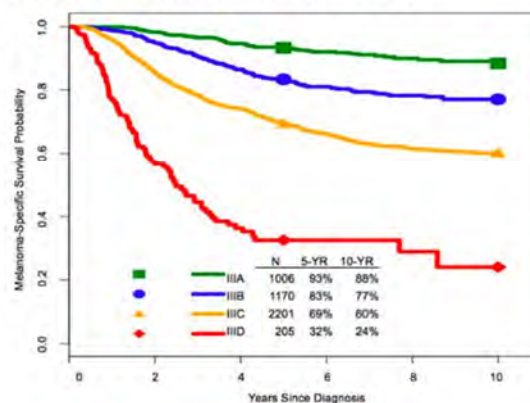
ADJUVANT TREATMENTS IN MELANOMA

Agenda

- Risk category
- 90s – 2016: Interferon
- 2016: Ipilimumab
- 2017: New treatments
 - Immunotherapy: AntiPD1
 - Nivolumab
 - Pembrolizumab
 - Targeted therapies:
 - Vemurafenib
 - Dabrafenib + trametinib

MSS according to Stage III Groups 8th Edition international melanoma database

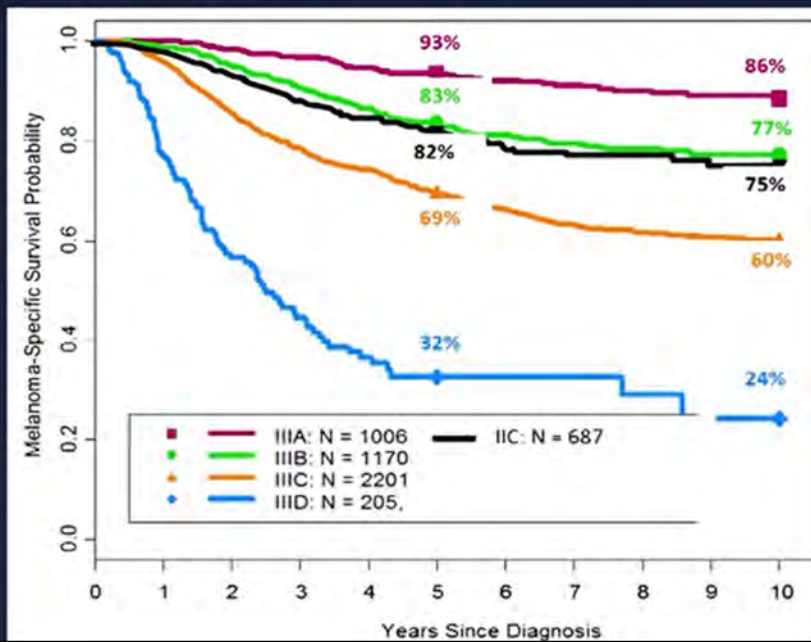
- Stage group stratification based on both T- and N-category criteria
 - Tumor thickness
 - Ulceration
 - # LNs
 - Microsatellite/ITM/satellites
- Recursive partitioning → final = 4 stage groups
- Significant heterogeneity



Gershenwald, Scolyer, Hess, Sondak et al. CA Cancer J Clin. 2017 Oct 13; doi: 10.3322/caac.21409. [Epub ahead of print]

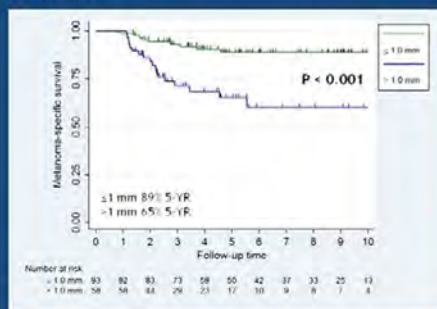
AJCC 2018: Stage III Survival

Willekind 2017, TNM handbook 2017

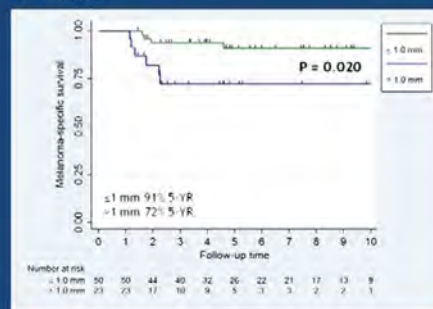


Survival differentiation in stage IIIA

7th edition



8th edition



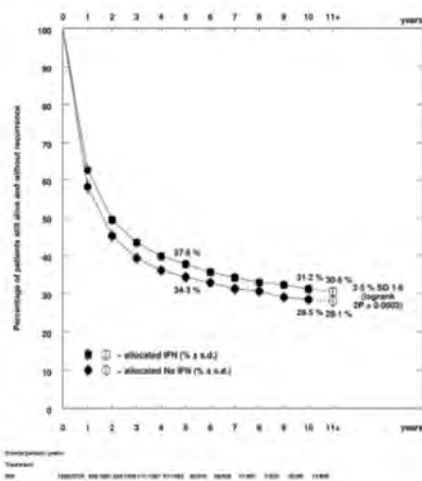


Schedule	Dose	Frequency	Duration
Low dose			
	3 miu	3 x weekly	18-24 months
Intermediate dose			
Induction	10 miu	5 x weekly	4 weeks
Maintenance	10 miu	3 x weekly	12-24 months
	5 miu	3 x weekly	24 months
High dose			
Induction	20 MIU/m ²	5 x weekly	4 weeks
Maintenance	10 MIU/m ²	3 x weekly	11 months
Short course			
Induction x 1	20 MIU/m ²	5 x weekly	4 weeks
Intermittent			
Induction x 3	20 MIU/m ²	5 x weekly	4 weeks Q4 months

Overall risk		
Dose	Event Free Survival	Overall Survival
High (N=1196)	0.83 (0.72-0.96)	0.93 (0.80-1.08)
Peg-IFN (N=1256)	0.83 (0.76-1.00)	0.96 (0.82-1.11)
Intermediate (N=2243)	0.84 (0.74-0.95)	0.91 (0.79-1.04)
Low (N=2732)	0.85 (0.77-0.94)	0.86 (0.77-0.96)
Very low (N=484)	0.99 (0.80-1.23)	0.96 (0.76-1.21)

INTERFERON A – META ANALYSIS 2017

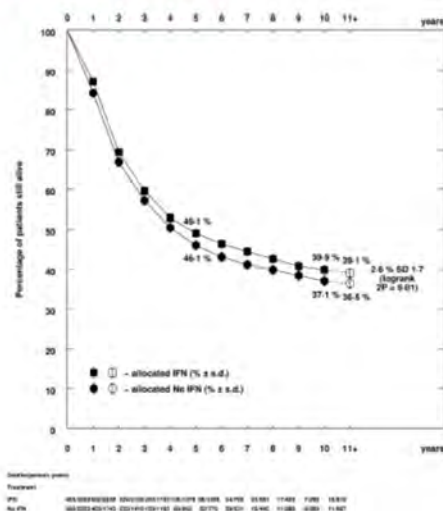
Survival curve for event-free survival



Reprinted from Eur Cancer, 82, Ives NJ, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis; 171-183. Copyright 2017, with permission from Elsevier.

INTERFERON A – META ANALYSIS 2017

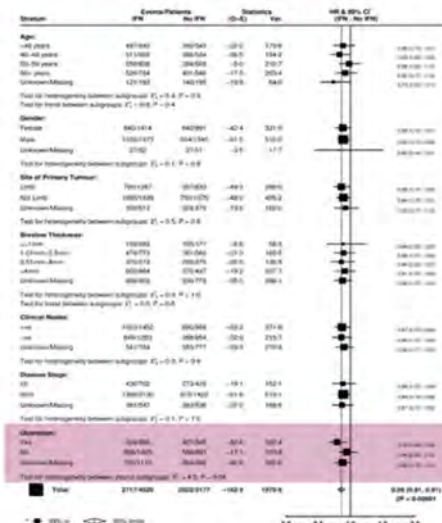
Survival curve for Overall Survival



Reprinted from Eur Cancer, 82, Ives NJ, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis; 171-183. Copyright 2017, with permission from Elsevier.

META ANALYSIS 2017

Subgroup analysis for relapse free survival



Reprinted from Eur Cancer, 82, Ives NJ, et al. Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis; 171-183. Copyright 2017, with permission from Elsevier.

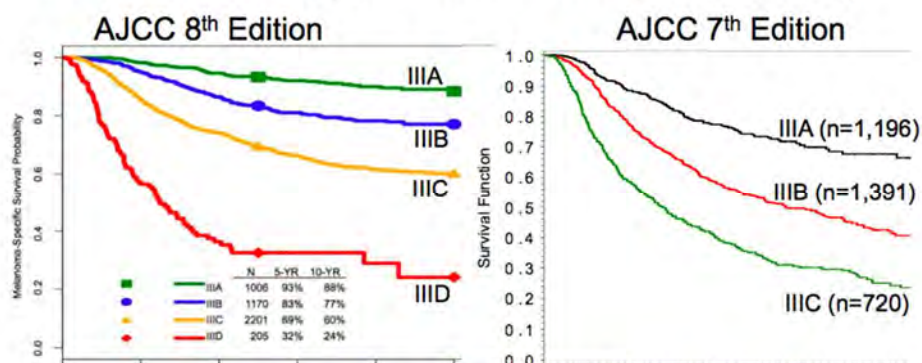
- Modest activity with relatively few adverse events (on low-dose IFN) and serious toxicity (on high-dose IFN)
- In Europe mainly LDI is still used for high-risk AJCC stage IIB/C (SN-negative pts)
- No longer used for stage III patients
- No future for interferons from 2021+!?

Adjuvant Melanoma Trials: Potential Pitfalls

All trials on stage III patients have been conducted

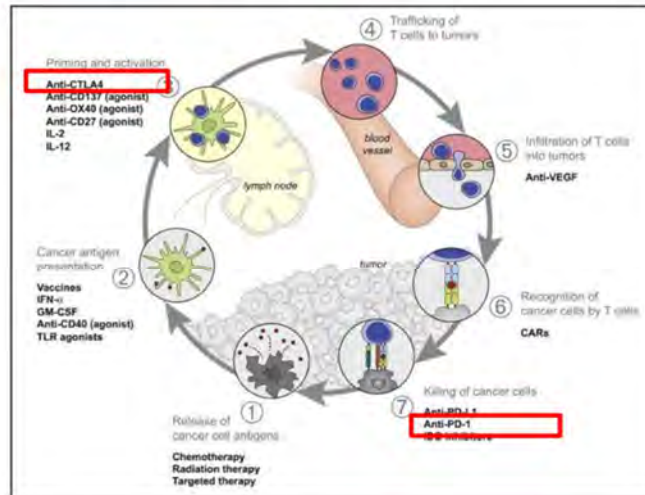
- with selection criteria based on the AJCC 7th edition melanoma classification
- with patients who received a complete lymphadenectomy (CLND)

MSS according to AJCC Stage III Group



Implications for Patient Counseling, Management & Contemporary Adjuvant Clinical Trial Design

Immune checkpoint inhibitors



Reprinted from Immunity 2013; 39(1), Chen DS, Mellman I, Oncology Meets Immunology: The Cancer-Immunity Cycle, 1-10. Copyright 2013, with permission from Elsevier.

CheckMate-238 Study Schema

Randomized, phase 3 study of adjuvant NIVO vs IPI after complete resection of high-risk stage III/IV melanoma

- ≥ 15 year old with melanoma
- Stage IIIb/c or IV before complete resection
- Complete surgical resection
- No prior medical therapy for melanoma treatment
- No ocular/uveal melanoma

RANDOMIZED
1:1

N = 453

N = 453

NIVO 3 mg/kg + IPI PBO IV
Q2 weeks x 4 doses, then
Q12 weeks starting at week 24

IPI 10 mg/kg + NIVO PBO IV
Q2 weeks x 4 doses, then
Q12 weeks starting at week 24

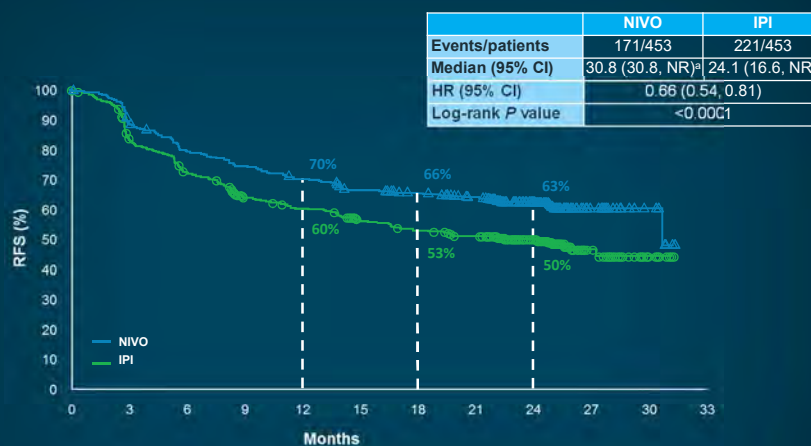
Trial dates: 3/2015 – 11/2019 (estimated)

- **Primary endpoint:** RFS (up to 36 months, ITT population).
- **Secondary endpoints:** OS (up to 48 months).

ITT = intention to treat.

NCT02388906. Weber J et al. *N Engl J Med*. 2017;377:1824-1835.

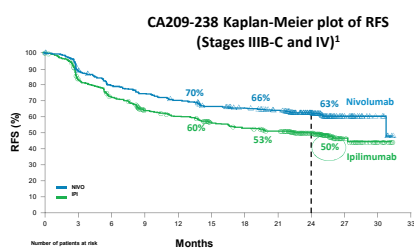
Adjuvant Nivolumab in CheckMate-238: RFS in All Patients



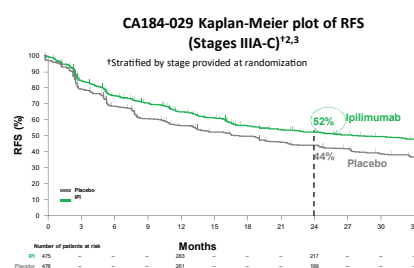
24-month RFS rates were significantly longer for NIVO vs IPI, with DMFS also remaining significantly longer for NIVO (70.5%) vs IPI (63.7%).

Weber J, et al ASCO 2018.

Nivolumab demonstrated superior RFS benefit vs. ipilimumab, an active comparator with proven 5-year OS benefit



NOTE: Stable censoring rate at milestone intervals confirm the robustness of the RFS curve and the potential for this to be predictive of long-term benefit



¹Stratified by stage provided at randomization

	Nivolumab	Ipilimumab		Ipilimumab	Placebo
Events/patients	171/453	221/453	Events/patients	264/475	323/476
Median (95% CI)	30.8 (30.8, NR)	24.1 (16.6, NR)	Median (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)
HR (95% CI), P value	0.66 (0.54, 0.81), <0.0001		HR (95% CI), P value	0.76 (0.64, 0.89), 0.0008	

- Significantly fewer patients experienced relapse or death with nivolumab than with active control, ipilimumab¹
- Nivolumab magnitude of benefit is durable through 2 years¹
- Informal comparison of CA209-238 and CA184-029 results suggests that nivolumab RFS rates are even greater than placebo^{1,2}

RFS: Pre-specified Subgroups



AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Acceptable toxicity profile

Safety Summary

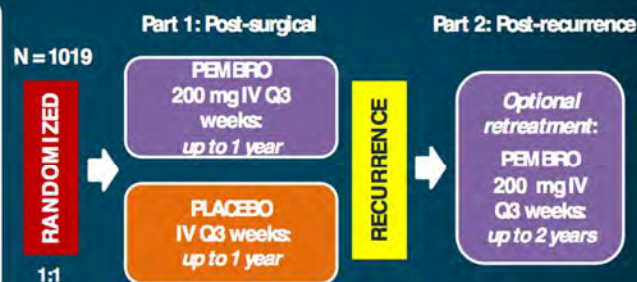
n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
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KEYNOTE-54 (EORTC1325) Study Schema

Randomized, phase 3 study of adjuvant PEMBRO after complete resection of high-risk stage III melanoma

- ≥ 18 year old with melanoma
- Complete surgical resection of stage III disease
- No ocular/mucosal melanoma
- No prior medical therapy for melanoma treatment
- No previous CTLA4 treatment



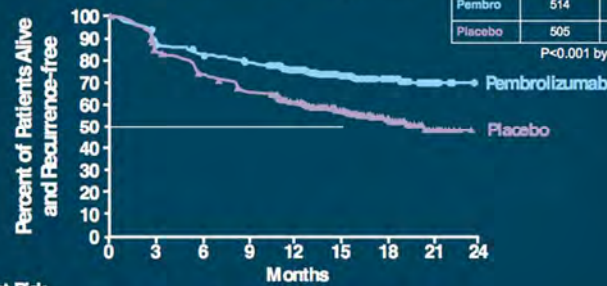
Trial dates: 7/2015 – 7/2023 (estimated)

- **Primary endpoint:** FFS(6 months), FFSpercentage with PD-L1 positive tumor expression.
- **Secondary endpoints:** DMFSand OS(overall vs PD-L1 tumor expression), AE

NCT02362594. Eggermont AMM, et al. *N Eng J Med*. 2018;378:1789-1801.

KEYNOTE-54 (EORTC1325): RFS ITT Population

Overall Intention-to-Treat Population



	Total No.	No. with Event	Hazard Ratio (95% CI)
Pembro	514	135	0.57 (0.43-0.74)
Placebo	505	216	1.00

P<0.001 by stratified log-rank test

No. at Risk

Pembrolizumab	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

RFS rates were longer for PEMBRO (71.4%) vs. PBO (53.2%) at 18 months, with distant metastasis incidence of 16.7% vs 29.7% respectively.

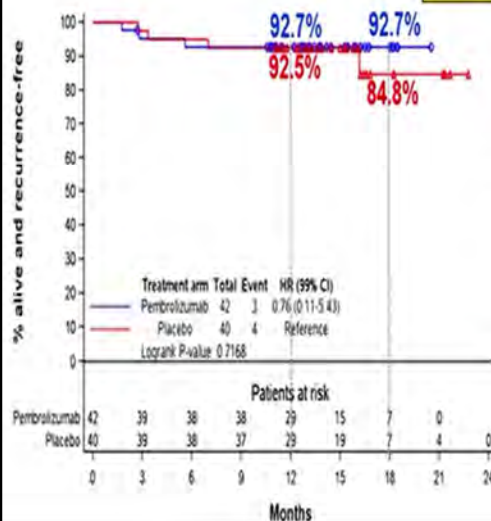
Eggermont AMM, et al. *N Engl J Med*. 2018;378:1789-1801.

Recurrence-Free Survival: subgroup analysis by AJCC-8

Eggermont KN054 SMR 2018

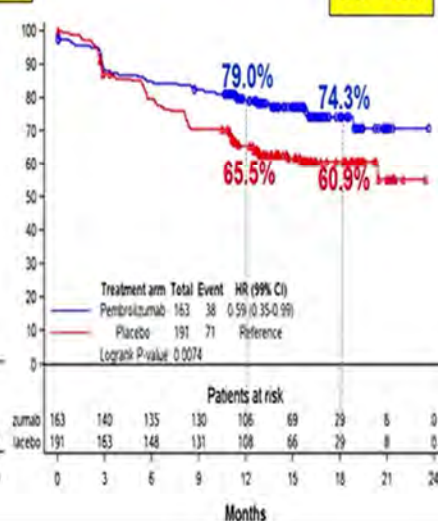
AJCC-8 Stage IIIA

HR 0.76

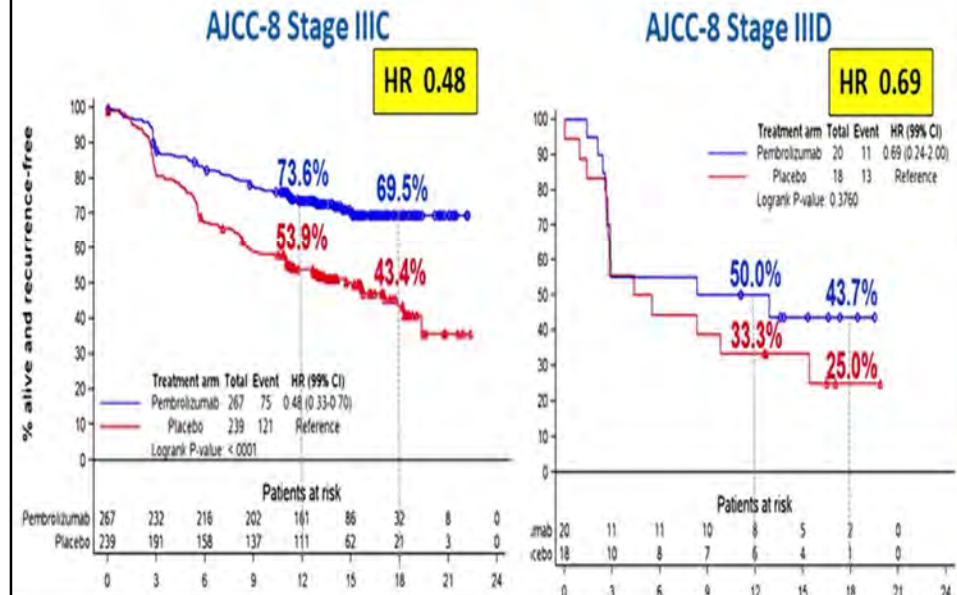


AJCC-8 Stage IIIB

HR 0.59



Recurrence-Free Survival: subgroup analysis by AJCC-8 (cont)



Patient Disposition and Treatment

J. Eggermont AACR 2018

	Pembrolizumab (N=514)	Placebo (N=505)
Started allocated treatment	N=509	N=502
Reasons for discontinuation, %	96.3%	98.8%
Normal completion	55.4	58.6
Disease recurrence	21.4	35.7
Adverse event	13.8	2.2
Patient/investigator decision	3.5	1.2
Other malignancy	0.8	1.0
Non-compliance/Other reason	1.3	0.2
Still on treatment, %	3.7	1.2
Median (IQR) doses received per patient	18 (9-18)	18 (8-18)

Event	Event				Pembrolizumab (N=509)		Placebo (N=502)	
	Any Grade		Grade ≥3		Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)		number of patients (percent)		number of patients (percent)		number of patients (percent)	
Immune-related adverse events, regardless of investigator attribution								
Any	190	(37.3)	36	(7.1)	43	(8.0)	3	(0.6)
Endocrine disorders	119	(23.4)	9	(1.8)	25	(5.0)	0	0
Hypothyroidism	73	(14.3)	0	0	14	(2.8)	0	0
Hyperthyroidism	52	(10.2)	1	(0.2)	6	(1.2)	0	0
Thyroiditis	16	(3.1)	0	0	1	(0.2)	0	0
Hypophysitis, including hypopituitarism	11	(2.2)	1	(0.2)	1	(0.2)	0	0
Type 1 diabetes mellitus	5	(1.0)	5	(1.0)	0	0	0	0
Adrenal insufficiency	5	(1.0)	1	(0.2)	4	(0.8)	0	0
Respiratory, thoracic and mediastinal disorders	24	(4.7)	4	(0.8)	3	(0.6)	0	0
Pneumonitis or interstitial lung disease	17	(3.3)	4	(0.8)	1	(0.2)	0	0
Sarcoidosis	7	(1.4)	0	0	0	0	0	0
Vitiligo or severe skin reactions	27	(5.3)	3	(0.6)	8	(1.6)	0	0
Vitiligo	24	(4.7)	0	0	8	(1.6)	0	0
Severe skin reactions	3	(0.6)	3	(0.6)	0	0	0	0
Gastrointestinal conditions	20	(3.9)	10	(2.0)	4	(0.8)	2	(0.4)
Colitis	19	(3.7)	10	(2.0)	3	(0.6)	1	(0.2)
Pancreatitis	2	(0.4)	1	(0.2)	1	(0.2)	1	(0.2)
Hepatobiliary disorders	9	(1.8)	7	(1.4)	1	(0.2)	1	(0.2)
Hepatitis	9	(1.8)	7	(1.4)	1	(0.2)	1	(0.2)
Other immune-related adverse events	15	(2.9)	5	(1.0)	5	(1.0)	0	0
Nephritis	2	(0.4)	2	(0.4)	1	(0.2)	0	0
Uveitis	2	(0.4)	0	0	0	0	0	0
Myositis	1	(0.2)	1	(0.2)	1	(0.2)	0	0
Myocarditis	1	(0.2)	1	(0.2)	0	0	0	0

Event	Pembrolizumab (N=509)		Placebo (N=502)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)		number of patients (percent)	
Any adverse event	475	(93.3)	453	(90.2)
Treatment-related adverse events				
Any	196	(38.5)	17	(3.4)
Fatigue or asthenia	189	(37.1)	4	(0.8)
Skin reactions	144	(28.3)	1	(0.2)
Rash	82	(16.1)	1	(0.2)
Pruritus	90	(17.7)	0	0
Diarrhea	97	(19.1)	4	(0.8)
Arthralgia	61	(12.0)	3	(0.6)
Nausea	58	(11.4)	0	0
Dyspnea	30	(5.9)	1	(0.2)

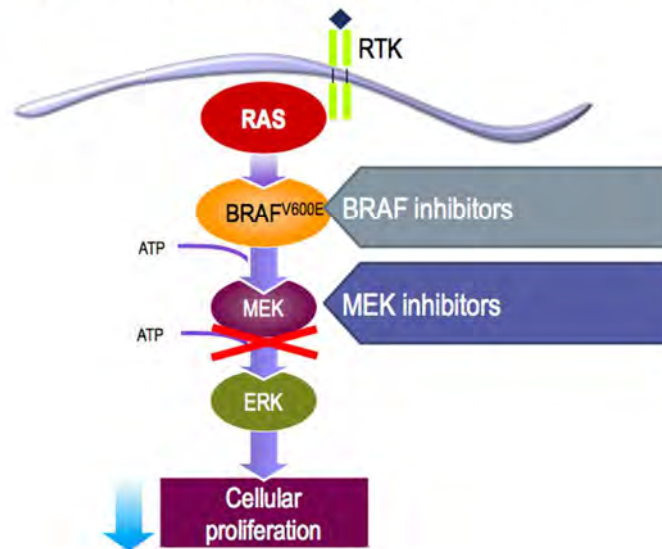
Adjuvant Nivolumab and Pembrolizumab

Effective in both BRAF mutated and wild-type melanoma pts in stage III/IV!

Well-tolerated in general (10-14% treatment discontinuations), but some rare, irreversible AEs

BRAF AND MEK INHIBITORS

Mechanism of action of BRAF and MEK inhibitors



BRAF MONOTHERAPY IN THE ADJUVANT SETTING

MADRID 2017 **ESMO** congress

BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients with completely resected *BRAF*^{V600+} melanoma at high risk for recurrence

Karl Lewis,¹ Michele Maio,² Lev Demidov,³ Mario Mandalà,⁴ Paolo A. Ascierto,⁵ Christopher Herbert,⁶ Andrzej Mackiewicz,⁷ Piotr Rutkowski,⁸ Alexander Guminski,⁹ Grant Goodman,¹⁰ Brian Simmons,¹⁰ Chenglin Ye,¹⁰ Yibing Yan,¹⁰ Dirk Schadendorf¹¹

¹University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; ²Division of Medical Oncology and Immunotherapy, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; ³N N Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russia; ⁴Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; ⁵Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; ⁶Bristol Haematology and Oncology Centre, Bristol, UK; ⁷Department of Cancer Immunology, Poznan University for Medical Sciences, Med-POLONIA, Poznan, Poland; ⁸Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie Institute – Oncology Center, Warsaw, Poland; ⁹Melanoma Translational Research Group, Melanoma Institute Australia, Wollstonecraft, NSW, Australia; ¹⁰Genentech, Inc., South San Francisco, CA, USA; ¹¹Department of Dermatology, University Hospital Essen, Essen, Germany; German Cancer Consortium, Heidelberg, Germany

BRAF MONOTHERAPY IN THE ADJUVANT SETTING

BRIM8 study design

Phase III, International, multicentre, double-blind, randomised, placebo-controlled study



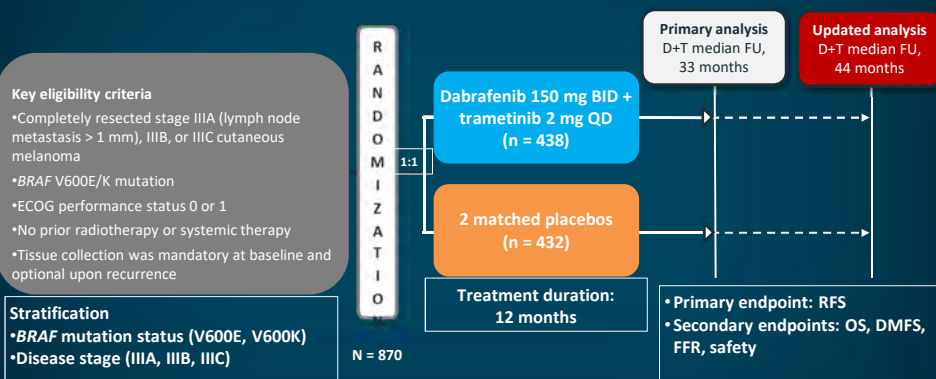
BID, twice daily; DFS, disease-free survival; DMFS, distant metastasis-free survival; HRQoL, Health-related quality of life; OS, overall survival.

*Patients with stage IIIA melanoma were eligible if they had one or more nodal metastasis >1mm in diameter.

Presented by Lewis K at ESMO 2017. Courtesy of Dr Lewis



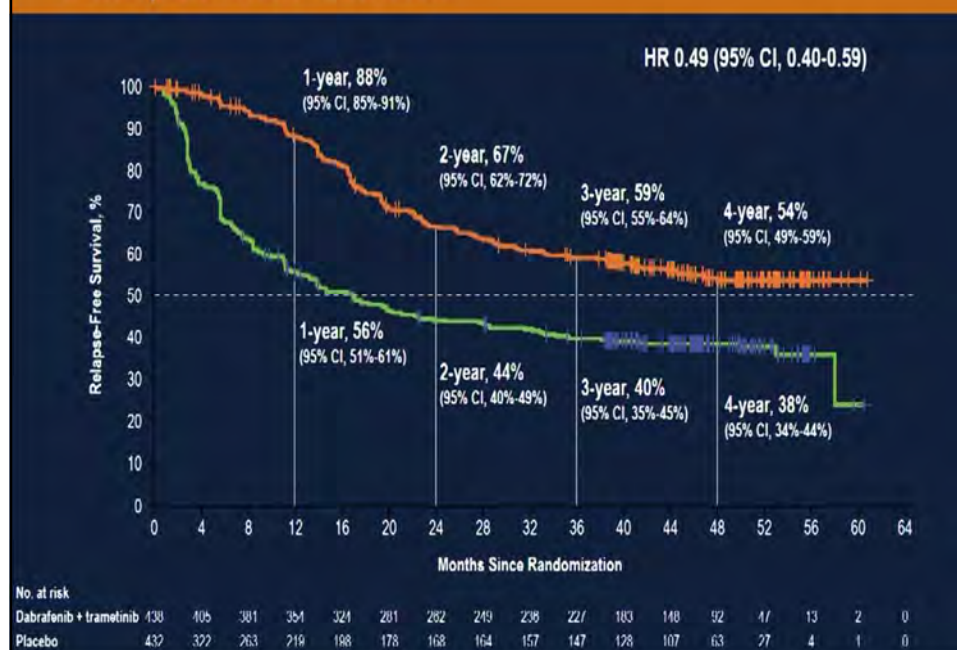
COMBI-AD: STUDY DESIGN—AND EXTENDED FOLLOW-UP ANALYSIS IN 2018



BID, twice daily; DMFS, distant metastasis-free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.
Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

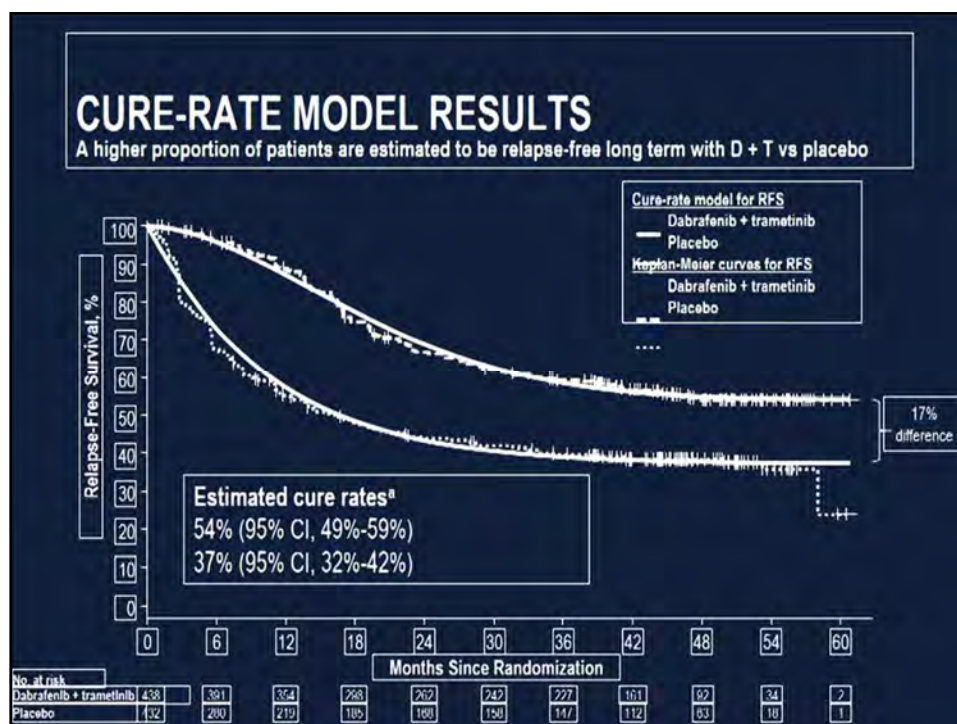
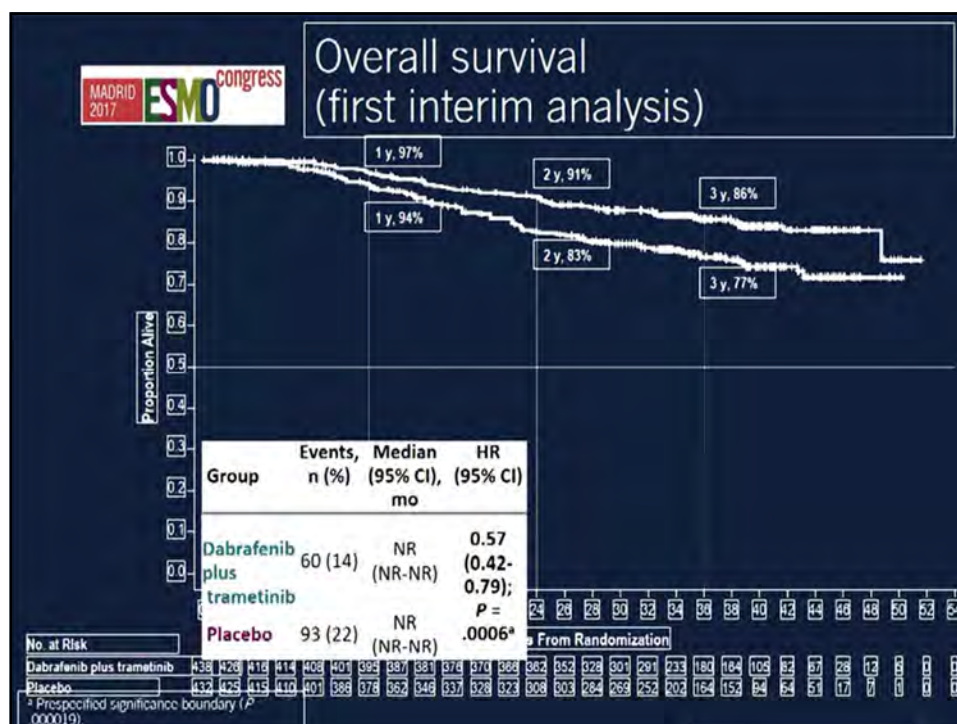
PRESENTED BY GV LONG AT ESMO 2018

Relapse-Free survival



Distant metastasis-free survival





Incorporation of frailties into a cure rate regression model and its diagnostics and application to melanoma data

Jeremias Leão¹ | Victor Leiva² | Helton Saulo^{3,4} | Vera Tomazella⁵

$$S_{ij}(u; \mu, \delta) = \frac{1}{2} \Phi \left(\frac{u + \delta(u - \mu)}{2\sqrt{u(1 + \delta)\mu}} \right), \quad u > 0,$$

$$h_{ij}(u; \mu, \delta) = \frac{\exp \left(-\frac{(\delta\mu + \delta u + u)^2}{4(\delta + 1)\mu u} \right) (\delta\mu + \delta u + u)}{2\sqrt{\pi\mu(\delta + 1)\mu} \Phi \left(\frac{u + \delta(u - \mu)}{2\sqrt{u(1 + \delta)\mu}} \right)}, \quad u > 0,$$

$$O_{j+1} = O_j + M_{j+1}g(O_j), \quad j = 0, 1, \dots$$

$$Q(s) = \frac{\exp \left(\frac{\delta}{2} \left(1 - \sqrt{\delta + 4s + 1} / \sqrt{\delta + 1} \right) \right) \left(\sqrt{\delta + 4s + 1} + \sqrt{\delta + 1} \right)}{2\sqrt{\delta + 4s + 1}}$$

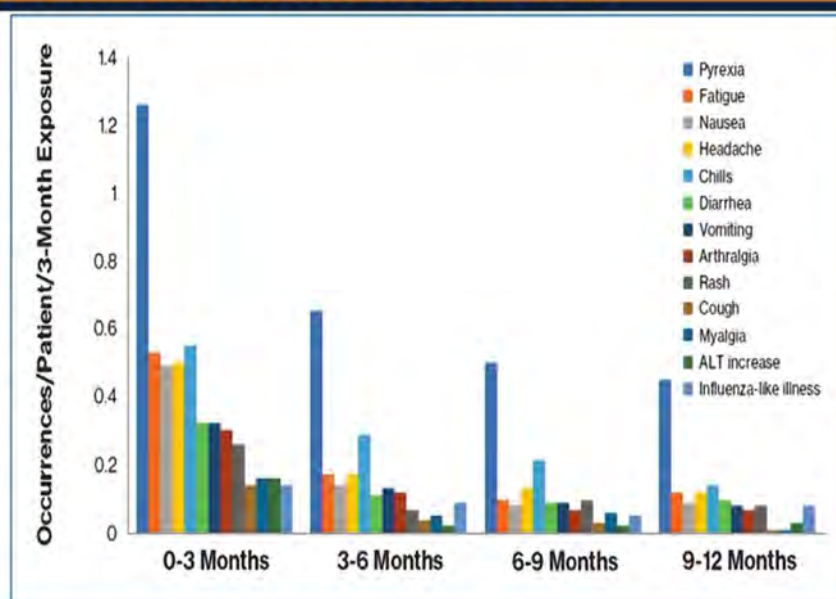
From (8) and evaluating (15) at $s = H_0(t)$, we get the unconditional SF under the BS frailty as

$$S_T(t; \delta) = \frac{\exp \left(\frac{\delta}{2} \left(1 - \sqrt{\delta + 4H_0(t) + 1} / \sqrt{\delta + 1} \right) \right) \left(\sqrt{\delta + 4H_0(t) + 1} + \sqrt{\delta + 1} \right)}{2\sqrt{\delta + 4H_0(t) + 1}}, \quad t > 0.$$

Safety summary

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Any grade 3/4 AE	180 (41)	61 (14)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
Fatal AEs related to study drug	0	0
AEs leading to dose interruption	289 (66)	65 (15)
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation ^a	114 (26)	12 (3)

Any Occurrence (exposure-adjusted) of AEs ($\geq 15\%$ of patients) Over Time in Patients Who Received Dabrafenib Plus Trametinib

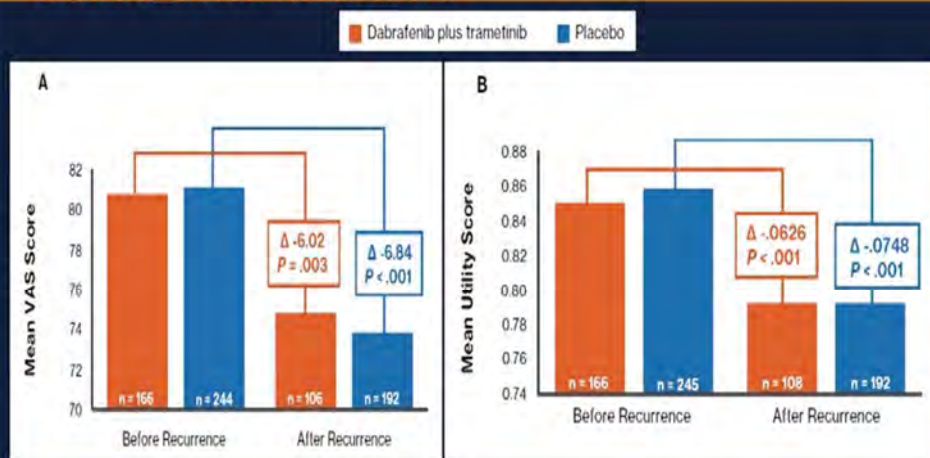


AE, adverse event.

Table 2. AEs Leading to Discontinuation ($\geq 1\%$ of patients)

	Dabrafenib + Trametinib N = 435	Placebo N = 432
Patients with any AE leading to discontinuation^a	114 (26)	12 (3)
Pyrexia	38 (9)	0
Chills	16 (4)	0
Fatigue	8 (2)	0
ALT increase	7 (2)	0
Headache	6 (1)	0
Arthralgia	5 (1)	0
AST increase	5 (1)	0
Nausea	5 (1)	1 (< 1)
Neutropenia	5 (1)	0

Mean EQ-5D VAS (A) and Utility (B) Scores at Assessments Before and After Recurrence^a



^a P-value was calculated using a paired t-test.

^a Regardless of whether recurrence occurred during or after the end of treatment.

Schmidinger et al. Effect on Health-Related Quality of Life of Adjuvant Treatment With Dabrafenib Plus Trametinib in Patients With Resected Stage III BRAF-Mutant Melanoma. Presented at ASCO 2018. Abstract 9591.

**Adjuvant
Dabrafenib and Trametinib:
highly effective and relatively well tolerated
(good QoL despite 26% treatment
discontinuations)!**

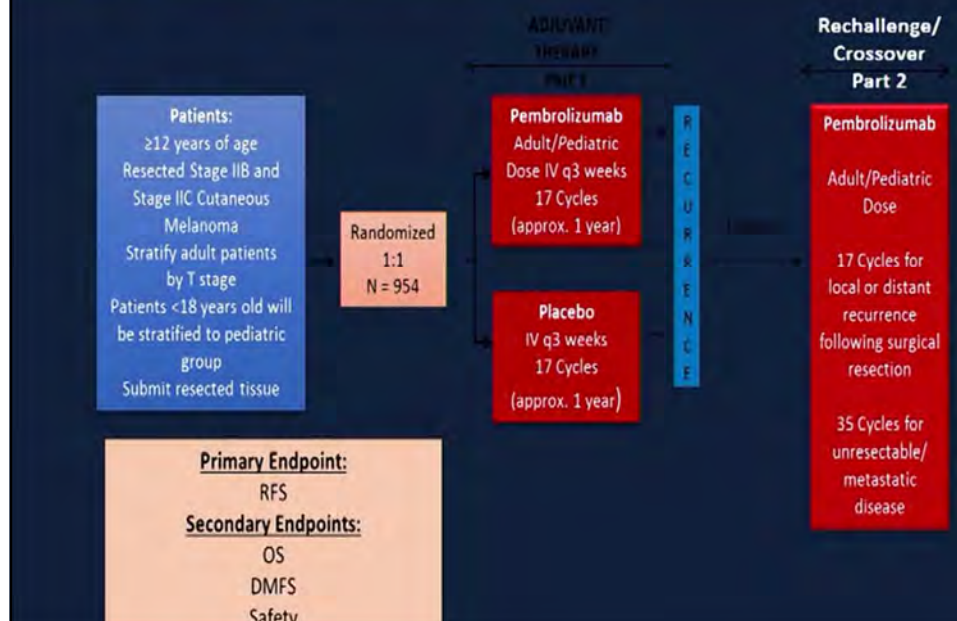
Adjuvant Melanoma Therapy: new jobs to do!

- Testing the new drugs for AJCC stage 2 melanomas („how much recurrence risk justifies how much risk for toxicities?“)
- Biomarker development for the selection of the best patients (and prediction of certain toxicities)
- Addressing the issue of induction for resistance for potential stage IV setting
- Neoadjuvant trials are mandatory!

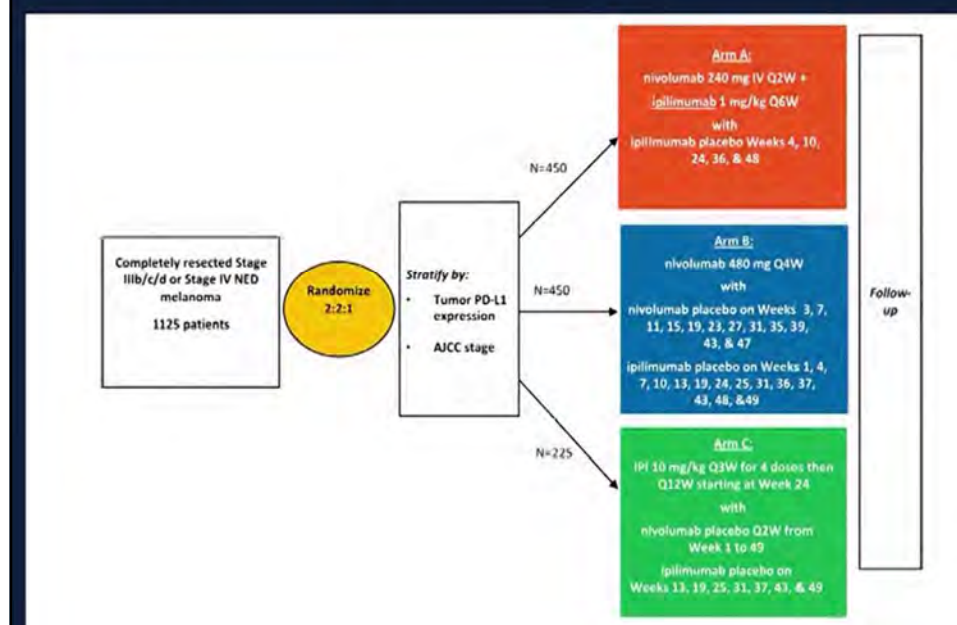
EXPLORATORY ANALYSIS OF THE PREDICTIVE VALUE OF TMB/IFN- γ



Stage II: MK3475-716 Study



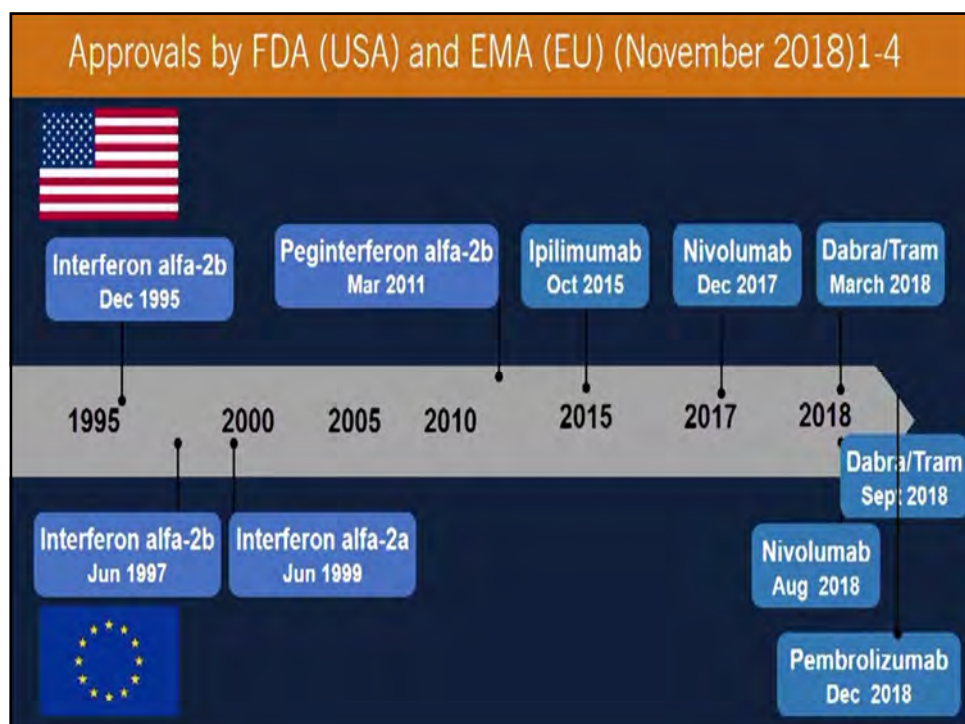
Ipi/Nivo combo: CA209-915 trial



	BRIM-8	Checkmate-238	Nivo+Ipi	Combi-AD	Keynote-054	EORTC 18071 - Ipi
Patients	IIc – IIIC (SN >1mm)	IIIB, IIIC or IV (no brain mets)	IIIC or IV (No Brain mets)	IIIA (>1mm), IIIB, IIIC	IIIA (>1mm), IIIB, IIIC (no Intransits)	IIIA (>1mm), IIIB, IIIC (no intransits)
Mucosal melanoma	excluded	3%	excluded	excluded	excluded	excluded
Duration of therapy	1 yr	1 yr	1 yr	1 yr	1 yr	1 yr
RFS	2yr DFS: 46.3% Vs 47.5% (IIIC)	1 yr 70% vs 60% HR 0.65	75 -80% at 2 yrs	3 yr 58% vs 39% HR 0.57	1 yr 75% vs 61% HR 0.57	5 yr 40% vs 30% HR 0.75
DMFS	NA	HR 0.73	NA	HR 0.51	NA	5yr 48% vs 38%
OS	NA	NA	NA	3 yr 86% vs 77% HR 0.57	NA	5yr 65% vs 54%

Patient selection for adjuvant treatment: potential criteria apart from efficacy

- Patient characteristics: age/gender
- Performance status
- Comorbidities
- Tumor characteristics: stage of metastasis (AJCC)
- Micro- versus macrometastases
- Mutational status
- Biomarkers (PD-L1 status)
- Treatment factors: oral vs. IV (intervals?)
- Potential toxicities (reversible vs irreversible)



1st

For more information visit conference web site:
www.seic2019.com

SOUTHEASTERN EUROPE IMMUNOTHERAPY CONFERENCE

Zagreb, 11-12 October 2019
Hotel Dubrovnik

Dear friends

On behalf of the 1st Southeastern European Immunotherapy Conference Organizing Committee, it is my great pleasure to invite you to the conference to be held on 11-12 October 2019 in Zagreb, Croatia. We hope that you will enjoy the conference and that your interaction with your colleagues from many different countries will stimulate a creative exchange of ideas and will be personally rewarding.

We thank you in advance for being part of this conference and hope to make the 1st Southeastern European Immunotherapy Conference in Zagreb a memorable experience for you.

Davorin Hecceg, MD, PhD

Melanoma 2020: standards of care and unmet needs

Prof dr Lidija Kandolf Sekulović
Medical Faculty, Medical Military Academy
Belgrade, Serbia

Metastatic melanoma: standards of care

SURGERY:

For solitary metastases: PET-CT and brain MRI necessary before decision for surgery
(+adjuvant therapy with anti-PD1)

SYSTEMIC THERAPY:

- Checkpoint inhibitor immunotherapy: anti-PD1 antibodies, anti-CTLA4 antibody
- Targeted therapy: BRAF and MEK inhibitors

RADIOTHERAPY :

STEREOTACTIC RADIOTHERAPY AND GAMMA KNIFE SURGERY for CNS and other distant sites

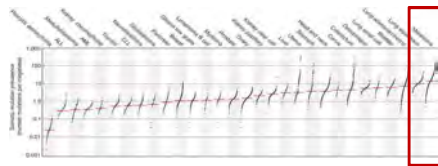
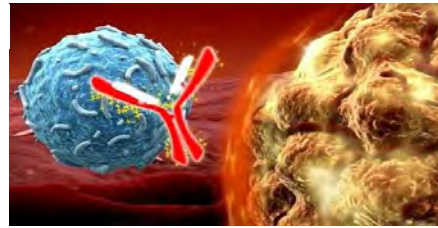
Palliative for bone metastases, lymph nodes and soft tissues, CNS metastases

SUPPORTIVE CARE

Systemic treatment of metastatic melanoma 2019



BRAF gene mutation
early event in oncogenesis



High mutational load =
Immunotherapy effective

Targeted therapy

Vemurafenib
Cobimetinib
Dabrafenib
Trametinib
Encorafenib
Binimetinib

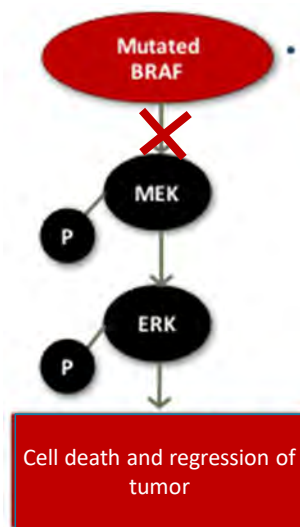
Checkpoint inhibitors

Ipilimumab
Nivolumab
Pembrolizumab
Atezolizumab
Avelumab
Durvalumab

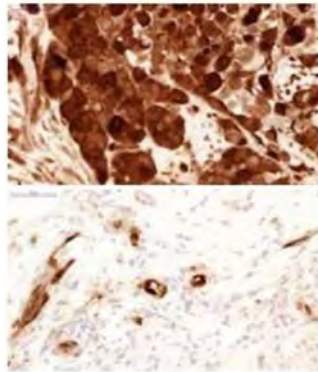
FDA APPROVED

**EMA
APPROVED**

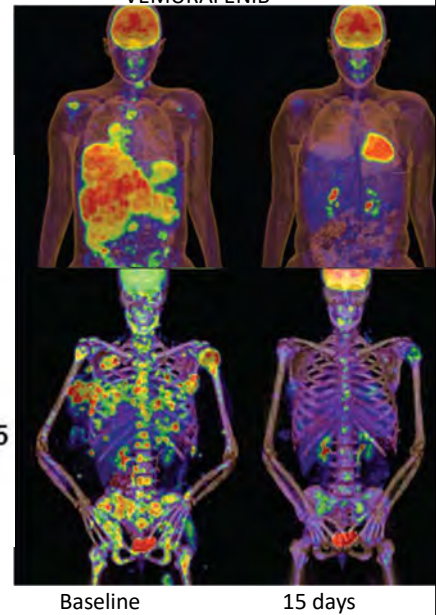
BRAF INHIBITOR



- Constant activation without control



VEMURAFENIB



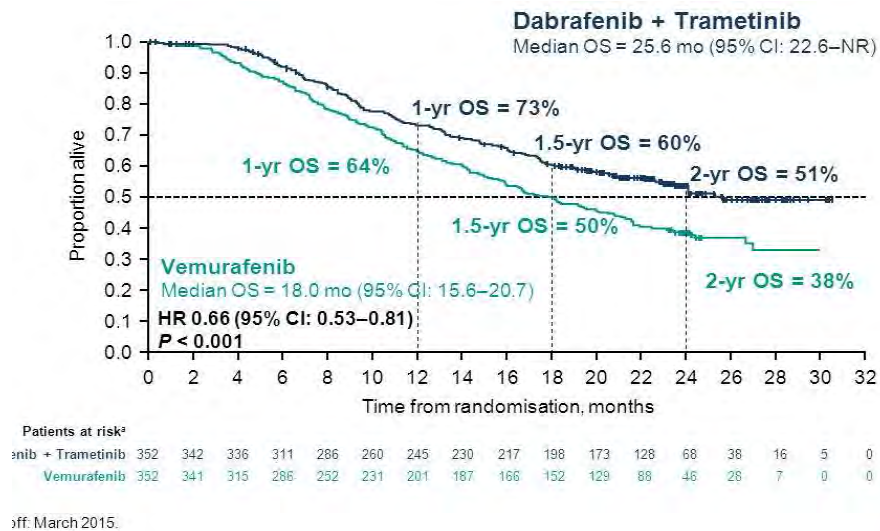
BRAF inhibitor: treatment resistance



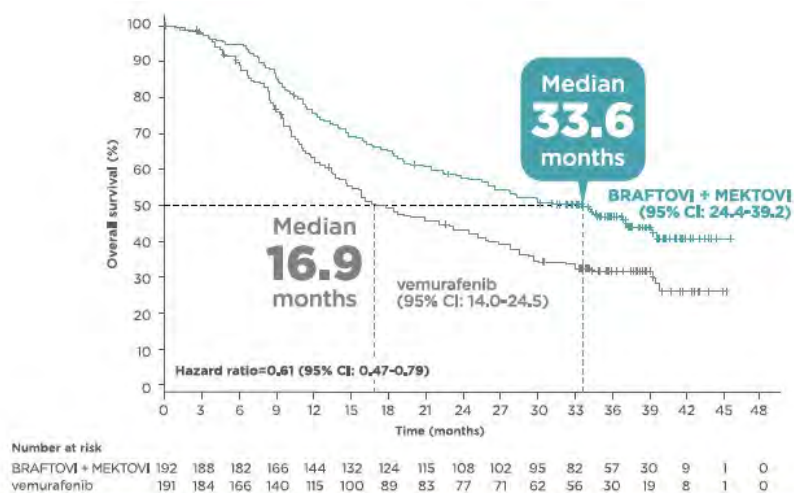
(Wagle et al, 2011, *J Clin Oncol* 29:3085)

- Strong initial effects vemurafenib
- Emerging drug resistancy
- Reccurence of aggressive tumors

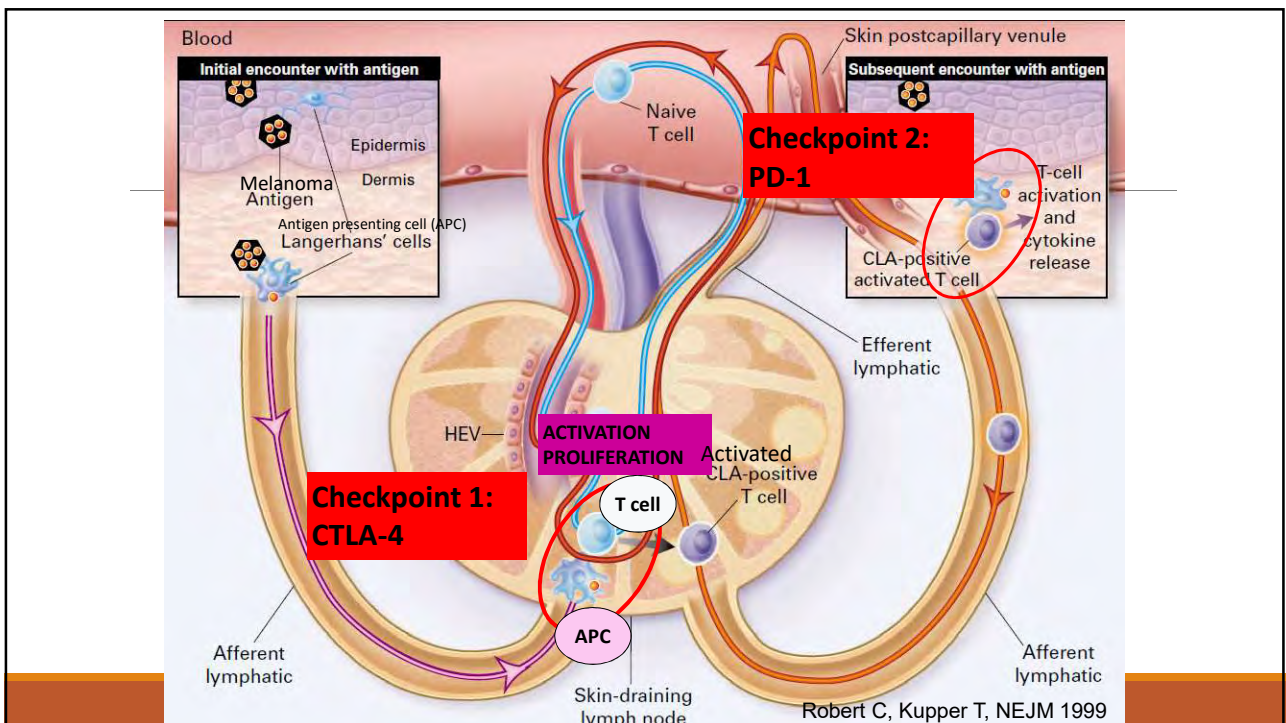
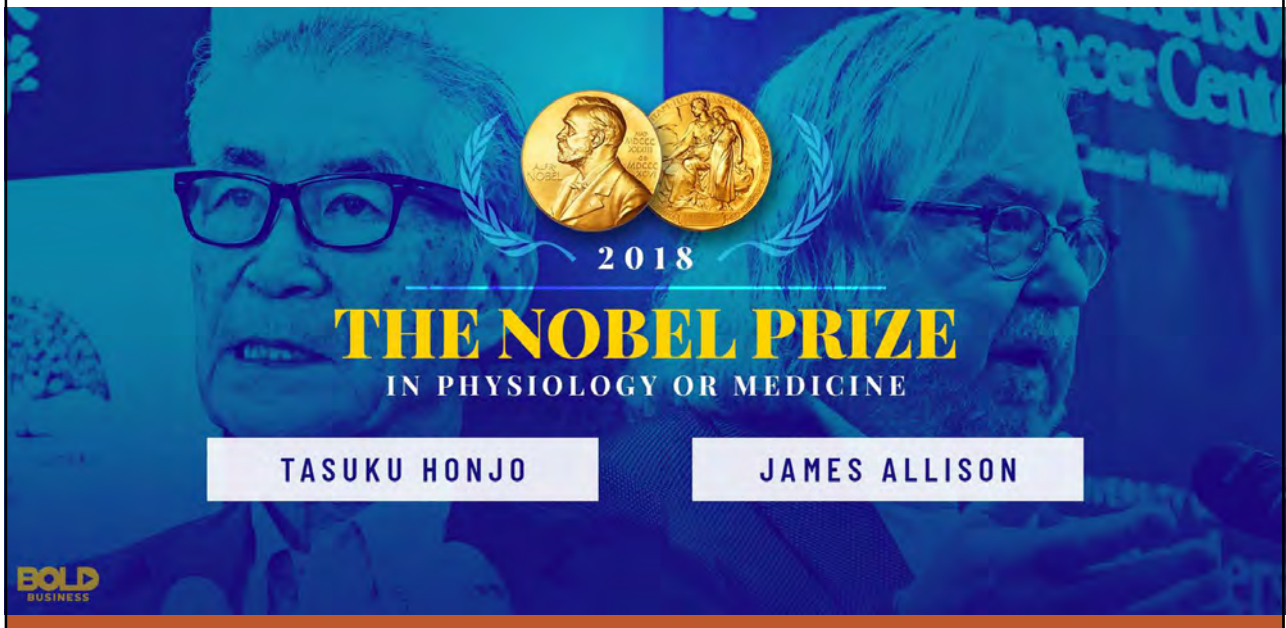
Dabrafenib trametinib versus vemurafenib



Encorafenib binimetinib versus vemurafenib

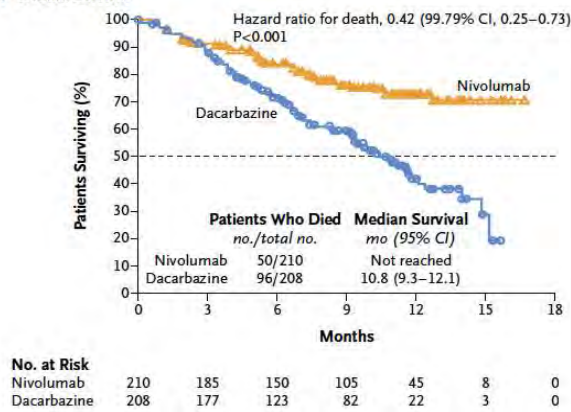


Checkpoint inhibitor immunotherapy: anti-PD1 and anti-CTLA4

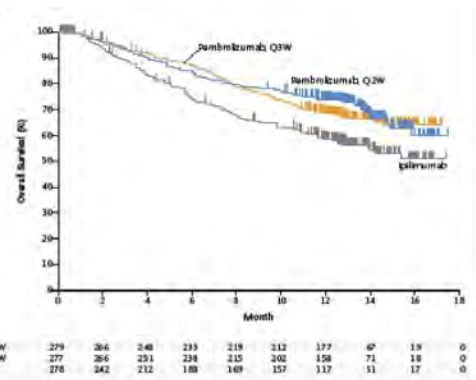


Anti PD1: efficacy

A Overall Survival



B Overall Survival



Robert C et al.

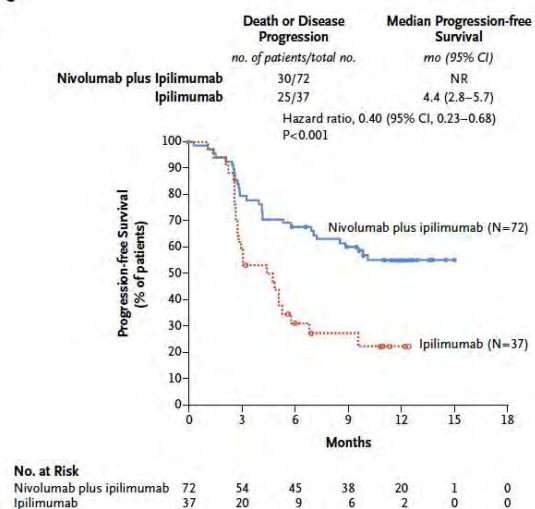
N Engl J Med 2015;372:320-30.

Robert C et al.

N Engl J Med 2015;372:2521-32.

Combination immunotherapy: anti-PD1 plus anti CTLA4

C



EMA, April 2016

anti-PD1+anti-CTLA4:

- Higher response rates
- Faster response
- Long-term responses
- More frequent and more severe side effects

Postow M et al. N Engl J Med 2015;372:2006-17.

Brain metastases

STAGE III: **10-13%** of patients already have CNS mets (CT/MRI necessary in follow-up!)

STAGE IV: **18-46%**

ON AUTOPSY **55-75%**

Frequent relapses in patients with regression of internal organ metastases

Overall survival: 4 months after diagnosis (*Fife et al, J Clin Oncol 2004*)

Fife KM. J Clin Oncol 2004; Sawaya RE, Brain Tumors. Philadelphia; 2001. Barnholtz-Sloan JS, 2004; Harrison BE, Am J Clin Oncol 2003;

The majority of patients with metastatic melanoma are not represented in pivotal phase III immunotherapy trials

Marco Donia ^{a,b,*}, Marie Louise Kimper-Karl ^c, Katrine Lundby Høyer ^d,
Lars Bastholt ^c, Henrik Schmidt ^d, Inge Marie Svane ^{a,b}

Table 2 Eligibility criteria in patients with MM (n = 276).	
Performance status	PS ≥ 2 81 (29.3%)
Brain metastases	Yes, active 62 (22.5%)
Comorbidities	Yes 58 (21.0%)
Other malignancies	Yes 24 (8.7%)
Autoimmunity	Yes 12 (4.3%)
Immunosuppression	Yes 46 (16.7%)

MM, metastatic melanoma.

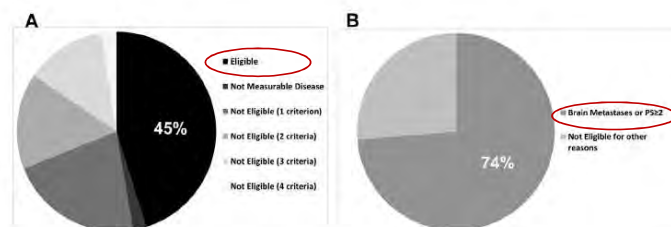


Fig. 1. Common eligibility criteria for immunotherapy trials may exclude over half of the patients diagnosed with metastatic melanoma. (A) The proportion of 'eligible' patients as well as 'not eligible' patients, because they do not meet one, two or more pre-defined criteria is shown. (B) About three quarters of patients 'not eligible' have PS ≥ 2 or active/untreated brain metastases.

Brain metastases

HIRURGIJA	8.7 meseci
Hirurgija + radioterapija celog mozga (WBRT)	8.9 meseci
Samo radioterapija celog mozga (WBRT)	3.4 meseci
Suportivna terapija	2.1 meseci

STEREOTAKSNA RADIOHIRURGIJA:
 Lokalna kontrola bolesti 90% slučajeva
 Efikasnost slična hirurgiji
 Ukupno preživljavanje 5-11 meseci

Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy

K. A. Ahmed¹, D. G. Stallworth², Y. Kim³, P. A. S. Johnstone¹, L. B. Harrison¹, J. J. Caudell¹, H. H. M. Yu¹, A. B. Etame⁴, J. S. Weber⁵ & G. T. Gibney^{6,7*}

Annals of Oncology 27: 434–441, 2016

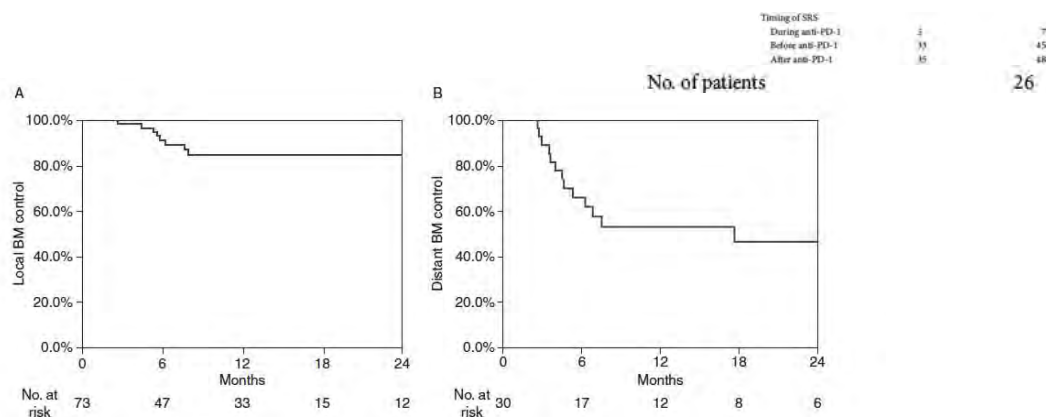


Figure 1. A) Kaplan-Meier curve for local BM control of 73 treated lesions and B) distant BM control following 30 treatment sessions.

Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies

European Journal of Cancer 75 (2017) 169–178

Ee Siang Choong ^{a,*}, Serigne Lo ^b, Martin Drummond ^b,
Gerald B. Fogarty ^{b,c,d,e}, Alexander M. Menzies ^{b,c,d},
Alexander Guminski ^{b,c,d}, Brindha Shivalingam ^{b,c,d}, Kathryn Clarke ^d,
Georgina V. Long ^{b,c,d}, Angela M. Hong ^{b,c,d,e,f}

Method: A total of 108 patients treated with SRS from 2010 to 2015 were included. Systemic treatment use within 6 weeks of SRS was noted. OS was defined as time from SRS to death or last follow-up, and BC was defined as absence of any active intracranial disease during follow-up. Univariate and multivariate Cox proportional hazard analyses were performed on clinicopathological prognostic features associated with OS and BC.

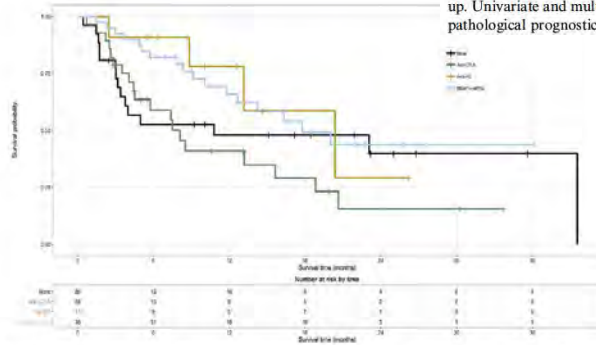


Fig. 1. Kaplan Meier plot for OS according to types of systemic treatment received – anti-CTLA4, anti-PD1 and BRAFi ± MEKi (n = 104). *The one patient who had MEKi alone was excluded in the survival analysis.

Table 5

Trials and retrospective series of systemic drug therapies in patients with active brain metastases.

Systemic therapy	Study	Year	No. of patients	Patients received SRS	Systemic therapy	Median OS	OS at 6 months	OS at 1 year	OS at 2 years
Anti-CTLA4	Choong <i>et al.</i>		28	Y	Ipilimumab	7.5	59%	41%	16%
	Kiess [26]	2014	46	Y	Ipilimumab	12.4	N/A	40–65%	N/A
	Knisely [14]	2012	27	Y	Ipilimumab	21.3	N/A	N/A	47.2%
	Mathew [34]	2013	25	Y	Ipilimumab	5.9	56%	N/A	N/A
	Margolin [15]	2012	72	N	Ipilimumab				
			51	Asymptomatic (cohort A)		7.0	55%	31%	26%
Anti-PD1			21	Symptomatic (cohort B)		3.7	38%	19%	10%
	Choong <i>et al.</i>		11	Y	Anti-PD1	20.4	91%	78%	29%
	Ahmed [27]	2016	19	Y	Nivolumab	11.8	78%	55%	N/A
BRAFi ± MEKi	Choong <i>et al.</i>		39	Y	BRAFi ± MEKi	15.6	82%	66%	44%
	Ly D [30]	2015	52	Y	BRAFi	11.2	N/A	N/A	N/A
	Wolf [31]	2015	31	Y	BRAFi – (23% MEKi)	11.2	54%	41%	N/A
	Ahmed [29]	2015	24	Y	BRAFi	7.2	N/A	N/A	N/A
	Patel [36]	2016	6	Y	BRAFi + MEKi	20.0	N/A	100%	N/A
	Long [21]	2012	172	N	BRAFi				
			89	No prior local therapy (cohort A)		8.3	61%	N/A	N/A
			83	Progressed after local therapy (cohort B)		7.9	61%	N/A	N/A

OS, overall survival; N/A, not reported.

Only trials or series with reported relevant endpoints included.

Anti CTLA4 i anti PD1 u metastazama mozga (IVD)

	Cohort A		Cohort B		Cohort C (n=16)
	Drug* naive (n=27)	Overall (n=35)	Drug* naive (n=19)	Overall (n=25)	
Intracranial response					
Overall (%; 95% CI)	15 (56%; 35-75)	16 (46%; 29-63)	4 (21%; 6-46)	5 (20%; 7-41)	1 (6%; 0-30)
Complete response	5 (19%)	6 (17%)	2 (11%)	3 (12%)	0
Partial response	10 (37%)	10 (29%)	2 (11%)	2 (8%)	1 (6%)
Stable disease	3 (11%)	4 (11%)	0	0	2 (13%)
Progressive disease	8 (30%)	14 (40%)	14 (74%)	19 (76%)	13 (81%)
Non-evaluable	1 (4%)	1 (3%)	1 (5%)	1 (4%)	0

Side effects?

Class specific

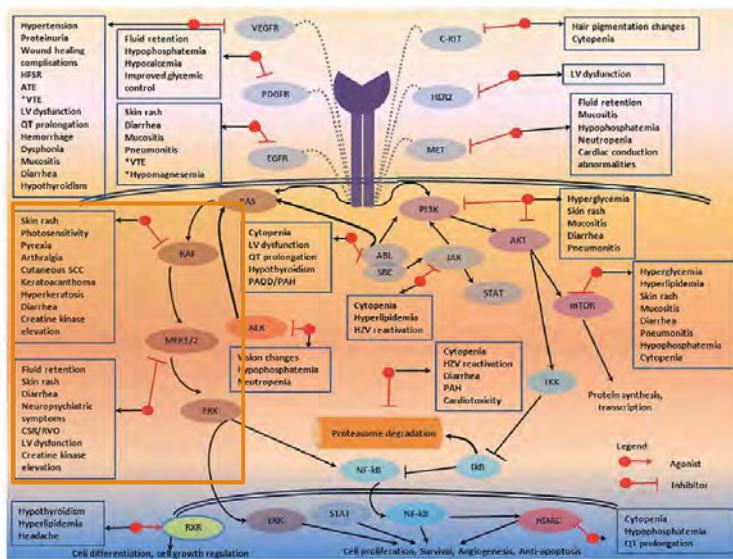
- Targeted therapy: primary drug target/pathway in cancer cells/tissues also mediates physiologic functions in normal cells/tissues.
- Checkpoint inhibitors: immune-mediated adverse effects; monoclonal antibody administration related side effects

Drug specific

- Other mechanisms
 - Vemurafenib: photosensitivity
 - Dabrafenib: Hemolytic anemia in patients with G6PD deficiency (dabrafenib has sulfonamide moiety)

Tumor specific:

- different frequencies of side effects of the same drug in different tumors



Targeted therapy toxicity

- Paradoxical activation of MAPK pathway in BRAFwt cells
- Additional oncogene mutations (Ras, p53, TGF-beta) or HPV cofactors
- Paradoxical cell proliferation
- Class effect

FIGURE 1. Toxicities Associated With Signal Transduction Inhibitors.*Associated predominantly with monoclonal antibodies. ATE indicates arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SCC, squamous cell cancer; VTE, venous thromboembolism.

CA CANCER J CLIN 2013;63:249-279

Targeted therapy: side-effects all grades % (grade 3-4 %)

	Vemurafenib	Dabrafenib	Encorafenib	Trametinib	Vemurafenib Cobimetinib	Dabrafenib Trametinib	Encorafenib Binimetinib (450)
Rash	68 (16)	30 (0)	45 (5)	57 (8)	73 (17)	27 (0)	23 (1)
Cutaneous SCC	21 (21)	10 (4)	9 (1)	0	6 (5)	7 (5)	4 (0)
Diarrhoea	33 (1)	8 (0.4)	14 (2)	43 (0)	33.3 (7)	36 (2)	36 (3)
Arthralgia	56 (6)	19 (<1)	44 (9)	NR	38 (3)	24 (0)	26 (1)
Fatigue	33 (3)	18 (1)	25 (1)	26 (4)	37 (5)	53 (4)	29 (2)
Nausea	37.3 (1)	13 (0.4)	NR	18 (1)	41.3	36(0.4)	NR
Vomiting	14 (1)	7 (<1)	NR	13 (1)	24.3	30.3 (0.4)	NR
Cardiac	10 (2)	3 (2)	2 (1)	7 (1)	17 (3)	9 (0)	8 (2)
Ophtalmologic	9 (4)	2 (0)	1 (0)	9 (<1)	27 (3)	2 (2)	13 (2)
Liver laboratory abnormalities	36 (11)	26 (2)	7 (2)	24 (2)	26 (11)	27(2)	14 (6)
CPK increase	3 (<1)	NR	1 (0)	NR	35 (12)	2.9	23 (7)
Photosensitivity	41.4(4)	3 (0)	4 (0)	NR	28 (2)	4 (0)	5 (1)
Pyrexia	22.8 (<1)	32(4)	15 (1)	NR	26 (2)	52 (7)	18 (4)

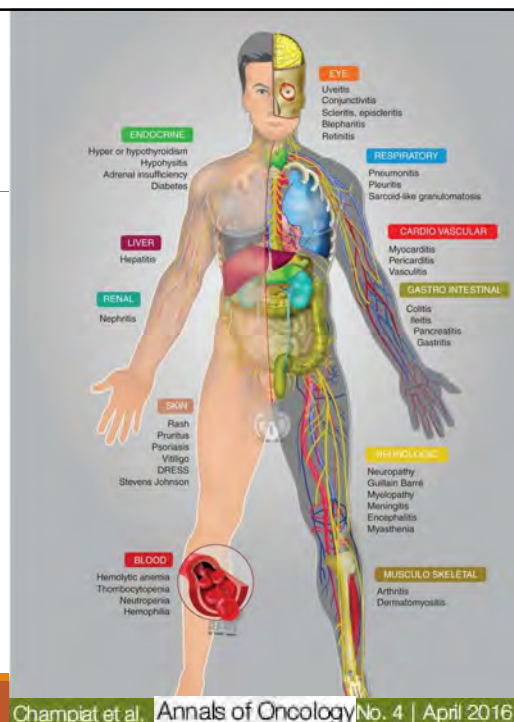
Checkpoint-inhibitors: immune-related adverse effects

Inhibitory immune-checkpoints are associated with tolerance mechanisms and prevention of autoimmunity

In the setting of CTLA-4 and anti-PD1-PDL-1 blockade immune related adverse events develop

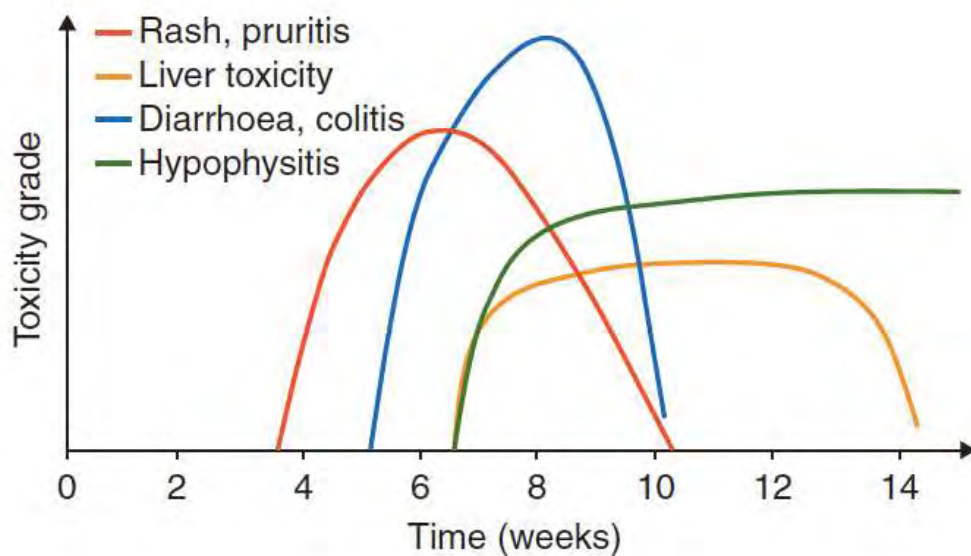
Most frequent: skin ,GI, liver, endocrine

Less common: pneumonitis, neurotoxicity, ocular, etc.

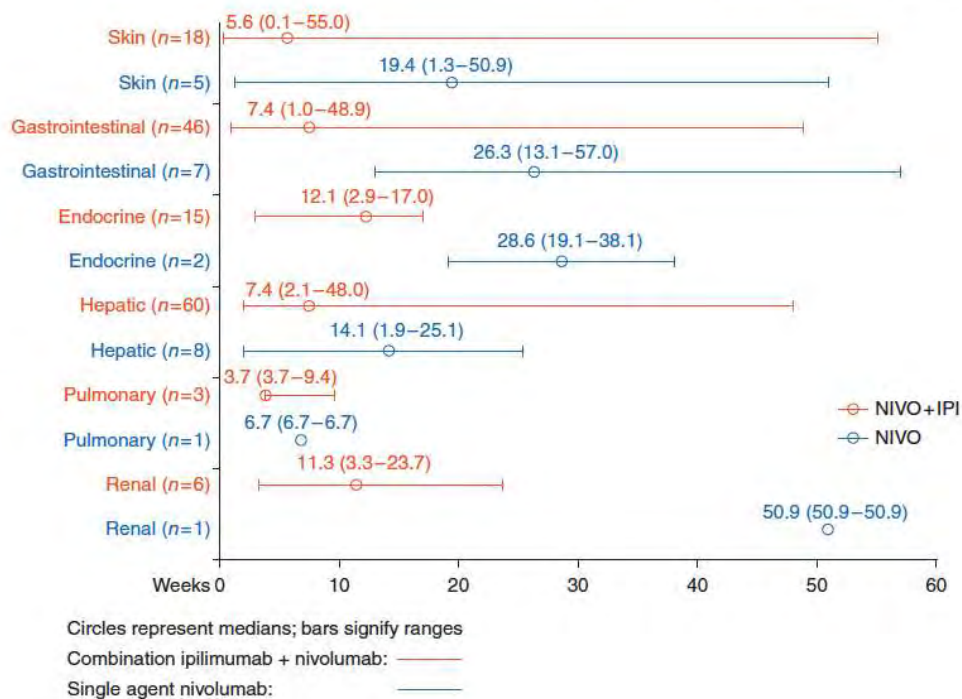


Immune related side effects: frequency

	Ipilimumab all % (gr 3-4%)	Nivolumab all, % (gr 3-4%)	Pembrolizumab all % (gr 3-4, %)	Nivolumab Ipilimumab all % (gr 3-4%)
Skin	54.6 (2.5)	38.4 (1.1)		61.9 (6.4)
Rash	21.6 (1.4)	16.9 (0.4)	21 (1)	31.2 (3.2)
Pruritus	34.4 (0.3)	18.4 (0.1)	21 (1)	33.4 (1.7)
Gastrointestinal	42.3 (11.5)	17.7 (1.7)		46.4 (15.7)
Diarrhea	43 (8.8)	17.2 (1.3)	20 (1)	33.6 (6.2)
Colitis	14 (9.6)	1.1 (0.6)		11.8 (8.4)
Pulmonary	2.2 (0.6)	2 (0.1)		7.6 (1.2)
Pneumonitis	2 (0.6)	1.8 (0.1)	4 (1)	6.9 (1.2)
Endocrine	11.8 (2.5)	10.8 (0.6)		29.7 (4.9)
Thyroid	6.4 (0)	10.1 (0.1)	8 (1)	18.9 (0.9)
Hypophysitis	4.2 (2.2)	0.4 (0.3)	NR	8.6 (1.7)
Renal	NR	1.5 (0.5)	2 (1)	4.7 (1.7)
Hepatic	0.7 (0.1)	6.9 (2.2)		29 (17.4)
Lab abnormal.	NR	0.4 (0.1)	18(1)	18.2 (8.4)
Infusion reactions	NR	4.8 (0.3)	NR	2.5 (0)
irAE	86.2 (27.7)	86.3 (20.8)		95.8 (58.5%)
Treatment discontinuation	16.1 (14.1)	11.5 (7.7)		39.6 (31)



Puzanov et al. *Journal for ImmunoTherapy of Cancer* (2017) 5:95



Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review

Annals of Oncology 28: 2377–2385, 2017

L. Khoja^{1,2†}, D. Day^{3,4,5†}, T. Wei-Wu Chen^{6,7,8}, L. L. Siu^{3,4} & A. R. Hansen^{3,4*}

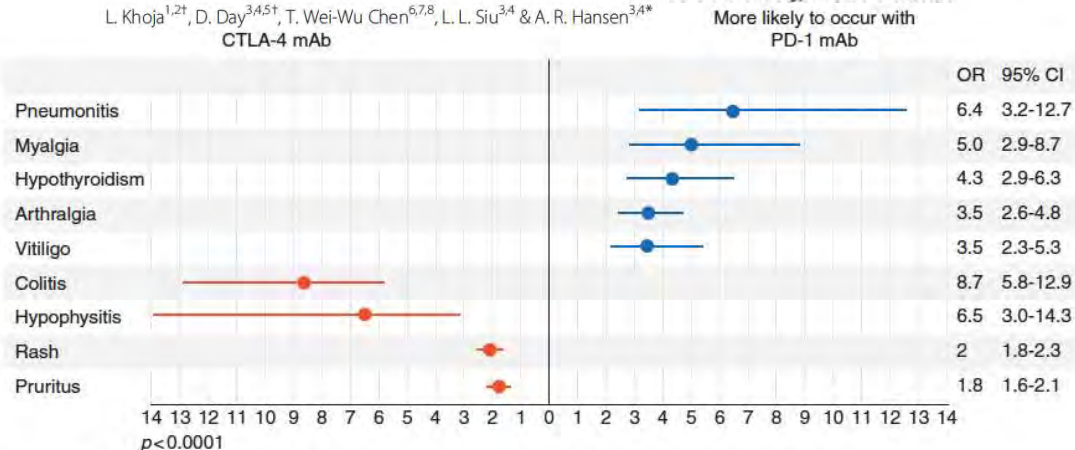


Figure 2. The odds ratio (OR) of different immune-related adverse events (all grades) comparing PD-1/PD-L1 versus CTLA-4 immune checkpoint inhibitors.



Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

J. B. A. G. Haanen¹, F. Carbone², C. Robert³, K. M. Kerr⁴, S. Peters⁵, J. Larkin⁶ & K. Jordan⁷, on behalf of the ESMO Guidelines Committee*



Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov^{1†}, A. Diab^{2†}, K. Abdallah³, C. O. Bingham III⁴, C. Brogdon⁵, R. Dadu², L. Hamad¹, S. Kim², M. E. Lacouture⁶, N. R. LeBoeuf⁷, D. Lenihan⁸, C. Onofrei⁹, V. Shannon², R. Sharma¹, A. W. Silk¹², D. Skondra¹⁰, M. E. Suarez-Almazor², Y. Wang², K. Wiley¹¹, H. L. Kaufman^{12†}, M. S. Ernst^{1††} and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Puzanov et al. *Journal for Immunotherapy of Cancer* (2017) 5:95

The
Oncologist®

Melanoma and Cutaneous Malignancies

Management of Treatment-Related Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma

ADIL DAUD, KATY TSAI

The Oncologist 2017;22:1–11

Optimizing combination dabrafenib and trametinib therapy in BRAF mutation-positive advanced melanoma patients: Guidelines from Australian melanoma medical oncologists

Victoria ATKINSON,¹ Georgina V. LONG,² Alexander M. MENZIES,³ Grant MCARTHUR,¹ Matteo S. CARLINO,⁴ Michael MILLWARD,⁵ Rachel ROBERTS-THOMSON,⁶ Benjamin BRADY,³ Richard KEFFORD,⁷ Andrew HAYDON⁸ and Jonathan CEBON⁹

Asia-Pacific Journal of Clinical Oncology 2016; 12(Suppl. 7): 5–

Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma

Ther Adv Med Oncol

2015, Vol. 7(2) 122–136

Sarah J. Welsh and Pippa G. Corrie

Cutaneous adverse effects of targeted therapies

Part II: Inhibitors of intracellular molecular signaling pathways

James B. Macdonald, MD,^{a,b} Brooke Macdonald, BA,^c Loren E. Golitz, MD,^{d,e}

J AM ACAD DERMATOL
FEBRUARY 2015

General management principles

Targeted therapy

Grade 1: continue TT, symptomatic therapy, diagnostic work-up

Grade 2:

- Interruption of treatment, until grade 1, then reintroduce in decreased dose
- If reappear, second interruption until grade 1 than reintroduce with further dose reduction
- Diagnostic work-up
- Symptomatic therapy

Grade 3 and 4

- Interruption of treatment until grade 1, then reintroduce in decreased dose
- Diagnostic work-up
- Symptomatic therapy
- Consider switching to other BRAFi+MEKi

Dose reductions for BRAFi MEKi

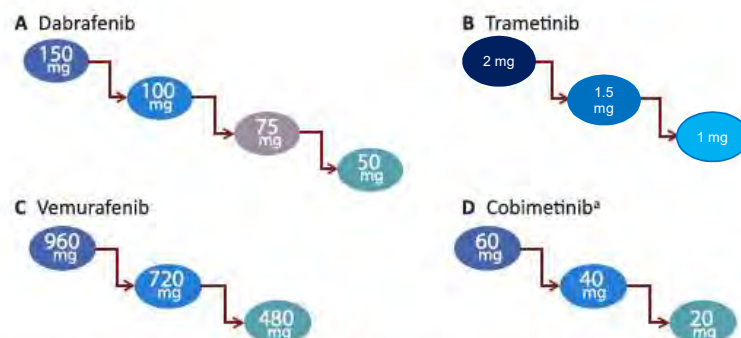


Figure 1. Recommended dose adjustments and modifications for dabrafenib (A), trametinib (B), vemurafenib (C), and cobimetinib (D).

General management principles

Immunotherapy

Grade 1: continue ICI therapy, symptomatic therapy, close follow-up

Grade 2:

- hold ICI therapy
- diagnostic work-up
- start corticosteroid therapy and resume ICI when corticosteroid is tapered to ≤ 10 mg/day and patient remains symptom-free (grade 1)
- If irAE returns on resuming ICI:
 - Grade ≤ 2 : temporarily hold ICI
 - Grade ≥ 3 : permanently discontinue ICI
- If using combination anti-CTLA-4/anti-PD-1 immunotherapy, continue anti-PD-1 agent only

Grade 3:

- withhold ICI; consider resuming ICI when
- corticosteroid is tapered to ≤ 10 mg/day and patient remains symptom-free (grade ≤ 1)
- If irAE returns: permanently discontinue ICI
- consider hospitalization

Grade 4: permanently discontinue ICI and hospitalize

Corticosteroid use for irAE

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2-3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to \leq grade 1 AE, start 4-6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to \leq grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2-3 days, add additional/alternative immune suppressant • Once improved to \leq grade 1, start 4-6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4-6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2-3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

Dermatologic toxicities

Targeted therapy

Targeted therapy:

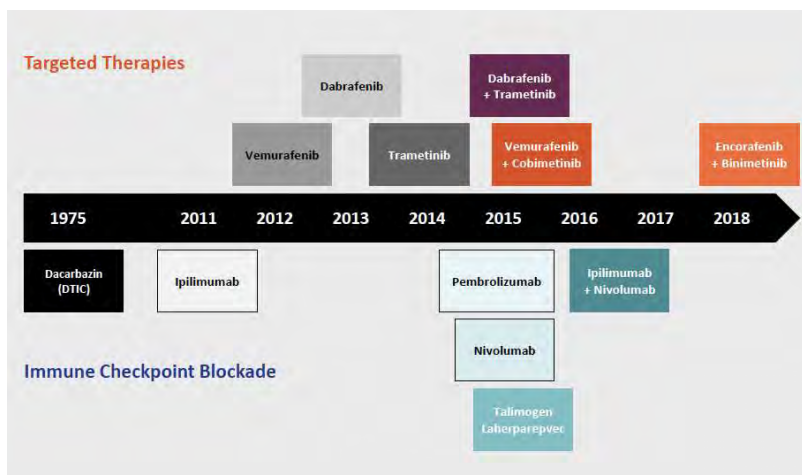
- BRAFi
 - Follicular rash
 - Maculopapular rash
 - Hair thinning and curling
 - cuSCC
 - Palmar-plantar dysesthesia syndrome
- MEKi
 - Papulopustular rash
 - Palmar-plantar dysesthesia syndrome

Immunotherapy

- Checkpoint inhibitor therapy
 - Pruritus
 - Maculopapular rash
 - Vitiligo
 - Rare
 - Neutrophilic dermatoses
 - Lichenoid reactions
 - Bullous pemphigoid
 - AGEP
 - Alopecia areata/universalis

TYPE > GRADE > MANAGEMENT

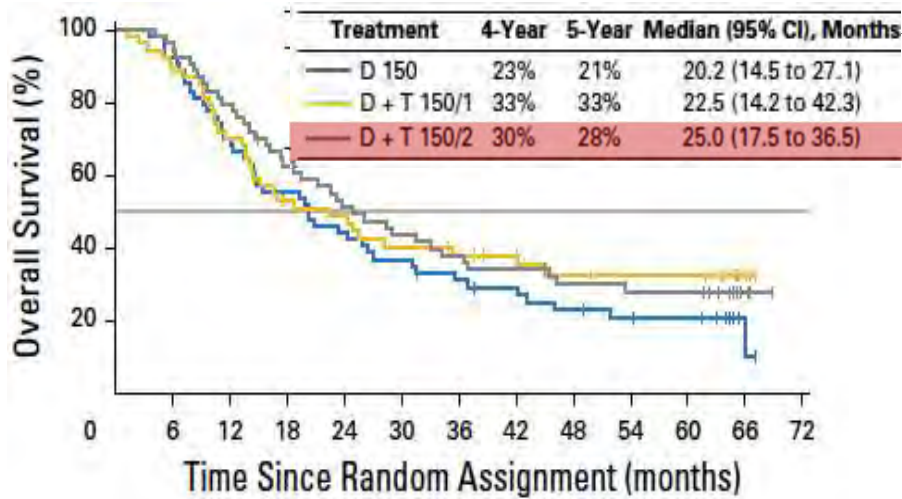
Melanoma 2020: standards of care and unmet needs



2020?

Hauschild A. EADO 2018

Dabrafenib trametinib 5-year OS update (phase II, BRF113220, part C)

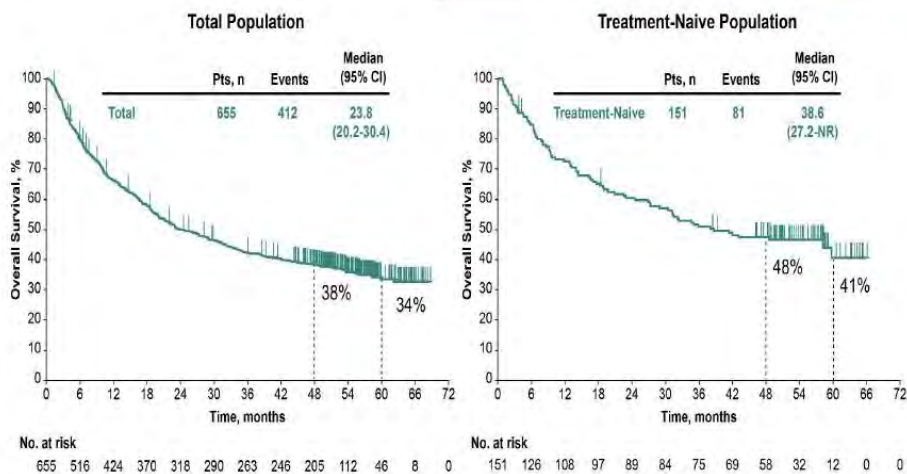


VOLUME 36 • NUMBER 7 • MARCH 1, 2018

Long G et al. *J Clin Oncol* 36:667-673.

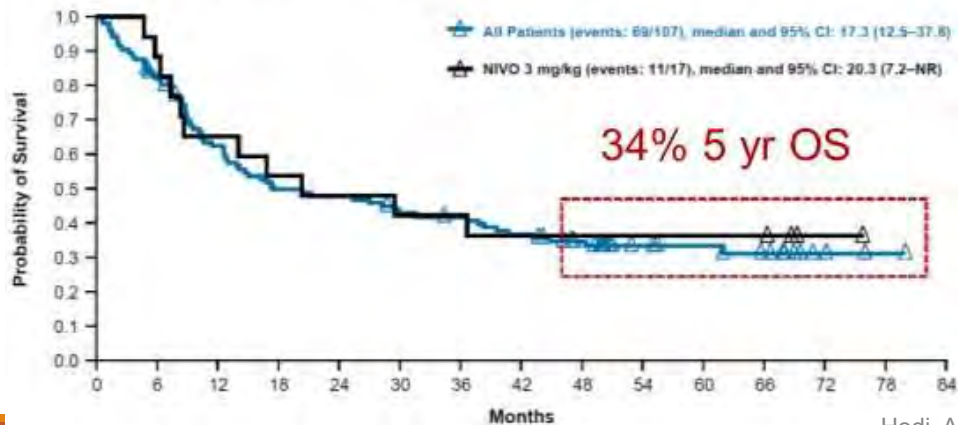
5-y-Overall Survival Pembro (KN-001 trial)

5-year survival:
Untreated pts 41%
Pre-treated and naive: 34%



Nivolumab: heavily pretreated patients

Overall Survival at 5 Years of Follow-up



Hodi, AACR April, 2016

Metastatic melanoma treatment 2019

- Five year OS rates: 30-35%, 65-70% do not survive

Questions:

1. Duration of treatment?
2. Discontinuation of treatment?

Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma

Caroline Robert, Antoni Ribas, Omid Hamid, Adil Daud, Jedd D. Wolchok, Anthony M. Joshua, Wen-Jen Hwu, Jeffrey S. Weber, Tara C. Gangadhar, Richard W. Joseph, Roxana Dronca, Amita Patnaik, Hassane Zarour, Richard Kefford, Peter Hersey, Jin Zhang, James Anderson, Scott J. Dieder, Scot Ebbinghaus, and F. Stephen Hodi

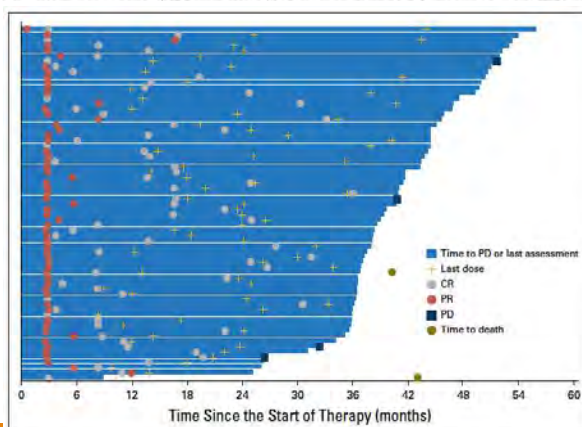


Fig 2. Time to response and durability of response from the start of therapy in complete responders who discontinued pembrolizumab and proceeded to observation (n = 67). Bar length is equivalent to the time to the last imaging assessment by investigator review. CR, complete response; PD, progressive disease; PR, partial response.

J Clin Oncol 36:1668-1674.

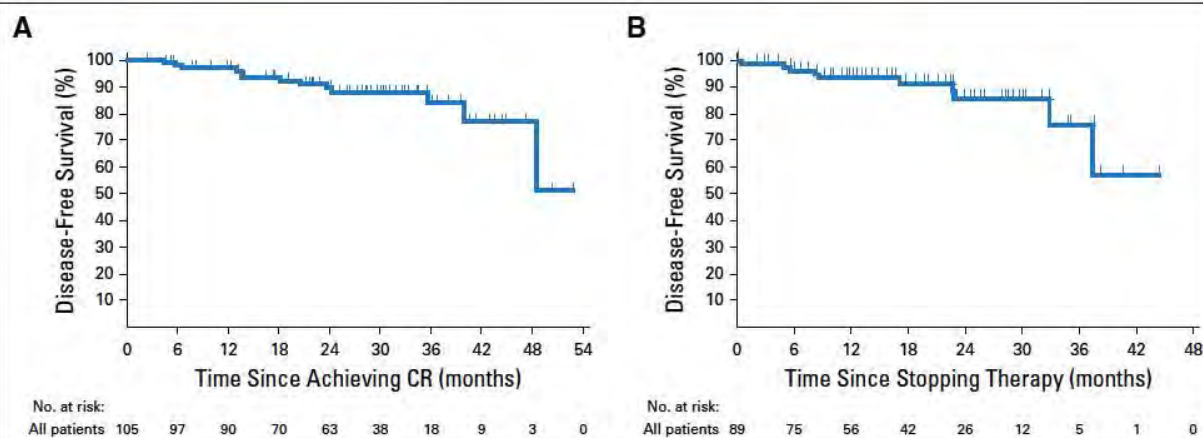


Fig 3. Disease-free survival (A) from time of experiencing complete response (CR) in all patients who achieved CR (n = 105) and (B) from time of discontinuation of pembrolizumab in patients who discontinued after CR for reasons other than progression (n = 89). The hash marks designate patients who were censored at that time point.

J Clin Oncol 36:1668-1674.

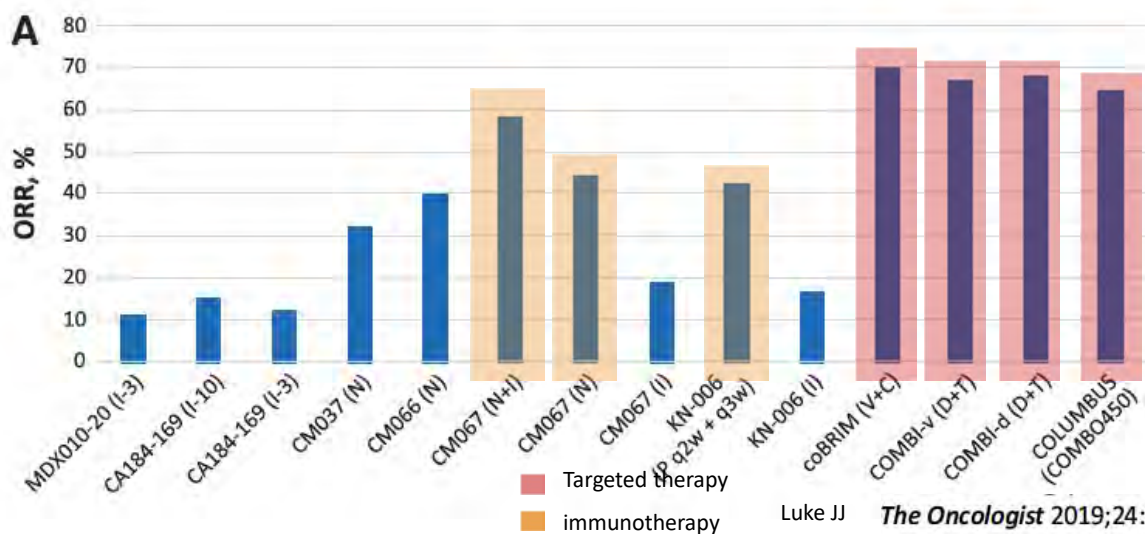
Metastatic melanoma treatment 2019

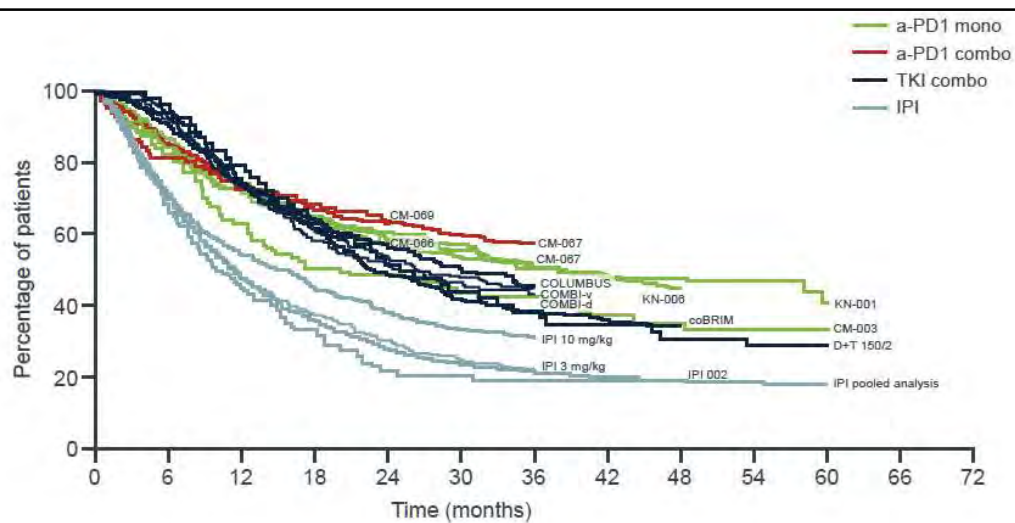
- Five year OS rates: 30-35%, **65-70% do not survive**

Questions:

1. Can we improve further treatment outcomes?
2. Are there evidence available to guide our treatment decision on choosing the first line treatment?
3. Does sequencing matters?

Metastatic melanoma: ORR





KN-006: Long GV et al. ASCO 2018; abstract 9503
 KN-001: Hamid O et al. ASCO 2018; abstract 9516
 CM-066: Atkinson V et al. SMR 2015
 CM-003: Hodi FS et al. AACR 2016; abstract CT001
 CM-067: Wolchok JD et al. N Engl J Med 2017; 377(14): 1345-56
 CM-069: Hodi FS et al. Lancet Oncol 2016; 17(11): 1558-68
 COLUMBUS: Dummer R et al. ASCO 2018; abstract 9504

D+T 150/2: Long GV et al. J Clin Oncol 2018; 36(7): 667-73
 COMBI-d: Long GV et al. Ann Oncol 2017; 28(7): 1631-39
 COMBI-v: Long GV et al. Ann Oncol 2016; 27(6): 1-38
 coBRIM: Dreno B et al. ASCO 2018; abstract 6522
 IPI 002: Hodi FS et al. N Engl J Med 2010; 363(8): 711-23
 IPI pooled: Schadendorf D et al. J Clin Oncol 2015; 33(17): 1889-94
 IPI 3/10mg: Ascierto PA et al. Lancet Oncol 2017; 18(5): 611-22

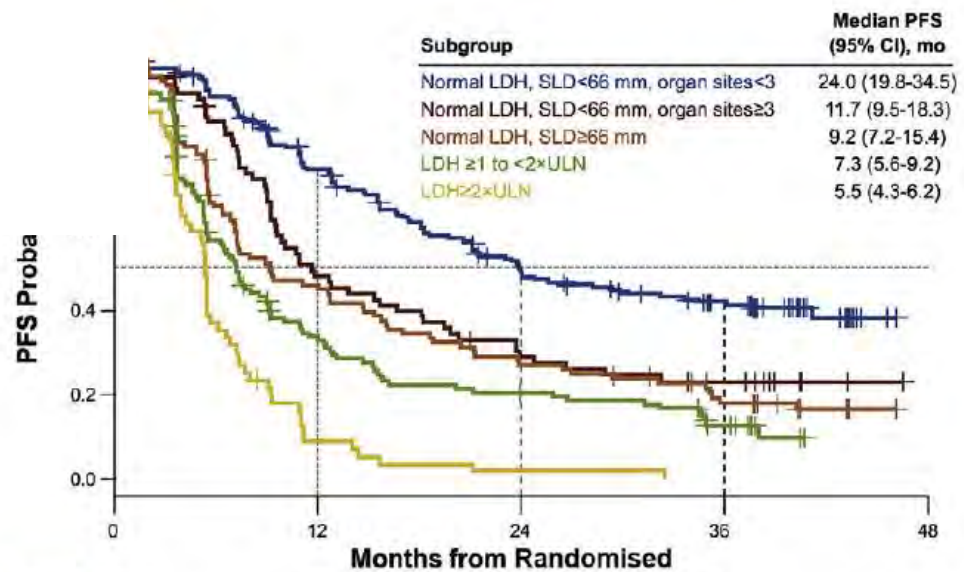
Important note: all curves are representative interpretations of source data from different studies. Curves from different studies cannot be compared directly.

OS rates: 1st line treatment

	3-year OS rate	4-year OS rate	5-year OS rate
Dabrafenib trametinib	45	37	34
Pembrolizumab	51	45	40
Nivolumab	51	45	-
Nivolumab+ipilimumab	58	52	-

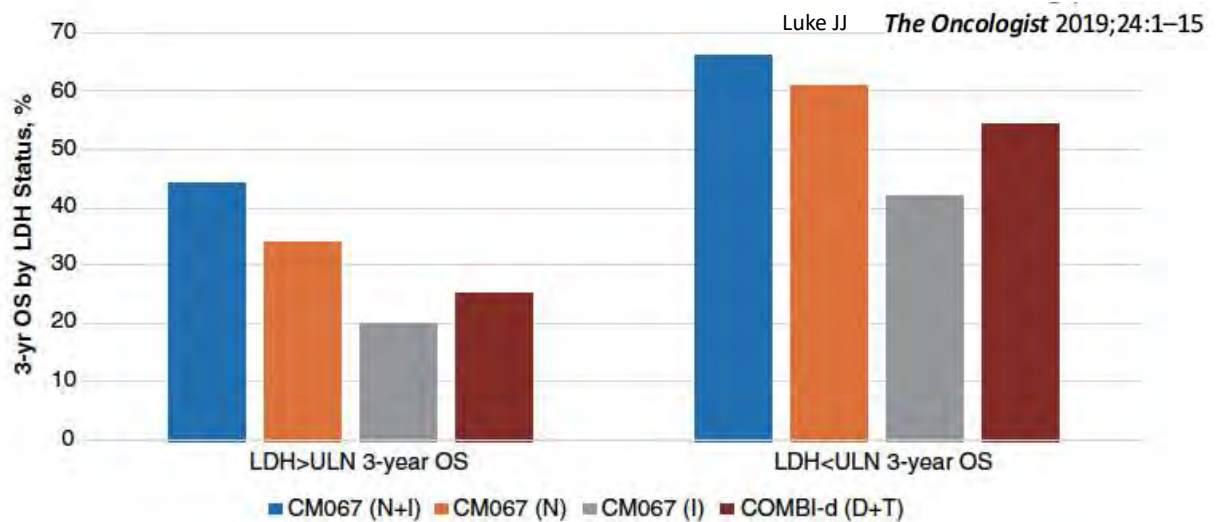
COMBI-D

Schadendorf D et al.
Eur J Cancer 2017



No. at risk					
Normal LDH, SLD < 66 mm, organ sites < 3	183	124	79	55	0
Normal LDH, SLD < 66 mm, organ sites ≥ 3	81	35	20	12	0
Normal LDH, SLD ≥ 66 mm	102	44	26	16	0
LDH ≥ 1 to < 2 x ULN	132	38	22	11	0
LDH ≥ 2 x ULN	65	5	4	0	0

3-year OS and clinical factors



Sequencing and treatment outcome

- Only retrospective data available!
- Biased data due to the preference that for high tumor burden BRAFi+MEKi should be the 1st treatment option

Targeted agents or immuno-oncology therapies as first-line therapy for BRAF-mutated metastatic melanoma: a real-world study

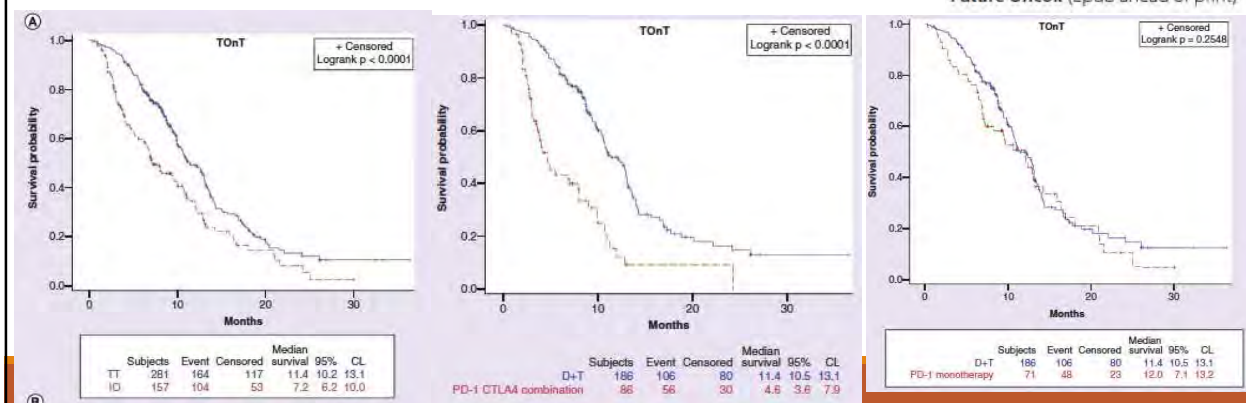
440 patients

IO-treated had a RECIST-determined response rate of 45.9 versus 60.1% for TT and time on treatment of 7.2 versus 11.4 months, respectively

There was no survival difference between cohorts ($p = 0.664$).

Luke JJ Feb2019

Future Oncol. (Epub ahead of print)



Comparative efficacy of combination immunotherapy and targeted therapy in the treatment of BRAF-mutant advanced melanoma: a matching-adjusted indirect comparison

Atkins et al.

Immunotherapy (2019) 11(7), 617–629

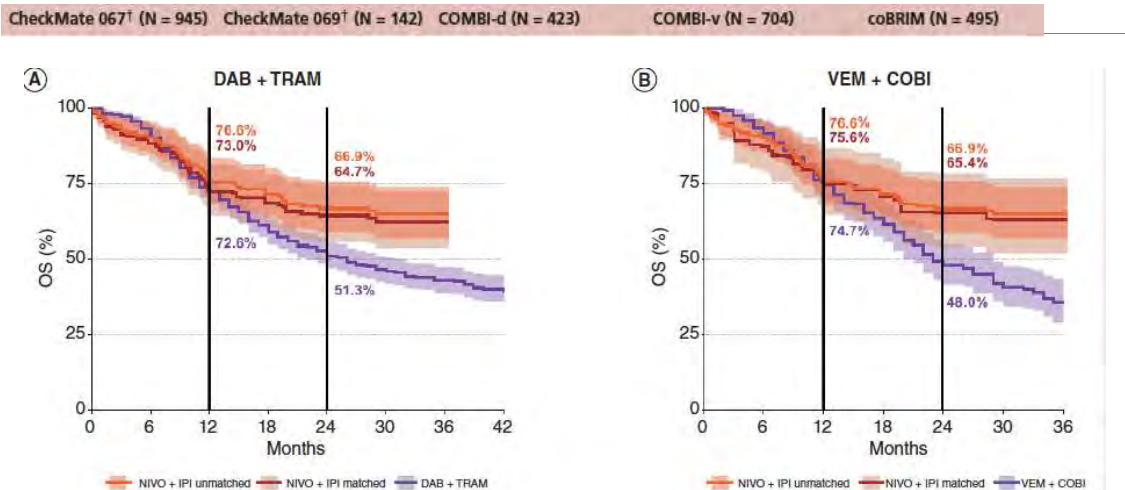


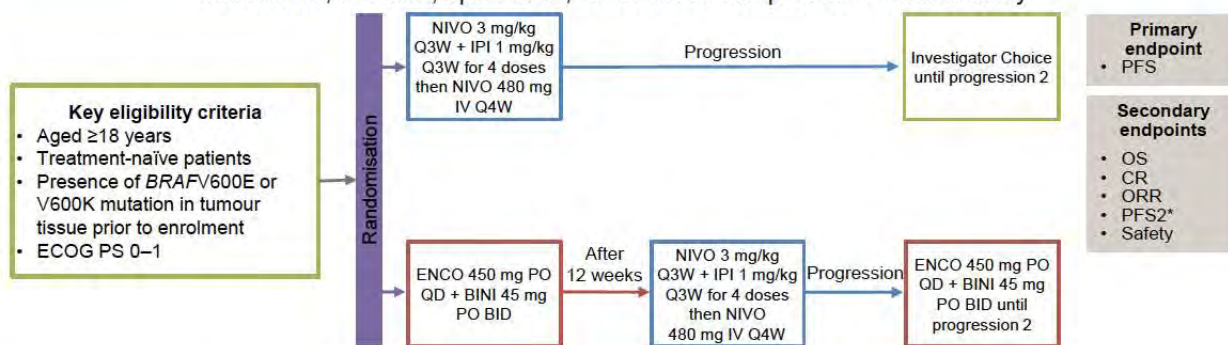
Figure 2. Overall survival comparisons. Comparison of OS before and after matching for nivolumab + ipilimumab versus dabrafenib + trametinib (A) and nivolumab + ipilimumab versus vemurafenib + cobimetinib (B).

Need for prospective data!

EORTC 1216: study design

Objective: to assess whether PFS can be improved with a sequential approach, using a 12-week induction of encorafenib + binimetinib, followed by combination nivolumab + ipilimumab, compared with nivolumab + ipilimumab alone, in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma

Multicentre, two-arm, open-label, randomised comparative Phase 2 study

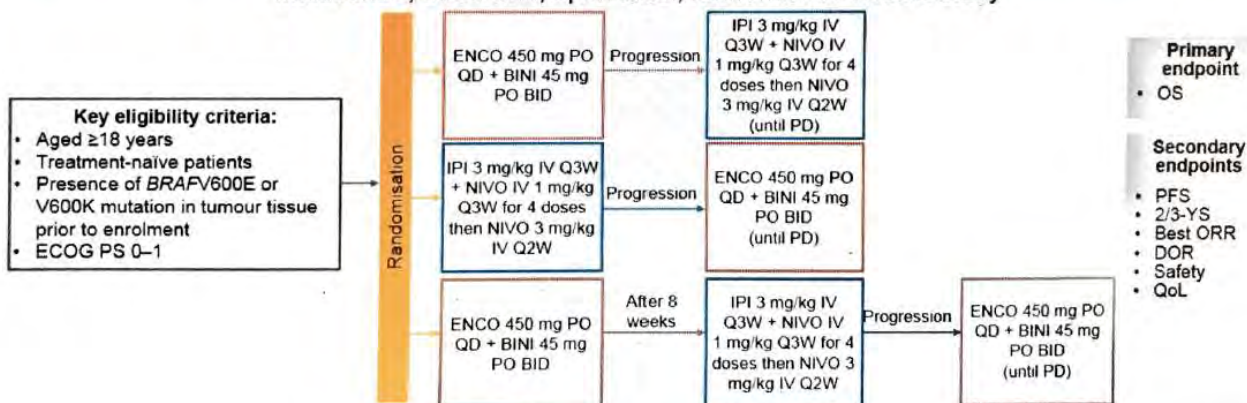


*PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first.
 BID, twice daily; BINI, binimetinib; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENCO, encorafenib; IPI, ipilimumab; IV, intravenous; NIVO, nivolumab; ORR, overall response rate; OS, overall survival;
 PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily
 ClinicalTrials.gov, NCT03235245. Available from: <https://clinicaltrials.gov/> (Accessed 15 October 2018).

SECOMBIT: study design

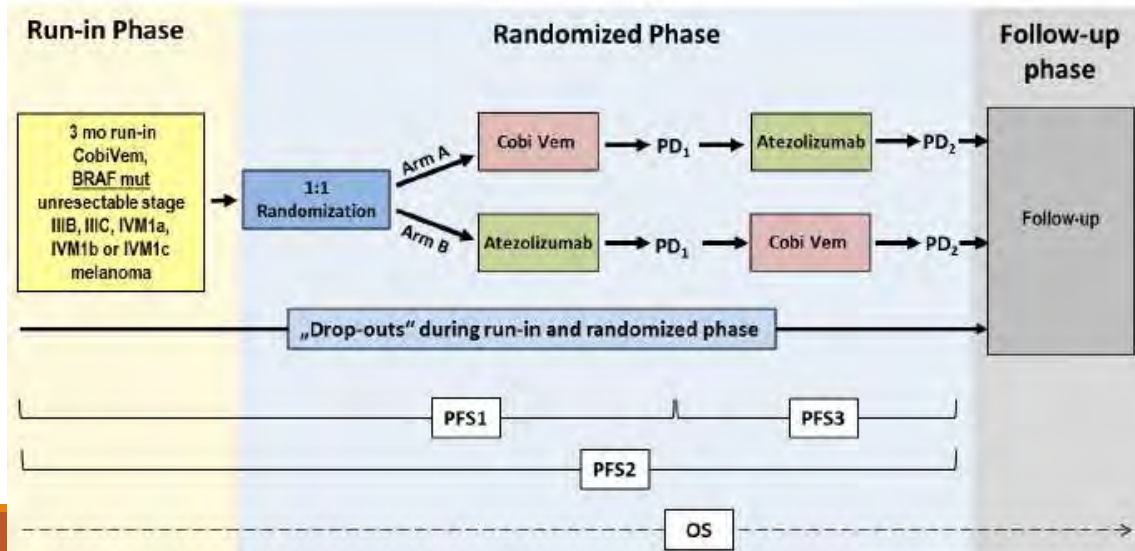
Objective: to evaluate the best sequential approach with combination immunotherapy (ipilimumab + nivolumab) and combination target therapy (encorafenib + binimetinib) in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma

Multicentre, three-arm, open-label, randomised Phase 2 study



SECOMBIT is a Phase 2, multicentre, three-arm, open-label, randomised controlled trial comparing two sequential approaches with combination immunotherapy (ipilimumab + nivolumab) and combination target therapy (encorafenib + binimetinib) in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma. The trial is registered at ClinicalTrials.gov (NCT03235245).

ImmunoCobiVem (Germany, France, Greece, Serbia-VMA)



NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600 mutant melanoma



Actual Study Start Date : July 13, 2015

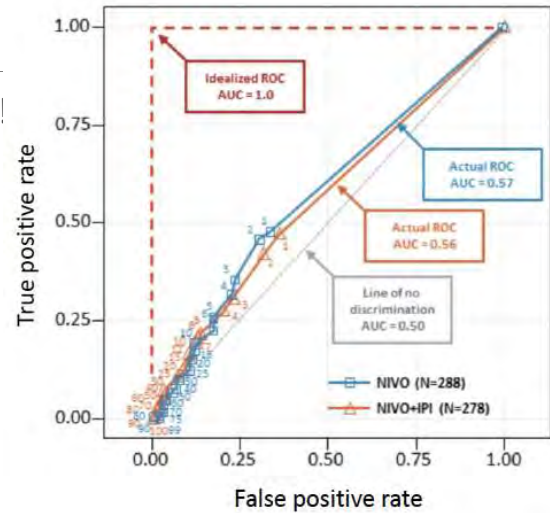
Estimated Primary Completion Date : October 2, 2022

Predictive biomarkers?

No validated markers for IO in melanoma!

- PD-L1: not standard of care
- MSI-high: not routine
- TMB mostly high in melanoma
- Main limitation:
negative predictive value

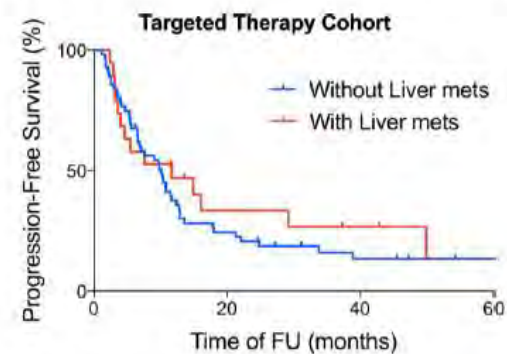
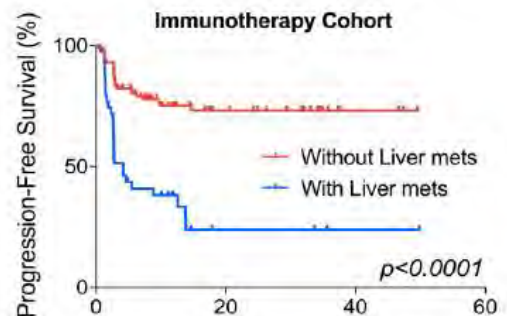
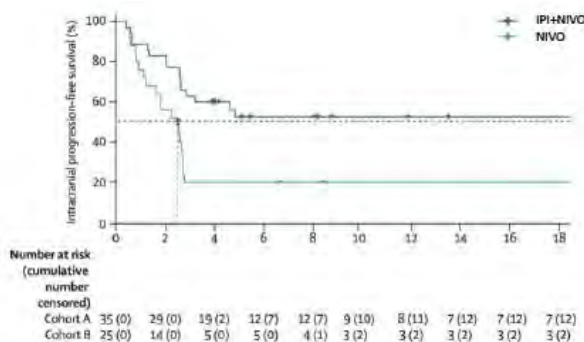
ROC curves confirm the poor performance of PD-L1 to guide patient selection: Fig. S4



¹Wolchok, *NEJM* 2017

Site of metastases

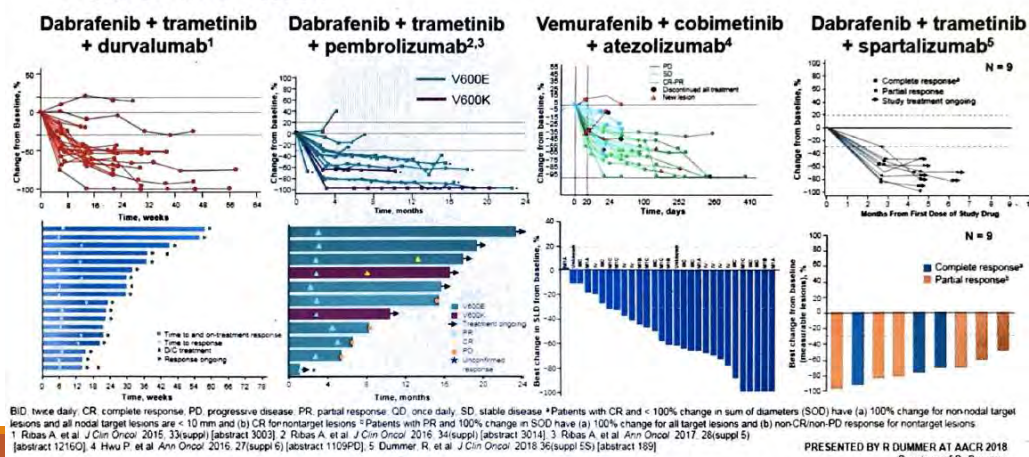
BRAIN METS



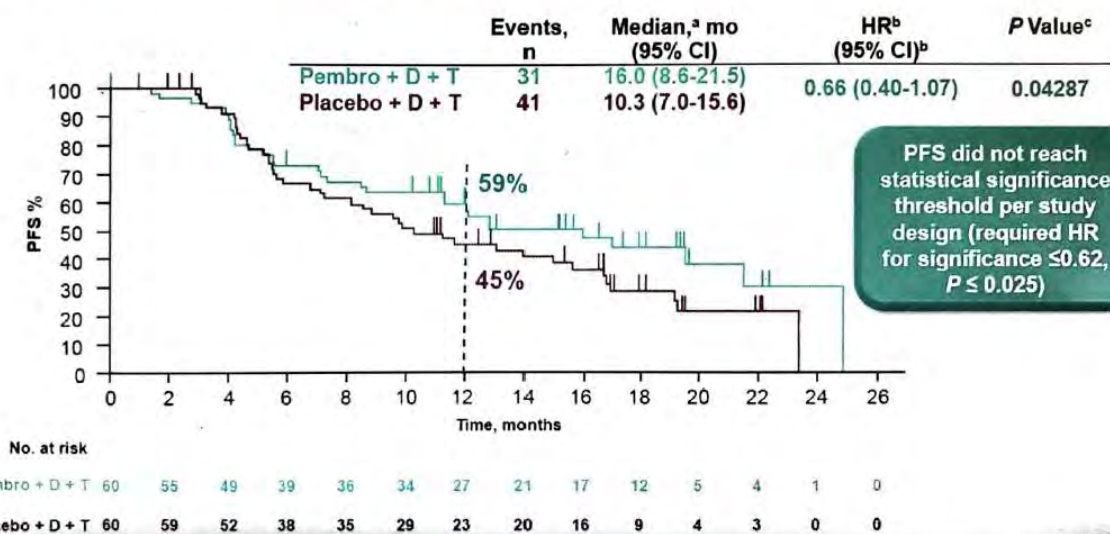
¹ Tawbi, *NEJM* 2018; ² Long, *Lancet Oncol* 2018

Combination!

Clinical Trials Combining BRAFi + MEKi + anti-PD-1/L1



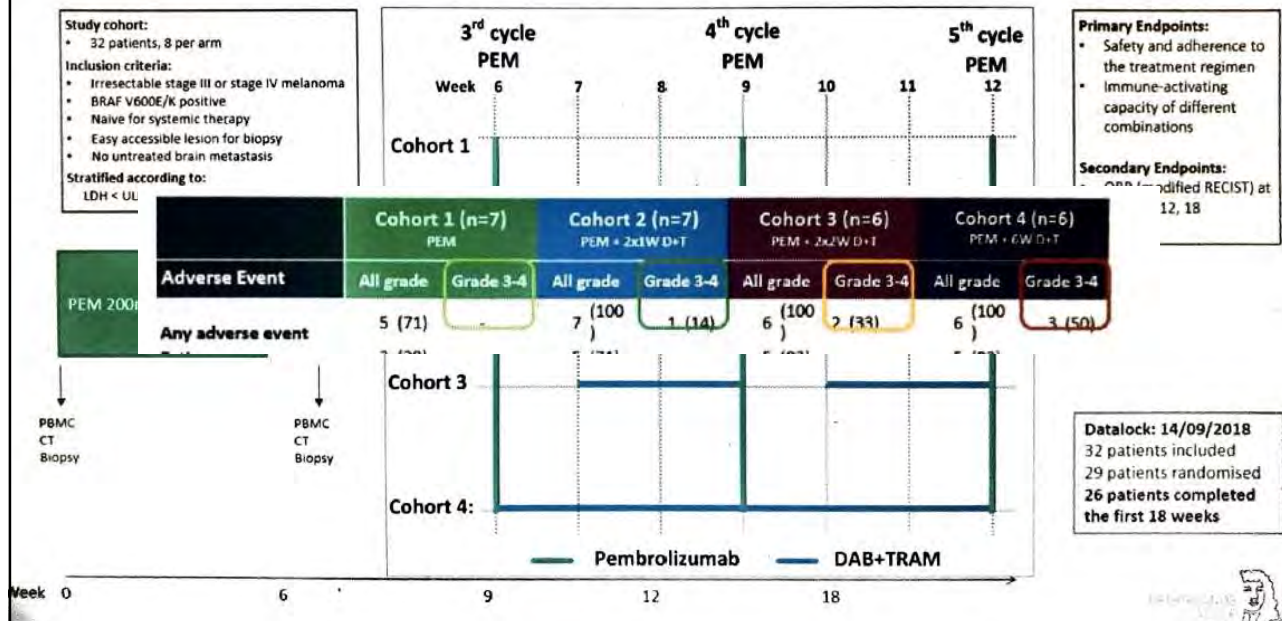
Progression-Free Survival



Based on Kaplan-Meier estimate of PFS, per investigator assessment

IMPEMBRA- STUDY DESIGN

Rozeman et al ESMO 2018



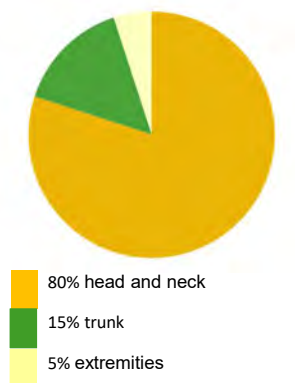
Systemic treatment of non-melanoma skin cancer

Janja Ocvirk
Institute of Oncology Ljubljana

Ljubljana, 5.9.2019

Basal cell carcinoma - BCC

- Basal cell carcinoma (BCC) grows from the basal layer of the epidermis and is the most commonly diagnosed malignant tumor and the most common form of skin cancer in the white population¹⁻⁴
- The risk of occurrence of BCC in the white population is 30%^{1,2}
- Poor reporting in registers
- The main cause of BCC is the exposure to UV radiation leading to cumulative DNA damage and gene mutations¹⁻⁵



1. Rubin AJ et al. N Engl J Med 2005;353:2262-9
2. Wong CSM et al. Br Med J 2003;327:794-8
3. Roewert-Huber J et al. Br J Dermatol 2007;157:47-51
4. Lear JT et al. J R Soc Med 1998;91:585-8
5. Caro J, Low JA. Clin Cancer Res 2010;16:3335-9

Treatment of basal cell carcinoma

- Curettage and cautery, cryosurgery
- Imiquimod

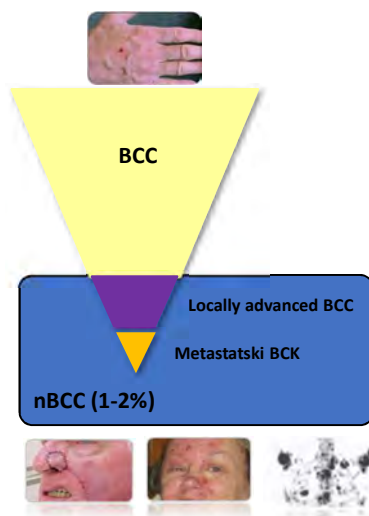
- Surgical excision
- Electrochemotherapy
- Radiotherapy
- Targeted therapy -Vismodegib

nBCC



3

Advanced basal cell carcinoma



Locally advanced basal cell carcinoma (lnBCC)

Aggressive disease with local tissue damage
Frequent recurrences after surgery
The operation would cause deformation



Metastatic BCC (mBCC)

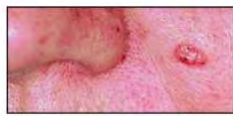
Rare but serious form of BCC
It involves the presence of metastases (e.g., lymph nodes, bones, lungs, liver)¹
Weak outcome (median survival: 8-14 months)²⁻³
5-year survival rate: 10%^{3,4}

1. Ting PT et al. J Cutan Med Surg 2005;9:10-15
2. von Domarus H, Stevens PL. J Am Acad Dermatol 1984;10:1043-60
3. Lo JS et al. J Am Acad Dermatol 1991;24:715-19
4. Wong CSM et al. Br Med J 2003;327:794-8

4

Criteria for defining advanced form of BCC

- The lesion size ≥ 10 mm
- Growth of the tumor in the surrounding tissues and structures
- Surgical treatment / irradiation is contraindicated due to the position of the tumor or would lead to significant morbidity / deformation / loss of function
- Two or more repeated lesions in the same place ¹



1. Basset-Seguín N. et al. Mol Cancer Ther 2015; 1–9

5

BCC and Hedgehog signal pathway



- The pathway of cell growth and differentiation that controls the formation of organs in embryonic development
- The Hedgehog signaling pathway is inactive in most of the tissue of the adult
- Abnormal activation (mutation) of the Hedgehog signal pathway plays an important role in pathogenesis BCC¹
- Hedgehog signaling pathway inhibitors provide a new treatment option for advanced patients BCC (vismodegib, sonidegib)



6

Table 1. Risk factors for recurrence[†].

	Clinical	Histological
Location	Low risk: trunk and limbs Intermediate risk: forehead, cheek, chin, scalp and neck High risk: nose and periorificial areas on the head and neck	Aggressive subtype [‡] : – Morpheaform – Infiltrating – Basosquamous – Multifocal
Size (largest tumor diameter)	>1 cm for high-risk location >2 cm for low- or intermediate-risk location	
Clinical aspect	Ill-defined lesions or morpheaform subtypes	
Disease status	Recurrent	

[†]Level of evidence 3 (i.e., based on case-control studies).
[‡]When several subtypes are associated, global prognosis depends on the component with the poorest prognosis.
 Adapted with permission from [26].

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial



Nicole Bassot-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunzfeld, Brigitte Dréno, Laurent Mortier, Paolo A Ascierto, Lisa Liotta, Caroline Durrain, Luc Thomas, Thomas Jouary, Nicolas Meyer, Bernard Guilha, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto F Fitzgibbon, Ioannis Xynos, Johan Hansson

Summary
 Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal *Lancet Oncol* 2015; 16: 729-36

	All patients (n=482*)	Patients with locally advanced basal cell carcinoma (n=453)	Patients with metastatic basal cell carcinoma (n=29)
Complete	155 (32%)	153 (34%)	2 (7%)
Partial	158 (33%)	149 (33%)	9 (31%)
Stable disease	128 (27%)	118 (26%)	10 (34%)
Progressive disease	15 (3%)	11 (2%)	4 (14%)
Missing/not evaluable	26 (5%)	22 (5%)	4 (14%)

Data are n (%). *Excludes patients without histologically confirmed disease (n=3) and without measurable disease (n=14).

Table 4: Best response to treatment

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial



Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunzfeld, Brigitte Dréno, Laurent Morlier, Paolo A Ascierto, Lisa Lickra, Caroline Duvicq, Luc Thomas, Thomas Jovary, Nicolas Meyer, Bernard Guilha, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto Fittipaldi, Ioannis Xynos, Johan Hansson

Summary

Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal

Lancet Oncol 2015; 16: 729-36

	All TEAEs		Grade 3-5 TEAEs	
	<12 months' exposure (n=314)	≥12 months' exposure (n=185)	<12 months' exposure (n=314)	≥12 months' exposure (n=185)
Any TEAE	307 (98%)	184 (99%)	130 (41%)	84 (45%)
Muscle spasms	169 (54%)	148 (80%)	21 (7%)	17 (9%)
Alopecia	154 (49%)	153 (83%)	1 (<1%)	1 (<1%)
Dysgeusia	139 (44%)	130 (70%)	8 (3%)	3 (2%)
Weight loss	80 (25%)	82 (44%)	4 (1%)	14 (8%)
Asthenia	76 (24%)	65 (35%)	9 (3%)	5 (3%)
Decreased appetite	74 (24%)	52 (28%)	7 (2%)	4 (2%)
Ageusia	75 (24%)	37 (20%)	6 (2%)	5 (3%)
Fatigue	50 (16%)	30 (16%)	9 (3%)	3 (2%)
Nausea	38 (12%)	47 (23%)	0	1 (<1%)
Diarrhoea	32 (10%)	51 (28%)	1 (<1%)	2 (1%)

Data are n (%). For the most common treatment-emergent adverse events (TEAEs) of any grade, event occurring in 10% or more of patients are reported. Events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version (version 4.0).

Table 3: Incidence of treatment-emergent adverse events according to duration of vismodegib exposure (≥12 months vs <12 months; n=499)

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial



Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunzfeld, Brigitte Dréno, Laurent Morlier, Paolo A Ascierto, Lisa Lickra, Caroline Duvicq, Luc Thomas, Thomas Jovary, Nicolas Meyer, Bernard Guilha, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto Fittipaldi, Ioannis Xynos, Johan Hansson

Summary

Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal

Lancet Oncol 2015; 16: 729-36

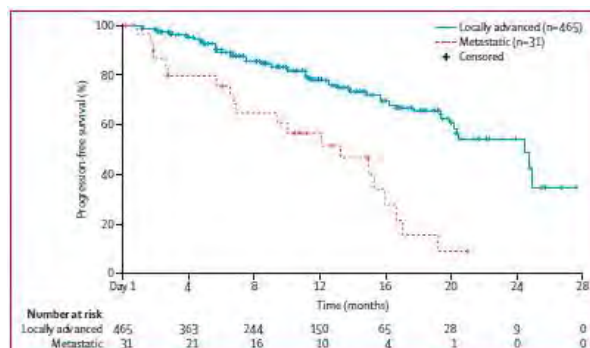


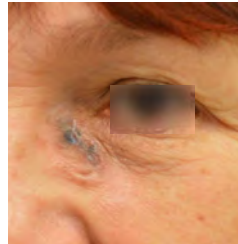
Figure 2: Kaplan-Meier plot of progression-free survival in patients who had histologically confirmed basal cell carcinoma

Case from OIL

23. 9. 2013



19. 12. 2013



31. 7. 2014



Quick response to high-dose treatment

Side effects: alopecia gr. 2 after one year of treatment, increased CPK gr.1, muscle cramps gr.1

11

Case from OIL



8. 11. 2012

Patient with Gorlin syndrome (multiple BCC)



16. 10. 2014



Side effects: alopecia gr.1 weight loss gr.2 increased CPK gr.1-3



Merkel's cells carcinoma (MCC)

- MCC is a rare, aggressive and often deadly neuroendocrine skin cancer.
- Growing incidence (in the United States it tripled between 1986 and 2001).
- Possible connection with recently discovered polyomavirus (80% of MCC cells).
- It often occurs in the sun exposed areas of the skin.

There are two reasons for MCC

- Through onco- proteins encoded with the Merckel's Cell Polycom virus (MCPyV)
- The accumulation of mutations caused by UV radiation.
- More often in immunosuppressed patients



PRINCIPLES OF SYSTEMIC THERAPY¹

Local Disease:

- Adjuvant chemotherapy not recommended

Regional Disease:

- Clinical trial (preferred)
- Adjuvant chemotherapy not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgement dictates
 - › Cisplatin ± etoposide
 - › Carboplatin ± etoposide

Disseminated Disease:

- Clinical trial (preferred)
- Avelumab²
- Pembrolizumab²
- Nivolumab²
- As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
 - › Cisplatin ± etoposide
 - › Carboplatin ± etoposide
 - › Topotecan
 - › (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

¹When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

²Preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy. The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies. Consult prescribing information for recommendations on detection and management of immune-related adverse events associated with checkpoint immunotherapies. Clinician and patient education is critical for safe administration of checkpoint immunotherapies.

Reason for use of immunotherapy in mMCC

- PD-L1 is expressed in MCC tumor cells and infiltrates of adjacent immune cells¹
- Dysfunction of MCPyV-specific T cells²
 - Levels of CD8 T cells increase with a higher tumor load
 - Exhausted phenotype (PD-1 +, Tim-3 +)
- MCPyV-negative tumors have a higher burden on mutations and neoantigens³

1. Lipson EJ, et al. *Cancer Immunol Res.* 2013;1(1):54-63; 2. Afanasiev O, et al. *Clin Cancer Res.* 2014;19(19):5351-60; 3. Goh G, et al. *Oncotarget.* 2016;7(3):3403-15.

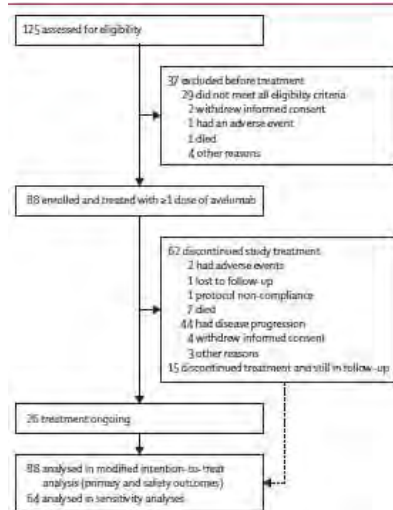
Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailesh Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Cécile Lebbié, Gerald P Linette, Michele Mihaly, Isaac Brownell, Karl D Lewis, Jochen H Larch, Kevin Chin, Lisa Mahoney, Arja von Haydebreck, Jean-Marie Cullerot, Paul Nghiem

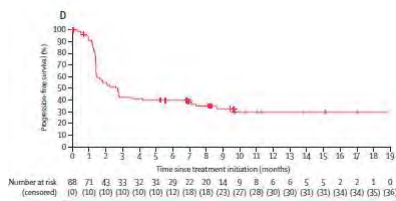
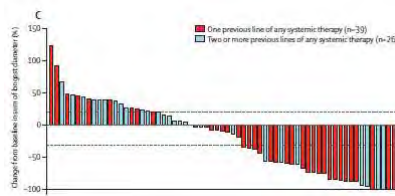
- 88 patients were enrolled and received at least one dose of avelumab.
- Patients were followed up for a median of 10 • 4 months (IQR 8 • 6–13 • 1).
- The proportion of patients who achieved an objective response was 28 (31 • 8% [95 • 9% CI 21 • 9–43 • 1]) of 88 patients, including eight complete responses and 20 partial responses. Responses were ongoing in 23 (82%) of 28 patients at the time of analysis.
- Five grade 3 treatment-related adverse events occurred in four (5%) patients: lymphopenia in two patients, blood creatine phosphokinase increase in one patient, aminotransferase increase in one patient, and blood cholesterol increase in one patient; there were no treatment-related grade 4 adverse events or treatment-related deaths. Serious treatment-related adverse events were reported in five patients (6%): enterocolitis, infusion-related reaction, aminotransferases increased, chondrocalcinosis, synovitis, and interstitial nephritis (n=1 each).

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaurman, Jeffery Russell, Omid Hamid, Shalender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Cdeste Lebbe, Gerald P Linette, Michele Midis, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Haydebreck, Jean-Marie Grilleat, Paul Nghiem



Lancet Oncol 2016; 17: 1374–85



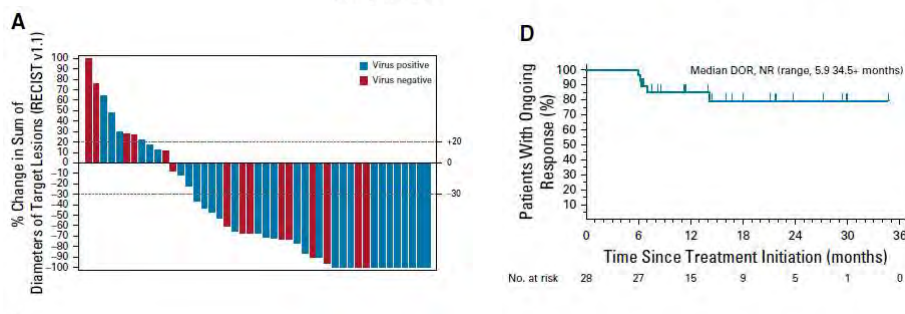
Lancet Oncol 2016; 17: 1374–85

- ORR to pembrolizumab was 56% (complete response [24%] plus partial response [32%]; 95% CI, 41.3% to 70.0%), with ORRs of 59% in virus-positive and 53% in virus-negative tumors.
- Median follow-up time was 14.9 months (range, 0.4 to 36.4+ months).
- Among 28 responders, median response duration was not reached (range, 5.9 to 34.5+ months).
- The 24-month PFS rate was 48.3%, and median PFS time was 16.8 months (95% CI, 4.6 months to not estimable).
- The 24-month OS rate was 68.7%, and median OS time was not reached.
- Although tumor viral status did not correlate with ORR, PFS, or OS, there was a trend toward improved PFS and OS in patients with programmed death ligand-1-positive tumors.
- Grade 3 or greater treatment-related adverse events occurred in 14 (28%) of 50 patients and led to treatment discontinuation in seven (14%) of 50 patients, including one treatment-related death.

J Clin Oncol 37:693-702. 2019

Durable Tumor Regression and Overall Survival in Patients With Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy

Paul Nghiem, MD, PhD¹; Shalender Bhatia, MD¹; Evan J. Lipson, MD¹; William H. Sharfman, MD¹; Ragini R. Kurchadkar, MD¹; Andrew S. Brohl, MD¹; Phillip A. Friedlander, MD²; Adil Daud, MD³; Hamlet M. Kluger, MD⁴; Sonil A. Reddy, MD⁵; Brian C. Boukay, MD⁶; Adam L. Riker, MD⁷; Melissa A. Burgess, MD⁸; Brent A. Hanks, MD, PhD⁹; Thomas Olencki, DO¹⁰; Kim Margolin, MD¹¹; Lisa M. Lundgren, MS¹²; Abba Soti, DO¹³; Nirasha Ramchurn, PhD¹⁴; Candice Church, PhD¹⁵; Sang Y. Park, MD¹⁶; Michi M. Shirahata, MD¹⁷; Bob Salim, PhD¹⁸; Janis M. Taube, MD¹⁹; Steven R. Bird, MS²⁰; Nagatle Ibrahim, MD²¹; Steven P. Fling, PhD²²; Blanca Homet Moreno, MD, PhD²³; Ead Shanon, MD, MPH²⁴; Martin A. Cheever, MD²⁵; and Suzanne L. Topalian, MD²⁶



J Clin Oncol 37:693-702. 2019

In patients with aMCC receiving first-line anti-programmed cell death-1 therapy - Pembrolizumab demonstrated durable tumor control, a generally manageable safety profile, and favorable OS compared with historical data from patients treated with first-line chemotherapy.

J Clin Oncol 37:693-702. 2019

Table 2. Summary of data from trials of immunotherapy for the treatment of patients with advanced MCC

Parameter	Pembrolizumab Study ⁷	Avelumab Study ⁸
Patient population	Treatment naïve (first-line treatment)	Chemotherapy refractory (second-line or later treatment)
N	20 ^a	88
Primary end point	Objective response rate by RECIST v1.1	Confirmed best overall response by independent review committee per RECIST v1.1
Patient and disease characteristics		
Median age (range), years	68 (57–91)	73 (55–88)
Stage IIIb MCC, n (%)	2 (8)	0
Stage IV MCC, n (%)	24 (92)	88 (100)
Prior lines of systemic therapy, n (%)		
0	26 (100)	0
1	0	52 (59)
≥ 2	0	36 (41)
Median baseline extent of disease (range), mm	69 (13–182)	79 (16–404)
MCPyV-positive, n (%)	17 (85)	46 (52) ^b
Median duration of follow-up (range), months	7.6 (1.6–12.2)	10.4 (6–19)
Minimum duration of follow-up, months	1.6	6
Objective response rate		
Overall, % (95% CI)	56 (35–76)	32 (22–43) ^c
MCPyV-positive, % (n/N) ^d	62 (10/16)	26 (12/46)
MCPyV-negative, % (n/N)	44 (4/9)	36 (11/31)
Response durability		
Number of patients with ongoing response at data cutoff, % (n/N)	86 (12/14)	82 (23/28)
Median duration of response (range), months ^e	Not reached (2+ to 10+)	Not reached (3+ to 18+)
Kaplan-Meier estimate of proportion of responses with ≥ 6 months' duration, % (95% CI)	Not reported	92 (70–98)
Durable response rate, % (95% CI) ^f	Not reported	29 (20–39) ^g
Progression-free survival		
Median, months (95% CI)	9 (5–not reached)	2.7 (1.4–6.9)
6-month rate, % (95% CI)	67 (49–84)	48 (29–70)
Overall survival		
Median, months (95% CI)	Not reported	11.3 (7.5–14.8)
6-month rate, % (95% CI)	Not reported	69 (58–78)
Treatment-related AEs, n (%)		
Any grade	20 (77)	62 (70)
grade 3	2 (8)	4 (5)
grade 4	2 (8)	0 (0)

^a25/26 patients had ≥ 1 tumor assessment during treatment.

^b77/88 patients were evaluable for MCPyV status.

^cA repeated CI for the ORR in the modified intent-to-treat analysis set (95.9% CI for the primary analysis) was calculated to account for the group sequential testing approach.

^dN1, number evaluable.

^e– denotes a censored observation for durability of response.

^fDurable response rate defined as the proportion of patients with a response of at least 6 months' duration and was estimated as the product of the objective response and the Kaplan-Meier estimate of 6 months' durability of response.

ONCOLOGY
2019; 37(10): 693-702
DOI: 10.1200/JCO.2018.16.10001

Taylor & Francis
Taylor & Francis Group

REVIEW

Immune evasion mechanisms and immune checkpoint inhibition in advanced merkel cell carcinoma

Drk Schoderf, Paul Nghiem, Shalender Bhatia, Axel Hauschild, Philippe Saiag, Lisa Mahler, Subramanian Hariharan, and Howard L. Kaufman

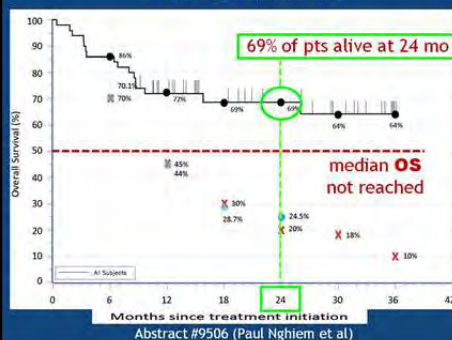
Immune Checkpoint Inhibition Trials in MCC: Advanced Metastatic Disease

Drug / Trial	Target	n	Prior chemo	Objective response	Median follow-up	Median PFS	Median OS
Pembrolizumab first-line ¹ (NCT02267603) CITN-09	PD-1	26	No	56%	8 mo	Not reached	Not reached
Avelumab first-line ² (NCT02155647) JAVELIN Merkel 200	PD-L1	29	No	63%	3 mo	Not reached	Not reached
Nivolumab first/second-line ³ (NCT02488759) CheckMate-358	PD-1	15 10	No Yes	73% 1st-L 50% 2nd-L	3+ mo	Not reached	Not reached
Avelumab second-line ^{4,5} (NCT02155647) JAVELIN Merkel 200	PD-L1	88	Yes	33%	16 mo	3 mo	13 mo

1. Nghiem PT et al.: *N Engl J Med* 374:2542 (2016); 2. D'Angelo SP et al.: ASCO abstract 9530 (2017); 3. Topalian S et al.: *Cancer Res* 77(13 Suppl): abstract CT074 (2017); 4. Kaufman HL et al.: *Lancet Oncol* 17:1374 (2016); 5. Kaufman H et al.: *J Immunother Cancer* 6:7 (2018).

Anti-PD-1/PD-L1 in advanced MCC: first-line or second-line (chemo-naïve or chemo-pretreated) ?

1st line (pembrolizumab)



2nd line (avelumab) after previous chemo



Anti PD-1/PD-L1 in advanced MCC

- **ORR** 1st line 56-73%
2nd line 33-50%
- **PFS** 1st line 17 mo (median)
2nd line 3 mo (median)
- **OS** 1st line median not reached
2nd line 13 mo (median)
- Previous ChT impairs outcome of anti-PD-1/PD-L1
- anti-PD-1/PD-L1 should be applied as first-line treatment
- ChT should be postponed to 2nd line

SCC

- Second most common NMSC (20%)
- Incidence is rising in last 30 years (50-200%)
- Head and neck 80-90%
- 90% have good prognosis





SCC in transplanted patients

36 x higher incidence than usual (BCC: SCC 4: 1)
Aggressive behavior - poor prognosis



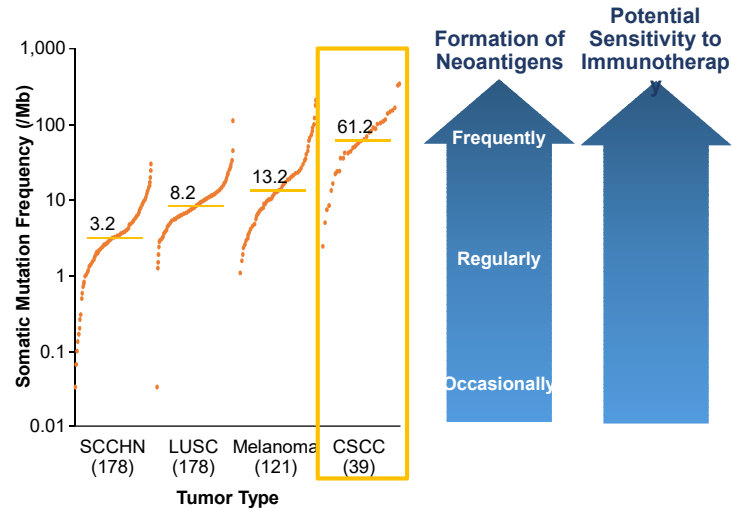
- Localized disease – surgery, electrochemotherapy
- Radiotherapy
- Advance disease - locally in systemic
- Pplatinum based chemotherapy – no standard schemas, shorter durance of remissions – 3 months
- Targeterd therapy: cetuximab (RR 21%), Panitumumab (31%)

NCCN Guidelines. V2.2018. https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf.



Presented By Axel Hauschild at 2017 ASCO Annual Meeting

Tumor Mutational Burden in CSCC



Red horizontal line and associated number in figure = median mutations per Mb.
 CSCC, cutaneous squamous cell carcinoma; LUSC, lung squamous cell carcinoma; Mb, megabase of DNA; SCCHN, Squamous cell carcinoma of the head and neck.
 Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582-6592.

Rationale for Evaluating Checkpoint Inhibition in CSCC

- High tumor mutation burden (TMB) and immunogenic cancer
 - High TMB may contribute to increased neoantigen production, which may increase tumor antigenicity¹
- Immunosuppression is a well-described risk factor for CSCC (especially in solid-organ transplant patients)²
- PD-L1 expression has been observed in advanced CSCC³

1. Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582-92; 2. Euvrard E, et al. *N Engl J Med*. 2003;348:1681-1691.
 3. Slater NA, et al. *J Cutan Pathol*. 2016;43:663-70.

Candidates for Immunotherapy for Advanced CSCC

- Patients with advanced CSCC
 - Locally advanced / metastatic disease
- Patients who have failed prior surgeries
- Patients who are not surgical candidates due to morbidity / potential disfigurement or low confidence of clear margins
- Patients not candidates for radiotherapy



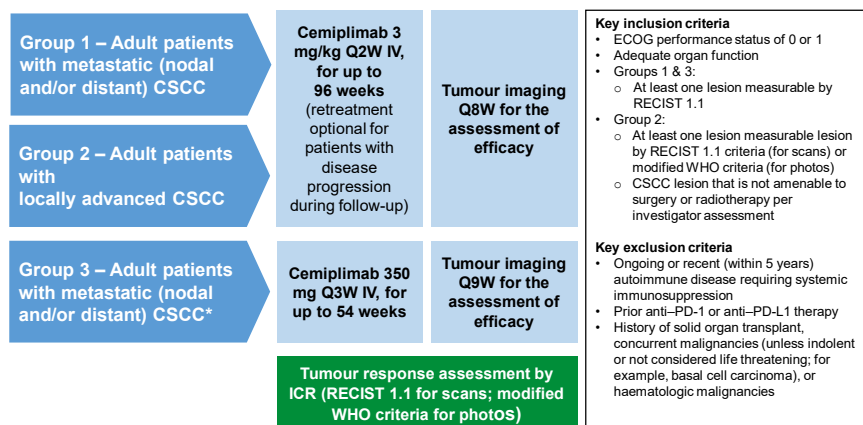
The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowitz, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohari, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homs, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

EMPOWER-CSCC-1 Study Design (NCT02760498)



*Data not yet available

CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, programmed cell death; PD-L, PD-ligand; Q[n]W, every [n] weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; WHO, World Health Organisation.

1. Guminski et al. *J Clin Oncol*. 2019;37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol*. 2019;37 (suppl; abstr 6015) [poster presentation].

Group 1: Data cut-off date: September 20, 2018
Group 2: Data cut-off date: October 10, 2018

Baseline Characteristics in EMPOWER-CSCC-1 with Advanced CSCC (Group 1 and Group 2)

	Metastatic CSCC (N=59) ¹	Locally advanced CSCC (N=78) ²
Median age, years (range)	71 (38–93)	74 (45–96)
≥ 65 years, n (%)	43 (72.9)	59 (75.6)
Male sex, n (%)	54 (91.5)	59 (75.6)
ECOG performance status, n (%)		
0 / 1	23 (39.0) / 36 (61.0)	38 (48.7) / 40 (51.3)
Primary CSCC site, n (%)		
Head/neck	38 (64.4)	62 (79.5)
Extremity	12 (20.3)	14 (17.9)
Trunk	9 (15.3)	2 (2.6)
Prior systemic therapy for CSCC, n (%)		
Any	33 (55.9)	12 (15.4)
1	22 (37.3)	10 (12.8)
≥2	11 (18.6)	2 (2.6)
Prior radiotherapy for CSCC, n (%)	50 (84.7)	43 (55.1)
Median duration of follow-up, months (range)	16.5 (1.1–26.6)	9.3 (0.8–27.9)

Data cut-off date: Sept 20, 2018 (Group 1)¹; Oct 10, 2018 (Group 2)

CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group

¹excludes ear and temple ²includes arms/hands and legs/feet

1. Guminski et al. *J Clin Oncol*. 2019;37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol*. 2019;37 (suppl; abstr 6015) [poster presentation].

Tumor Response Assessment by Independent Central Review in Patients with Advanced CSCC (Group 1 and 2)

	Metastatic CSCC (N=59) ¹	Locally Advanced CSCC (N=78) ²
Median duration of follow-up, months (range)	16.5 (1.1 – 26.6)	9.3 (0.8 – 27.9)
Best overall response, n (%)		
Complete Response (CR)	10 (16.9)	10 (12.8)
Partial Response	19 (32.2)	24 (30.8)
Stable Disease	9 (15.3)	28 (35.9)
Non-CR/non-PD [†]	4 (6.8)	0
Progressive Disease (PD)	10 (16.9)	9 (11.5)
Not evaluable [‡]	7 (11.9)	7 (9.0)
Objective response rate (ORR), % (95% CI)	49.2 (35.9–62.5)	43.6 (32.4–55.3)
ORR by INV % (95% CI)	49.2 (35.9–62.6)	52.6 (40.9–64.0)
Complete Response / Partial Response	4 (6.8) / 25 (42.3)	13 (16.7) / 28 (35.9)
Disease control rate, % (95% CI)	71.2 (57.9–82.2)	79.5 (68.8–87.8)
Durable disease control rate, % (95% CI) [§]	62.7 (49.1–75.0)	62.8 (51.1–73.5)
Median observed time to response, months (range) [¶]	1.9 (1.7–9.1)	1.9 (1.8–8.8)

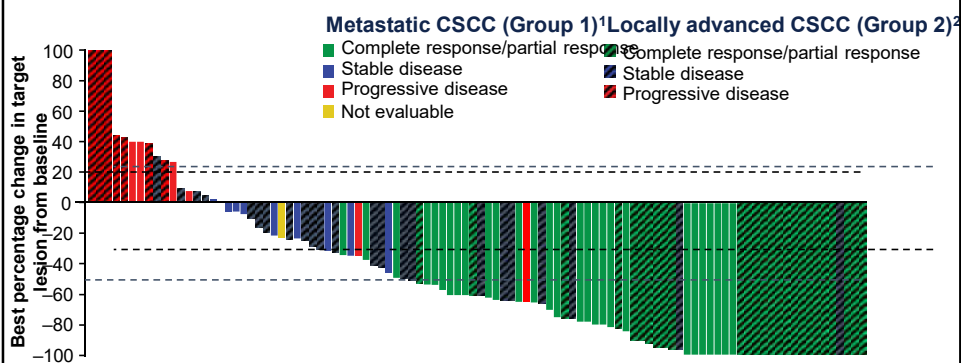
Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)

[†]Patients with non-measurable disease on central review of baseline imaging. [‡]Include missing and unknown tumor response. [§]Defined as the proportion of patients without progressive disease for at least 105 days. [¶]Data shown are from patients with confirmed responses.

INV investigator assessment

1. Guminski et al. *J Clin Oncol* 2019;37 (suppl: abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol* 2019;37 (suppl: abstr 6015) [poster presentation].

Best Percentage Change in Target Lesion in Patients with Advanced CSCC per ICR



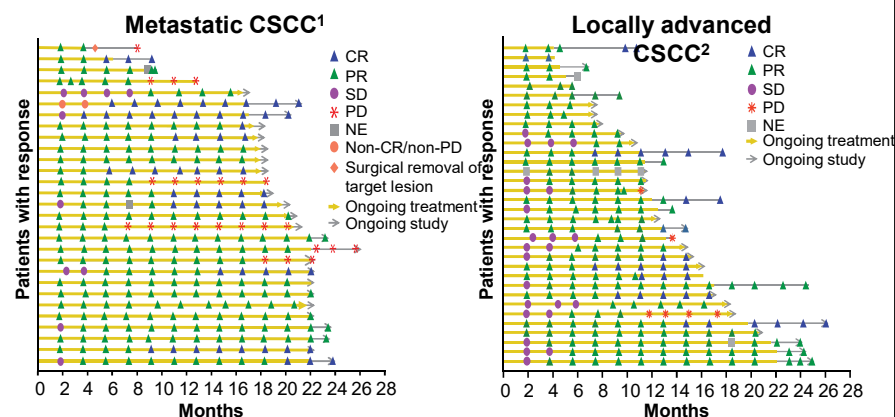
Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)

Bars show the best percentage change in the sum of target lesion diameters from baseline for 45 patients with metastatic CSCC who underwent radiologic evaluation per ICR and 56 patients with locally advanced CSCC who underwent photography evaluation per modified WHO criteria by ICR after treatment initiation. Lesion measurements after progression were excluded. Black horizontal dashed lines indicate RECIST 1.1 criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥25% increase in the sum of target lesion diameters). Blue horizontal dashed lines indicate WHO criteria for partial response (≥50% decrease in the sum of target lesion diameters) and progressive disease (≥25% increase in the sum of target lesion diameters).

CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

1. Guminski AD, et al. *J Clin Oncol* 2019;37 (suppl: abstr 9526); 2. Migden MR, et al. *J Clin Oncol* 2019;37 (suppl: abstr 6015)

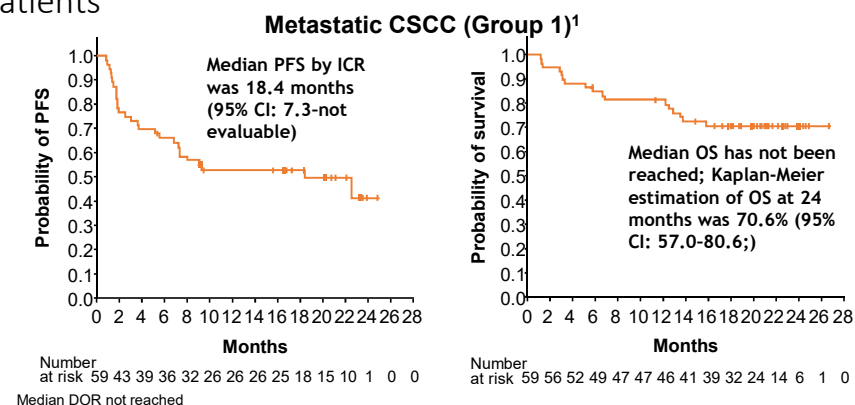
Time to Response and Duration of Response in the Responding Patients with Advanced CSCC



Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
¹Twenty-three of the 29 patients remain in response at time of data cut-off; of the 23 patients, 10 were still on study, 11 were in post-treatment follow-up and two were off study.
 Multiple progression events for a single patient were possible due to discrepancies between investigator and ICR assessments of tumour response and because the protocol allowed option for treatment past progression in patients whom the investigator felt were experiencing clinical benefits. ²Of the 34 responding patients, three had subsequent progressive disease. Among the remaining 31 patients who were in response at the time of data cut-off, 12 were still on study treatment, nine were in post-treatment follow-up, and 10 were off study. One patient (sixth from bottom) had four progressive disease assessments due to discordance between investigator and ICR assessments of tumour response.
 CR, complete response; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; NE, not evaluable;
 PD, progressive disease; PR, partial response; SD, stable disease.

1. Guminski et al. *J Clin Oncol*. 2019;37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol*. 2019;37 (suppl; abstr 6015) [poster presentation].

Kaplan-Meier Estimation Overall Survival, Progression-Free Survival, and Duration of Response in Advanced CSCC Patients



	Locally Advanced CSCC (Group 2) ²
Median PFS	NR
K-M Estimated PFS at 12 months	58.1% (95% CI: 43.7-70.0)
Median OS	NR
K-M Estimated OS at 12 months	93.2% (95% CI: 84.4-97.1)
Median DOR	NR

Group 1: Median duration of follow-up = 16.5 mos (range 1.1 – 26.6); Group 2: Median duration of follow-up = 9.3 mos (range 0.8 – 27.9)
 Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
 CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; OS, overall survival; PFS, progression-free survival;
 NR, not reached
 1. Guminski et al. *J Clin Oncol*. 2019;37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol*. 2019;37 (suppl; abstr 6015) [poster presentation].

Treatment-emergent Adverse Events (TEAEs), Regardless of Attribution, in Patients with Advanced CSCC

	Group 1 Metastatic CSCC (N=59) ¹		Group 2 Locally advanced CSCC (N=78) ²		Overall (N=137) ³	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	59 (100.0)	30 (50.8)	78 (100.0)	34 (43.6)	137 (100.0)	64 (46.7)
Serious	24 (40.7)	20 (33.9)	23 (29.5)	19 (24.4)	47 (34.3)	39 (28.5)
Led to discontinuation	6 (10.2)	4 (6.8)	6 (7.7)	5 (6.4)	12 (8.8)	9 (6.6)

Metastatic CSCC (Group 1)¹

Grade ≥3 TEAEs occurring in >1 patient

- Cellulitis (n=4; 6.8%)
- Pneumonitis (n=3; 5.1%)
- Anemia, dyspnea, hypercalcemia, new primary CSCC, pleural effusion, and pneumonia (each n=2; 3.4%)

Grade ≥3 TEAEs leading to treatment discontinuation

- Pneumonitis (n=3; 5.1%)
- Aseptic meningitis, confusional state, and neck pain (all in the same patient: n=1; 1.7%)

Locally advanced CSCC (Group 2)²

Grade ≥3 TEAEs occurring in >1 patient

- Hypertension (n=6; 7.7%)
- Pneumonia (n=4; 5.1%)
- Hyperglycemia and cellulitis (each n=3; 3.8%)
- Breast cancer, fall, hyponatremia, lymphopenia, muscular weakness, pneumonitis, sepsis, and urinary tract infection (each n=2; 2.6%)

Grade ≥3 TEAEs leading to treatment discontinuation

- Pneumonitis (n=2; 2.6%)
- Encephalitis, hepatitis, increased aspartate aminotransferase, pneumonia, and proctitis (each n=1; 1.3%)

Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)

CSCC, cutaneous squamous cell carcinoma; TEAE, treatment-emergent adverse event.

1. Guminski et al. J Clin Oncol. 2019;37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. J Clin Oncol. 2019;37 (suppl; abstr 6015) [poster presentation]. 3. Data on File, Regeneron Pharmaceuticals Inc.

PD 1 antibodies in SCC

Before treatment



After treatment

Summary

- NMSC - the most common cancer
- Incidence is rising
- Numerous mutations in UV-induced cancer
- Surgery is a standard therapy for non-complicated cases
- Limited role of radiotherapy despite radiosensitivity in MCC

NCCN Guidelines. V2.2018.
https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed 29 Aug 2018.

Thank you



SKIN TOXICITY OF IMMUNOTHERAPY CASE PRESENTATION

1st Summer School in medical oncology

Vermiglio Lucija, MD
Dr. Mesti Tanja, MD

PRESENTATION

- › B. L., male, 58 years
- › History of illness Ø
- › PS WHO 1
- › July 2017 – **painful mass in the right armpit (12x10x9cm)**
- › Biopsy – **Malignant melanoma metastasis**
- › Primary tumour Ø
- › T S-100, normal LDH
- › **BRAF +**
- › PET-CT

FIRST LINE TREATMENT

- › **BRAF/MEK inhibitors:** vemurafenib 960mg/12h/cont + cobimetinib 60mg/day/3weeks
 - July to Oct 2017
 - Tumor size ↓ 50%
- › November 2017 – **Axillary lymph node resection.**
50% ↓ (3x3x3cm), R2 resection, N(9/22)
- › December 2017 – **BRAF/MEK inhibitors**
- › January – March 2018, **RT** TD 60Gy

SECOND LINE TREATMENT

- › May 2018 – **PD** on PET-CT
- › Immunotherapy – **Pembrolizumab** 200 mg
- › Palliative RT TD 15Gy
- › June 2018 – *the last application of immunotherapy*

Locoregional status

June 2018:

- › 4x3cm painfull mass in the right armpit, exulcerated, purulent discharge, right arm red, swollen + osteolytic areas in the right humerus, no fracture
- › US arm – no DVT
- › Amoxicillin + clavulanic acid
- › Antibiotogram: Aerobic (Enterococcus faecalis, Staphylococcus lugdunensis, Staphylococcus caprae, Corynebacterium simulans) + Anaerobic bacteria (Prevotella bivia, Peptoniphilus harei, Finegoldia magna, Veillonella atypica)
- › Vancomycin + Metronidazol + Ciprofloxacin
- › **Severe generalized epidermolysis bullosa** (50 – 60%)
- › July 2018 – ICU
- › **Septic shock and multiorgan failure**

SKIN BIOPSY

- › Total necrosis of the epidermis – **toxic epidermal necrolysis**
- › Immunofluorescence analysis: **IgA mediated Epidermolysis bullosa**
- › Negative anti BP180 and anti BP230 (pemphigus bullosa)
- › Possible anti-P450 pemphigus bullosa or pemphigus bullosa mediated by anti-Plectin Ab



Severe bullous pemphigoid associated with pembrolizumab therapy of metastatic melanoma with complete regression
 D. Ritzke,¹ G. Bär-Sauer,² Z. K. Kasper,³ T. Seitz,⁴ C. D. Sauer,⁵ and R. Bergner¹

¹Department of Dermatology, University of Würzburg, Würzburg, Germany; ²Department of Dermatology, University of Würzburg, Würzburg, Germany; ³Department of Dermatology, University of Würzburg, Würzburg, Germany; ⁴Department of Dermatology, University of Würzburg, Würzburg, Germany; ⁵Department of Dermatology, University of Würzburg, Würzburg, Germany

Case Reports in Dermatology

Bullous Pemphigoid as an Adverse Reaction to Pembrolizumab: Two Case Reports

Keywords: Bullous pemphigoid, Pembrolizumab, Adverse reaction, Immunotherapy

Abstract: Two patients with severe bullous pemphigoid (BP) developed during pembrolizumab (pembro) therapy for metastatic melanoma. Both patients achieved complete regression of their melanoma lesions. The clinical and histopathologic features, frequency, and impact on cancer therapy are discussed.

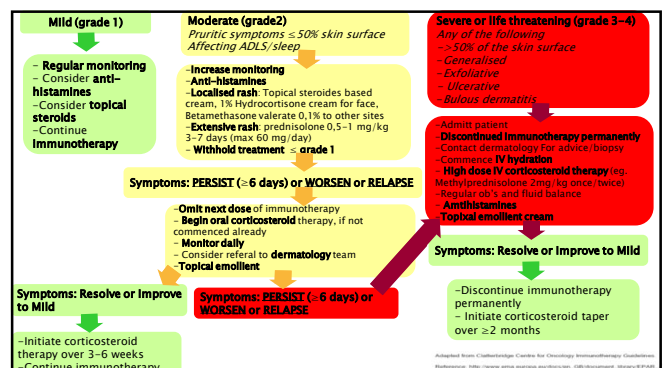
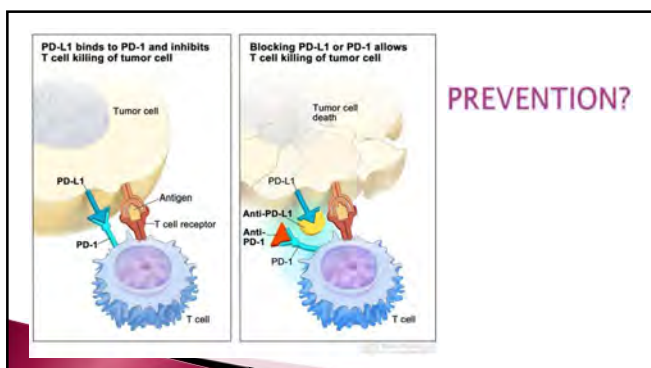
Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy: A retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy

Abstract: Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy are rare. We performed a retrospective analysis of 10 patients with bullous disorders who received anti-PD-1 or anti-PD-L1 therapy. The clinical and histopathologic features, frequency, and impact on cancer therapy are discussed.

Melanoma Research 2015, 26:265-268

A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab

Abstract: A patient with metastatic melanoma treated with pembrolizumab developed bullous pemphigoid. The clinical and histopathologic features, frequency, and impact on cancer therapy are discussed.



Thank you





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Systemic treatment of ovarian cancer

Erik Škof



1st Summer School in medical oncology – Standards and open questions
Institute of Oncology Ljubljana
6th september 2019



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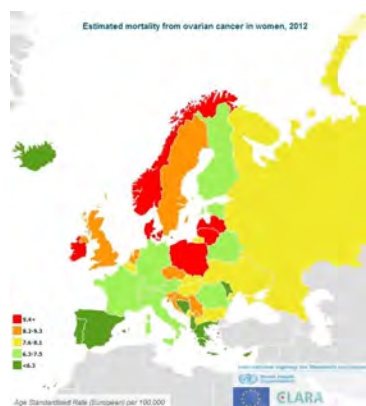
Ovarian cancer burden in Europe



INCIDENCE (per 100.000)

EU : 13,1

SLO: 13,8



MORTALITY (per 100.000)

EU: 7,6

SLO: 9,3



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Ovarian cancer - characteristics

- Despite many improvements in medicine:
 - No effective prevention
 - No effective screening
 - no proven benefit from many studies
 - No early detection
 - no symptoms at early stage
- Result*:
 - >75% of patients have advanced stage at diagnosis (IIIC, IV)
 - 80% of patients have relapse of the disease
 - 5-year overall survival is only about 40%

* Slovenian cancer registry 2016



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WHO classification of ovarian cancer (2014)

- EPITHELIAL
- STROMAL
- SEX CORD
- GERM CELL TUMORS
- MONODERMAL TERATOMA
- MESOTHELIAL
- SOFT TISSUE
- LIMFATIC AND IN MIELOIC
- SECONDARY (METASTATIC)

MANY COMBINATIONS POSSIBLE
- MORE THAN **80** HISTOLOGY TYPES!



■ Epithelial Tumors 90%
■ Stromal Tumors 7%
■ Germ Cell Tumors 3%



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Epithelial ovarian cancer- 5 types

WHO 2014 Diagnostic Criteria per Cancer Type

TYPE	% of total	MOLECULAR CHARACTERISTICS	OTHER NOTES
HGSOC	70%	TP53 ^{mut} , genomic instability	STIC precursor, no BOT
LGSOC	3.5%	KRAS ^{mut} , BRAF ^{mut}	Mutations more common in SBOT
CCC	10%	ARID1a ^{mut} , PIK3CA ^{mut} , PIK3CA ^{amp}	15-30% with endometriosis
ENDO ↓gr	10%	ARID1a ^{mut} , PIK3CA ^{mut} , PTEN LOH, β catenin ^{mut}	EBOT frequency of mutations similar to invasive, 15-30% associated with endometriosis
ENDO ↑gr		TP53 ^{mut}	Recategorized as HGSOC
Mucinous	3.6%	80%+ KRAS ^{mut}	Intestinal type only

BRCA - 20+%

HGSOC: high-grade serous ovarian cancer, LGSOC: low-grade serous ovarian cancer,
CCC: clear cell ovarian cancer, ENDO: endometrial ovarian cancer

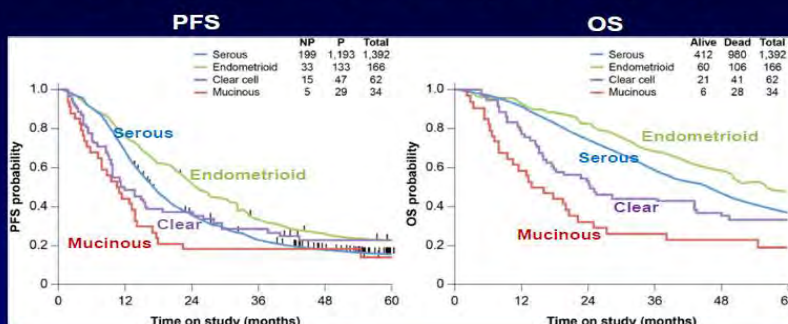


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Prognosis depends on histology type

Outcome FIGO Stage III Ovarian Cancer (GOG Trials #111, 114, 132, 152, 158, 172)





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Systemic treatment of epithelial ovarian cancer

Treatment guidance by histologic type

TYPE	% Early stage presentation	Histology-specific treatment guidance
HGSOC	20%	Chemotherapy, anti-angiogenic therapy, DNA repair inhibition therapy, radiation
LGSOC	30+%	*Consensus conference: chemotx or clinical trial
CCC	25%	*
ENDO	30%	*, **
Mucinous	? all	*Is advanced stage/metastatic ovarian? r/o GI source

Bevacizumab
Olaparib

HT

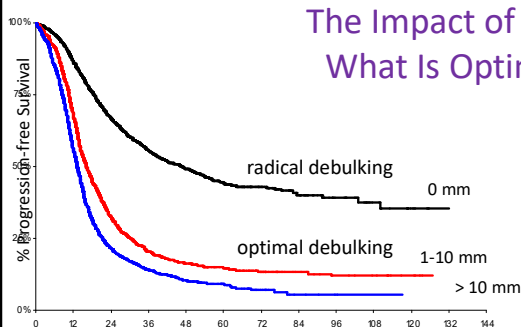
HT

* No validated type-specific treatment

**High grade reclassified and treated as HGSOC

HGSOC: high-grade serous ovarian cancer, LGSOC: low-grade serous ovarian cancer,
CCC: clear cell ovarian cancer, ENDO: endometrial ovarian cancer

The Impact of Residual Tumor: What Is Optimal Debulking?



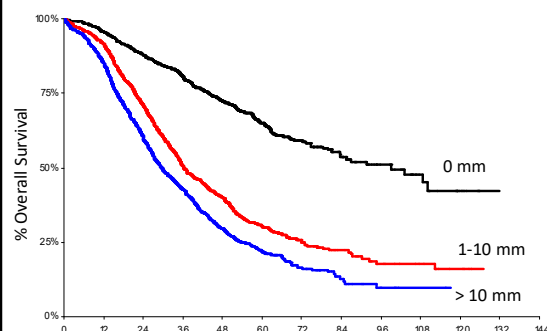
HR (95%CI)

1-10 mm vs. 0 mm: 2.52 (2.26;2.81)

>10 mm vs. 1-10 mm: 1.36 (1.24;1.50)

log-rank: $p < 0.0001$

Generated from 3 prospective
Phase III trials (OVAR 3,5, & 7)
N = 3126 pts



HR (95%CI)

1-10 mm vs. 0 mm: 2.70 (2.37; 3.07)

>10 mm vs. 1-10 mm: 1.34 (1.21; 1.49)

log-rank: $p < 0.0001$

DuBois, Cancer (2009)115:1234



Ovarian cancer: primary systemic treatment

- **Postoperative (adjuvant)**
 - goal is cure (stage I-III)
 - goal is life prolongation (stage IV)
- **Preoperative (neoadjuvant)**
 - goal is radical debulking at interval surgery - cure?
- **Paliative**
 - goal is decrease disease symptoms
 - goal is improvement of QoL



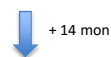
Ovarian cancer: primary systemic treatment

- **Chemotherapy**
 - platinum + taxane
 - majority of patients (except stage IA, grade I)



OS – overall survival
QoL – quality of life

Cisplatin+ Ciklofosamid: OS 24 months.



Cisplatin+ Paklitaksel: **OS 38 months.**



Karboplatin + Paklitaksel:

- standard
- all histology types

OS similar
less toxic
better QoL



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Ovarian cancer: primary systemic treatment

Bevacizumab

Recombinant humanised monoclonal anti-VEGF antibody developed from the mice anti-VEGF antibody (MAb A4.6.1)

- 93% of antibody has human origin
- Recognises all human isomorphes of human VEGF molecule
- Blood half-time is 21 days



VEGF = vascular endothelial growth factor
MAb = monoclonal antibody

Presta LG, et al. Cancer Res 1997;57:4593-9



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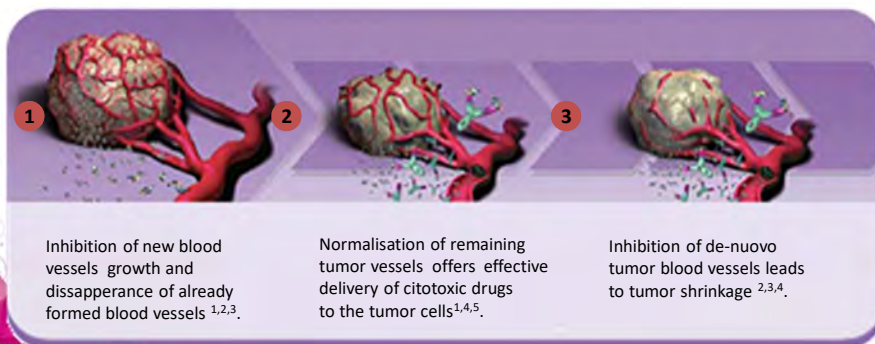
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Ovarian cancer: primary systemic treatment

Bevacizumab – mechanism of action

Early effect

Late effect



1. Willet et al. Nat Med 2004; 2. Baluk, et al. Curr Opin Genet Dev 2005; 3. Inai, et al. Am J Pathol 2004; 4. Gerber, et al. Cancer Res 2005; 5. Jain, et al. Science 2005



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Ovarian cancer: primary systemic treatment

The role of bevacizumab



NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D.,
Gini F. Fleming, M.D., Bradley J. Monk, M.D., Heeun Huang, M.D.,
Robert C. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D.,
Benjamin E. Goss, M.D., Matthew Poole, M.D., Michael J. Sinner, M.D., Ph.D.,
and Shaohu X. Liang, M.D., for the Gynecologic Oncology Group

GOG-218
Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483.

NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

A Phase 3 Trial of Bevacizumab in Ovarian Cancer

Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D.,
Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D.,
Mark S. Carey, M.D., Philip Beale, M.D., Anders Carver, M.D.,
Christian Ruzader, M.D., Andrea du Bois, M.D., Jalid Sehouli, M.D.,
Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D.,
Sharifah Ezzamel, M.D., Charles Gouley, M.D., Alain Lortholary, M.D.,
Frederic Selle, M.D., Hansoon R. Hitz, M.D., Arto Leinonen, M.D.,
Maria Pianta, M.D., Dan Stanic, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D.,
and Amit M. Ozols, M.D., for the ICON7 Investigators

ICON-7
Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.

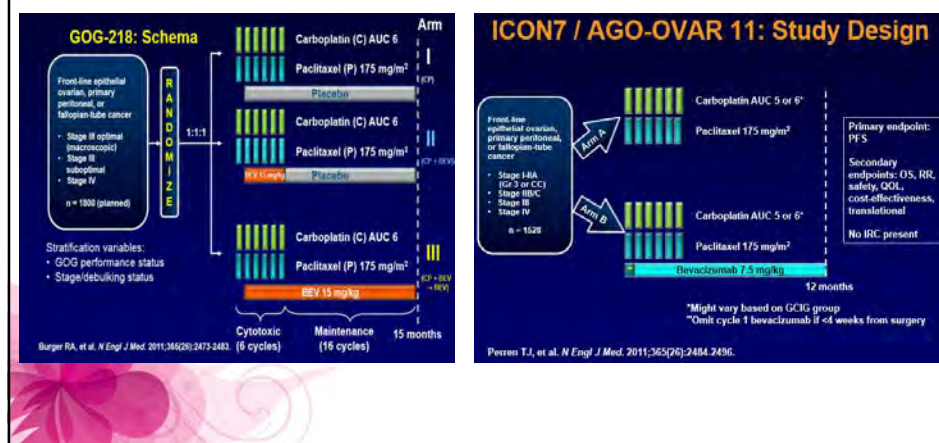


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Ovarian cancer: primary systemic treatment

The role of bevacizumab:



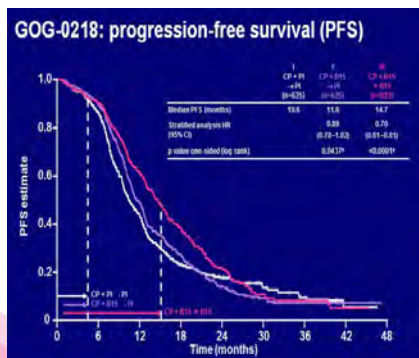


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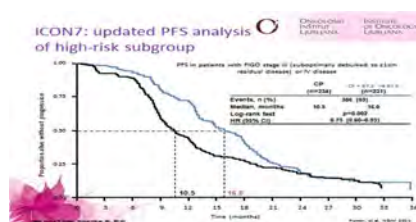
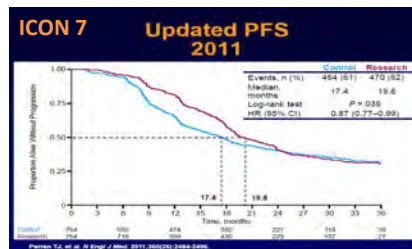
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Ovarian cancer: primary systemic treatment

The role of bevacizumab – prolongs PFS



PFS – progression-free survival

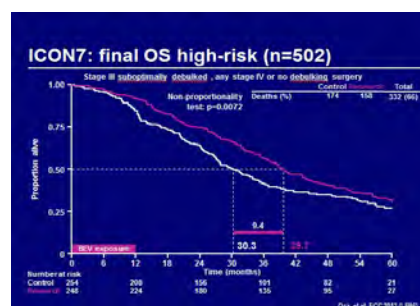
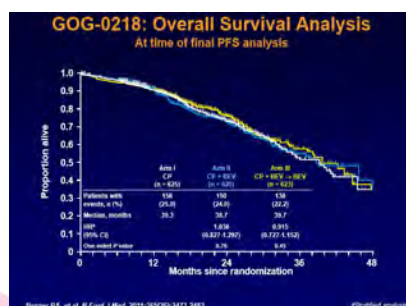


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Ovarian cancer: primary systemic treatment

The role of bevacizumab



– overall survival benefit in ICON 7 „high-risk patients“



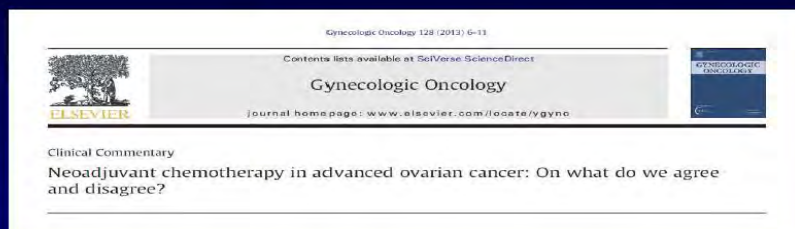
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The role of neoadjuvant chemotherapy

- definition of operable/inoperable disease?

Role of Radical Surgery and Neoadjuvant Chemotherapy in Advanced Ovarian Cancer: Report on the Consensus Paper



Vergote I, du Bois A, et al. *Gynecol Oncol.* 2013;128(1):6-11.

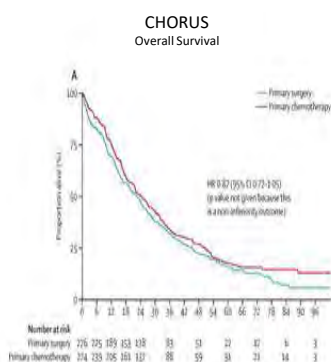


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The role of neoadjuvant chemotherapy

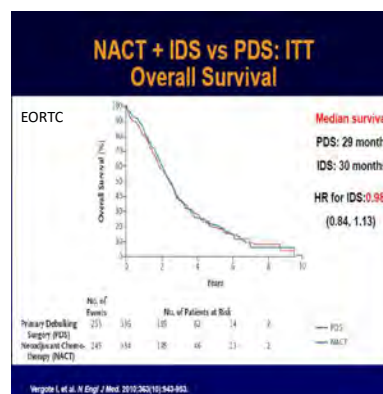
- two randomised studies: no difference in OS



Kehoe S, et al. *Lancet* 2015

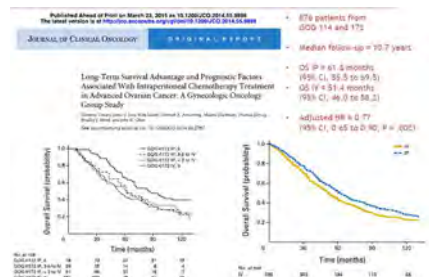
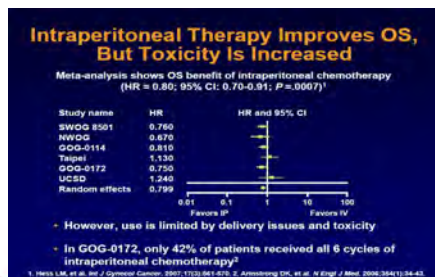
Criticism:

- poor surgery in both studies
- only 20% of pts had radical primary debulking



The role of intraperitoneal chemotherapy-1

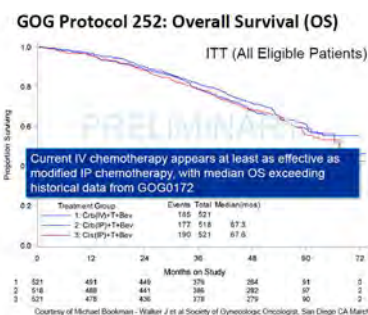
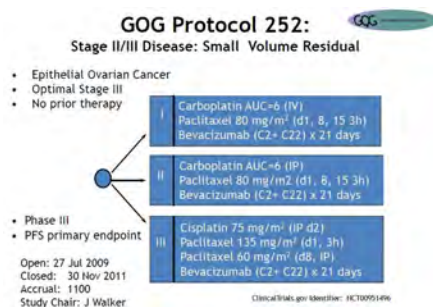
Effective but toxic



Criticism:

- old i.v. chemotherapy used,
- inappropriate doses of i.v. chemotherapy,...

The role of intraperitoneal chemotherapy-2



Conclusions:

- Up-to date i.v. chemotherapy with bevacizumab is:
- as effective as i.p. cht (the same OS)
 - less toxic
 - In EU intraperitoneal cht is experimental only treatment



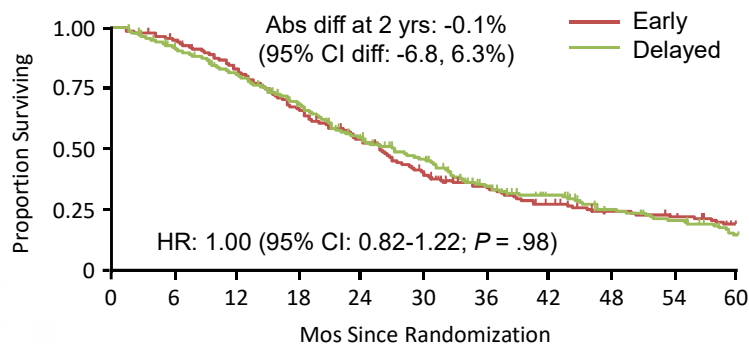
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Systemic treatment of relapsed ovarian cancer

When to treat relapsed disease?

EORTC 55955 – CA 125 elevation vs. **Clinical/radiologic relapse**



Patients at Risk, n

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

Rustin G, et al. ASCO 2009.



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Systemic treatment of relapsed ovarian cancer:

Predictive and prognostic factors that influence the treatment selection:

Disease related:

- Platinum-free interval
- Response to prior chemotherapy
- Histology type
- Molecular (BRCA)
- Symptoms

Patient related:

- Performance status
- Age
- Side effects
- Comorbidities
- Patient wishes (hair, etc.)



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Systemic treatment of relapsed ovarian cancer:

Resistance to platinum (PFI<6 months)

Non-platinum cht

- monotherapy
- ORR: 10-30%
- OS: <12 months

PLD

- Docetaxel
- Etoposide (oral)
- Gemcitabine
- Topotecan
- Paclitaxel (weekly)
- bevacizumab

Partial sensitivity to platinum (PFI 6-12 months)

Cht – platinum comb.

- ORR: 30-60%
- PFS: 7 months
- OS: 23 months

Pakli + Karbo
PLD + Karbo
Gem + Karbo
PLD + trabektidin

olaparib
bevacizumab

Full sensitivity to platinum (PFI>12 months)

Surgery

Cht – platinum comb.

- ORR: 60+%
- OS: 30+ months

- Pakli + Karbo
- PLD + Karbo
- Gem + Karbo
- Olaparib
- bevacizumab

ORR – objective response rate; PFS – progression-free survival, OS – overall survival



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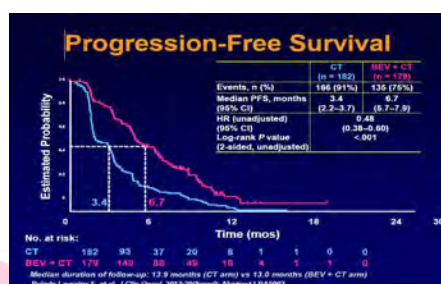
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Systemic treatment of relapsed ovarian cancer

Bevacizumab

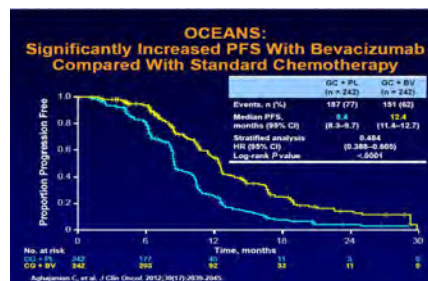
PFI<6 mes:

AURELIA: prolongs PFS for 3 months



PFI>6mes:

OCEANS: prolongs PFS for 4 months



PFS – progression-free survival
OS – overall survival

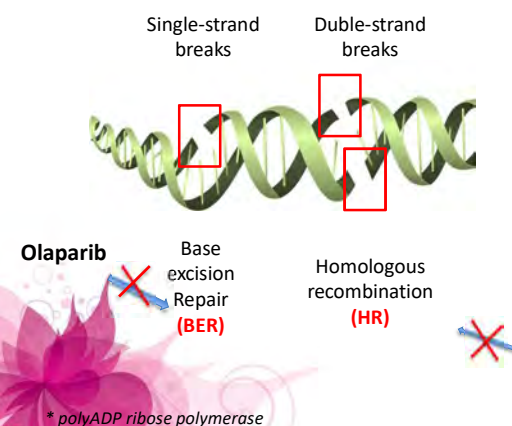
No benefit in OS



Systemic treatment of relapsed ovarian cancer

Olaparib - PARP* inhibitor

INHIBITS SINGLE-STRAND DNA REPAIR



- In base excision repair (BER), a damaged base is excised resulting in the formation of a single-strand break, which is enzymatically repaired.
- Two principal mechanisms are used in the repair of double-strand breaks: homologous recombination (HR) and non-homologous end joining (NHEJ)

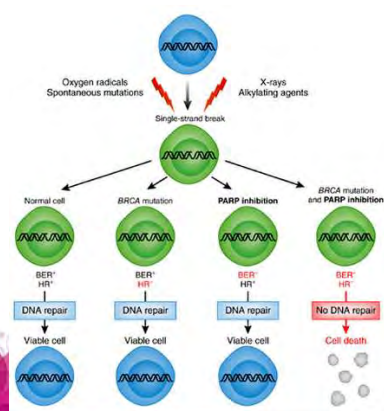
BRCA 1/2 mutation

Jackson SP and Bartek J. Nature
2009;461:1071–1078



PARP inhibition in preexisting HR deficit:

Olaparib – the princip of synthetic lethality



PARP - polyADP ribose polymerase; HR – homologous recombination

Synthetic lethality

Synthetic lethality is the term used when defects in two pathways lead to cell death, while a defect in either of the individual pathways is not deleterious²

PARP inhibition impairs the repair of single-strand breaks¹

Single-strand breaks lead to replication fork collapse and the occurrence of double-strand DNA breaks during DNA replication²

HR mechanism repairs double-strand DNA breaks

1. Jackson SP and Bartek J. Nature 2009;461:1071–1078;
2. De Lorenzo SB et al. Front Oncol 2013;3:228;



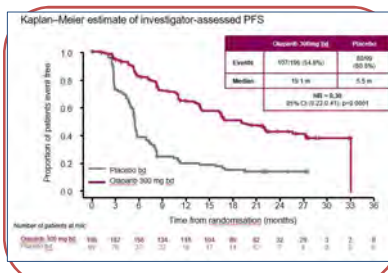
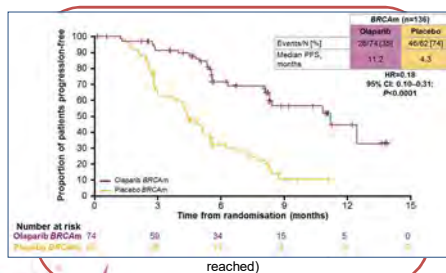
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Systemic treatment of relapsed ovarian cancer

Olaparib maintenance treatment improves PFS in patients with platinum sensitive
relapsed ovarian cancer¹⁻³

Study 19



* PFS = progression-free survival; CR = complete response; PR = partial response; po = per oral; bid = twice a day; HR = hazard ratio; CI = confidence interval
1. Pujade-Loraine J, et al. N Engl J Med. 2012;366(15):1382-1392; 2. Gourley C, et al. J Clin Oncol 2017;35(suppl); poster related to abstr 5533; 3. Pujade-Loraine J, et al. J Clin Oncol 2017;35(suppl); poster related to abstr 5533



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Ovarian cancer: Slovenia

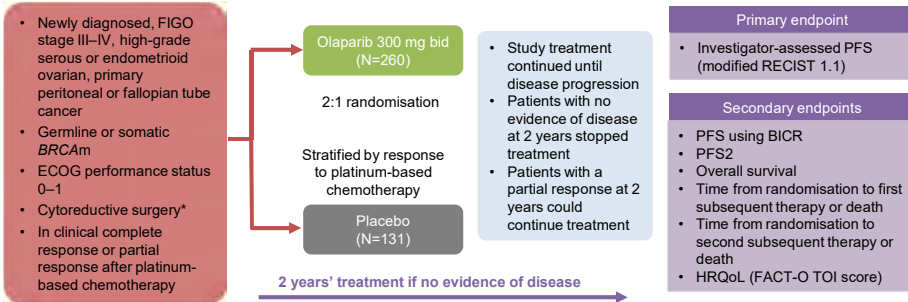
- Since 2014:
 - All patients with HGS* cancer of ovaries, fallopian tubes or PPSC are offered to perform **germline** BRCA genetic testing **at diagnosis** (or at relapse)
 - The aim of BRCA genetic testing is **treatment with olaparib** (not just prevention of breast and ovarian cancer)
 - Active searching for BRCA+ patients (confidential data)
- Since 2019:
 - All patients with HGS* cancer of ovaries have **somatic** BRCA testing **at diagnosis**

HGS* - high-grade serous

Zhang S, et al. Gynecol Oncol. 2011;121(2)

SOLO-1 - Phase III trial to investigate maintenance therapy with olaparib in newly diagnosed BRCAm ovarian cancer

SOLO-1 is a global randomised multicentre placebo controlled Phase III study

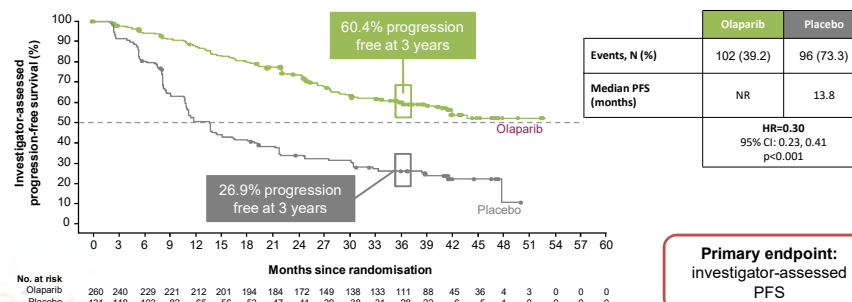


* Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease
BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; FACT-O = Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO = International Federation of Gynecology and Obstetrics; HRQoL = health-related quality of life; PFS = progression-free survival; PFS2 = time to second progression or death; RECIST = Response Evaluation Criteria in Solid Tumours; TOI = Trial Outcome Index; PARP = poly (ADP-ribose) polymerase; BRCAm = BRCA gene mutation
1. Moore K et al. N Engl J Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

Systemic treatment of ovarian cancer

SOLO 1: Olaparib reduced the risk of progression or death by 70% vs. placebo¹

After a median follow-up of 41 months, the median PFS had not been reached in the olaparib arm (vs. 13.8 months in the placebo arm)¹



DCO: May 2018; Median FU: olaparib, 40.7 months; placebo, 41.2 months
Analysis was performed after 198 progression events had occurred (in 50.6% of patients)
PFS = progression-free survival; DCO = data cut-off; HR = hazard ratio; CI = confidence interval
1. Moore K et al. N Engl J Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)



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Conclusions

- Platinum based chemotherapy remains backbone in systemic therapy of patients with ovarian cancer
- Bevacizumab and olaparib are used in maintenance setting
- BRCA 1/2 (germline or somatic) testing is recommended in every patient with epithelial ovarian cancer
- Intraperitoneal chemotherapy is „experimental“ treatment in EU



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- Thank you!



APPROACH TO THE PATIENT WITH CANCER AND RENAL IMPAIRMENT/INSUFFICIENCY

Tomaž Milanez

Institute of Oncology Ljubljana
University Medical Center Ljubljana

Epidemiology: renal impairment in patients with cancer

- Elderly patients (65)-higher rate of chronic kidney disease
 - Despite normal serum creatinine levels prevalence of renal in most of those patients is high
 - IRMA study- 65% of patients had renal insufficiency
- NHANES III study -30% (age 53) of patients had renal insufficiency
- IRMA-2 study-
 - renal insufficiency (MDRD - $eGFR < 60 \text{ ml/min/1.73m}^2$) is independent risk factor for reduced survival
 - Renal insufficiency in the whole was associated with 8.6 reduced median survival compared with normal function (16.4 vs. 25 months: $HR = 1.27$; $p < .0002$)

Patients with cancer and renal insufficiency

- Acute kidney injury
- Renal impairment
- Chronic kidney disease (CKD)/Renal insufficiency
 - End stage kidney disease (ESKD)
 - Patients with renal failure on renal replacement therapy
 - Hemodialysis/Peritoneal dialysis
 - Kidney transplantation

How to manage patients with renal impairment

- Acute kidney injury
 - Determining the cause of impairment
 - Managing the life threatening features (hyperkalemia, overhydration/hypervolemia, acidosis, uremic pericarditis)
 - Look for and treat the reversible conditions
 - Lower urinary tract obstruction
 - Intrarenal toxic effects of systemic treatment
 - Avoiding (further) toxic factors
- Chronic renal impairment

How to monitoring renal function in patients with cancer

- Glomerular filtration rate (GFR)
 - Estimation GFR (eGFR)
 - Reference method
 - Different equations (mathematical models)
 - “New model” of eGFR/cisplatin/carboplatin
- Estimating creatinine clearance (CrCl)
- Serum creatinine level

Stages of chronic kidney disease and complications

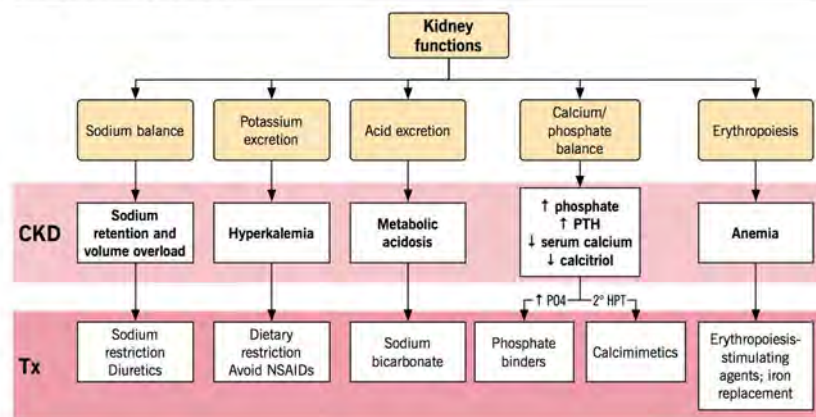
Table 1. Stages of chronic kidney disease.

Stage	Description	eGFR (mL/min)	Potential complications of reduced GFR (in alphabetical order)
1	Kidney damage with normal or ↑ GFR	≥90	<ul style="list-style-type: none">• Anemia, including functional iron deficiency• Blood pressure increases• Calcium absorption decreases• Dyslipidemia /heart failure/volume overload• Hyperkalemia• Hyperparathyroidism• Hyperphosphatemia• Left ventricular hypertrophy• Metabolic acidosis• Malnutrition potential (late)
2	Kidney damage with mild ↓ GFR	60–89	
3	Moderate ↓ GFR	30–59	
4	Severe ↓ GFR	15–29	
5	Kidney failure	<15 or dialysis	

Source: Adapted from Identification, Evaluation and Management of Chronic Kidney Disease (www.health.gov.bc.ca/gpac/pdf/ckd.pdf)

Managing complication of CKD

Complications of CKD



How to manage the patients with renal impairment and cancer

- Plan of systemic oncological treatment
 - Lack of evidence for systemic treatment for patients with severe renal impairment-insufficiency
 - Patients were excluded from prospective randomized trials
- Managing complications of reduced GFR
- Managing the risk factors of decline of renal function
- Adjusting dose of systemic therapy to renal function/replacement kidney therapy

Patients with cancer and renal insufficiency

- Acute renal failure
 - definition
- Chronic kidney disease (CKD)
 - End stage kidney disease (ESKD)
 - Patients with renal failure on renal replacement therapy
 - Hemodialysis
 - Peritoneal dialysis
 - Kidney transplantation

Profile of cancer patients with renal insufficiency/CKD

- Definition
 - Guidelines of CKD (KDOQI)
- Risk factors (CKD)
 - Comorbidities
- Kidney failure
 - Chronic dialysis treatment (hemodialysis/peritoneal dialysis)
 - Kidney transplant treatment
- Agents known to adversely affect renal function
- “Polypharmacy”

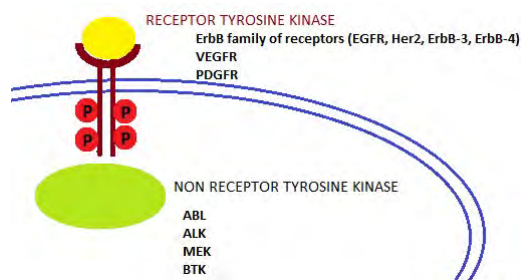
Conclusions

- Follow the goal of systemic oncological treatment-clinical end points/ extend meaning
- Preserve kidney function/capacity of organs/maintain organ function
- Lack of guidelines for systemic treatment in patients with severe renal impairment (recommendation)
- Adjust systemic treatment to renal function
 - Use the most appropriate equation for estimating GFR (systemic treatment – derivatives of platinum)
 - Estimate and monitor renal function (patients with renal failure/insufficiency)/modalities
 - Pharmacokinetics of systemic drugs (guidelines/recommendation)
 - Adjust systemic treatment to replacement therapy i.e. dialysis (recommendation)
- Managing comorbidities and complication of CKD
- Avoiding/replace potential renal toxic drugs/agents
- Looking for reversible factors during the treatment
- Balancing/weighing between potential effectiveness and harm in patients with severe renal impairment (case reports, retrospective analysis)

Toxicity of tyrosine kinase inhibitors and the management

Urška Bokal, MD,
Institute of Oncology, Ljubljana
1st Summer School of Medical Oncology, 6. 9. 2019

Tyrosine kinase inhibitors



- Other protein kinases:
 - B Raf (serine threonine kinase)

Tyrosine kinases:

- active proteins/autoactivates by phosphorylation
- important for signal transduction and cell cycle regulation

Tyrosine kinase inhibitors:

- Small molecules, oral application
- act mostly by blocking ATP binding site, therefore inhibit phosphorylation
- bind reversibly or irreversibly

ATC classification system

L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01 ANTINEOPLASTIC AGENTS
L01X OTHER ANTINEOPLASTIC AGENTS
L01XE Protein kinase inhibitors

ATC code	Name
L01XE01	imatinib
L01XE02	gefitinib
L01XE03	erlotinib
L01XE04	sunitinib
L01XE05	sorafenib
L01XE06	dasatinib
L01XE07	lapatinib
L01XE08	nilotinib



WHO Collaborating Centre for
Drug Statistics Methodology

https://www.whocc.no/atc_ddd_index/?code=L01XE&showdescription=no

On and off target toxicity

- On target:
 - due to inhibition of the desired target (mechanism based)
 - class effect: shared with all agent that inhibit specific target
 - VEGFR TKI: hypertension
 - EGFR TKI: rash
- Off target:
 - due to inhibition of other unintended targets
 - sunitib: hematologic toxicity (FLT3 inhibition)

CA Cancer J Clin. 2013;63:249-79

The good news: toxicity may correlate with response/better survival

- rash due to EGFR TKI in lung cancer
- hypertension and hypothyroidism due to VEGFR inhibitors in renal cell carcinoma

[PLoS One](#). 2013;8(1):e55128. doi: 10.1371/journal.pone.0055128. Epub 2013 Jan 30.

Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis.

[Liu HB¹](#), [Wu Y](#), [Lv TF](#), [Yao YW](#), [Xiao YY](#), [Yuan DM](#), [Song Y](#)

[J Natl Cancer Inst](#). 2011 May 4;103(9):763-73. doi: 10.1093/jnci/djr128. Epub 2011 Apr 28.

Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib.

[Cancer](#). 2011 Feb 1;117(3):534-44. doi: 10.1002/cncr.25422. Epub 2010 Sep 15.

Hypothyroidism in patients with renal cell carcinoma: blessing or curse?

[Schmidinger M¹](#), [Voigt UM](#), [Bojic M](#), [Lamm W](#), [Heinzel H](#), [Haitel A](#), [Clodi M](#), [Kramer G](#), [Zielinski CC](#).

[Liu S et al. Cancer Treat Rev. 2014; 40: 883-91](#)

Anti Her tyrosine kinase inhibitors

Compound	Target inhibition	Specific toxicity
erlotinib gefitinib	1 st generation EGFR TKI (mutant EGFR, reversible)	skin related toxicity (rash, acne, pruritus, dry skin) diarrhea interstitial pneumonitis
afatinib dacomitinib	2 nd generation EGFR TKI (EGFR, Her2 and Her4, irreversible)	
osimertinib	3 rd generation EGFR TKI (mutant EGFR including mutation T790M, irreversible)	
lapatinib	EGFR and Her2, reversible	diarrhea nausea, vomiting rash cardiomyopathy
neratinib	EGFR, Her2 and Her4, irreversible	

anti ALK tyrosine kinase inhibitors

CPK – creatine phosphokinase
AP – alkaline phosphatase

ALL: interstitial lung disease!!

Compound	Target inhibition	The most common toxicity (incidence of all grades)	Other toxicity
crizotinib (+ ROS1, cMET)	1 st generation ALK TKI	nausea, vomiting, diarrhea, constipation, edema, fatigue, ↓ appetite, neuropathy, dizziness hepatotoxicity, vision disorder, (≥ 25%)	neutropenia, QT prolongation, bradycardia, cardiac failure, GIT perforation, renal impairment
ceritinib (+ ROS1)		nausea, vomiting, diarrhea, constipation, fatigue, ↓ appetite, ↓ weight, abdominal pain, hepatotoxicity, ↑ creatinine, rash, anemia, esophageal disorder (≥ 10%)	QT prolongation, bradycardia, hyperglycemia, ↑ amylase and lipase
alectinib (+ RET)	2 nd generation ALK TKI	constipation, edema, myalgia (≥ 20%)	hepatotoxicity, ↑ CPK, bradycardia, photosensitivity
brigatinib (+ ROS1)		↑ glucose, insulin, CPK, lipase, amylase, AP, aPTT, ↓ lymphocytes, phosphate, leucocytes, anemia, nausea, diarrhea, fatigue, cough, headache, rash, vomiting, dyspnea, hypertension, myalgia, peripheral neuropathy (≥ 25%)	bradycardia visual disturbance
lorlatinib (+ ROS1)	3 rd generation ALK TKI	hyperlipidemia, peripheral neuropathy, cognitive effects, edema, fatigue, weight increase, diarrhea, arthralgia (≥ 20%)	↑ amylase, lipase, AV block, LVEF decrease

anti VEGFR tyrosine kinase inhibitors

Compound	Specific toxicity
sunitinib	thyroid dysfunction, dysphonia, palmar-plantar erythrodysesthesia syndrome thromboembolism, hypertension, cardiac failure, QT prolongation hemorrhages, GIT perforation/fistulas, impaired wound healing liver toxicity, proteinuria, fatigue, taste disorder
pazopanib	
axitinib	
tivozanib	
cabozantinib	
sorafenib	
regorafenib	

Take home message

- Toxicity varies between patients.
 - Beware of drug interactions!
- During its management patients may be referred to doctors of other specialities.
- Low grade toxicity importantly influence the quality of life of patients.

IMMUNE-RELATED ADVERSE EVENTS OF IMMUNE CHECKPOINT INHIBITORS

Nežka Hribnik, MD
Martina Reberšek, MD, PhD
Institute of Oncology Ljubljana

1st Summer School in Medical Oncology
September 2019

Characteristics of irAE

- They are reversible if treated promptly
- If left untreated they progress to more severe state
- If treated early, severity and duration decreases
- Any organ can be affected
- Average 6 – 12 weeks after initiation of therapy
- Can occur
 - Within days of the first dose
 - After several months of therapy
 - After discontinuation of therapy

Pre-treatment evaluation and diagnostic tests to consider

- **WHO PS**
- **History**
 - Detailed questioning for autoimmune, infectious disease, endocrine and organ-specific disease history (**NOT** contraindication, but should be well controlled!)
 - History of base line bowel habit (frequency of bowel movements, usual stool consistency)
- **Blood tests:**
 - **CBC, CMP, TSH/T3/T4**, HbA1c, total CK
 - **Infectious disease screen:** HBsAg/sAb/cAb, HCAb, CMV Ab, HIV Ab/Ag p24
- Dermatologic examination
- Pulmonary test (SaO₂), cardiac tests (ECG, Trop I/T)
- Additional screening tests recommended in patients with pre-existing organ disease/at risk of organ-specific toxicity (8 am ACTH, cortisol, NT pro-BNP, 6MWT ...)

General approach to management of irAEs

Grade	Management	ICI	Notes
1	Supportive measures Close monitoring	Continue (except some: pneumonitis/ neurological/ cardiac irAEs)	Outpatient
2	Corticosteroids Immediate vs delayed	Withhold ICI (continued once AEs ≤ G1)	Outpatient with close team contact or inpatient
3	Immediate corticosteroids and additional IMA if required	Withhold or discontinue ICI	Inpatient (except some: skin/ hepatitis)
4	Immediate corticosteroids With early use of additional IMA	Discontinue ICI	Inpatient Consider transfer to experienced centre!

- Development of irAE is not required for ICIs benefit; some irAE (e.g., vitiligo) may be more clearly associated with **ICIs efficacy**.
- **The clinical outcome** of patients on ICIs is not affected by the use of immunosuppressive agents or the management of irAE.
- **Reintroducing ICIs** should be made on an individual basis, taking into account the clinical setting and specific clinical need of each patient (severity of initial irAE, age).
- **Age** alone should not be used to exclude patients from treatment, benefit appears to be similar regardless of age.

TAKE-HOME MESSAGES!

- MULTIDISCIPLINARY APPROACH
 - Baseline assessment
 - Ongoing assessment
 - PATIENT & PHYSICIAN EDUCATION
 - Management protocols
 - Collaboration with emergency departments, GPs, specialists, visiting nurses!!
- AWARENESS IS NEEDED AMONG CLINICIANS ACROSS DISCIPLINES GIVEN THE INCREASE IN USE OF THESE AGENTS.

APENDIX:

Dr. Dobrila: Systemic treatment of metastatic gastric cancer
(Tuesday 03.09.)

Dr. Pleština: Systemic treatment of metastatic colorectal cancer
(Tuesday 03.09.)

Dr. Škrbinc: Systemic treatment of germinal tumors
(Wednesday 04.09.)

Systemic treatment in advanced gastric cancer

*Prof. Renata Dobrila-Dintinjana, MD.PhD.
Clinical Hospital Center, Rijeka
School of Medicine, Rijeka
Croatia*

Advanced Gastric Cancer

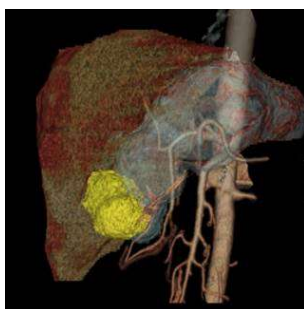
Locally advanced

OS: 11 months

Resectability

(Same survival of initially resectable patients)

A 3-drug regimen (tumor response)



Metastatic

OS: 3 months

Palliation

QoL; Survival

*A 2-drug regimen
(no toxic regimen)*

Locally advanced disease:

1. The most active regimen?

2. The role of surgery?

Triplet vs doublet:

Better Response

40/50% vs 20/30%

Which regimen?

FLOT

pCR

FLOT 16%

ECX 11%

CDDP/5FU 3%

Full Paper

High curative resection rate with weekly cisplatin, 5-fluorouracil, epirubicin, 6S-leucovorin, glutathione, and filgrastim in patients with locally advanced, unresectable gastric cancer: a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD)

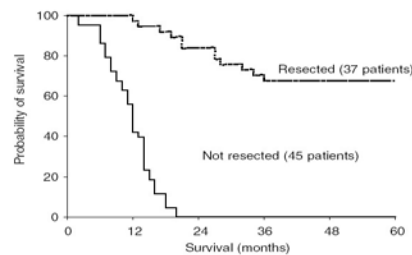


Figure 2 (A) Kaplan-Meier overall survival (OS) curve for the whole group of 82 patients. (B) Kaplan-Meier survival curves for patients who underwent curative resection of primary gastric tumour after chemotherapy (resected, - - - - -), and for not resected patients (not resected, ———).

Cascinu S, et al. *Br J Cancer* 2004.

Molecular Characterization of Gastric Carcinoma: Therapeutic Implications for Biomarkers and Targets

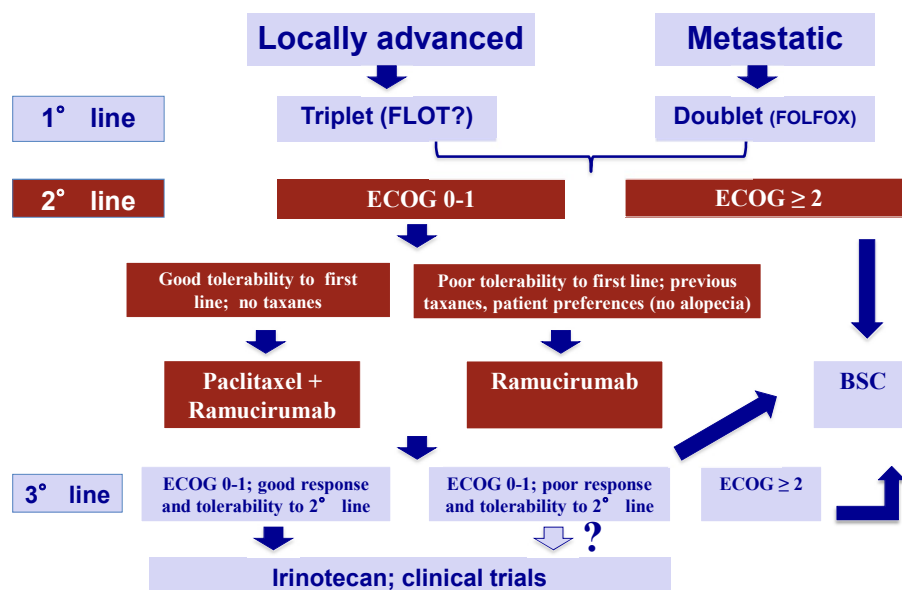
- *NO biomarker is available for predicting treatment response in the individual patient except human epidermal growth factor receptor 2 (HER2) amplification and programmed death-ligand 1 (PD-L1) expression for effectiveness of trastuzumab and pembrolizumab.....*
- *Molecular classification of GC by The Cancer Genome Atlas Research Network and the Asian Cancer Research Group is expected to identify therapeutic targets and predictive biomarkers.*

<i>Subtypes</i>	<i>Targets</i>	<i>Targeted Agents</i>
EBV	PIK3CA PD-L1/L2	Idelalisib, Taselisib Pembrolizumab, Nivolumab, Durvalumab, Avelumab, Atezolizumab
MSI	MLH1 silencing PIK3CA, EGFR ERBB2 ERBB3 PD-L1	Pembrolizumab, Nivolumab, Durvalumab, Avelumab, Atezolizumab Idelalisib, Taselisib Erlotinib, Gefitinib Trastuzumab Pertuzumab Pembrolizumab, Nivolumab, Durvalumab, Avelumab, Atezolizumab
CIN	EGFR VEGFA CCNE1, CCND1, CDK6	Erlotinib, Gefitinib Bevacizumab, Ramucirumab Palbociclib, Ribociclib, Abemaciclib
GS	RHOA - CLDN18 -	

Lionel Kankeu Fonkoua I and Nelson S. Yee 2,**Molecular Characterization of Gastric Carcinoma: Therapeutic Implications for Biomarkers and Targets*, *Biomedicines* 2018, 6, 32; doi:10.3390/biomedicines6010032www.mdpi.com/journal/biomedicines

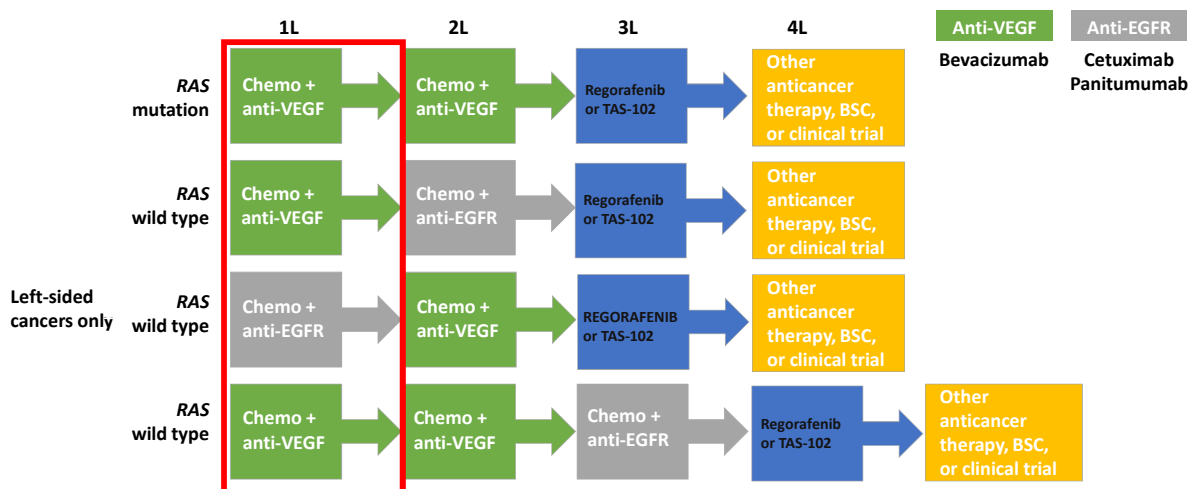
Proposed treatment algorithm

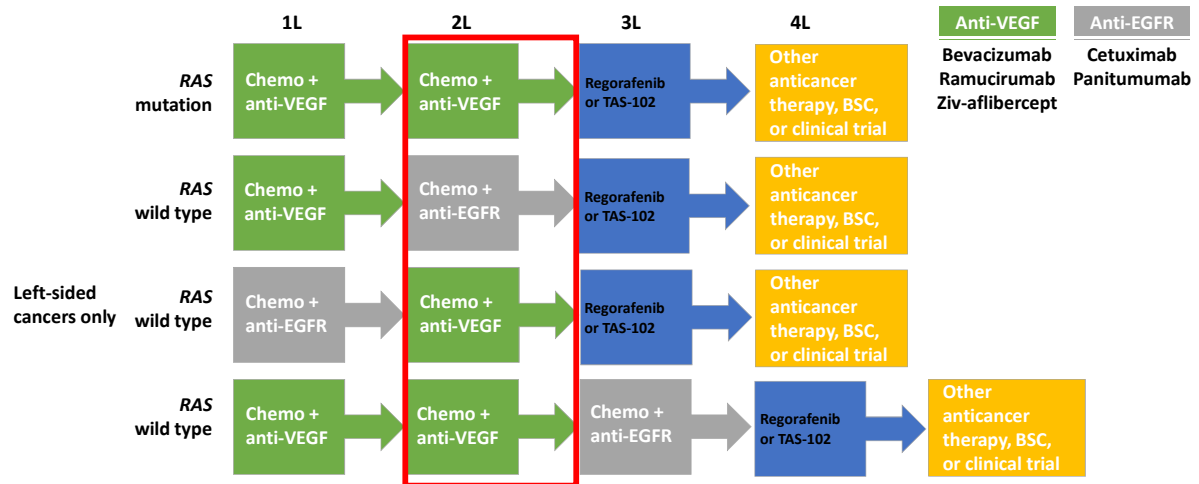
(Salati et al. *ESMO Open* 2017;2:e000206. doi:10.1136/esmoopen-2017-000206)



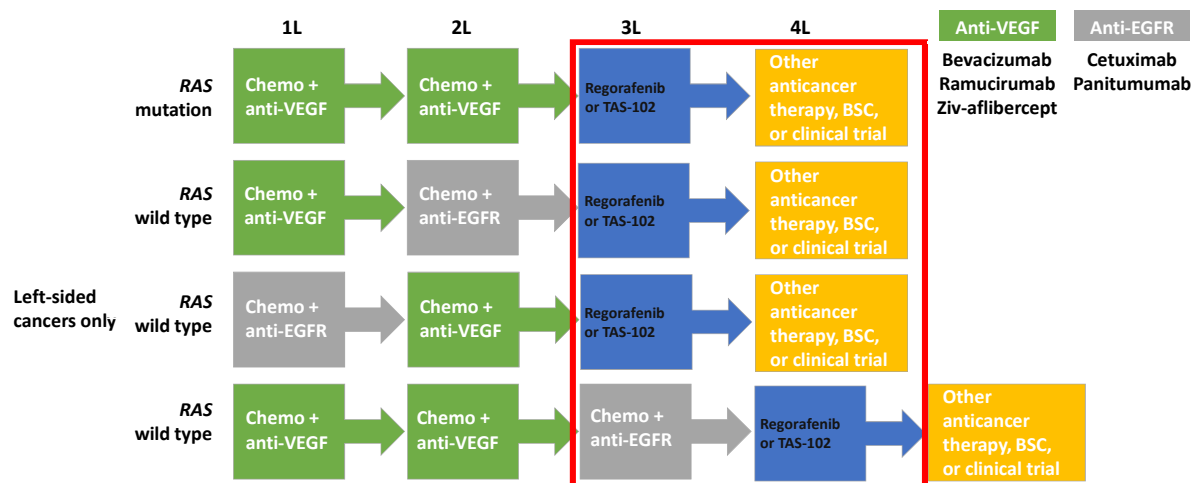
Systemic treatment of metastatic colorectal cancer

prof.dr.Stjepko Pleština
Department of Oncology
UHC Zagreb, Croatia





van Cutsem. Ann Oncol. 2016;27:1386.



van Cutsem. Ann Oncol. 2016;27:1386.

- A wealth of evidence indicates that primary tumour location is prognostic
 - Patients with left-sided tumours have longer survival outcomes than patients with right-sided tumours
 - The prognostic value appears independent of chemotherapy backbone
- Genetic differences between right- and left-sided tumours may account for some of the prognostic effect
 - Right-sided primary tumours occur more frequently with increasing age and are more likely to have concomitant genetic features associated with poor outcomes: BRAF MT, MSI-H, and increased methylation
- Both clinical trial and real-world data suggest that bevacizumab provides clinical benefit regardless of primary tumour location
- The totality of data suggests that cetuximab and panitumumab have efficacy in left-sided CRC, but EGFR inhibitors are not equally beneficial to patients with right-sided primary tumours
 - The NCCN guidelines draw the same conclusion that bevacizumab works regardless of tumour location whereas anti-EGFRs are only effective in left-sided tumours: "only patients whose primary tumours originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease"

Overview of CMS Predictive Data in mCRC

CALGB80405	1st line	RAS wild-type	RCT (n=392)	FOLFOX-cetuximab vs. FOLFOX bevacizumab	CMS1 > OS with FOLFOX-bevacizumab, CMS2 > OS with FOLFOX-cetuximab	Almac Xcell FFPE
FIRE-3	1st line	RAS wild-type	RCT (n=385)	FOLFIRI-cetuximab vs. FOLFIRI bevacizumab	CMS4 > OS with FOLFIRI-cetuximab	Custom Nanostring FFPE
CAIRO2	1st line	all-comers	RCT (n=311)	CAPOX-bevacizumab vs. CAPOX-bevacizumab-cetuximab	CMS2/CMS3 > OS with cetuximab (RAS/BRAF wt)	IHC FFPE
MAX	1st line	all-comers	RCT (n=237)	Capecitabine +/- mitomycin +/- bevacizumab	CMS2/CMS3 > PFS with bevacizumab	Almac Xcell FFPE
Japan	1st line	all-comers	Retrospective (n=193)	Oxaliplatin vs. Irinotecan	CMS4 > PFS and OS with Irinotecan	Agilent FF
CORRECT	3rd line	all-comers	RCT (n=)	Regorafenib vs placebo	CMS4 > OS with Regorafenib	Affimetrix Array FFPE

FFPE, Formalin-Fixed Paraffin-Embedded; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial.

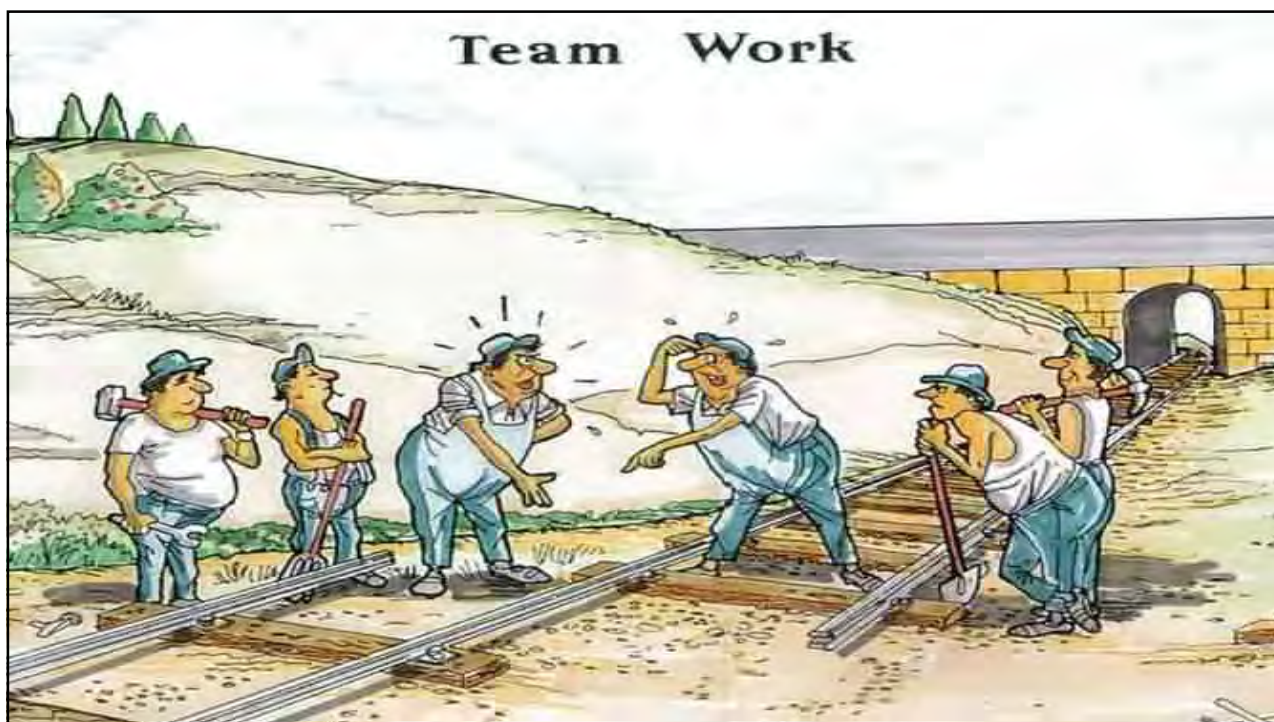
Stintzing S, et al. *J Clin Oncol.* 2017;35(suppl; abstr 3510); Lenz HJ, et al. *J Clin Oncol.* 2017;35(suppl; abstr 3511); Okita A, et al. *Oncotarget.* 2018;9:18698-18711; Teufel M, et al. *J Clin Oncol.* 2015;33(suppl; abstr 3558).

Current Treatment Paradigms in Metastatic Colorectal Cancer

- Better, but still pure prognosis
- Some patients with “limited” stage IV disease can be cured by an interdisciplinary approach
- Addition of biologics to chemotherapy has improved outcomes, but to a more limited extent than hoped
- Identification of molecular predictive factors is improving potential for individualized therapy
- Attempts are under way to expand the role of immunotherapy beyond treating patients with microsatellite instability-high CRC

mCRC – Multidisciplinary Therapeutic Decision.....





ESMO 2017 GUIDELINES

Category	Fit patients						Unfit	
							May be unfit	Unfit
Treatment goal	Cytoreduction (tumor shrinkage)			Disease control (control of progression)			Palliation	
Molecular profile	RAS WT	RAS MT	BRAF MT	RAS WT	RAS MT	BRAF MT	Any	Any
First line								
Preferred choice(s)	ChT doublet + EGFR antibody	ChT doublet + bevacizumab	FOLFOXIRI + bevacizumab	ChT doublet + bevacizumab or ChT doublet + EGFR antibody	ChT doublet + bevacizumab	FOLFOXIRI +/- bevacizumab	FP + bevacizumab	BSC
Second choice(s)	FOLFOXIRI +/- bevacizumab	FOLFOXIRI +/- bevacizumab	ChT doublet + bevacizumab	FP + bevacizumab		ChT doublet + bevacizumab	Reduced-dose ChT doublet	–
Third choice(s)	ChT doublet + bevacizumab	FOLFOXIRI	FOLFOXIRI				If RAS WT may consider EGFR antibody therapy	–
Maintenance								
Preferred choice	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	–
Second choice	Pause	Pause	Pause	Pause	Pause	Pause	FP	–
Second line								
Preferred choice(s)	ChT doublet + bevacizumab	ChT doublet + bevacizumab	ChT doublet + bevacizumab	ChT doublet + bevacizumab or ChT doublet + EGFR antibody	ChT doublet + bevacizumab	ChT doublet + bevacizumab		–
Second choice(s)	ChT doublet + EGFR antibody or FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ramucirumab	FOLFIRI + aflibercept/ramucirumab		–
Third line								
Preferred choice(s)	ChT doublet + EGFR antibody or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil	ChT doublet + EGFR antibody or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil		–
Second choice(s)	EGFR antibody monotherapy			EGFR antibody monotherapy				–
Third choice(s)	Regorafenib or trifluridine/tipiracil			Regorafenib or trifluridine/tipiracil				–



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Systemic treatment of germ-cell tumors

Dr. Breda Škrbinc, dr.med.

OI Ljubljana, 4.9.2019

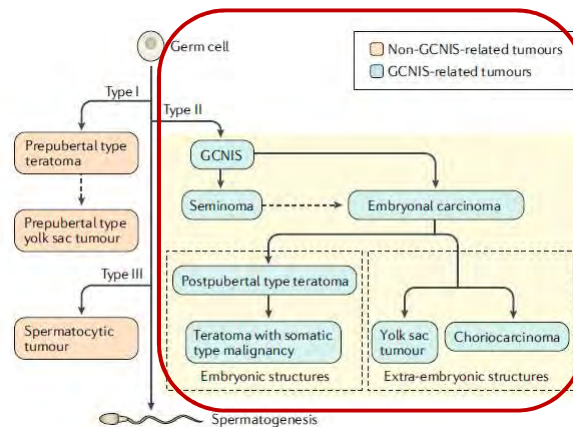


Fig. 1 | Schematic representation of the types of testicular germ cell tumours

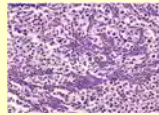
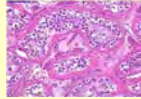


<https://doi.org/10.1038/s41572-018-0029-0>
NATURE REVIEWS | DISEASE PRIMERS (2018)

GCT histopathology

Testicular cancers are one of the most diverse areas of human pathology

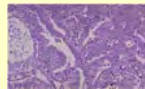
GCNIS



Seminoma (50 %)

Nonseminoma (40 %)

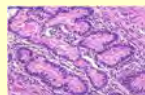
Embryonal carcinoma



Yolk sac tumor

Choriocarcinoma

Teratoma postpubertal type



Mixed germ cell tumors (10 %)

Multidisciplinary treatment

Treatment For Testicular Cancer



Orchiectomy
(Removal of testicles)



Chemotherapy



Radiation Therapy



Stem Cell
Transplantation



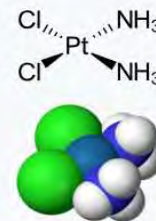
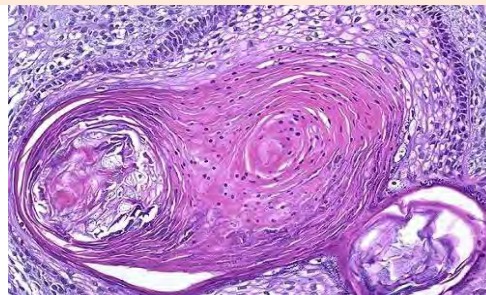
Lymph Node
Block Dissection



Teratoma postpubertal type

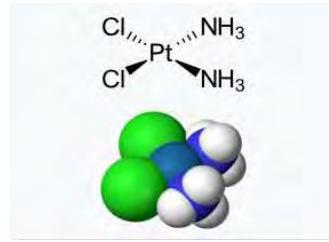


- Chemoresistant
- Exclusive treatment modality – radical surgery



- Cisplatin based chemotherapy
- Success story in metastatic GCT treatment
- 70% of mGCT patients cured with first line ChT
- 30% mGCT relapsing
 - up to 70% long term survivors – one salvage ChT line
 - up to 25% long term survivors – 2 or more ChT lines
- 10–15% of primarily advanced and 3–5% of all GCC patients fail established platinum-based standard treatments and potentially die of the disease





- **Adjuvant chemotherapy**
- **Chemotherapy for the metastatic disease**
- **Salvage treatment**



Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial



*RT D Oliver, MD Mason, GM Mead, H von der Maase, GJS Rustin, JK Joffe, R de Wit, N Aass, JD Graham, R Coleman, SJ Kirk, SP Stenning, for the MRC TE19 collaborators and the EORTC 30982 collaborators**

1477 patients from 70 hospitals in 14 countries randomly assigned to receive:

- **Radiotherapy** (para-aortic strip or dog-leg field)
- or
- **one injection of carboplatin**
dose based on the formula: **7 X [glomerular filtration rate X 25] mg**

The primary outcome measure - **the relapse-free rate**,
with the trial powered to exclude absolute differences in 2-year rates of more than 3%.



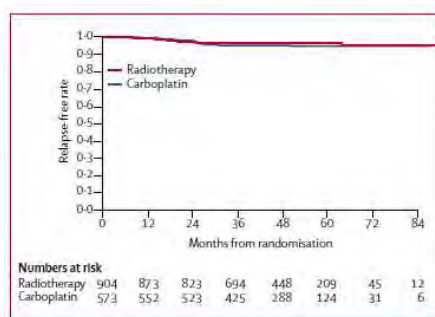
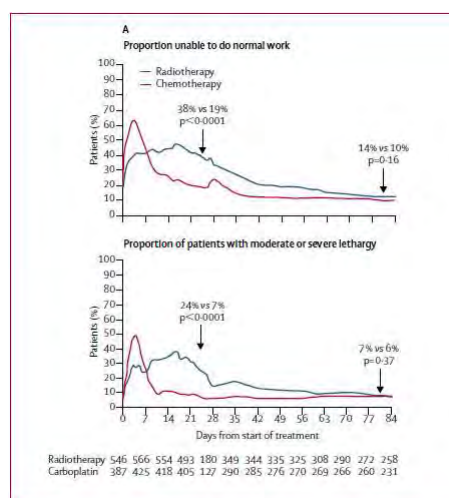


Figure 3: Relapse-free rate by allocated treatment

Patients' diary card data
Comparison between radiotherapy and carboplatin treatment



At 2 years' follow-up, the absolute differences in relapse-free rates (radiotherapy–chemotherapy) were :

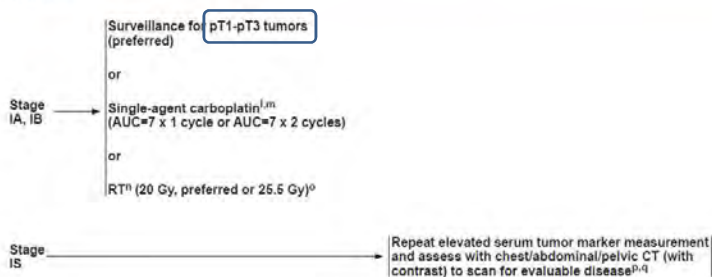


- –1.0% (90% CI –2.5 to 0.5) by direct comparison of proportions
- 0.9% (–0.5 to 3.0) by a hazard-ratio-based approach.
- Patients given carboplatin were less lethargic and less likely to take time off work than those given radiotherapy.

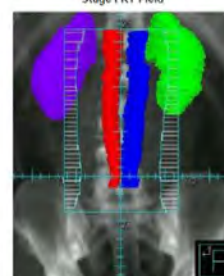
NCCN Guidelines Version 1.2019 Testicular Cancer - Pure Seminoma

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CLINICAL STAGE PRIMARY TREATMENT^a



Target Volumes by Stage (or location)
Figure 1: Stage I RT Field



^a Discuss sperm banking prior to chemotherapy or radiation treatment.



Risk factors

- Tu size (no definite cut off value)
- Stromal invasion in rete testis
- 12% RR - no RF
- 16% RR - either of two RF
- 32% RR - both RF
- Both RF should be considered



8. Who should be offered adjuvant chemotherapy?

Seminoma. In clinical stage I seminoma, several studies have found a low risk of relapse (~5%) in patients without RFs [87, 88, 93]. In these patients, adjuvant chemotherapy will therefore result in over-treatment in ~95% of cases. In patients with a higher risk of relapse, adjuvant chemotherapy remains an option. Adjuvant carboplatin reduces the risk of relapse by ~60% [93], which provides a number-needed-to-treat (NNT) value in the range of 15–20 to prevent one relapse.

Recommendation 8.1: Patients with seminoma and a low risk of relapse should **not** be offered adjuvant chemotherapy.

Level of evidence: III

Strength of recommendation: C

Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

Recommendation 8.2: In patients with seminoma and a higher risk of relapse, surveillance or adjuvant carboplatin are options.

Level of evidence: III

Strength of recommendation: C

Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

Recommendation 8.3: In patients with seminoma, patient autonomy should be taken into account following thorough provision of information regarding the pros and cons of the alternative treatment strategies.

Level of evidence: III

Strength of recommendation: C

Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

Lymphovascular invasion – validated RF

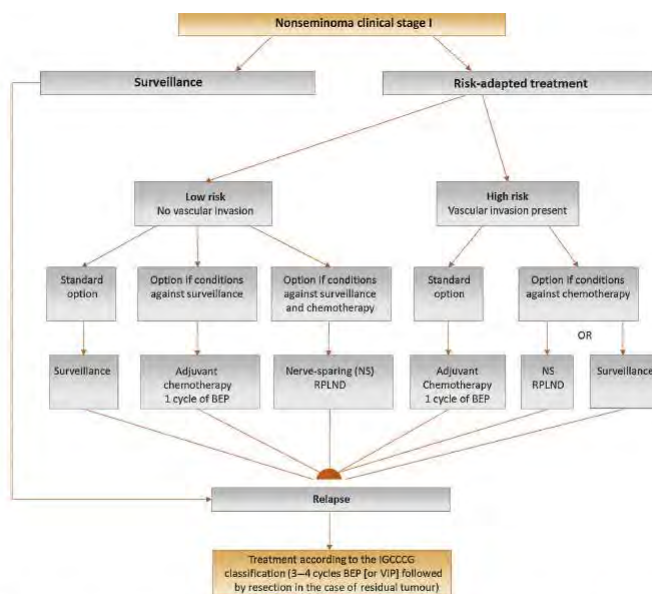


Fig. 1 – Risk-adapted treatment in patients with clinical stage I nonseminoma. All treatment options need to be discussed with individual patients to allow them to make an informed decision as to their further care. BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RPLND = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.



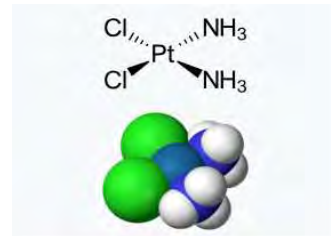
Serum Levels of MicroRNA-371a-3p (M371 Test) as a New Biomarker of Testicular Germ Cell Tumors: Results of a Prospective Multicentric Study

Klaus-Peter Dieckmann, Prof^{1,2}; Arlo Radtke, PhD³; Lajos Geczi, MD, PhD⁴; Cord Matthies, MD⁵; Petra Anheuser, MD⁶; Ulrike Eckardt, MD⁷; Jörg Sommer, MD⁸; Friedemann Zengerling, MD⁹; Emanuela Trenti, MD⁹; Renate Pichler, PhD¹⁰; Hanjo Belz, MD¹¹; Stefan Zastrow, MD¹²; Alexander Winter, MD¹³; Sebastian Melchior, Prof¹⁴; Johannes Hammel, MD¹⁵; Jennifer Kianz, MD¹⁵; Marius Boltz, MD¹⁶; Susanne Kreye, Prof¹⁷; Björn Haben, MD¹⁸; Wolfgang Loidl, MD¹⁹; Christian Guido Ruf, MD²⁰; Julia Heinzelbecker, MD²¹; Axel Heidenreich, Prof²²; Jann Frederik Cremers, MD²³; Christoph Oing, MD²⁴; Thomas Hermanns, MD²⁵; Christian Daniel Fankhauser, MD²⁶; Silke Gillissen, MD²⁶; Hermann Reichegger, MD²⁶; Richard Cathomas, MD²⁷; Martin Pichler, Prof²⁸; Marcus Henrich, MD²⁹; Klaus Eredics, MD³⁰; Anja Lorch, Prof³¹; Christian Wülfing, Prof¹; Sven Peine, MD³²; Werner Wosniok, PhD³; Carsten Bokemeyer, Prof²⁴; and Gazanfer Belge, PhD³

miR-371a-3p outperforms the classical biomarkers and represents a highly sensitive and specific new biomarker for TGCC



J Clin Oncol 2019



- Adjuvant chemotherapy
- **Chemotherapy for the metastatic disease**
- Salvage treatment



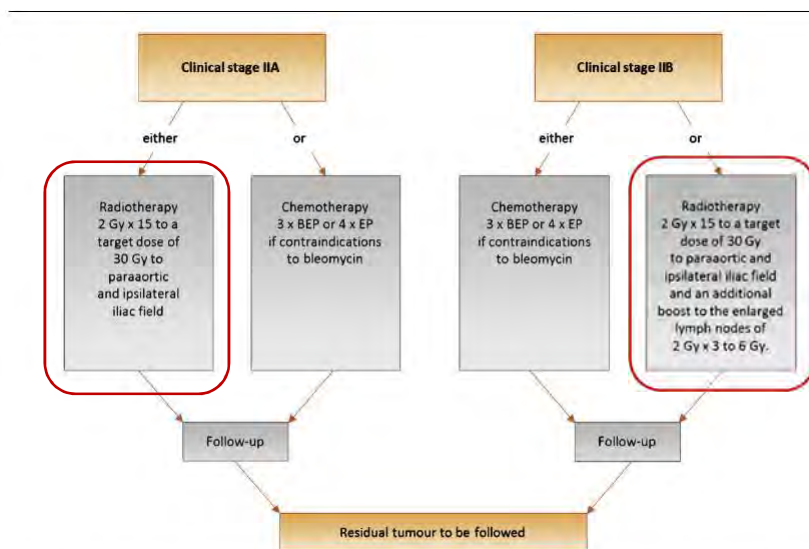


Fig. 2 – Treatment options for patients with clinical stage IIA and IIB seminoma. BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.



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NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019 Testicular Cancer

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RISK CLASSIFICATION FOR ADVANCED DISEASE (post-orchectomy) ^a		
Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and <u>Post-orchectomy markers</u> - all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and <u>Post-orchectomy markers</u> - any of: AFP 1,000–10,000 ng/mL hCG 5,000–50,000 iu/L LDH 1.5–10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or <u>Post-orchectomy markers</u> - any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol 1997;15(2):594-603. Reprinted with permission of the American Society of Clinical Oncology.

^a Markers used for risk classification are post-orchectomy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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TEST-D



Table 1 | Serum AFP and hCG levels in GCTs²²

GCT histological subtype	AFP	hCG
Yolk sac tumour	++	-
Seminoma	-	±
Embryonal carcinoma	±	±
Choriocarcinoma	-	++
Teratoma	±	-

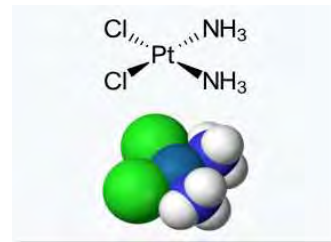
AFP, α-fetoprotein; GCT, germ cell tumour; hCG, human chorionic gonadotrophin. ++, strongly positive levels; ±, levels may be negative or moderately positive; -, negative levels.



Table 2. Chemotherapy regimens in metastatic seminoma and non-seminoma

BEP ^a (Repeat cycles every 3 weeks)		
Cisplatin	20 mg/m ²	Day 1-5
Etoposide	100 mg/m ²	Day 1-5
Bleomycin	30 mg	Day 1, 8, 15
EP ^b (Repeat cycles every 3 weeks)		
Cisplatin	20 mg/m ²	Day 1-5
Etoposide	100 mg/m ²	Day 1-5
VIP/PEI ^c (Repeat cycles every 3 weeks)		
Cisplatin	20 mg/m ²	Day 1-5
Etoposide	75 mg/m ²	Day 1-5
Ifosfamide	1.2 g	Day 1-5
TIP ^d (Repeat cycles every 3 weeks)		
Paclitaxel	250 mg/m ²	Day 1
Cisplatin	25 mg/m ²	Day 2-5
Ifosfamide	1.5 g	Day 2-5
VelP ^e (Repeat cycles every 3 weeks)		
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m ²	Day 1-5
Cisplatin	20 mg/m ²	Day 1-5
TI-CE ^f (TI cycles 1-2 every 2 weeks)		
Paclitaxel	200 mg/m ²	Day 1
Ifosfamide	2.0 g	Day 2-4
(CE cycles 3-5 every 3 weeks)		
Carboplatin	AUC = 7	Day 1-3
Etoposide	400 mg/m ²	Day 1-3
CE ^g (Two cycles, may be preceded by VelP)		
Carboplatin	700 mg/m ²	Day 1
Etoposide	750 mg/m ²	Day 1-3





- Adjuvant chemotherapy
- Chemotherapy for the metastatic disease
- Salvage treatment



Multidisciplinary treatment

Treatment For Testicular Cancer



*Orchiectomy
(Removal of testicles)*



Chemotherapy



Radiation Therapy



*Stem Cell
Transplantation*



*Lymph Node
Block Dissection*



Late relapse of mGCT

recurrent GCT more than 2 years from completion of initial chemotherapy in the absence of a second gonadal primary tumor

evidence of new lesions, or sequentially increasing serum tumour markers (AFP or HCG), more than 2 years after ≥ 3 cycles of cisplatin-based chemotherapy

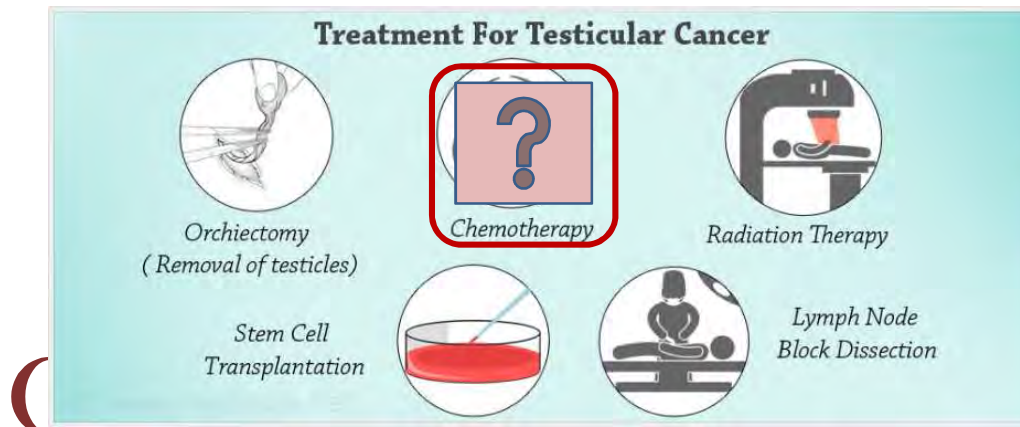


Table 2. Chemotherapy regimens in metastatic seminoma and non-seminoma

BEP ^a (Repeat cycles every 3 weeks)		
Cisplatin	20 mg/m ²	Day 1-5
Etoposide	100 mg/m ²	Day 1-5
Bleomycin	30 mg	Day 1, 8, 15
EP ^b (Repeat cycles every 3 weeks)		
Cisplatin	20 mg/m ²	Day 1-5
Etoposide	100 mg/m ²	Day 1-5
VIP/PEI ^c (Repeat cycles every 3 weeks)		
Cisplatin	20 mg/m ²	Day 1-5
Etoposide	75 mg/m ²	Day 1-5
Ifosfamide	1.2 g	Day 1-5
TIP ^d (Repeat cycles every 3 weeks)		
Paclitaxel	250 mg/m ²	Day 1
Cisplatin	25 mg/m ²	Day 2-5
Ifosfamide	1.5 g	Day 2-5
VIP ^e (Repeat cycles every 3 weeks)		
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m ²	Day 1-5
Cisplatin	20 mg/m ²	Day 1-5
TI-CE ^f (TI cycles 1-2 every 2 weeks)		
Paclitaxel	200 mg/m ²	Day 1
Ifosfamide	2.0 g	Day 2-4
(CE cycles 3-5 every 3 weeks)		
Carboplatin	AUC = 7	Day 1-3
Etoposide	400 mg/m ²	Day 1-3
CE ^g (Two cycles, may be preceded by VIP)		
Carboplatin	700 mg/m ²	Day 1
Etoposide	750 mg/m ²	Day 1-3



A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial

GM Mead^{a,1}, MH Cullen², R Huddart³, P Harper⁴, GJS Rustin⁵, PA Cook⁶, SP Stenning⁶ and M Mason⁷ on behalf of the MRC Testicular Tumour Working Party^a

^aMedical Oncology Unit, C Level West Wing, Southampton General Hospital, Southampton SO16 6YD, UK; ¹University Hospital Birmingham NHS Foundation Trust, Birmingham B15 2TH, UK; ²Royal Marsden Hospital, Sutton SW2 5PT, UK; ³Guy's Hospital, London SE1, UK; ⁴St Vincent's Hospital, Harlow HA6 3RL, UK; ⁵MRC Clinical Trials Unit, London NW1 2DA, UK; ⁶Velindre Hospital, Cardiff CF4 7XL, UK

43 eligible pts (relaps after BEP 1st line for mGCT)
TIP x 4 (G-CSF given at the discretion of the investigator)
Primary outcome measure – response to TIP

Table 2 Response rates, FFS and overall survival

Group	Response (N, %)					Favourable (CR+PR) response rate (FFR _p) (95% CI)	Favourable (CR+PR+CR(S)) response rate (FFR _c) (95% CI)	1-year FFS rate (95% CI)	1-year overall survival rate (95% CI)
	CR	PR MK-ve	Complete resection of viable malignancy CR(S)	IR	Treatment failure/early death				
All patients	8 (19%)	18 (42%)	5 (12%)	8 (19%)	4 (9%)	60% (44–75)	72% (56–85)	38% (23–53)	70% (56–84)



CR = complete response; PR = partial response; IR = incomplete response; FFS = failure-free survival; 95% CI = 95% confidence interval.

Table 2 Response rates, FFS and overall survival

Group	Response (N, %)					Favourable (CR+PR) response rate (FFR _p) (95% CI)	Favourable (CR+PR+CR(S)) response rate (FFR _c) (95% CI)	1-year FFS rate (95% CI)	1-year overall survival rate (95% CI)
	CR	PR MK-ve	Complete resection of viable malignancy CR(S)	IR	Treatment failure/early death				
All patients	8 (19%)	18 (42%)	5 (12%)	8 (19%)	4 (9%)	60% (44–75)	72% (56–85)	38% (23–53)	70% (56–84)
MSKCC good risk	7 (27%)	12 (46%)	2 (8%)	3 (12%)	2 (8%)	73% (52–88)	81% (61–93)	43% (23–63)	81% (64–98)
MSKCC poor risk	1 (6%)	6 (35%)	3 (18%)	5 (29%)	2 (12%)	41% (18–67)	59% (33–82)	29% (8–51)	53% (29–77)

CR = complete response; PR = partial response; IR = incomplete response; FFS = failure-free survival; 95% CI = 95% confidence interval.

Table 3. Patient Characteristics Found to be Predictive of Survival in the Univariate Analysis

Characteristic	No. of Patients	No. Alive	Median Survival (months)	P
All patients	58	17	11	NA
Primary tumor site				.04
Gonadal	51	16	12	
Extragenital	7	1	3	
Retroperitoneal metastases				.08
No	21	3	9	
Yes	37	14	12	
Prior best response				.04
Incomplete	36	8	8	
Complete	22	9	24	
Refractory status ¹⁰				.04
Absolute refractory	12	3	7	
Refractory	21	3	7	
Relapsed	25	11	24	
Pretreatment HCG continuous variable	58	NA	NA	.03

Abbreviation: NA, not applicable.

Figure 3 Survival, all eligible patients.

© 2005 Cancer Research UK

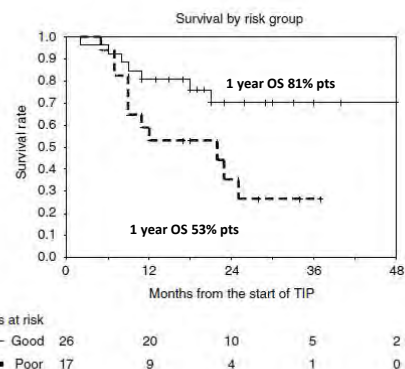


Figure 4 Survival by risk group.

British Journal of Cancer (2005) 93(2), 178 – 184

Salvage therapy of testicular cancer

High dose chemotherapy



ORIGINAL ARTICLE

High-Dose Chemotherapy and Stem-Cell Rescue for Metastatic Germ-Cell Tumors

Lawrence H. Einhorn, M.D., Stephen D. Williams, M.D., Amy Charness, B.A., Mary J. Brames, R.N., Susan M. Perkins, Ph.D., and Rafat Abonour, M.D.

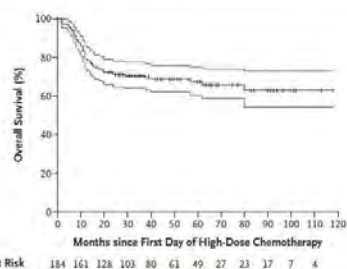


Figure 1. Kaplan-Meier Estimates of Overall Survival. The top and bottom lines show the 95% confidence interval.

Retrospective study

184 pts

2nd line (135)

3rd or subsequent lines (49)

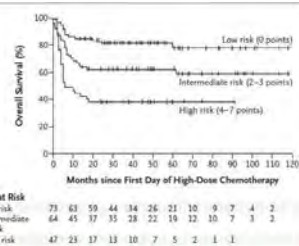


Figure 2. Disease-free Survival. The prognostic scoring algorithm, based on the three-variable model, assigned a score of 3 points for third-line chemotherapy, 2 points for platinum refractoriness, and 2 points for advanced International Germ Cell Cancer Collaborative Group stage. High scores indicated a low probability of disease-free survival.

Table 3. Results of Multivariate Cox Proportional-Hazards Analysis and Prognostic Score.*

Prognostic Variable	Hazard Ratio (95% CI)	P Value	β Regression Coefficient	Prognostic Score†
Third-line or subsequent chemotherapy	2.19 (1.35–3.56)	0.002	0.78	3
Platinum-refractory disease	1.74 (1.01–3.00)	0.05	0.55	2
IGCCCG high-risk stage	1.67 (1.00–2.78)	0.05	0.51	2

* The hazard ratio is for disease progression. IGCCCG denotes International Germ Cell Cancer Collaborative Group.

† The score was calculated by dividing the regression coefficient by 0.51, multiplying by 2.0, and rounding to the nearest whole number.

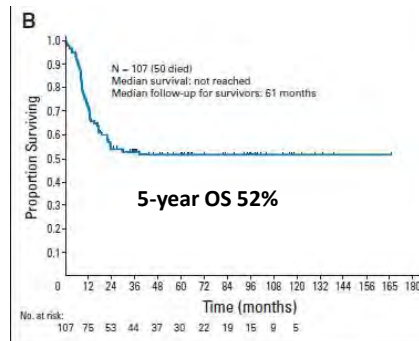
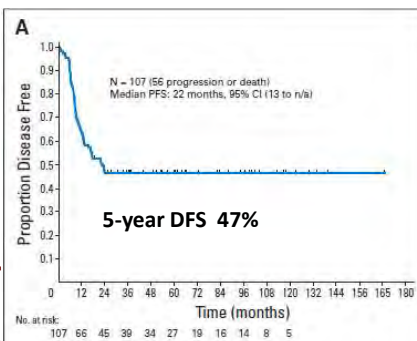
TI-CE High-Dose Chemotherapy for Patients With Previously Treated Germ Cell Tumors: Results and Prognostic Factor Analysis

Darren R. Feldman, Joel Sheinfeld, Dean F. Bajorin, Patricia Fischer, Stefan Turkula, Nicole Ishill, Sujata Patil, Manjit Bains, Lilian M. Reich, George J. Bosl, and Robert J. Motzer

Retrospective analysis: 107 pts

Unfavorable prognostic features (incomplete response to 1st line, relapse/incomplete response to cisplatin/ifosfamide based CDCT salvage, ekstragonadal primary)

- m follow-up: 61 months
- 50% CR and 8% PR neg TM;
- No relapses occurred after 2 years.
- 24 of primary mediastinal nonseminomatous GCTs are continuously disease free



Original article

Annals of Oncology 16: 1153-1159, 2005
doi:10.1093/annonc/mdh228
Published online 31 May 2005

A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours

IT-94 trial

J.-L. Pico¹, G. Rosti², A. Kramar^{3*}, H. Wandt⁴, V. Koza⁵, R. Salvioni⁶, C. Theodore¹, G. Lelli⁷, W. Sieger⁸, A. Horwich⁹, M. Marangolo², W. Linkesch¹⁰, G. Pizzocaro⁸, H.-J. Schmoll¹¹, J. Bouzy¹, J.-P. Droz¹² & P. Biron¹², for the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG-FNCLCC), France and the European Group for Blood and Marrow Transplantation (EBMT)

February 1994 and September 2001, 280 patients from 43 institutions in 11 countries

- arm A: four cycles of cisplatin, ifosfamide and etoposide (or vinblastine)
- arm B: three such cycles followed by high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC) with haematopoietic stem cell support

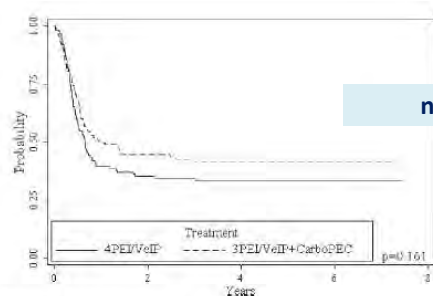


Figure 1. Event-free survival.

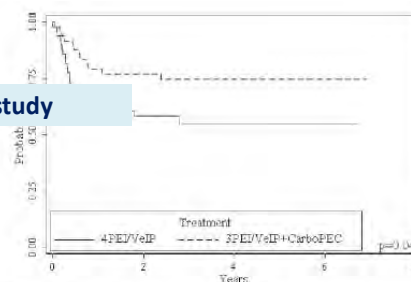
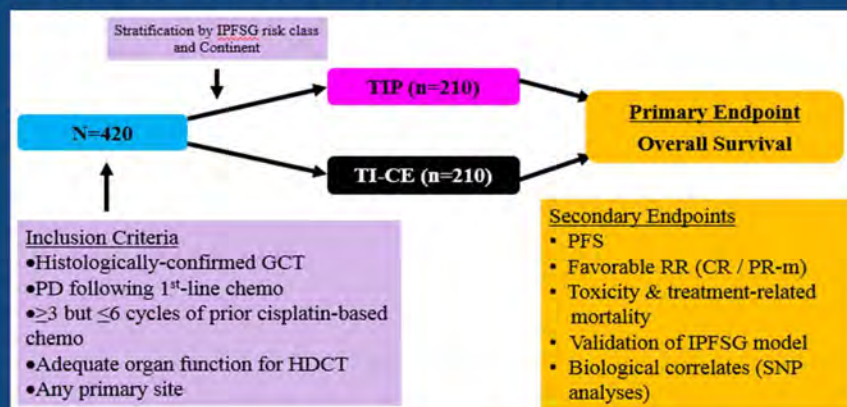


Figure 2. Disease-free survival from time of overall treatment evaluation among patients in complete remission.

TIGER: international, prospective Phase III trial



Sponsor: Alliance (USA, D. Feldman), EORTC (Europe, T. Powles), Movember

PRESENTED AT: 2018 ASCO ANNUAL MEETING

#ASCO18
All data are the property of the Society
of Medical Oncology and its members.

PRESENTED BY: DR. ANJA LORCH

23



Presented By Anja Lorch at 2018 ASCO Annual Meeting

Table 4. Relapsed GCC: International Prognostic Factors Study Group classification [1]

Parameter	Score points			
	0	1	2	3
Primary site	Gonadal	Extragenital	-	Mediastinal non-seminoma
Prior response	CR/PRm-	PRm+/SD	PD	-
PFI, months	>3	≤3	-	-
AFP salvage	Normal	≤1000	>1000	-
hCG salvage	≤1000	>1000	-	-
Score sum (values from 0 to 10)				
Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3				
Add histology score points: pure seminoma = -1; non-seminoma or mixed tumours = 0				
Final prognosis score (-1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)				

AFP, α -fetoprotein; CR, complete remission; GCC, germ cell cancer; hCG, human chorionic gonadotropin; PD, progressive disease; PFI, progression-free interval; PRm-, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease.



Annals of Oncology 29: 1658–1686, 2018 (supplements)

insufficient evidence to determine whether CDCT or HDCT produces superior outcomes as first-salvage chemotherapy → either CDCT or HDCT acceptable options for first-salvage chemotherapy



Table 3. 'Third-line' regimens used for second or subsequent salvage treatment

Single agent				
Regimen	Dose	Schedule	Reference	
Gemcitabine	1000 mg/m ²	d1, 8, 15 q3w	[241]	
	1200 mg/m ²	d1, 8, 15 q3w	[242]	
Oxaliplatin	60 mg/m ² or 85 mg/m ²	d1, 15 q4w	[243]	
Paclitaxel	170 mg/m ²	d1, q3w	[244]	
	225 mg/m ²	d1, q3w	[245]	
	250 mg/m ²	d1, q3w	[246]	
	250 mg/m ²	d1, q3w	[247]	
Oral etoposide	50 mg/m ² /day	Continuously	[248]	
Two drug combinations				
Regimen	Dose	Schedule	Reference	
Gemcitabine	1000 mg/m ² or 1250 mg/m ²	d1, 8 q3w	[249–251]	
Oxaliplatin	130 mg/m ²	d1, q3w		
Gemcitabine	1000 mg/m ²	d1, 8, 15 q4w	[252, 253]	
	Paclitaxel 100 mg/m ²			
Three drug combinations				
Regimen	Dose	Schedule	Reference	
Gemcitabine	800 mg/m ²	d1, 8 q3w	[254]	
Oxaliplatin	130 mg/m ²	d1, q3w		
Paclitaxel	80 mg/m ²	d1, 8 q3w		
Gemcitabine	800 mg/m ²	d1, 8 q3w	[255]	
	Cisplatin	50 mg/m ²		d1, 8 q3w
	Paclitaxel	80 mg/m ²		d1, 8 q3w

d, day; q3w, every 3 weeks; q4w, every 4 weeks.

d, day; q3w, every 3 weeks; q4w, every 4 weeks.



Palliative treatment in GCT

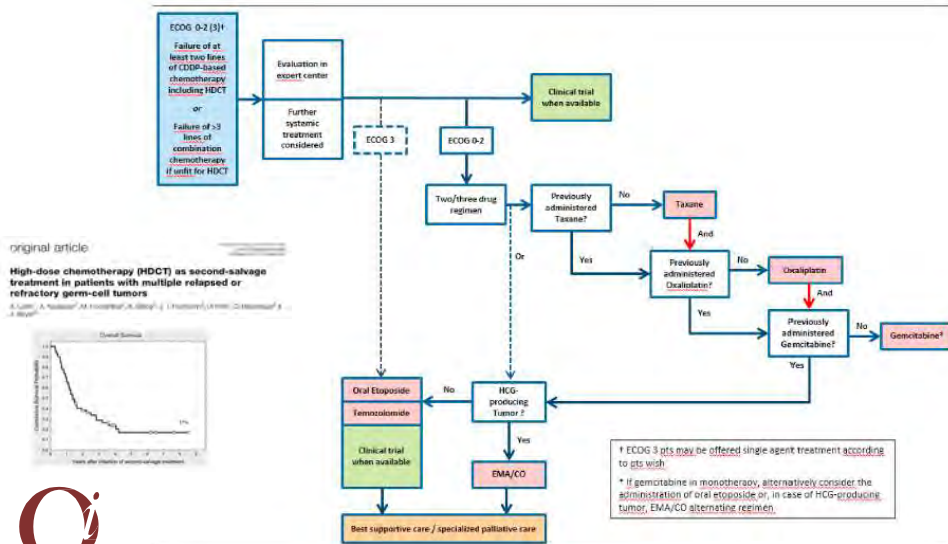


Fig. 1. Treatment algorithm for selection of palliative treatments.

Phase I / II studies

Kollmansberger C	trastuzumab	HER2/neu expressing GCT	Ann Oncol 1999
Rick O	thalidomid	platinum refractory	Eur J Cancer 2006
Feldman DR	sunitinib	relapsed refractory	Invest New Drugs 2010
Feldman DR	tivantinib	relapsed or refractory	Invest New Drugs 2013
Einhorn LH	imatinibmesil-	CTX refractory GCT expressing KIT	J Clin Oncol 2006
Necchi A	pazopanone	relapsed or refractory GCT	Ann Oncol 2017
Fenner M	regorafenib	multiply relapsed GCT	Journal of Cancer Research and Clinical Oncology, 2018
Adra N	pembrolizumab	multiply relapsed GCT, no other treatment option	Annals of Oncology, 2018

RESEARCH

CANCER BIOMARKERS

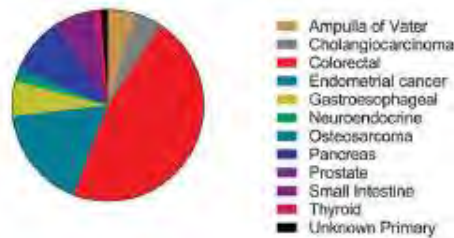
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Le et al., Science 357, 409–413 (2017)



the genomes of cancers deficient in MMR contain exceptionally high numbers of somatic mutations

→ sensitivity to immune checkpoint blockade



• 12 different tumor types

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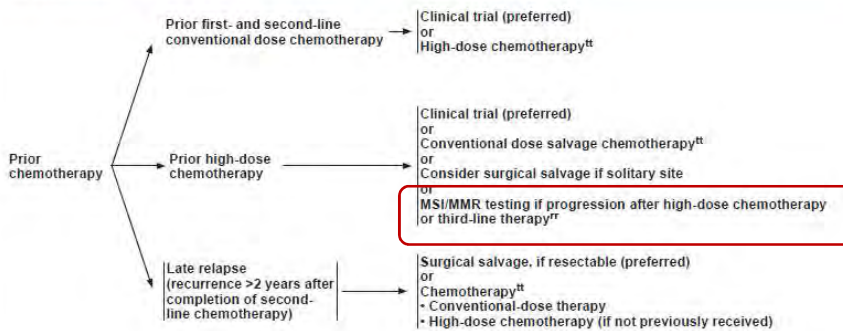
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RECURRENT⁹⁹

THIRD-LINE THERAPY^{kk,ss}



^{kk} To assess response after treatment, CT with contrast of chest/abdominal/pelvic and any other sites of disease is recommended.
⁹⁹ It is preferred that patients with recurrent nonseminoma be treated at centers with expertise in the management of this disease.

^{ss} Includes best supportive care.

^{tt} See Third-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-G).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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TEST-15

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THIRD-LINE CHEMOTHERAPY REGIMENS FOR METASTATIC GERM CELL TUMORS^a

High-Dose Chemotherapy NOT Previously Received
Preferred Regimens
High-Dose Chemotherapy

- Carboplatin 700 mg/m² (body surface area) IV
Etoposide 750 mg/m² IV
Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles¹
- Paclitaxel 200 mg/m² IV over 24 hours on Day 1
Ifosfamide 2000 mg/m² over 4 hours with mesna protection on Days 2–4
Repeat every 14 days for 2 cycles followed by
Carboplatin AUC 7–8 IV over 60 minutes on Days 1–3
Etoposide 400 mg/m² IV on Days 1–3
Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles²

Other Recommended Regimens^b

- Gemcitabine/paclitaxel/oxaliplatin³
- Gemcitabine/oxaliplatin^{4–6}
- Gemcitabine/paclitaxel^{7,8}
- Etoposide (oral)⁹

Useful in Certain Circumstances^b

- Pembrolizumab (for MSI-H/dMMR tumors)^{10,11}

High-Dose Chemotherapy Previously Received
Preferred Regimens^b

- Gemcitabine/paclitaxel/oxaliplatin³
- Gemcitabine/oxaliplatin^{4–6}
- Gemcitabine/paclitaxel^{7,8}
- Etoposide (oral)⁹

Useful in Certain Circumstances^b

- Pembrolizumab (for MSI-H/dMMR tumors)^{10,11}

^aIf VIP or TIP received as second-line therapy, high-dose chemotherapy is the preferred third-line option.
^bSee references on [TEST-G \(2 of 2\)](#) for dosing.

Note: All recommendations are category 2A unless otherwise indicated.
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TEST-G
1 OF 2

ESMO European Society for Medical Oncology

ORIGINAL ARTICLE

Phase II trial of pembrolizumab in patients with platinum refractory germ-cell tumors: a Hoosier Cancer Research Network Study GU14-206

N. Adia^{1*}, L. H. Bittorn², S. K. Athouroz³, N. R. Aramkhanova⁴, D. Muapatika⁵, C. Albany⁶, D. Vaughn⁷ & N. H. Hanna¹

Annals of Oncology 29, 206–214, 2018
doi:10.1093/annonc/mdx448
Published online 17 July 2018

- Single arm phase II trial investigating pembrolizumab 200mg i.v. Q3 weeks until disease progression
- Primary end point ORR using immune-related response criteria

- Patients with relapsed GCT and no curable options
- 12 patients enrolled, median age 38 years,
 - all patients had nonseminoma,
 - six patients had late relapse (>2 years)
- 2 patients had positive PD-L1 staining
- No CR or PR observed
- 2 pts radiographic SD (28 and 19 weeks),
 - both had continued rising AFP level despite radiographic stability and had negative PD-L1 staining

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