POST-ASCO MAMMACARCINOOM & GYNAECOLOGIE

GABE SONKE

Disclosures

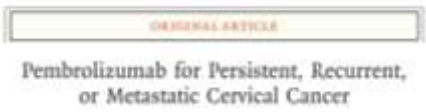
- Research funding: Agendia, AstraZeneca, Merck, Novartis, Roche
- Advisory role: Biovica, Seagen

Highlights

- Mamma
  - Trastuzumab-deruxtecan ++
  - Pembrolizumab +
  - Palbociclib -
- Cervix
  - Adjuvant chemotherapie -
  - Immuuntherapie 1e en 2e lijn +
- Endometrium
  - Pembrolizumab (+ lenvatinib) +
- Ovarium
  - PARP remming +
  - Mirvetuximab +


ORIGINAL ARTICLE

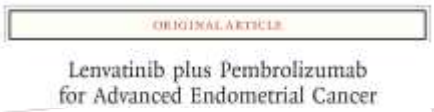
Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer


ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer


ORIGINAL ARTICLE

Survival with Cemiplimab in Recurrent Cervical Cancer


ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer

2022 ASCO ANNUAL MEETING

DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

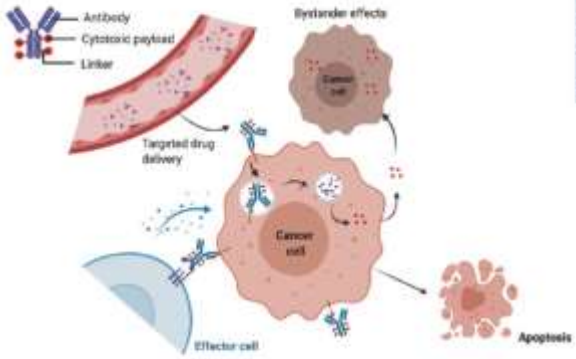
Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

June 5, 2022

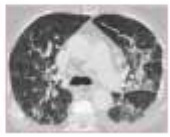
Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

Third generation ADC: bystander effect



- High potency
- **BUT** « off target » toxicities
- **Interstitial Lung Disease (ILD)**



Appropriate strategies for the management in clinical practice

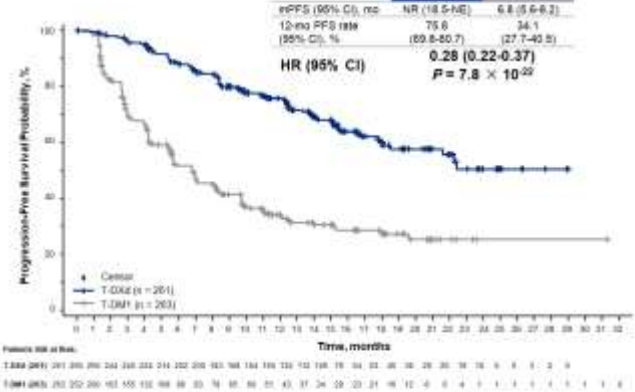
Fu Z et al. Signal transduction and Targeted therapy 2022

DESTINY-Breast03

Background

PFS by BICR[1,a]

	T-DXd	T-DM1
mPFS (95% CI), mo	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate (95% CI), %	75.6 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	



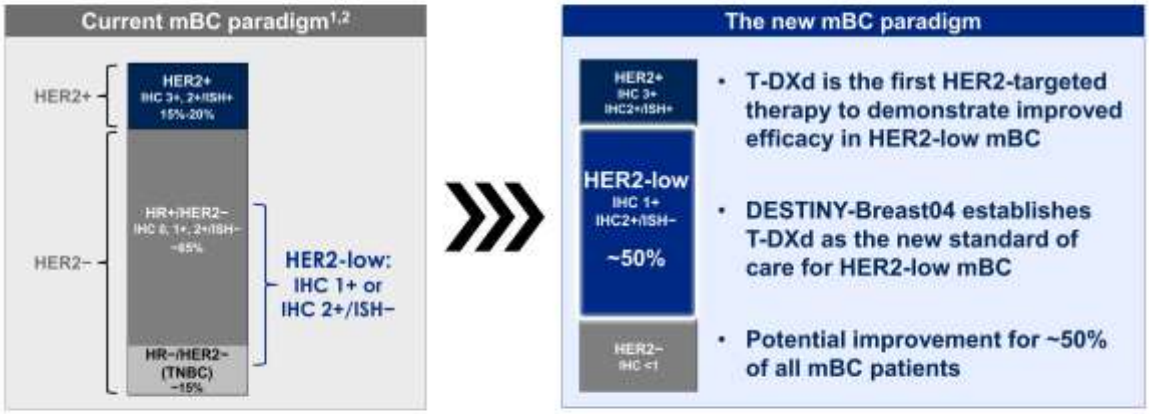
- T-DXd, a HER2-targeted ADC, was approved for the treatment of patients with HER2+ unresectable or mBC who have received a prior anti-HER2 therapy in the metastatic or neoadjuvant/adjuvant setting and had recurrence during or within 6 months after therapy[2]
- DESTINY-Breast03 (NCT03529110) investigated T-DXd vs T-DM1 in patients with HER2+ unresectable or mBC
  - In the primary analysis (May 21, 2021), T-DXd was superior to T-DM1 for PFS by BICR (primary endpoint)[1]
  - Overall health status and QoL was maintained with T-DXd and numerically favored T-DXd over T-DM1[3]

ADC, antibody-drug conjugate; BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression-free survival; PFS, progression-free survival; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. 1. Cortés J et al. *N Engl J Med* 2022;386:1143-1154. 2. Enhertu (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Daiichi Sankyo, Inc. 2022. 3. Curigliano G et al. Presented at ESMO Breast Cancer meeting; May 3-5, 2022; Berlin, Germany. Presentation 1030.

DESTINY-Breast04

DESTINY-Breast04 Summary and Impact

T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC



HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2022;38(17):1951–1962.

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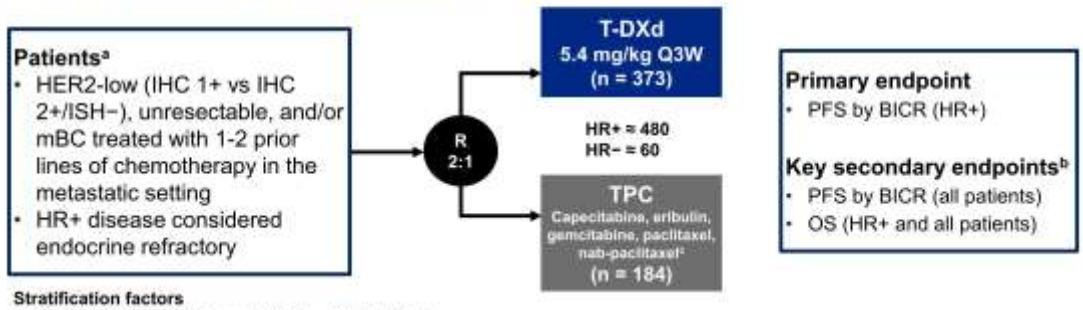
DESTINY-Breast04

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]All patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

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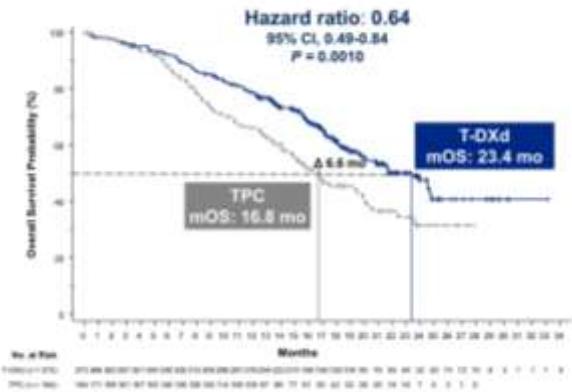
DESTINY-Breast04

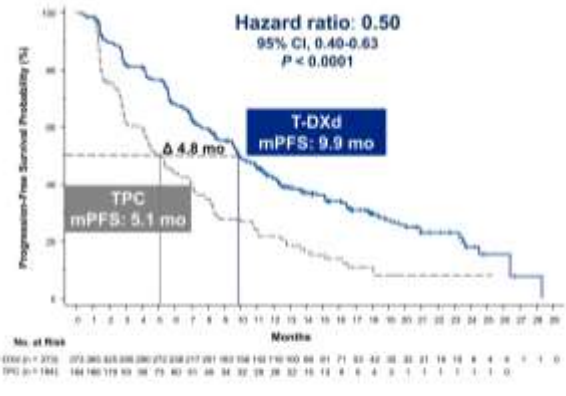
Prior Therapies

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

OS



PFS

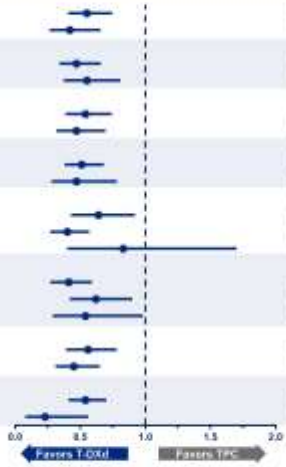


PFS by blinded independent central review.

DESTINY-Breast04

Subgroup Analysis: PFS in HR+

	No. of Events/No. of Patients T-DXd	TPC	PFS, median (95% CI), mo T-DXd	TPC	Hazard Ratio for Disease Progression or Death (95% CI)
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/18	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.29-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-8.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)

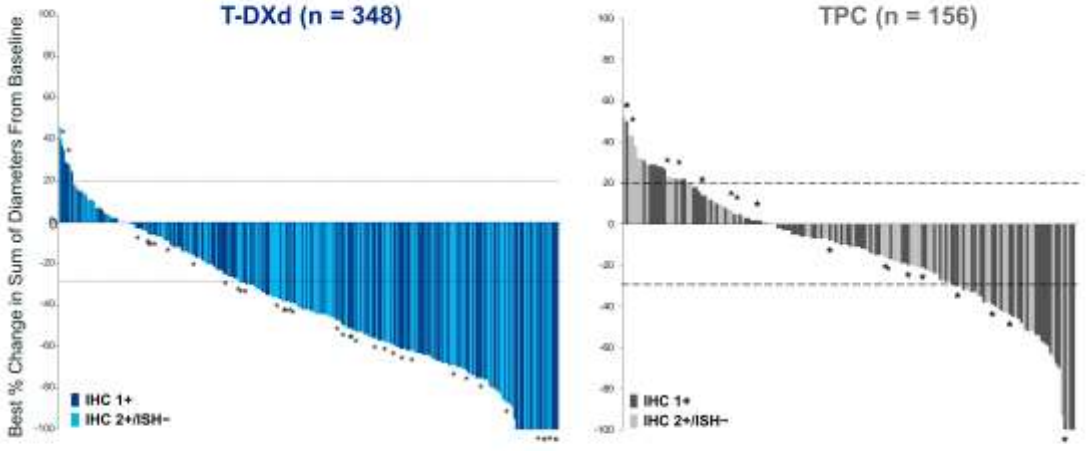


PFS by blinded independent central review. Based on derived data, which include protocol deviations.

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

DESTINY-Breast04

Best Change in Target Lesions (All Patients)



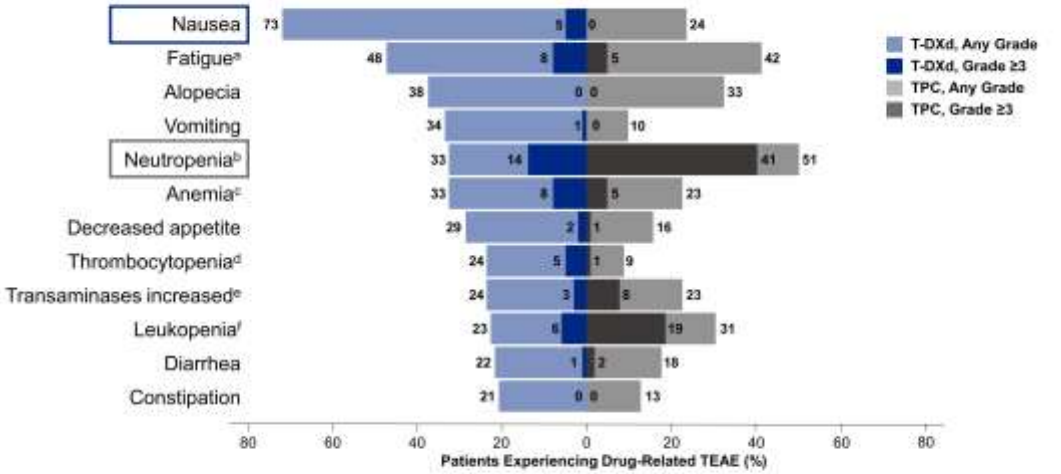
*Patients with HR− disease

Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).

HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

DESTINY-Breast04

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white cell count decreased and leukopenia.

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DESTINY-Breast04

Overall Safety Summary

n (%)	Safety analysis set[a] T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug, irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

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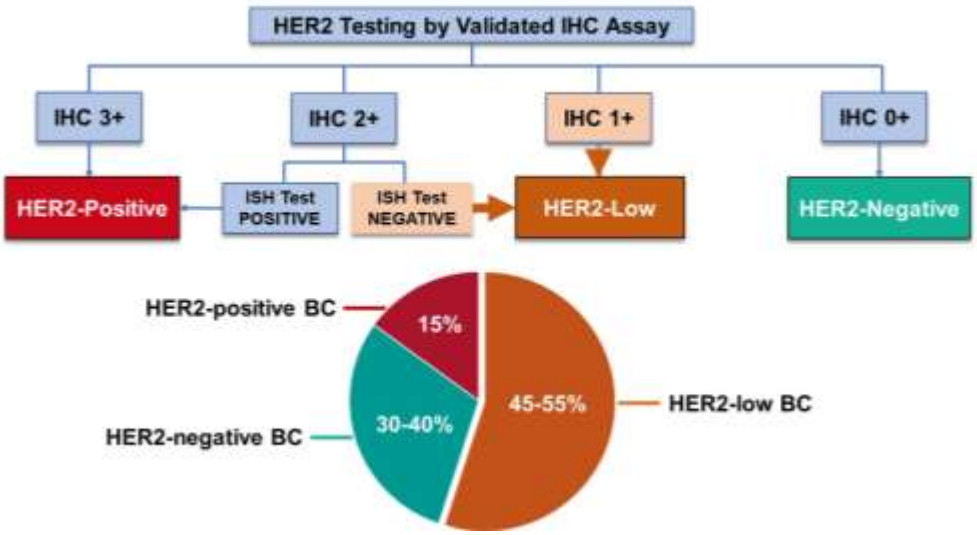
Trastuzumab-deruxtecan

Conclusies

- Zeer effectieve antibody drug conjugate
- Eerder al bij HER2+ mammacarcinoom
- Nu ook bij HER2-low mammacarcinoom belangrijke behandeloptie

- Bystander effect zorgt ook voor toxiciteit
  - doelgerichte chemotherapie = chemotherapie
- Resistentie mechanismen nog weinig bekend
- Nieuwe indicaties gaan ongetwijfeld volgen
- Kosten!

Gevolg voor pathologen



CDK 4/6 remmers in 1e lijn gemetastaseerd ER+ BC

	Median PFS Placebo	Median PFS CDK4/6i	HR (p value)
First line + AI:			
PALOMA-2 (Palbociclib)	14.5 mos	24.8 mos	0.58 (p<.001)
MONALEESA-2 (Ribociclib)	16 mos	25.3 mos	0.57 (p<.001)
MONARCH-3 (Abemaciclib)	14.8 mos	28.2 mos	0.54 (p<.001)

Overall Survival (OS) With First-Line Palbociclib Plus Letrozole (PAL+LET) Versus Placebo Plus Letrozole (PBO+LET) in Women With Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer (ER+/HER2− ABC): Analyses From PALOMA-2

Richard S. Finn,[1] Hope S. Rugo,[2] Veronique Diéras,[3] Nadia Harbeck,[4] Seock-Ah Im,[5] Karen A. Gelmon,[6] Janice M. Walshe,[7] Miguel Martin,[8] Mariana Chavez-MacGregor,[9] Eustratios Bananis,[10] Eric Gauthier,[11] Dongrui R. Lu,[12] Sindy Kim,[12] Dennis J. Slamon[1]

[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; [2]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [3]Centre Eugène Marquis, Rennes Cedex, France; [4]Brustzentrum, Frauenklinik and CCC Munich, LMU University Hospital, Munich, Germany; [5]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [6]BC Cancer, Vancouver, BC, Canada; [7]St. Vincent's University Hospital, Dublin, Cancer Trials, Ireland; [8]Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, CIBERONC, GEICAM, Madrid, Spain; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]Pfizer Inc, New York, NY, USA; [11]Pfizer Inc, San Francisco, CA, USA; [12]Pfizer Inc, San Diego, CA, USA

Presented at the 2022 ASCO Annual Meeting

PALOMA-2 Study Design

ELIGIBILITY CRITERIA
- Postmenopausal women with ER+/HER2− ABC
- No prior treatment for advanced disease
- ECOG PS 0–2

2:1 RANDOMIZATION N=666

Palbociclib 125 mg/day
3 weeks on, 1 week off
+
Letrozole 2.5 mg/day
(N=444)

Placebo 125 mg/day
3 weeks on, 1 week off
+
Letrozole 2.5 mg/day
(N=222)

Primary endpoint
Investigator-assessed PFS

Secondary endpoints
OS, Response, Safety, Biomarkers, PRO

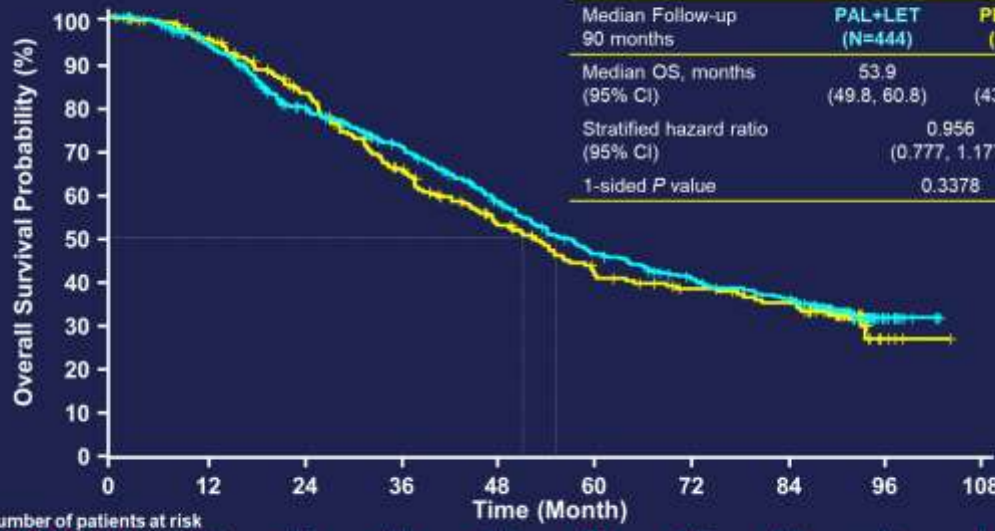
Stratification factors
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic, ≤12 mo, >12 mo)
- Prior neo/adjuvant hormonal therapy (yes, no)

Statistical Assumptions for PFS as Primary Endpoint:
- Sample size determined to detect ~44% improvement in median PFS from 9 months for the control arm to 13 months for the palbociclib arm
- Assuming a true hazard ratio of 0.69 in favor of the palbociclib arm (90% power with 1-sided α=0.025)

Statistical Assumptions for OS as Secondary Endpoint:
- Assumption for the control arm median OS of 34 to 46 months (~35% improvement)
- 390 events required to detect a hazard ratio of 0.74 or less (80% power with 1-sided α=0.025)

ABC=advanced breast cancer; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome.

Overall Survival – ITT



Median Follow-up 90 months	PAL+LET (N=444)	PBO+LET (N=222)
Median OS, months (95% CI)	53.9 (49.8, 60.8)	51.2 (43.7, 58.9)
Stratified hazard ratio (95% CI)	0.956 (0.777, 1.177)	
1-sided *P* value	0.3378	

ITT=intent-to-treat; LET=letrozole; OS=overall survival; PAL=palbociclib; PBO=placebo.

Why are there OS differences between the studies?

Randomized P3 Trials	PALOMA-2 Palbociclib	MONALEESA-2 Ribociclib	MONALEESA-7 Ribociclib	MONALEESA-3 Ribociclib 1L Cohort
De novo mBC	38%	34%	41%	20%
Disease-free interval				
DFI < 12 mos	22%	1%	7%	0%
DFI > 12 mos	40%	NR	53%	80%
DFI > 24 mos	NR	60%	NR	NR

- DFI ≤ 12 mos in Paloma 1 ~ 35%
- Combined OS analysis with PALOMA-1 planned
- Analysis by DFI subgroup unplanned

No substantial differences in prior therapy, visceral disease, use of subsequent CDK4/6i in placebo arm, other variables

Limitations:
- Post hoc analyses
- Definition of "missing survival data"

Finn et al NEJM 2016; Hortobagyi et al. NEJM 2016; Tripathy et al Lancet Oncol 2018; Slamon et al. NEJM 2020

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: Claudine Isaacs, MD, FRCPC

CDK4/6 remmers

- 1e lijn
  - OS voordeel voor ribociclib; niet voor palbociclib; onbekend abemaciclib
- 2e lijn
  - OS voordeel voor ribociclib en abemaciclib; niet voor palbociclib
- Adjuvant
  - DFS voordeel voor abemaciclib, niet voor palbociclib, onbekend ribociclib
- Hebben de drie middelen toch andere effectiviteit?
- Of komt het door verschil in studie populaties (bv TFI)?

OPTIMAL CANCER CARE ALLIANCE
Optimal Dosage. Best Outcome.

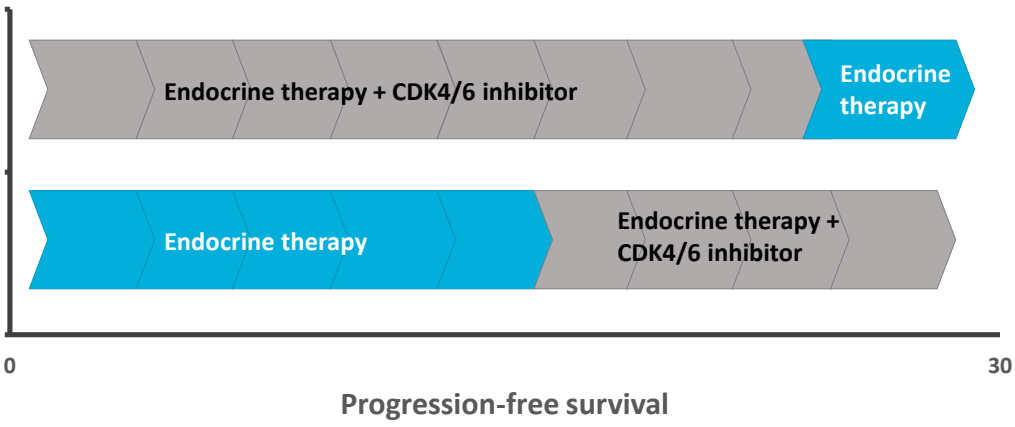
SONIA study

optimal use of CDK4/6 inhibitors in advanced breast cancer

iMTA · Amsterdam UMC · Erasmus MC · ZonMw · Netherlands Cancer Institute · BOOG · KNL · borstkankervereniging nederland · ZN

OPTIMAL CANCER CARE ALLIANCE
Optimal Dosage. Best Outcome.

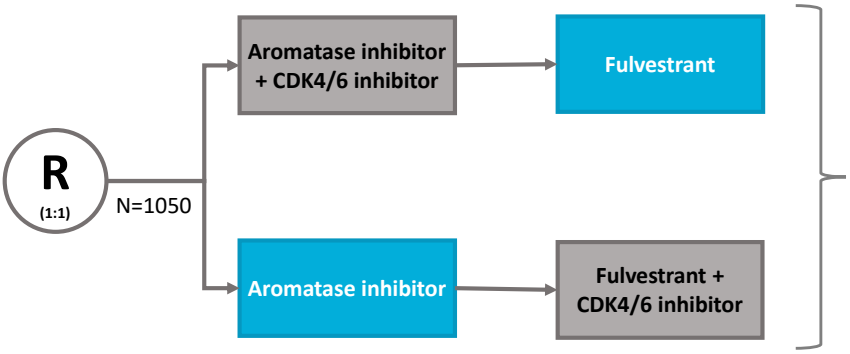
CDK4/6 inhibition as treatment in advanced breast cancer



Based on Paloma, Monaleesa and Monarch studies

OPTIMAL CANCER CARE ALLIANCE
Optimal Dosage. Best Outcome.

SONIA study design



Primary endpoint
- Progression-free survival after 2 lines (PFS2)

Secondary endpoints
- Quality of life
- Overall survival
- Cost-effectiveness

NCT03425838
BMC Cancer. 2018 Nov 20;18(1):1146

CDK4/6 remmers

- 1e lijn
  - OS voordeel voor ribociclib; niet voor palbociclib; onbekend abemaciclib
- 2e lijn
  - OS voordeel voor ribociclib en abemaciclib; niet voor palbociclib
- Adjuvant
  - DFS voordeel voor abemaciclib, niet voor palbociclib, onbekend ribociclib
- Hebben de drie middelen toch andere effectiviteit?
- Of komt het door verschil in studie populaties (bv TFI)?

2022 ASCO ANNUAL MEETING

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn L Hershman

Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1

N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

Primary Endpoint

- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

2022 ASCO ANNUAL MEETING #ASCO22
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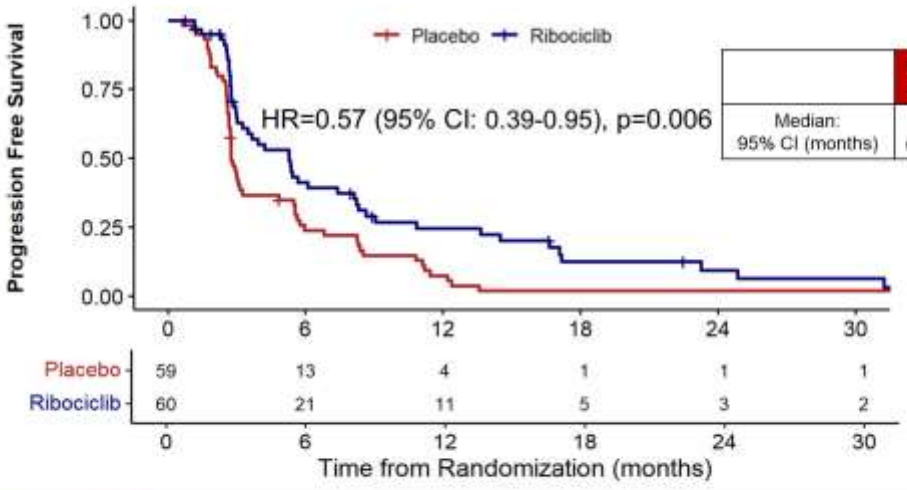
ASCO KNOWLEDGE CONQUERS CANCER

Primary Endpoint: Progression Free Survival (PFS)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	2.76 (2.66-3.25)	5.29 (3.02-8.12)

Conclusion

- **First randomized trial to show the benefit of ribociclib and switching ET after CDK 4/6 inhibitor progression**
  - Ribociclib + ET led to a statistically significant improvement in PFS compared to placebo + ET in pts with tumor progression following prior CDK 4/6 inhibitor
  - Palbociclib was the prior CDK4/6 inhibitor in 87% of pts
  - 43% risk reduction of progression or death with ribociclib vs. placebo in ITT population
  - Higher PFS rate at 6 months and 12 months, as well as improved clinical benefit rate, with ribociclib vs. placebo
  - Ribociclib + ET demonstrated a manageable safety profile

Optimale sequentie van CDK4/6 remmers

- 1e of 2e lijn volgt uit SONIA studie (verwacht volgend jaar)

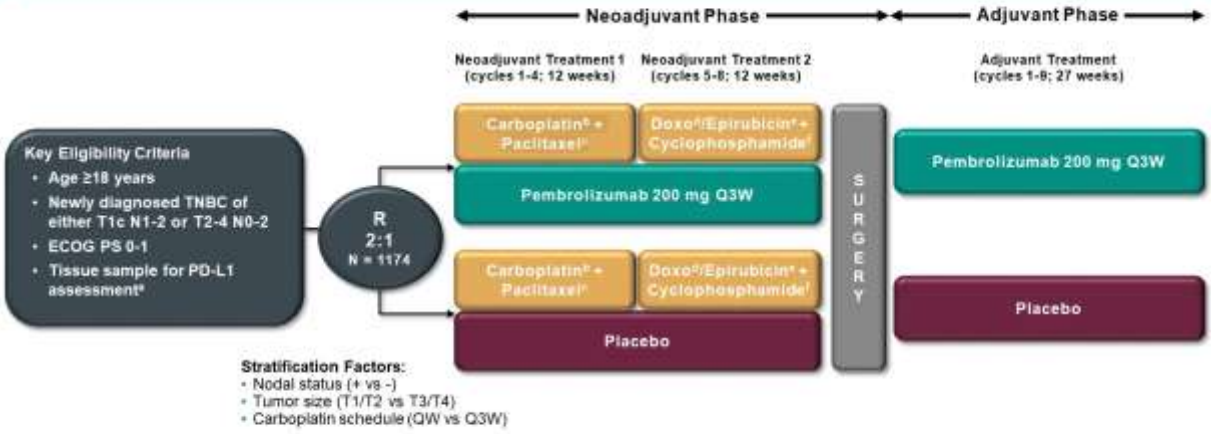
- Treatment beyond progression?
  - Maintain studie is hypothese genererend
  - Andere studies lopen, bv head tot head comparisons (Harmonia studie)

Event-free Survival by Residual Cancer Burden After Neoadjuvant Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy for Early-Stage TNBC: Exploratory Analysis From KEYNOTE-522

Lajos Pusztai[1], Carsten Denkert[2], Joyce O'Shaughnessy[3], Javier Cortes[4], Rebecca Dent[5], Heather McArthur[6], Sherko Kümmel[7], Jonas Bergh[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Michael Untch[13], Peter A. Fasching[14], Fatima Cardoso[15], Yalin Zhu[16], Wilbur Pan[16], Konstantinos Tryfonidis[16], Peter Schmid[17]

1. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 2. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany; 3. Baylor University Medical Center, Texas Oncology, US Oncology Network, Dallas, TX, USA; 4. International Breast Cancer Center, Quironsalud Group, Barcelona, Spain and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; 5. National Cancer Center Singapore, Duke – National University of Singapore Medical School, Singapore; 6. University of Texas Southwestern Medical Center, Dallas, TX, USA; 7. Breast Unit, Kliniken Essen-Mitte, Essen, Germany and Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany; 8. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer Theme, Karolinska University Hospital, Karolinska Comprehensive Cancer Center, Solna, Sweden; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, LMU University Hospital, Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; 14. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 15. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 16. Oncology, Merck & Co., Inc., Rahway, NJ, USA; 17. Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK

KEYNOTE-522 Study Design (NCT03036488)



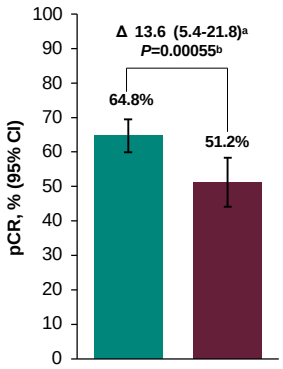
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

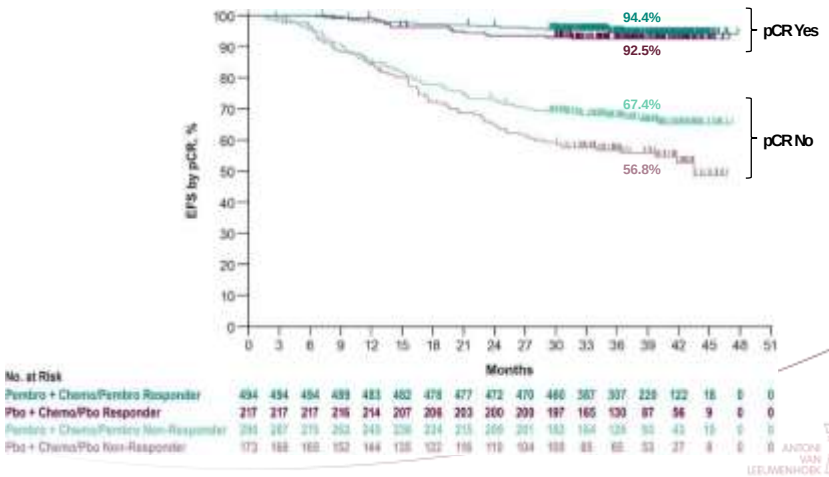
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m² QW. [d]Doxorubicin dose was 60 mg/m² Q3W. [e]Epirubicin dose was 90 mg/m² Q3W. [f]Cyclophosphamide dose was 600 mg/m² Q3W.

Eerdere resultaten uit KEYNOTE-522

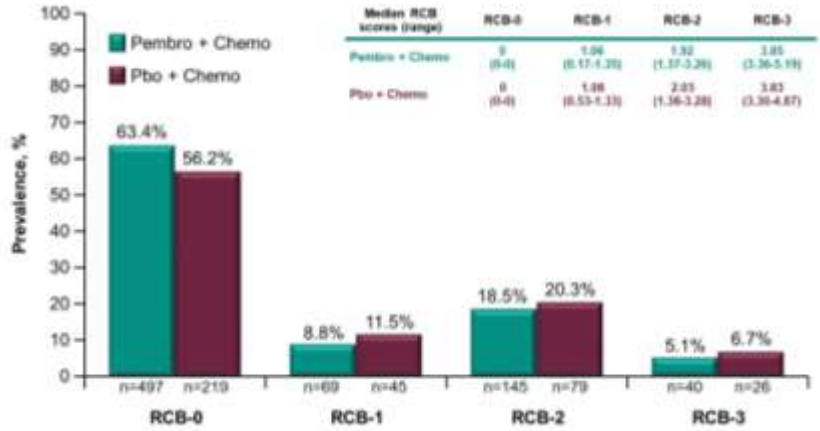
Pembro + Chemo (N = 401)
Pbo + Chemo (N = 201)



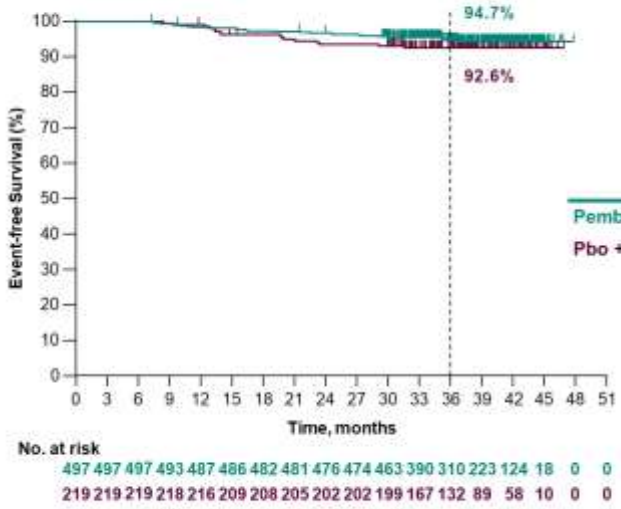


Residual cancer burden

- Semi kwantitatieve maat voor de hoeveelheid restziekte die over is op schaal 0-3



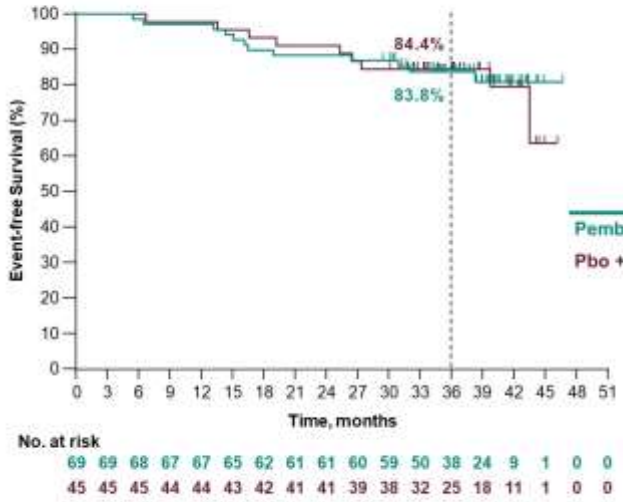
EFS in RCB-0



	n/N	Events	HR (95% CI)
Pembro + Chemo	26/497	5.2%	0.70[a] (0.38-1.31)
Pbo + Chemo	16/219	7.3%	

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

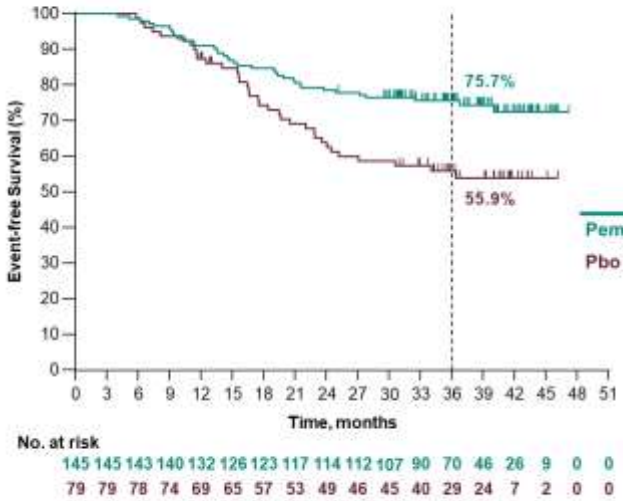
EFS in RCB-1



	n/N	Events	HR (95% CI)
Pembro + Chemo	12/69	17.4%	0.92[a] (0.39-2.20)
Pbo + Chemo	9/45	20.0%	

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

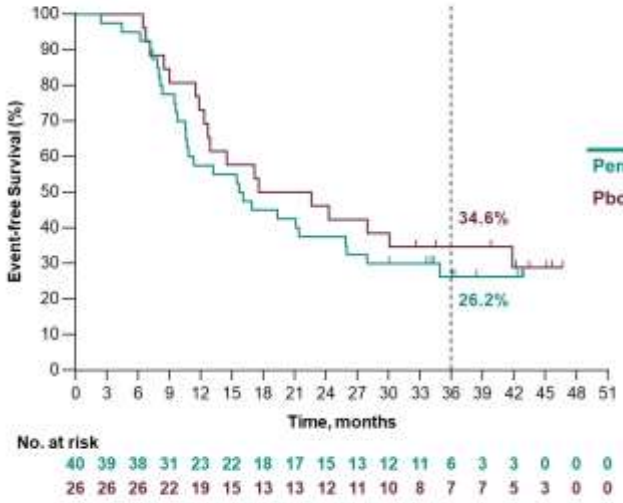
EFS in RCB-2



	n/N	Events	HR (95% CI)
Pembro + Chemo	37/145	25.5%	0.52[a] (0.32-0.82)
Pbo + Chemo	35/79	44.3%	

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

EFS in RCB-3



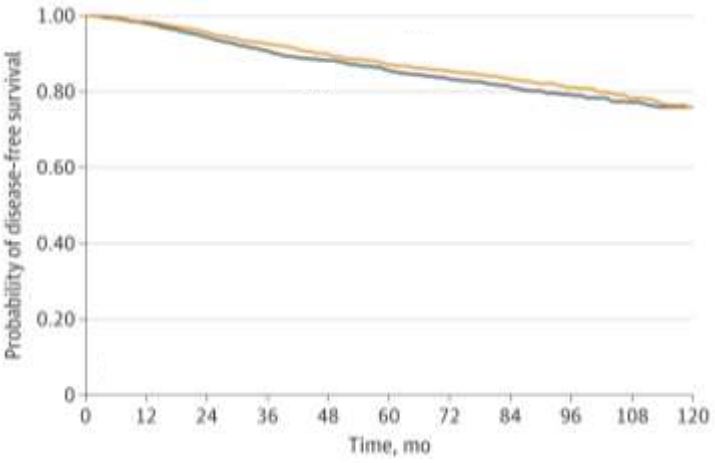
	n/N	Events	HR (95% CI)
Pembro + Chemo	29/40	72.5%	1.24[a] (0.69-2.23)
Pbo + Chemo	18/26	69.2%	

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

Pembrolizumab neo-adjuvant triple negatief

- Verbetert response (meer pCR)
- Als er goede response is dan voegt pembrolizumab niets toe
- Zeer onzeker of 12 maanden behandeling nodig is

VB: trastuzumab 6 vs 12 maanden adjuvant



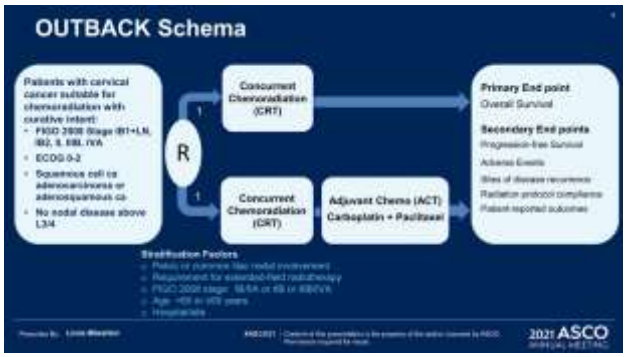
HR = 0,91 (0,81 – 1,01)

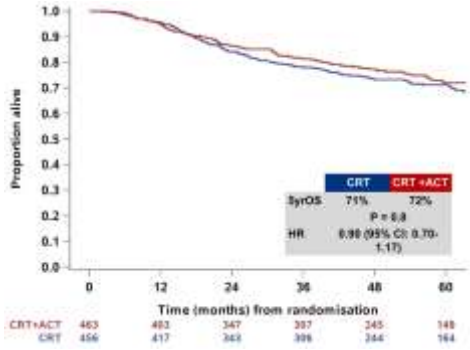
Cervixcarcinoom

Conclusies

- Geen indicatie adjuvant chemotherapie
  - neo-adjuvante studies lopen wel (ook met oog op fertiliteit)
- Anti-PD-(L)1 actief bij M+ in 1e en 2e lijn bij PD-L1+
  - EMA registratie, CieBOM en vergoeding volgen

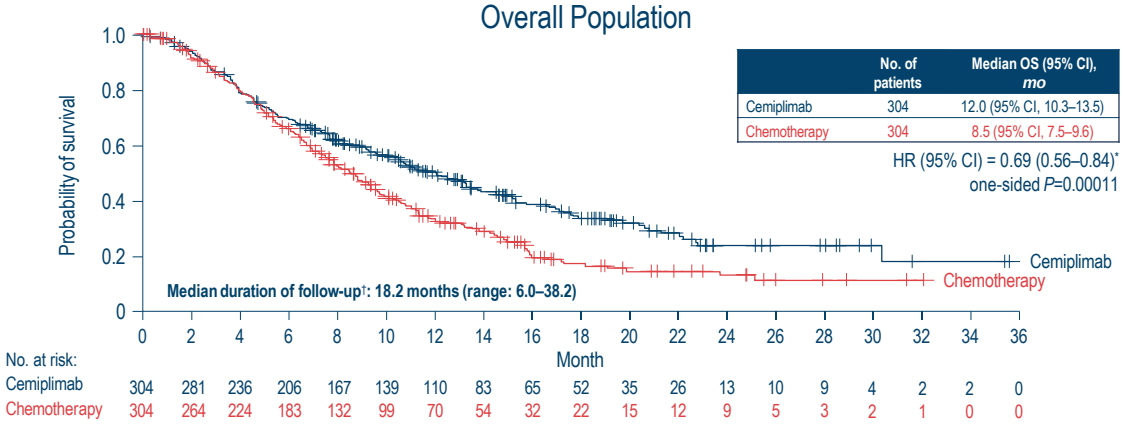
Chemoradiatie ± adjuvant chemotherapie bij cervixcarcinoom





Mileshkin. Abstract #LBA3

Cemiplimab 2e lijn cervixcarcinoom OVERALL SURVIVAL



	No. of patients	Median OS (95% CI), *mo*
Cemiplimab	304	12.0 (95% CI, 10.3–13.5)
Chemotherapy	304	8.5 (95% CI, 7.5–9.6)

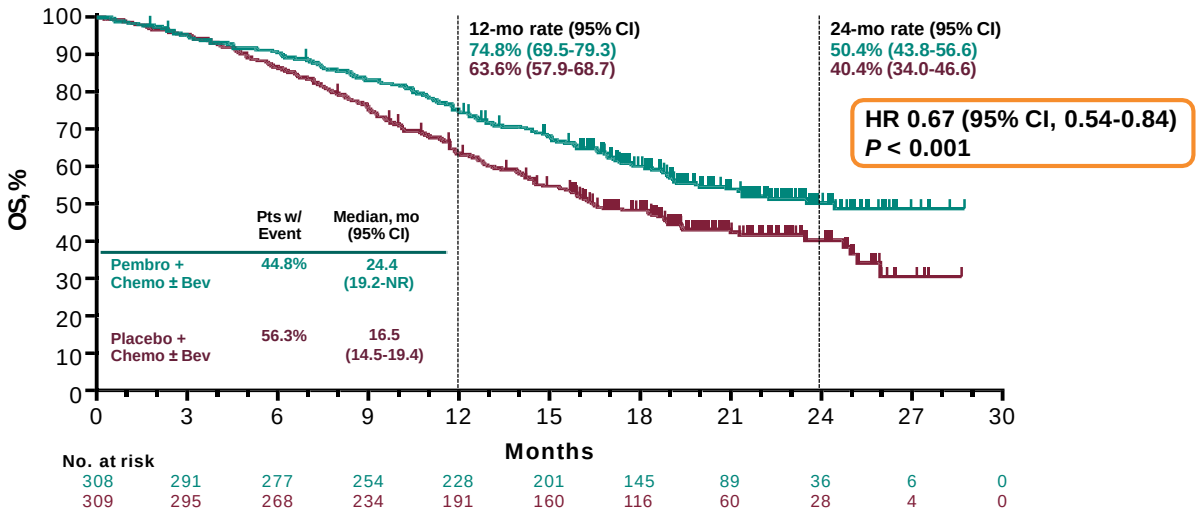
HR (95% CI) = 0.69 (0.56–0.84)*
one-sided *P*=0.00011

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system. †From randomisation to data cutoff date.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; ROW, rest of world; SCC, squamous cell carcinoma..

ESMO VIRTUAL PLENARY

Data cutoff date: 4 Jan 2021

Pembrolizumab 1e lijn cervixcarcinoom OS



Data cutoff date: May 3, 2021.

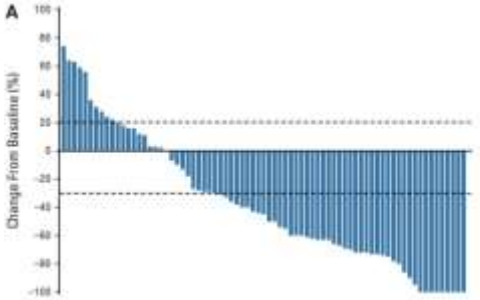
Endometriumcarcinoom

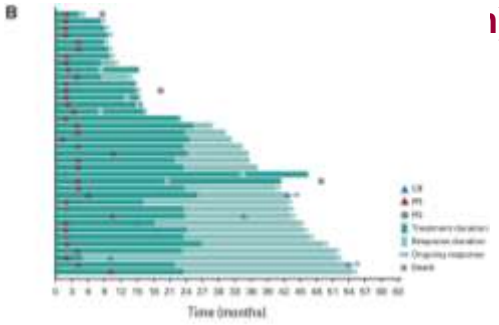
Conclusies

- Dostarlimab en Pembrolizumab 2e lijn monotherapie bij MSI tumoren
  - Dostarlimab EMA geregeistreerd, pembrolizumab nu ter beoordeling
  - voldoen aan CieBOM single arm criteria (?)

- Pembrolizumab + lenvatinib 2e lijn
  - EMA geregistreerd, CieBOM en ZINL volgen
  - toxisch
  - toegevoegde waarde lenvatinib bij dMMR?
  - toegevoegde waarde pembro bij pMMR?

Keynote-158 trial: ORR en DOR pembrolizumab in MSI-h



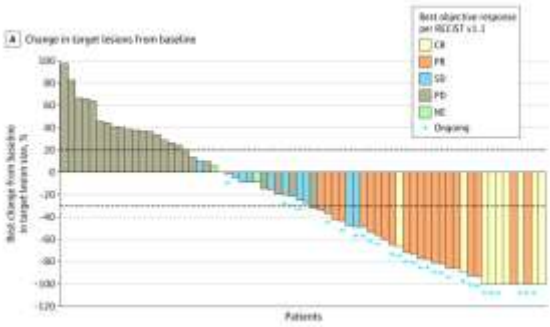


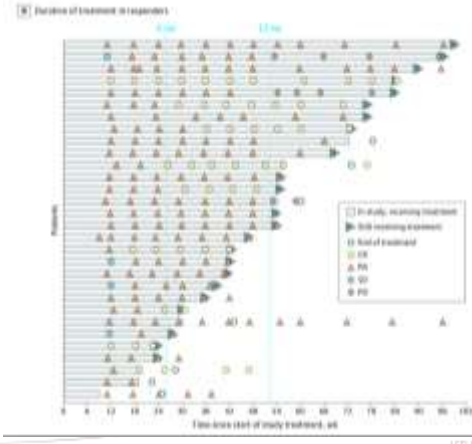
ORR 48% (37-60) mnd)

median DOR not reached (3-50

J Clin Oncol 2022; 7: 752-61

GARNET trial: ORR en DOR dostarlimab in MSI-h

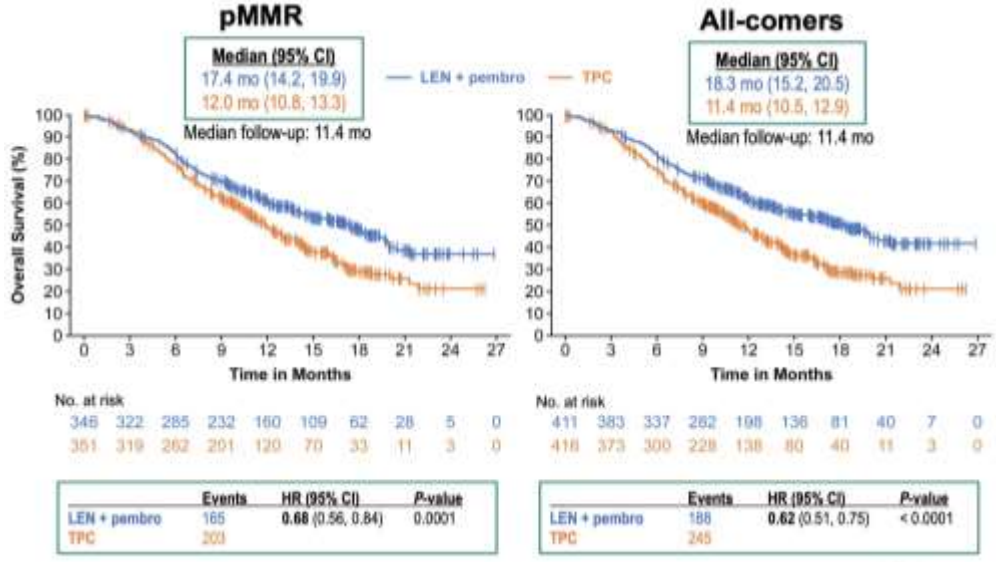




ORR 42%; 95% CI, 31%-55%
Median DOR not reached

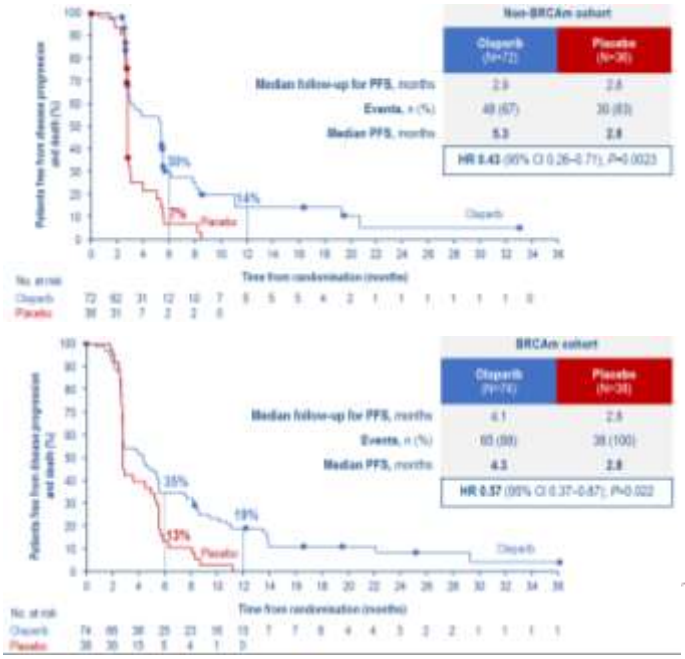
JAMA Oncol 2020; 6: 1-7

Lenvatinib + pembro vs physician's choice



Ovariumcarcinoom

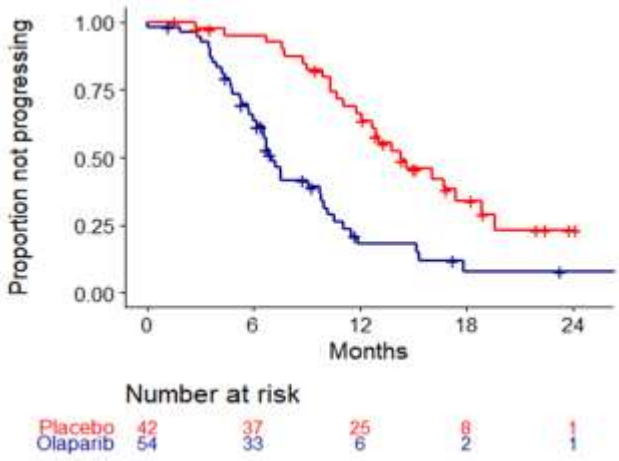
- Absolute winst van PARP na PARP beperkt bij ovariumcarcinoom
- Platinum minder effectief na eerder PARP (maar toch 1e keus bij interval >6mnd)
- Folaat receptor belangrijk voor imaging én behandeling



Pujade-Lauraine; ESMO 2021

Platinum na PARP: SOLO-2

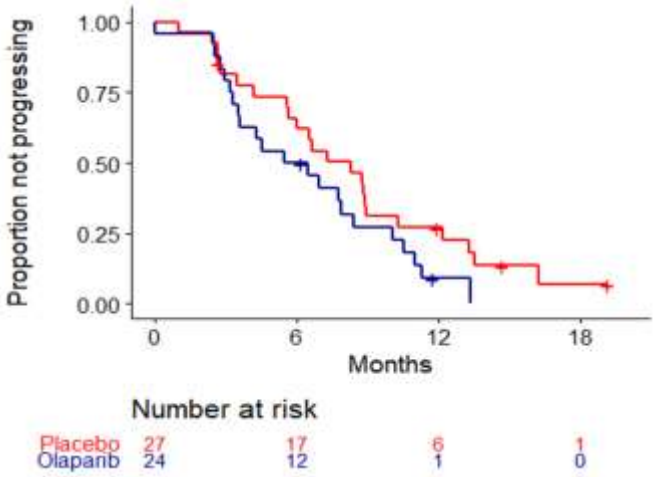
Olaparib vs Placebo
median 7.0 vs 14.3 months
HR=2.89; 95%CI [1.73, 4.82]



Frenel; ESMO 2020

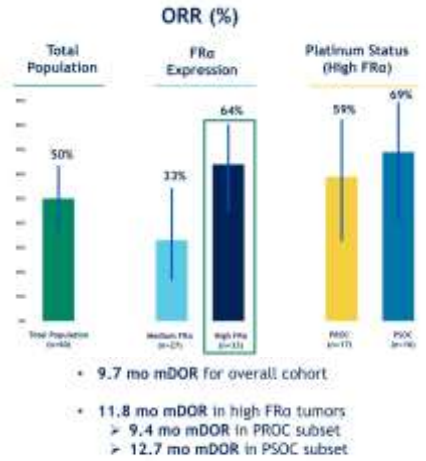
Non-platinum na PARP: SOLO-2

Olaparib vs Placebo
Median: 6.0 vs 8.3 months
HR=1.58; 95%CI [0.86,2.90]

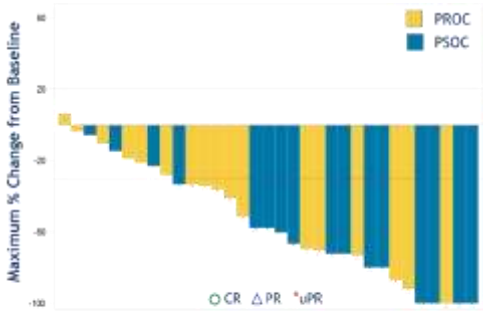


Frenel; ESMO 2020

Mirvetuximab soravtansine met bevacizumab bij ovariumcarcinoom



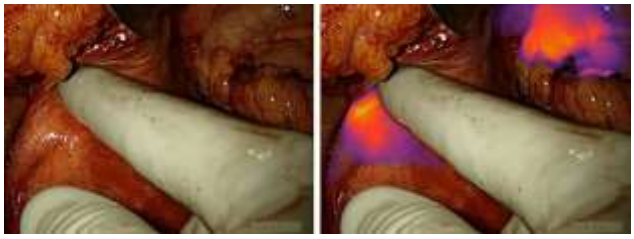
- 9.7 mo mDOR for overall cohort
- 11.8 mo mDOR in high FRα tumors
  - 9.4 mo mDOR in PROC subset
  - 12.7 mo mDOR in PSOC subset

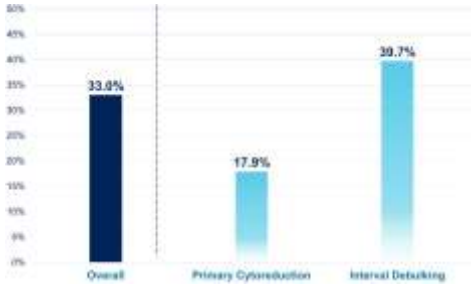


- **97% (32/33)** of patients demonstrated tumor burden reduction

O'Malley. Abstract #5504

Intra-operatieve imaging van folate receptor





Tanyi. Abstract #5503

Highlights

- Mamma
  - Trastuzumab-deruxtecan ++
  - Pembrolizumab +
  - Palbociclib -
- Cervix
  - Adjuvant chemotherapie -
  - Immuuntherapie 1e en 2e lijn +
- Endometrium
  - Pembrolizumab (+ lenvatinib) +
- Ovarium
  - PARP remming +
  - Mirvetuximab +


ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer


ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer


ORIGINAL ARTICLE

Survival with Cemiplimab in Recurrent Cervical Cancer


ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer