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Ethiopian Society of Obstetricians & Gynecologists

Principles of Chemotherapy in Gynecological Cancer

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UKH Universitätsklinikum Halle (Saale)

Conflicts of interest

Honoraria for lectures and advisory boards:

- Amgen
- Astra-Zeneca
- Celgene
- Daiichi-Sankyo
- Eisai
- Lilly
- MSD
- Mylan
- Nanostring
- Novartis
- Pfizer
- Pierre Fabre
- Puma
- Roche
- Vifor

Learning objectives

- Basic classification of chemotherapeutic agents
- Role of chemotherapy in ovarian cancer, uterine cancer, cervical cancer, vulvar cancer
- Assess the response for chemotherapy
- Management of toxicity

- General considerations

Chemotherapy in Gynecologcal Oncology Indications – Achievements - Challenges

Breast Cancer – high risk of distant metastases:

- Early breast cancer — Adjuvant therapy leads to >50% less mortality / 15yrs!
- Metastatic breast cancer — Prolongation of PFS, palliation; OS benefit possible

Gynaecological Cancers – mainly locoregional / abdominal diseases:

- Ovarian cancer — Prolongation of OS (1L and 2L)
- Cervical cancer — Radiochemotherapy – alternative to radical surgery in 1L. Prolongation of progression and OS in 2L. Role of ICPi
- Endometrial Cancer — OS benefit in 1L. Later: Small effects. Options: endocrine therapy, immune checkpoint inhibitors (ICPi)
- Vulvar cancer — Rare indication, palliation (analogue to cervical cancer)
- Gestational trophoblastic neoplasia (GTN) – Chemotherapy - high chance of cure

Classification of antineoplastic drugs - cytotoxic chemotherapy -

- Platin-salts (cisplatin - CDDP, carboplatin - CDBCA)
  - Interaction with DNA-replication
  - *Side effects: Nephrotoxicity, neurotoxicity, hearing loss, alopecia*
- Spindle poisons (taxanes, vinca-alkaloids)
  - Inhibiting microtubule depolymerization: paclitaxel, docetaxel
  - Inhibiting microtubule polymerization: vinorelbine
  - *Side effects: peripheral neuropathy, alopecia, myelosuppression*
- Anthracyclines (doxorubicin, pegylated doxorubicin)
  - DNA-intercalation, topoisomerase II-inhibition
  - *Side effects: vein toxicity, heart failure, alopecia, myelosupression*
- Alkylating compounds (cyclophosphamide)
  - DNA interstrand and intrastrand crosslinkages => apoptosis
  - *Side effects: Myelosuppression, urotoxicitiy (in higher doses)*

Chemistry: Coordination Complex (cis-diamino-dichloro-platinum)

Natural products (taxanes: yew tree, vinorelbine: vinca plants (periwinkle)

Bacterial product (Streptomyces)

Chemistry: nitrogen mustard–derived alkylating agent like ifosfamide

Classification of antineoplastic drugs - targeted drugs -

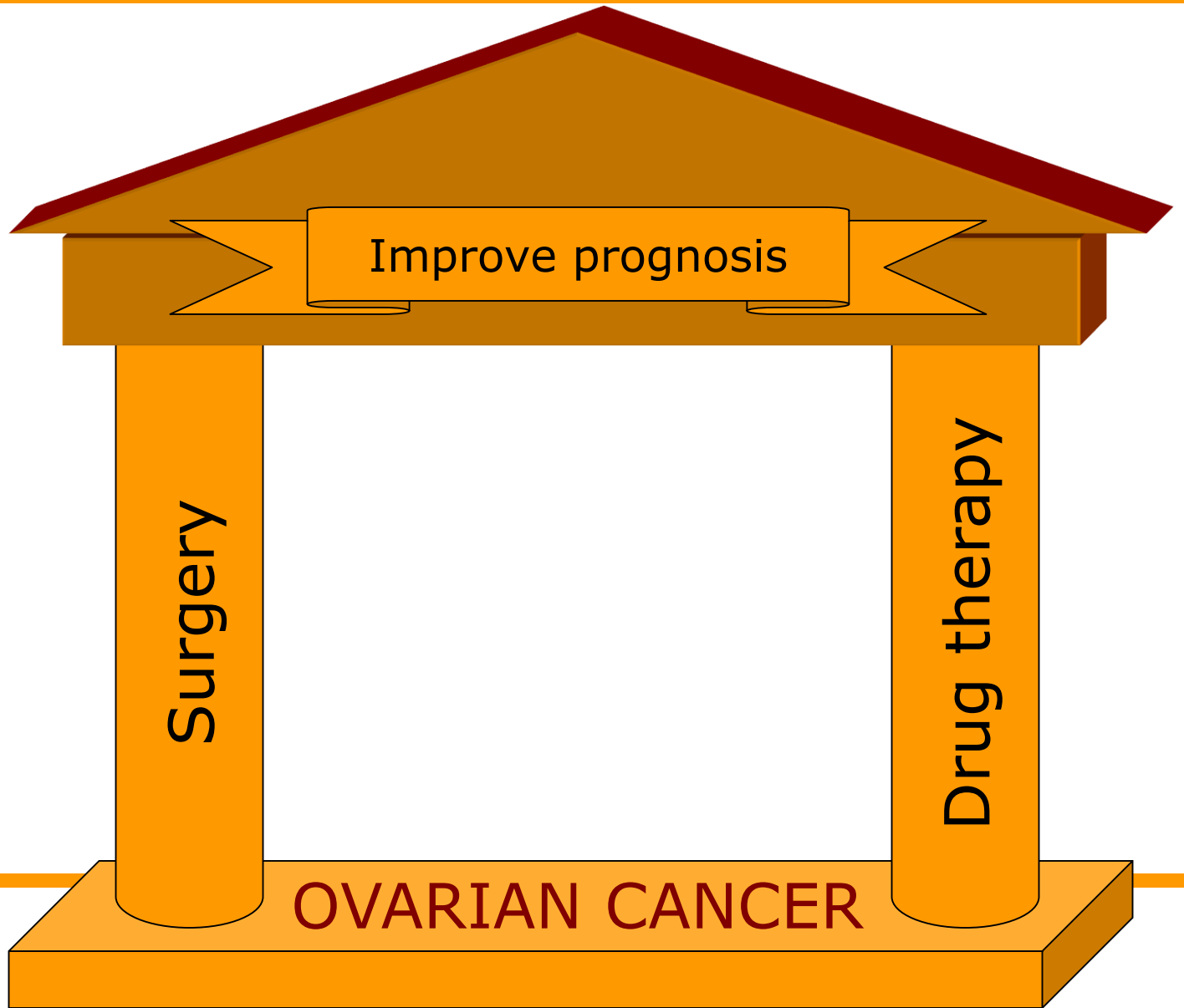
- Anti-angiogenetic drugs
  - **Bevacizumab**: Antibody against VEGF (ligand capture to inhibit VEGF-R based activation of vessel growth) => tumour hypoxia
  - *Side effects: nephrotoxicity (protein loss), hypertension, impaired wound healing, GI-perforations; thrombo-embolic events*
- PARP-inhibitors
  - **Olaparib, niraparib, rucaparib**: Single strand DNA repair, most effective, if double strand repair is impaired (homologous repair deficiency - HRD, BRCA-mutation) – „synthetic lethality"
  - *Side effects: myelotoxicity, fatigue*
- Immune checkpoint inhibitors (anti-PD1-/antiPD-L1-antibodies)
  - **Pembrolizumab, nivolumab, durvalumab** (antiPD1-MoAb): blocking interaction between immune cells and tumor cells => activation of immune reaction
  - *Side effects: autoimmune-like (hypo-/hyperthyreodism, hepatitis, colitis, etc.)*
- Tyrosine kinase inhibitors (TKI)
  - **Lenvatinib**: oral multikinase inhibitor that targets VEGFR 1–3, FGFR 1–4, PDGFRα, RET, and KIT
  - *Side effects: hypertension, fatigue, diarrhea, stomatitis, decreased appetite*

Medical therapy in cancer - Toxicity

- Toxic drugs – indication important
- Tolerance depends on supportive care
  - Nausea, emesis - prophylactic anti-emetic drugs
  - Myelosuppression - dose, interval; G-CSF
  - Peripheral neuropathy - compression gloves (& stocking)
  - Alopecia - artificial hairs, wig
  - Renal failure - hydration (also IV)
  - Pain - analgetics (incl. opioids)

- Ovarian Cancer (EOC) – First-line

Current Treatment Concepts for Ovarian Cancer



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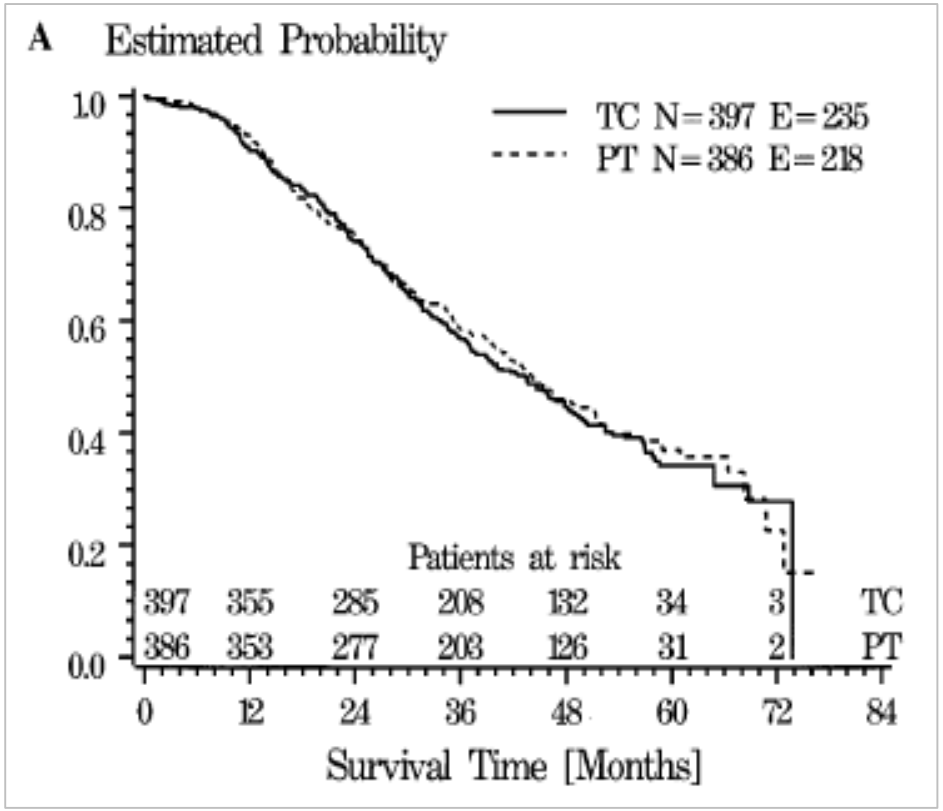
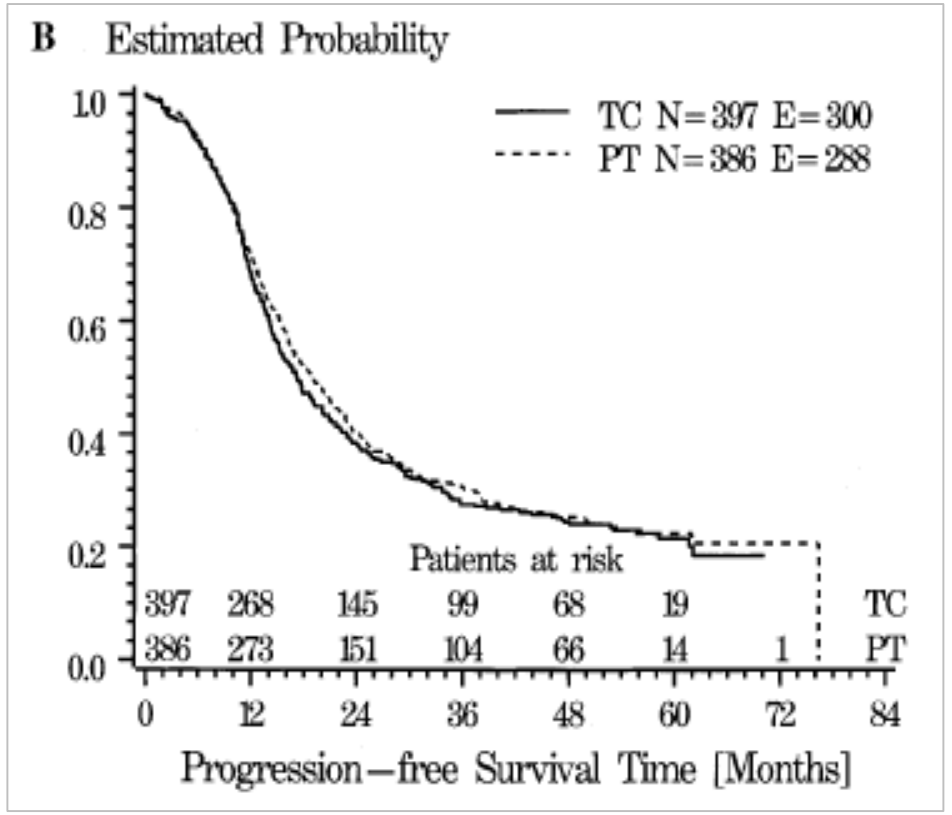
Ovarian cancer – Standards in first-line

- Standard
  - Surgery — Macroscopically tumor free
  - Medical therapy
    - Chemotherapy — $Carboplatin_{AUC5}$/$Paclitaxel_{175mg/m^2}$ q3w *6
    - antiVEGF-th. — $Bevacizumab_{7,5mg/kg}$ q3w for 15m (FIGO IIC+)
- New
  - Additional PARP-inhibitor (Niraparib, Olaparib) tablets for 2 years in pts with homologous repair deficiency (HRD) or germline BRCA1/2-mutation ($BRCA1/2^{MUT}$)

Cisplatin/Paclitaxel (PT) vs Carboplatin/Paclitaxel (TC) (AGO Ovar-3 trial)





TC: Higher frequency of hematologic toxicity, but a lower frequency of gastrointestinal and neurologic toxicity, than in PT.
TC: Higher mean global quality-of-life scores at end of treatment than in the PT arm.

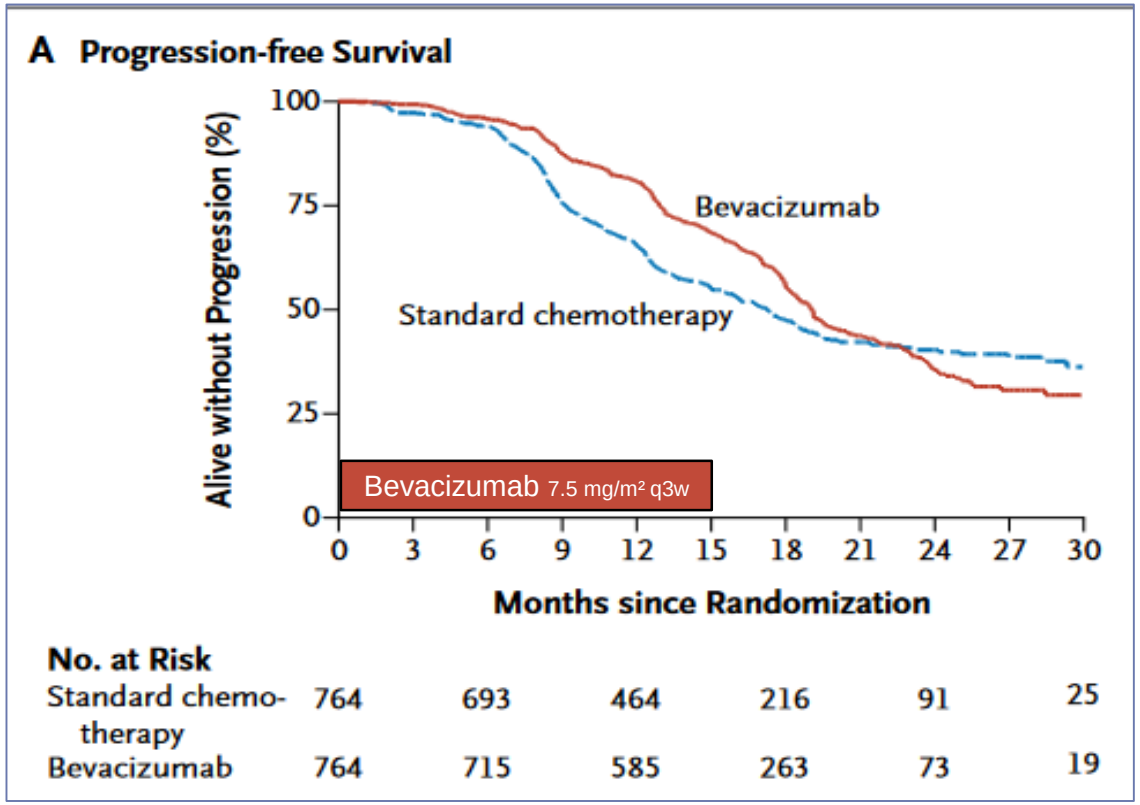
du Bois A et al., JNCI 2003;95:1320–30

Ovarian Cancer (FIGO IIB+) – First-Line Therapy Extension with Bevacizumab

Inhibition of angiogenesis

–VEGF, secreted by tumor cells, activates vessel growth

=>Anti-VEGF-MoAb (bevacizumab) catches the ligand VEGF, thus inhibiting its function by binding to the receptor VEGF-R and inhibiting vessel growth („Tumor starving“)



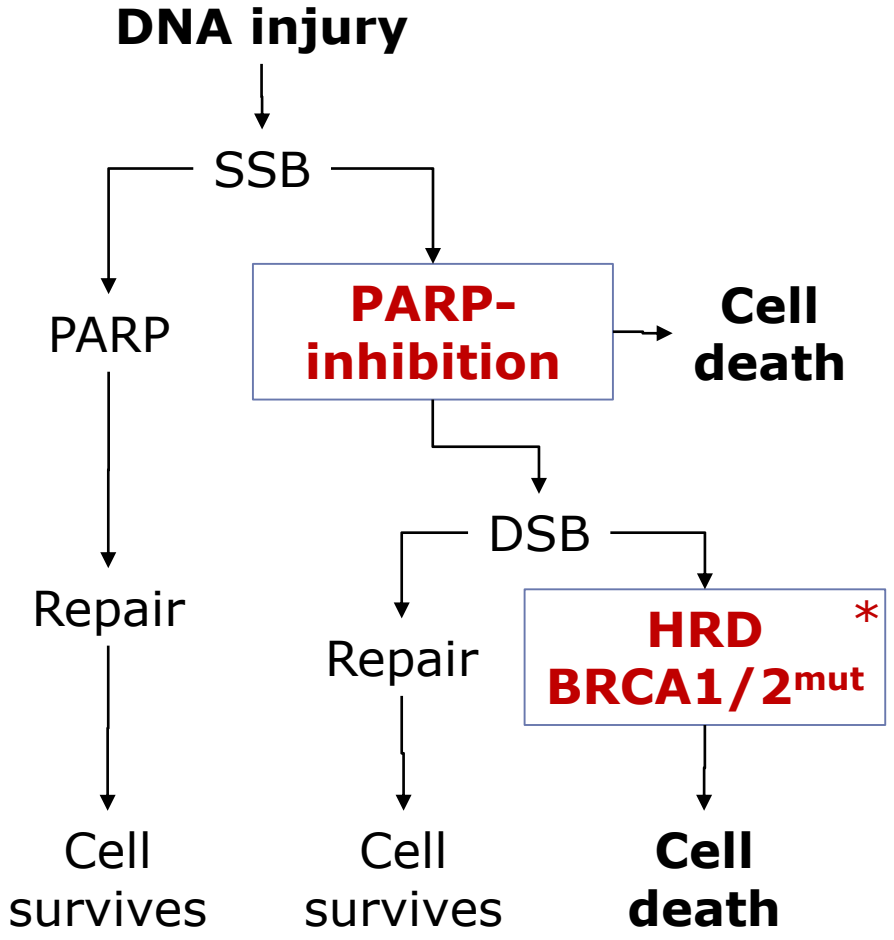
Oza AM et al.; ICON7 trial investigators. Lancet Oncol. 2015 Aug;16(8):928-36.

Ovarian cancer – Synthetic lethality

„Synthetic lethality“

- PARP-inhibition (no repair of single-strand DNA-breaks),
- Homologous recombination deficiency (no repair of double strand DNA-breaks)

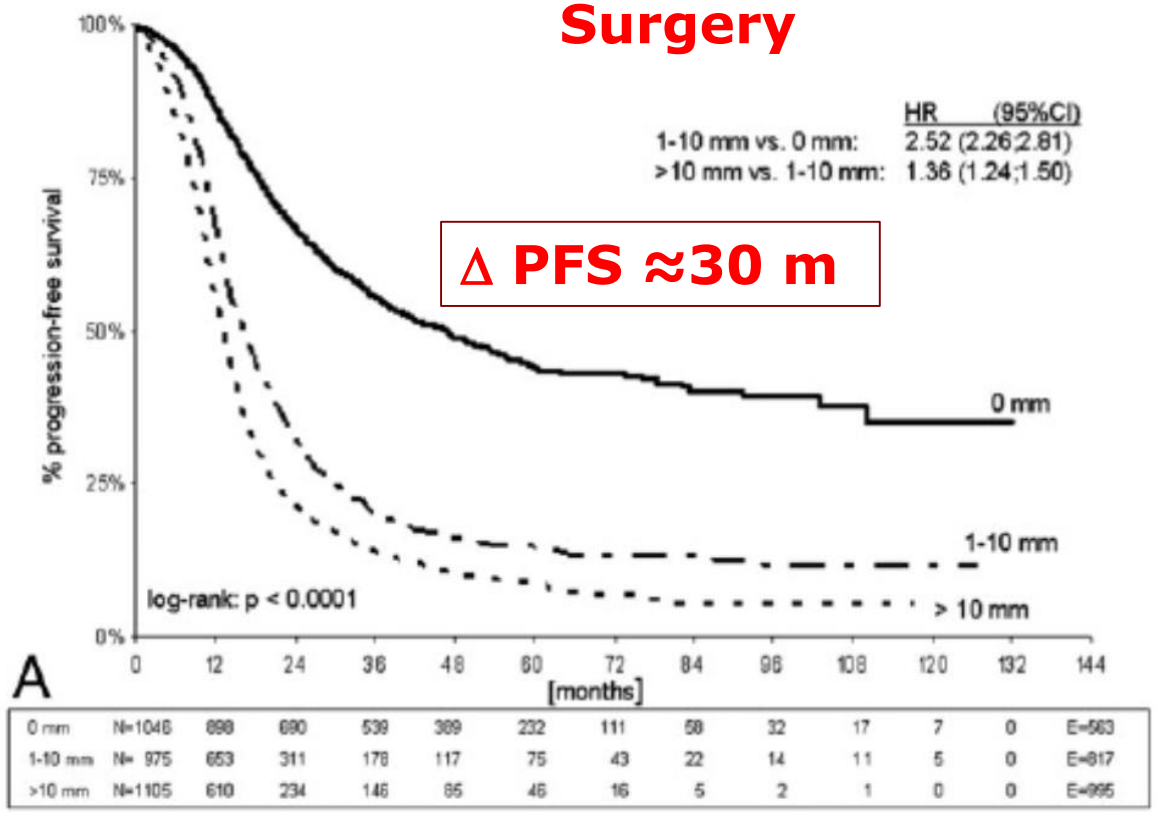
=> PARP-Inhibition (niraparib, olaparib, rucaparib) effective in pts. with homologous repair deficiency (HRD, BRCA1/2^{mut})



* 20% in pts <50yrs with HG-EOC without family history
20-40% in pts with family history for EOC or BC

FIGO III/IV: Effect on PFS by surgery (residual tumor) and PARP-inhibitor (olaparib)

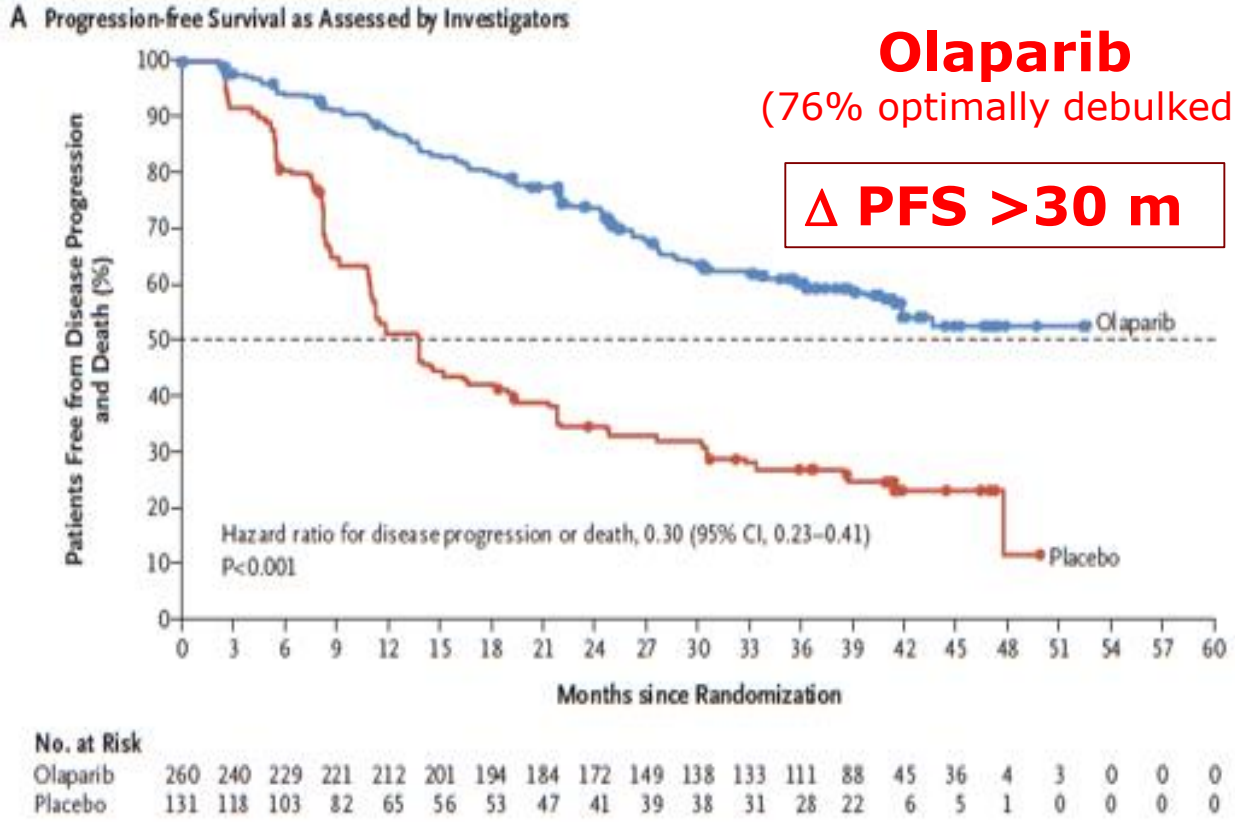
Surgery



Postoperative residual tumor

Olaparib

(76% optimally debulked)



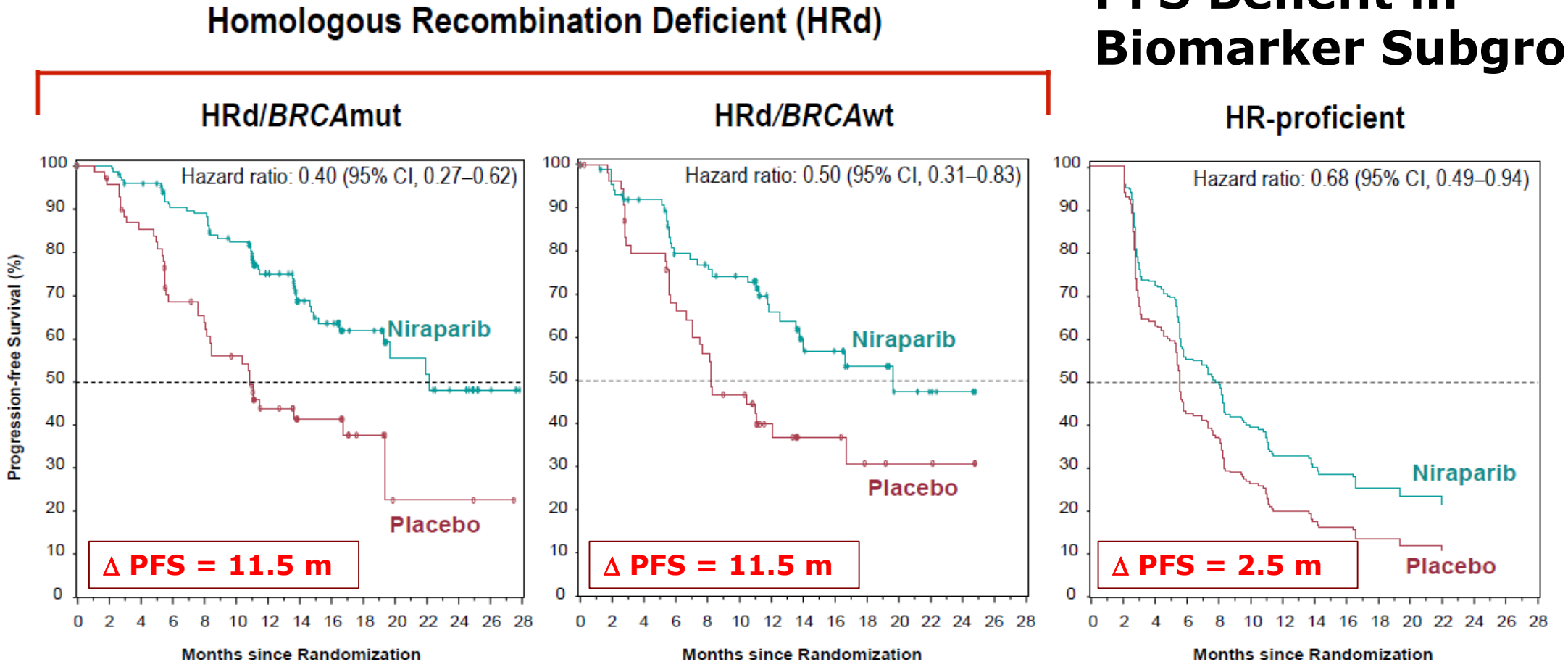
Olaparib maintenance therapy after primary therapy in BRCA^{mut}- pts. (OP + CBDCA/Paclitaxel)

du Bois A et al. Cancer. 2009 Mar 15;115(6):1234-44.
Moore K et al. N Engl J Med. 2018 Dec 27;379(26):2495-2505.

PRIMA (niraparib vs placebo – FIGO III/IV)

(HG-serous, FIGO III / optimally debulked excluded)

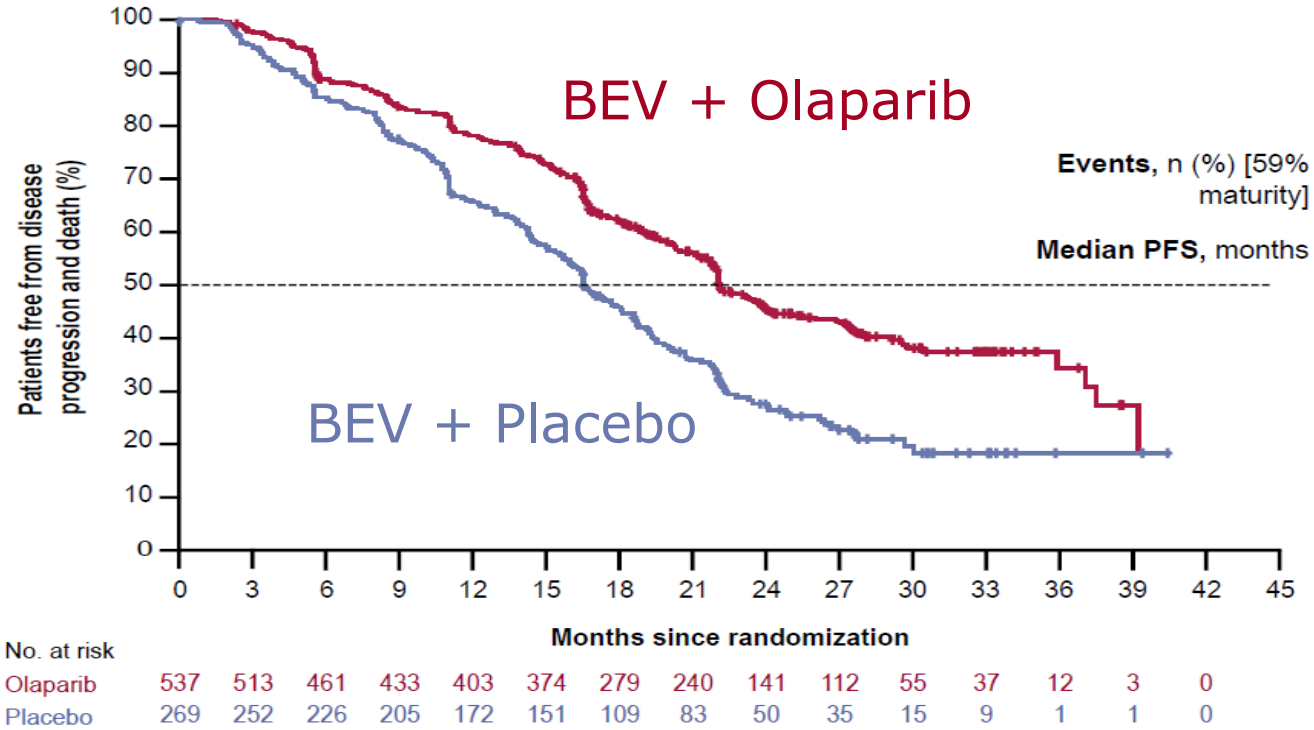
PFS Benefit in Biomarker Subgroups



González-Martín A et al. PRIMA/ENGOT-OV26/GOG-3012 Investigators. N Engl J Med. 2019 Dec 19;381(25):2391-2402. & Abstract No. LBA1 – ESMO 2019

PAOLA-1 (bevacizumab ± olaparib)
(HG-serous, FIGO III/IV, 60% optimal debulking)

PFS by investigator assessment: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	**22.1**	**16.6**

HR 0.59 (95% CI 0.49–0.72; *P*<0.0001)

Δ PFS = 5.5 m

Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intent-to-treat population

BARCELONA 2019 ESMO congress

Ray-Coquard I et al.; PAOLA-1 Investigators. N Engl J Med. 2019 Dec 19;381(25):2416-2428.

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Therapy 1L EOC – standards and perspectives

- Optimal surgery (without residual disease) plus 1L-therapy with carboplatin / paclitaxel – standard of care in EOC

- Molecular oncology provides new prospects of therapy (e.g. VEGF-inhibition, PARP-inhibition)
  - Inhibition of angiogenesis prolongs DFS (Bevacizumab)
  - Inhibition of PARP in HRD/BRCA^{mut} prolongs PFS (HG-EOC)
    - Patients with EOC should undergo genetic counseling and analysis (probability of BRCA1/2-mutation: up to 20%!)
      - Higher frequencies (-40%) with high-grade, family history, younger age
    - PARP-inhibitors - a substantial benefit in HRD/BRCA^{mut} patients

Paradiso AV et al. BMC Cancer 2019;19:641
Fumagalli C et al. Cancers (Basel) 2019;11:1641

- Ovarian Cancer (EOC) – Second-line

Recurrent ovarian cancer

First question: Platinum sensitive or not?

- Platinum-sensitive (≥6 months therapy-free)
  - consider re-operation
  - re-challenge platinum-combinations (e.g. carboplatin-PEG-liposomal doxorubicin)
  - consider bevacizumab-containing regimen
  - consider PARP-inhibitors (independent from BRCA^{mut})
- Platinum-resistant (<6 months therapy-free)
  - topotecan
  - consider molecular tumorboard (NGS-analysis)
- Platinum resistant and low grade
  - Consider re-operation and chemotherapy. With low-grade disease consider maintenance with endocrine therapy (e.g. aromatase inhibitors)

Platin-combinations in platinum-sensitive recurrences of ovarian cancer

- Re-challenge regimen with similar efficacy
  - Carboplatin – paclitaxel*
  - Carboplatin – gemcitabine*
  - Carboplatin – pegylated doxorubicin

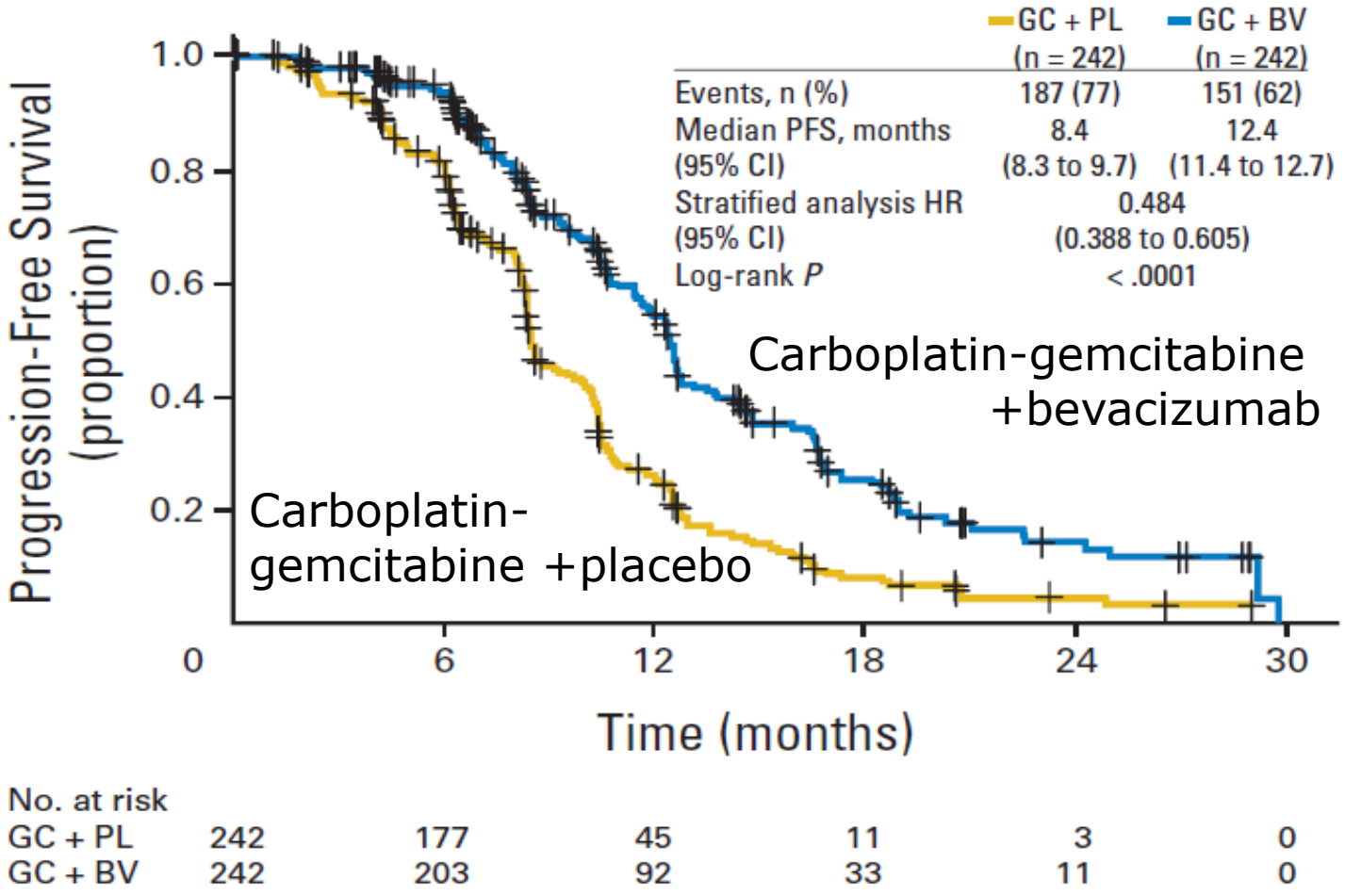
Limitation neurotoxicity

Positive data with bevacizumab-maintenance

Preference for slightly improved efficacy

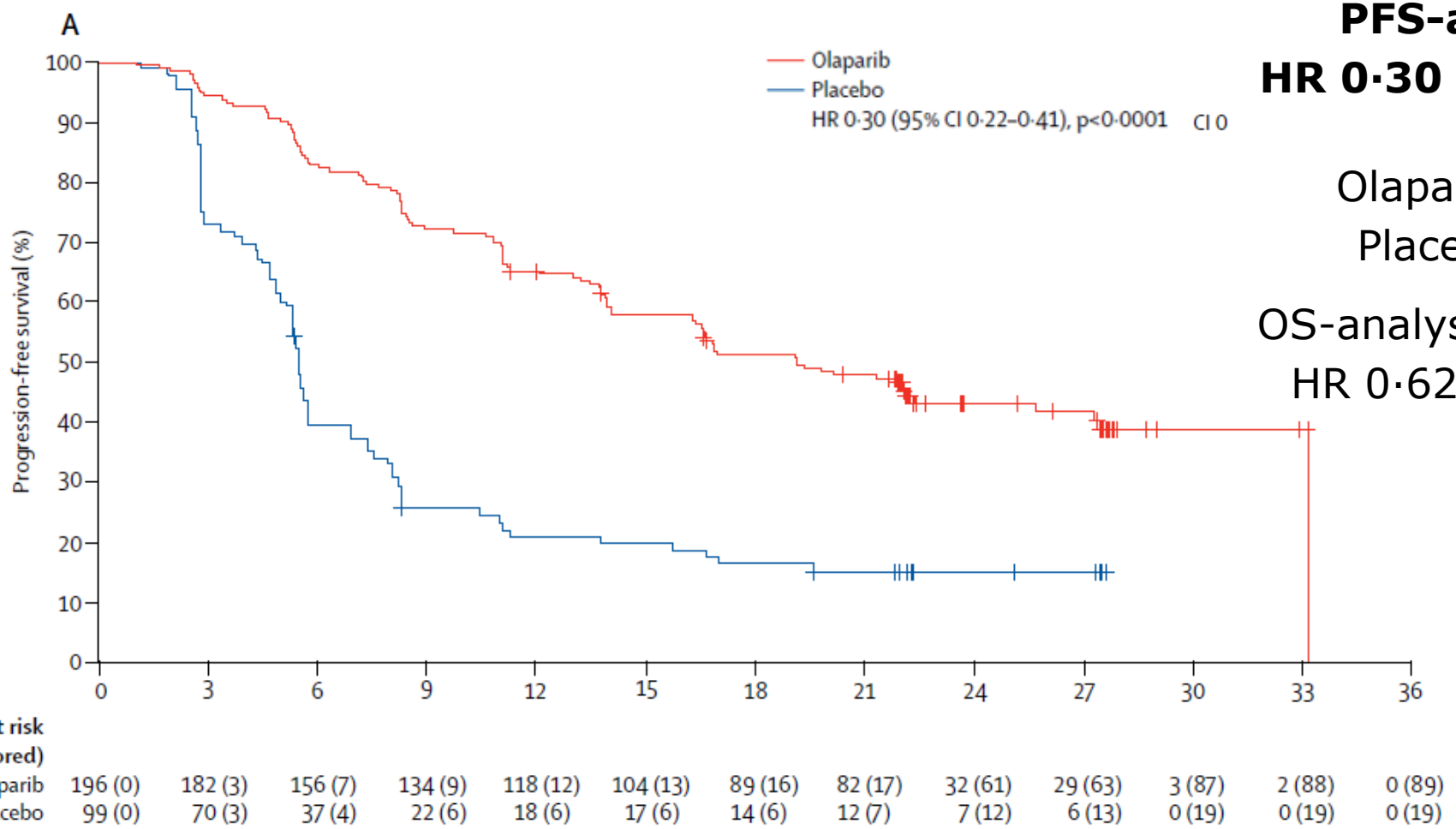
*analyzed also in combination with bevacizumab (antiVEGF-MoAb), if not given during 1L-therapy

OCEANS-trial: Bevacizumab-maintenance after carboplatin-gemcitabine



- Role of PARP-inhibitors in therapy of relapse of HG-EOC *(high grade serous ovarian cancer)*

Olaparib maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation **(SOLO2/ENGOT-Ov21 – Phase 3)**



PFS-analysis (SOLO2)

HR 0·30 (95% CI 0·22–0·41)

p<0·0001

Olaparib PFS_{median} 19.1m

Placebo PFS_{median} 5.5m

OS-analysis (Study 19–Phase 2)

HR 0·62 (95% CI 0·41–0·94)

Pujade-Lauraine E et al. Lancet Oncol 2017; 18: 1274–84 (SOLO2 - Phase 3)
Ledermann JA et al. Lancet Oncol 2016; 17: 1579–89 – (Study19 - Phase 3)

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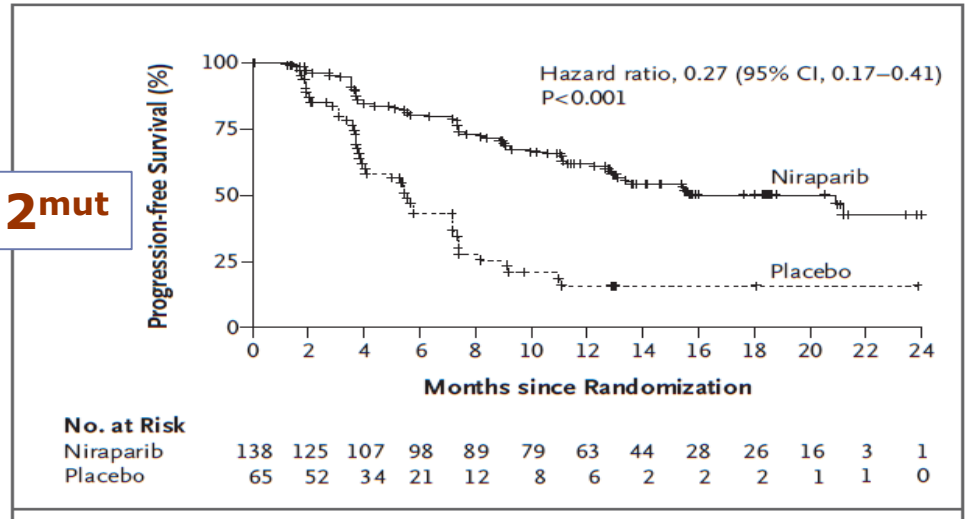
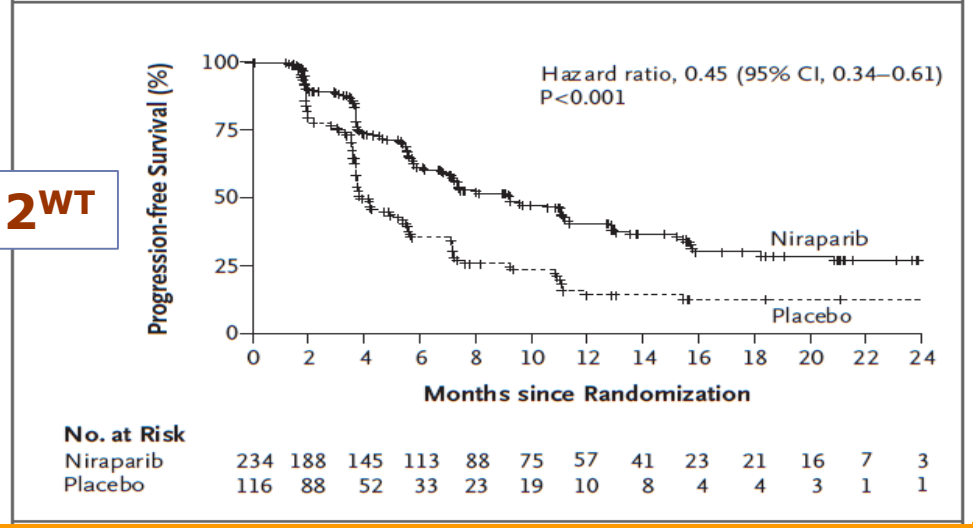
PARP-inhibition (niraparib) only with BRCA^{mut}?

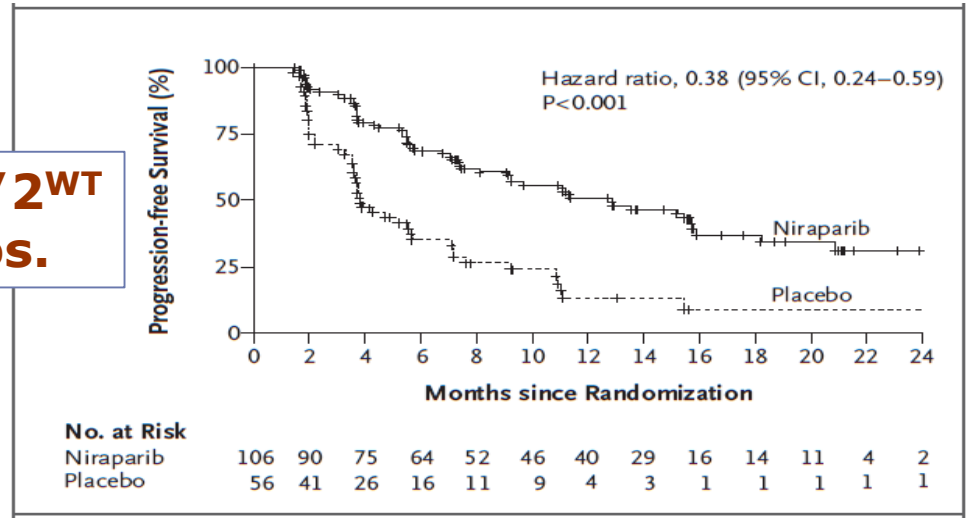
BRCA1/2^{mut}



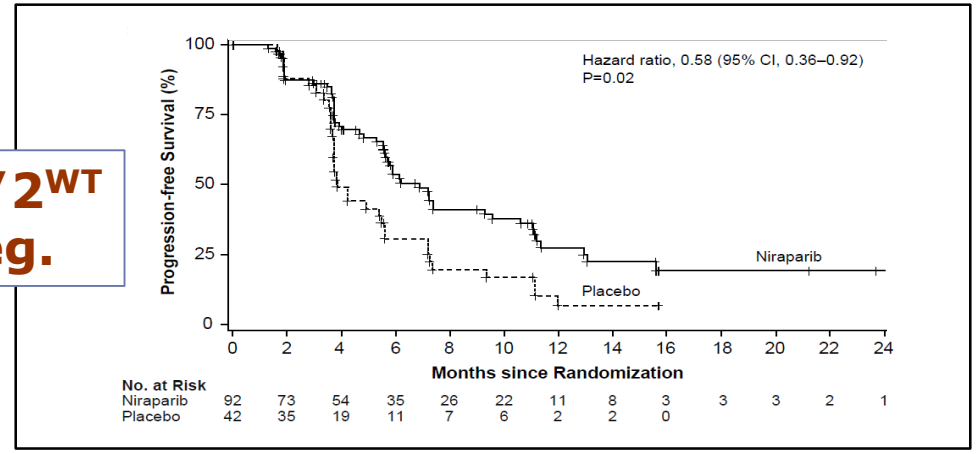
BRCA1/2^{WT}



BRCA1/2^{WT} HRD-pos.



BRCA1/2^{WT} HRD-neg.



Mirza MR et al. N Engl J Med. 2016 Dec 1;375(22):2154-2164.

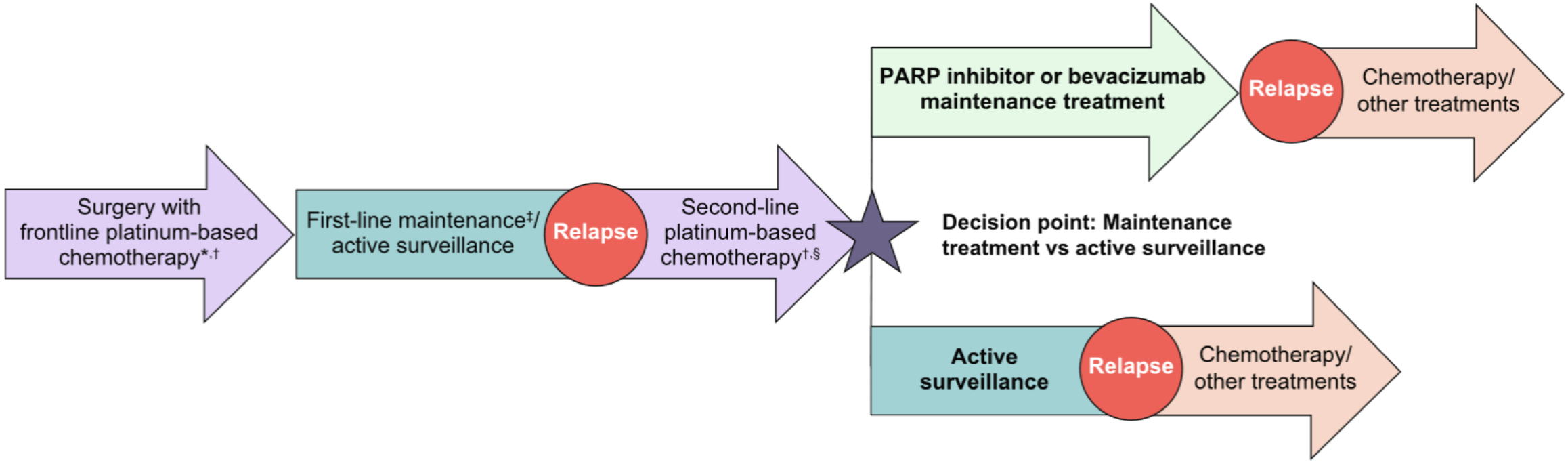
Treatment of **platinum-sensitive** recurrent ovarian cancer

- Re-challenge with a carboplatin-containing combination *(preference carboplatin-pegyl. doxorubicin)*
  - if not done before, add bevacizumab-maintenance (effect: HR= 0.48)

- Targeted option:

  PARP-inhibitors (niraparib, olaparib) should be given as maintenance therapy until disease progression (effect: HR=0,27$^{\text{BRCAmut}}$–HR=0.058$^{\text{BRCAwt-HRDneg}}$)
  - combination with bevacizumab (unknown)

Treatment sequence in Ovarian Cancer



Ray-Coquard I et al. Cancer Treat Rev. 2020 Nov;90:102107.

Platinum-resistant recurrence of ovarian cancer (<6 months therapy-free)

Chemotherapy (combination not better than single agent)

- Pegyliertes liposomales Doxorubicin (±Bevacizumab)
- Topotecan (±Bevacizumab)
- Gemcitabin
- Paclitaxel wöchentlich (±Bevacizumab)

Particularly in low-grade ovarian cancer (LGSC)

- Endocrine therapy (aromatase inhibitors; >70% stable disease, 7-11m PFS)

Molecular tumor board (Next Generation Sequencing)

- e.g. KRAS, BRAF etc. (MEK-inhibitors)

- Endometrial Cancer

Endometrial cancer

- Differentiate endometrial cancer types
  - Type 1 (low-grade, endocrine sensitive)
  - Type 2 (high grade, ER-negative)
- 1L-therapy:
  - Type 1: no endocrine adjuvant therapy
  - Type 1/2: chemotherapy, depending on stage and histology
- 2L-therapy (metastases)
  - Type 1: MPA 200mg/d or MGA 160mg/d – high CR rate
  - Type 2: chemotherapy, immune-checkpoint inhibitors

Adjuvant/additive concepts in endometrial cancer

Regimen: Carboplatin AUC5(or 6) + paclitaxel 175mg/m² q3w*6

• Type 1 pT1a/b cN0 G1/G2	=> no chemotherapy
• Type 1 pT1a G3 cN0	=> no data
• Type 1 pT1b pN0 G3	=> chemotherapy as option
• Type 1 pT2 pN0	=> chemotherapy as option
• Type 2 any stage	=> chemotherapy as option
– Carcinosarcoma, serous EC	=> chemotherapy recommended*
• pT3 or pN1	=> chemotherapy recommended
• pT4a or M1 (no tumorrest)	=> chemotherapy recommended

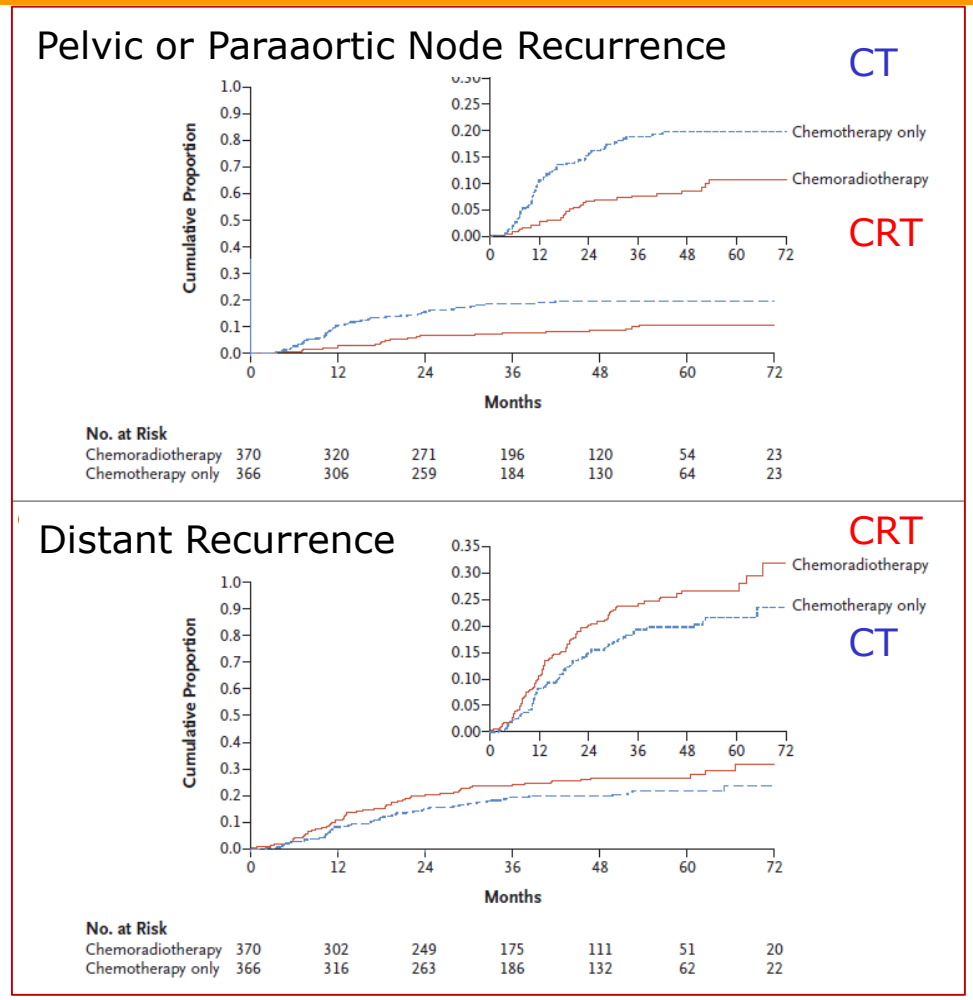
(*for carcinosarcoma alternatively: ifosfamide 1,6 g/m² d1–4 + cisplatin 20 mg/m² d1–4)

Endometrial cancer – high risk (FIGO III or G3 LVI or serous/clear cell)

GOG 258

- Chemoradiotherapy* (CRT) vs chemotherapy** (CT)

- Overall:
  - Recurrence-free survival: **Hazard ratio 0.90** (90% CI, 0.74–1.10); **p=0.20**



Median follow-up 47.0 months

* Cisplatin 50 mg/m² q4w *2 during radiotherapy followed by carboplatin AUC5 / Paclitaxel 175 mg/m² q3w *4.
Target (45 Gy): cN0 only pelvic, cN1 lower or upper aortic fields

** Carboplatin AUC6 / Paclitaxel 175 mg/m² q3w *6

Adjuvant concepts for high risk endometrial cancer
(FIGO III or G3 LVI or serous/clear cell)

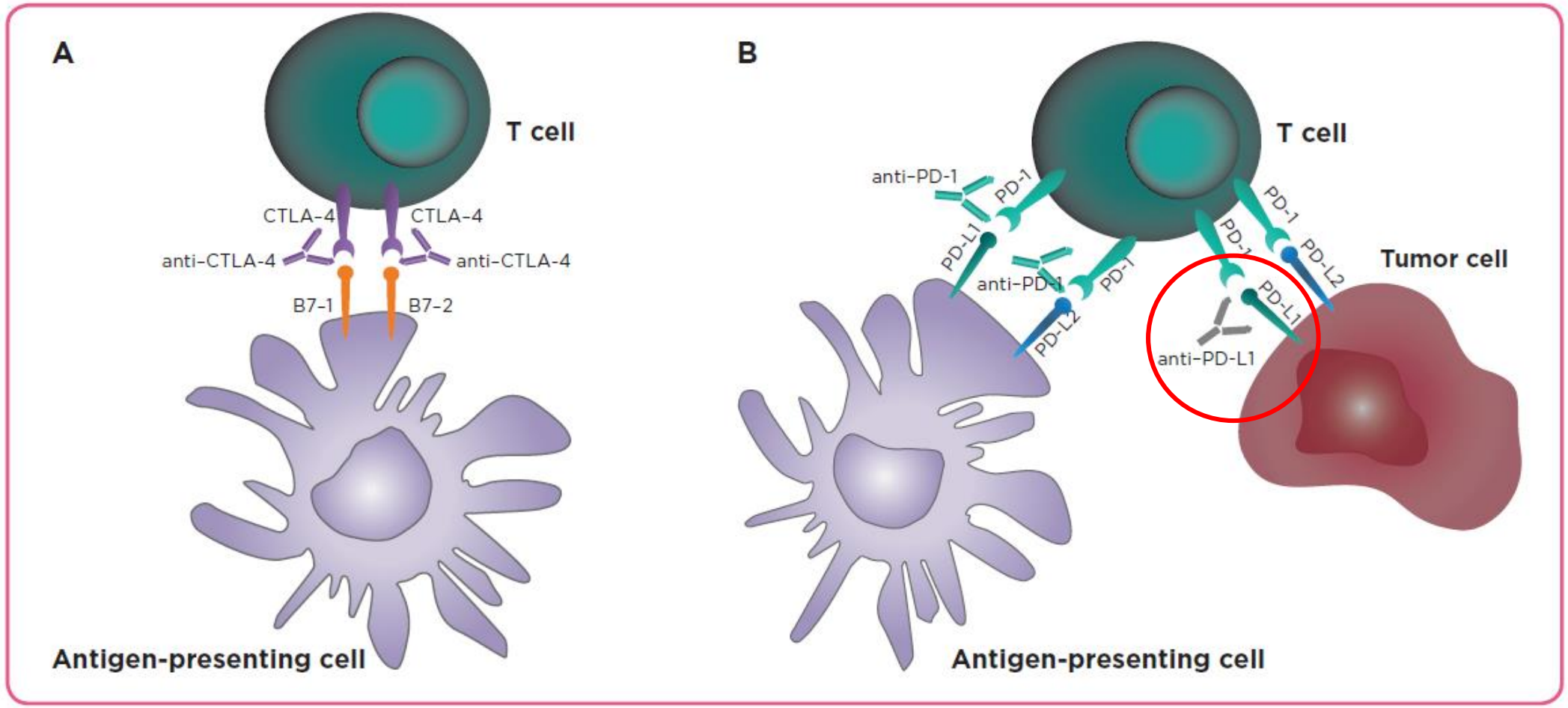
- Adjuvant chemotherapy with carboplatin/paclitaxel (*6)
  - FIGO III
  - Serous/clear cell cancer
- Vaginal brachytherapy optional (also in high risk FIGO I)
- Percutaneous radiotherapy
  - May reduce locoregional recurrences
  - May enhance rate of distant metastases
  - Can be reserved for secondary irradiation in case of particularly as pelvic and/or paraaortic recurrence

Endometrial cancer – recurrence / metastases

- Most effective chemotherapy regimen
  - **Carboplatin / paclitaxel**, also as re-challenge
  - Alternative: doxorubicin / cisplatinum
- Other options
  - G1, ER-positive: MPA 200mg/d or MGA 160mg/d
  - dMMR (mismatch-repair deficiency)
    - Pembrolizumab
    - Pembrolizumab plus Lenvatinib
  - Trastuzumab if HER2-positive (serous EC)

=> molecular analysis in recurrent diesease

Immune checkpoint-inhibitor (ICPIs)



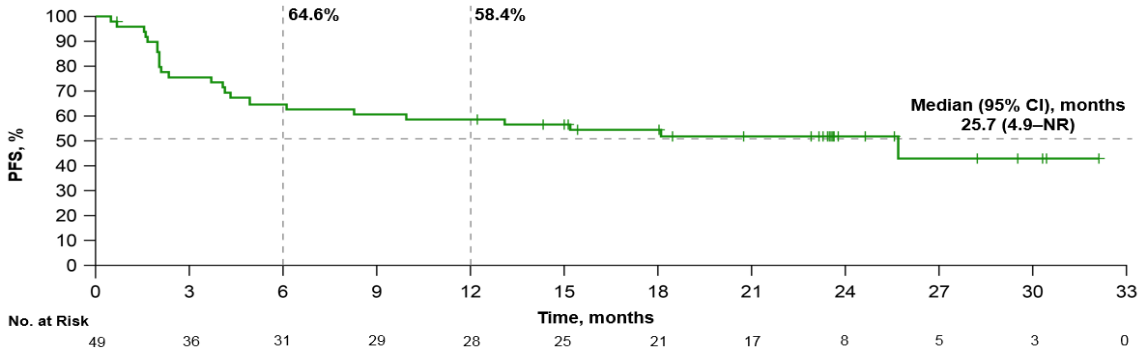
Kreamer KM et al. J Adv Pract Oncol 2014;5:418–431

Advanced endometrial cancer
KEYNOTE-158 / KEYNOTE-146

KEYNOTE-158 (Pembrolizumab 200 mg q3w for 35 cycles (approx 2 yrs) or PD, tox, withdrawal)

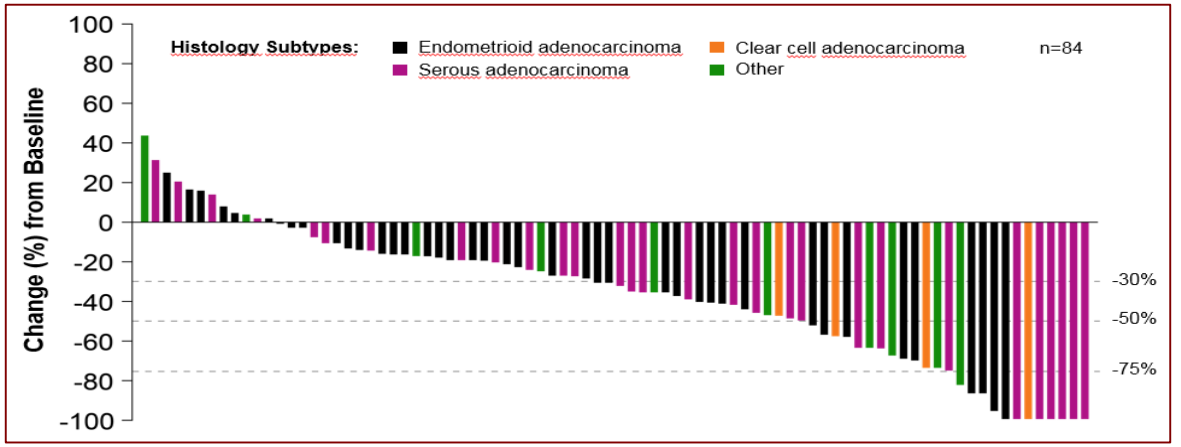
	MSI-H, N=49 (cohorts D+K)	Cohort D, N=107 (Biomarker unsel.)
ORR, % (95% CI)	57.1 (42.2–71.2)[a]	11.2 (5.9–18.8)
Best overall response, n (%)		
Complete response	8 (16.3)	0
Partial response	20 (40.8)	12 (11.2)
Stable disease	8 (16.3)	26 (24.4)
Progressive disease	11 (22.4)	56 (52.3)
Not evaluable[b]	1 (2.0)	2 (1.9)
Not assessed[c]	1 (2.0)	11 (10.3)

Progression-free survival assessed by RECIST v1.1 per central review for participants with MSI-H endometrial cancer

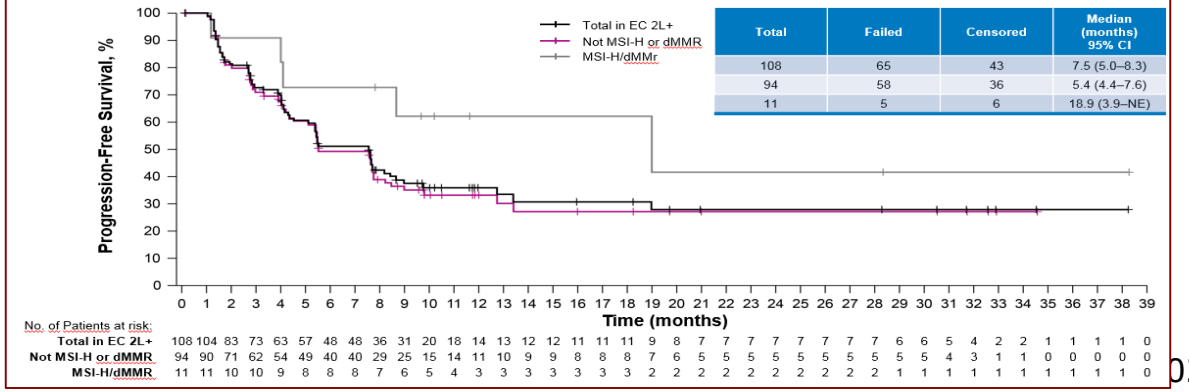


KEYNOTE-146 (Lenvatinib and Pembrolizumab)

Change in Sum of Diameters of Target Lesions at Postbaseline Nadir



Progression-Free Survival (Independent Imaging Review; RECIST v1.1)



021

O'Malley D et al. ESMO 2019, Abstract No. 1044P (mod.)
Makker V et al. ESMO 2019, Abstract No. 994O (mod.)

Lenvatinib: oral multikinase inhibitor that targets VEGFR 1–3, FGFR 1–4, PDGFRα, RET, and KIT

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- Cervical cancer

Cervical cancer

- **Radiochemotherapy** (instead of radiotherpy alone) if indication of irradiation is given (primary or adjuvant / recurrence)
  - **Cisplatinum 40 mg/m² IV q1w** during irradiation (5-7 weeks, minimum 5 applications)
  - Alternatively (e.g in kidney failure) **vinorelbine** (15mg/m² IV q1w or 40 mg/m² PO q1w) (5-7 weeks, minimum 5 applications)

Adjuvant therapy after radical surgery
in high-risk early-stage cancer of the cervix

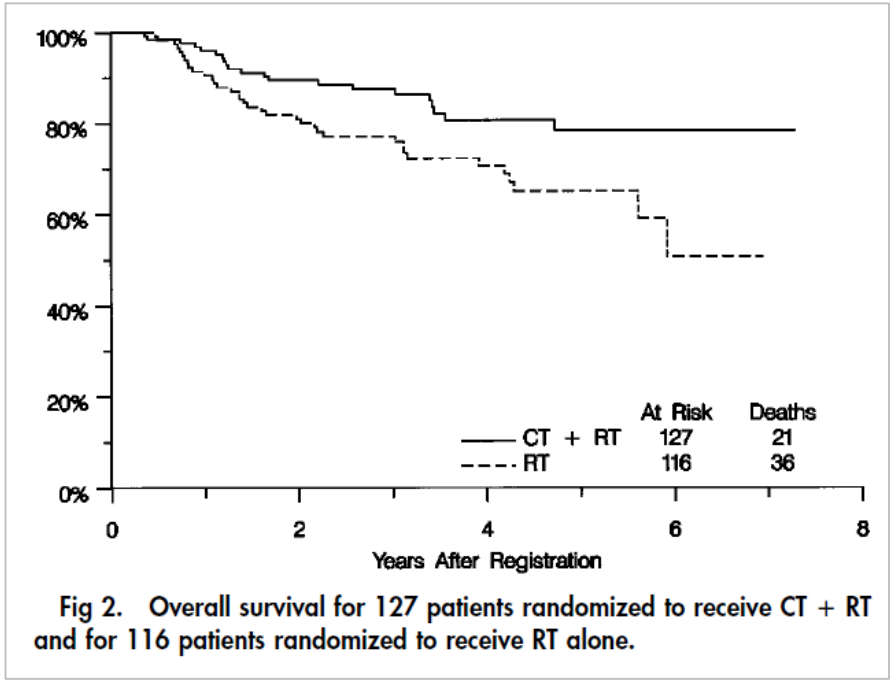


Fig 2. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

Peters WA 3rd et al. J Clin Oncol. 2000 Apr;18(8):1606-13

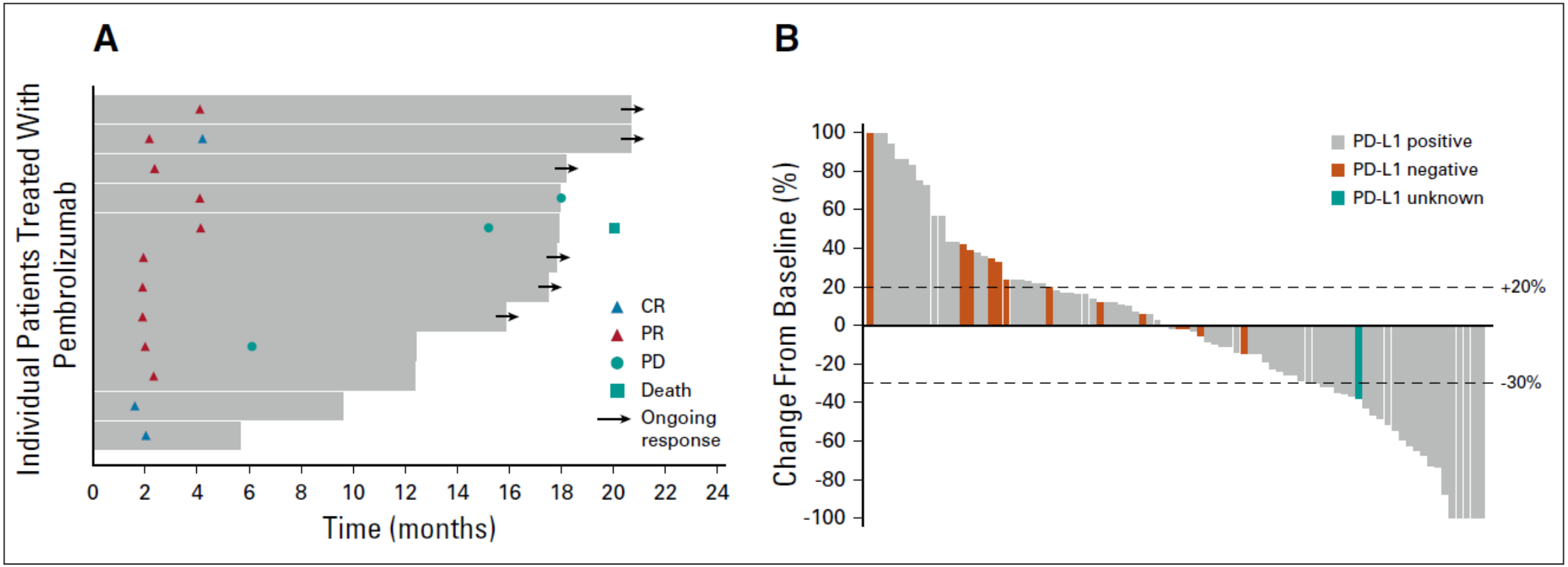
Cervical cancer advanced/metastatic

- OS-Benefit shown for
  - **CDDP / topotecan** vs CDDP alone
    - CDDP-containing regimen less effective if CDDP-pretreated
  - Adding **bevacizumab** to standard regimen (CDDP/paclitaxel, topotecan/paclitaxel, carboplatin/paclitaxel)

- NEW!
  - Immune checkpoint inhibitors (Pembrolizumab, Nivolumab)

*CDDP = cisplatinum

Antitumor activity of pembrolizumab (Keynote-158)



N=98; 3rd-line 65,3%; 82 (84%) PD-L1 pos.

Clinical Benefit (CR+PR+CSD) 33%; OS_{median} 9,4 m; duration of response >12m: 75% (9 of 12)

Chung HC et al. J Clin Oncol 2019;37:1470-1478.

Medical therapy in gynaecological cancer

- Adjuvant / first-line (incl. RCT) use provides survival benefit
  - Ovarian cancer, endometrial cancer, cervical cancer
- Early use of targeted drugs (BEV, PARPi) is effective
  - Ovarian cancer (1l and 2L)
- Combination chemotherapy effective in 2L-situations
  - Ovarian cancer, cervical cancer, endometrial cancer
- Immune-checkpoint inhibitors in 2L
  - Cervical cancer, endometrial cancer
- Individualised effective therapy in GTN
  - Curative intention