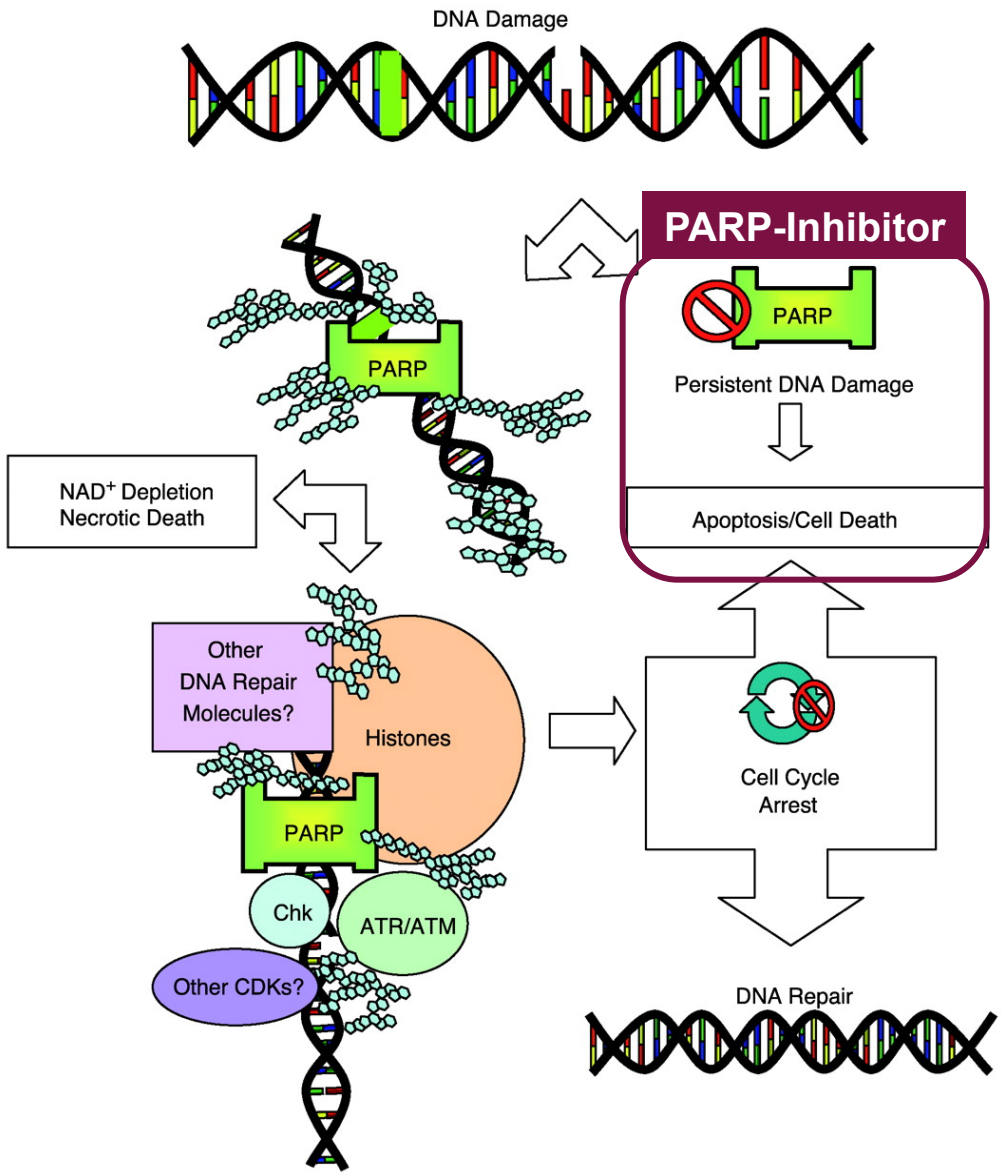
Highlights - ASCO 2016

PARP-Inhibitoren (Ovarialkarzinom)

Immuntherapie (Endometrium-, Zervix-Ca)

Alain G. Zeimet

P A R P - Inhibitoren



PARP = poly (**A**DP-**r**ibose) **p**olymerase, ubiquitäres nukleäres Enzym = Regulator der **Einzelstrang Reparatur**. Hemmung → Doppelstrang Brüchen.

Wirksamkeit besonders bei Defekten in der ***Homologen Rekombination*** (Reparatur v. DNA-Doppelstrang Brüchen) i.e. Mutation v. **BRCA1/2** und anderen (RAD1C) (sog. BRCAness)

BRCAness = Prediktor für Wirkung v. PARP-Inhibitoren + v. Platine

The NEW ENGLAND JOURNAL of MEDICINE

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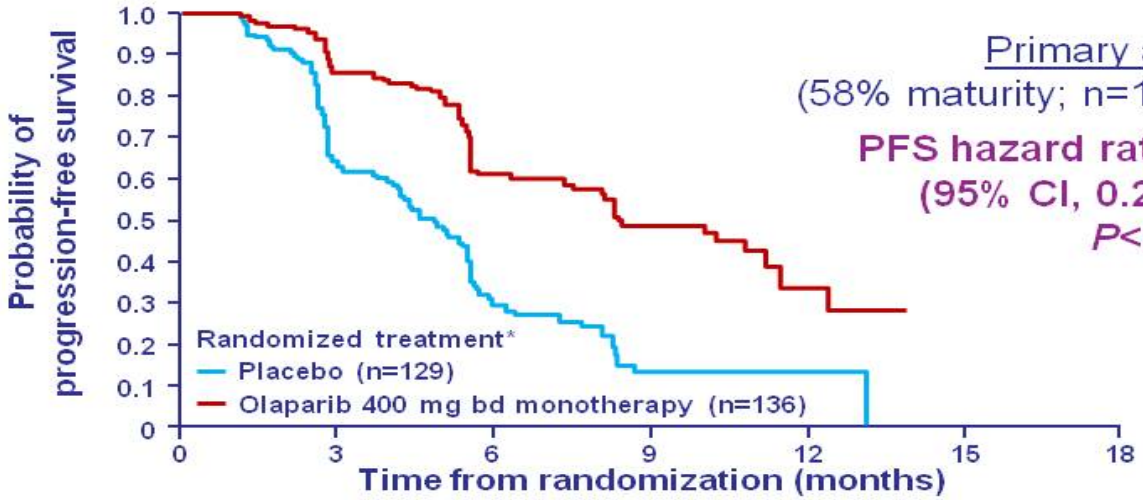
ORIGINAL ARTICLE

Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer

- Patients were randomized after response to platinum-based chemotherapy



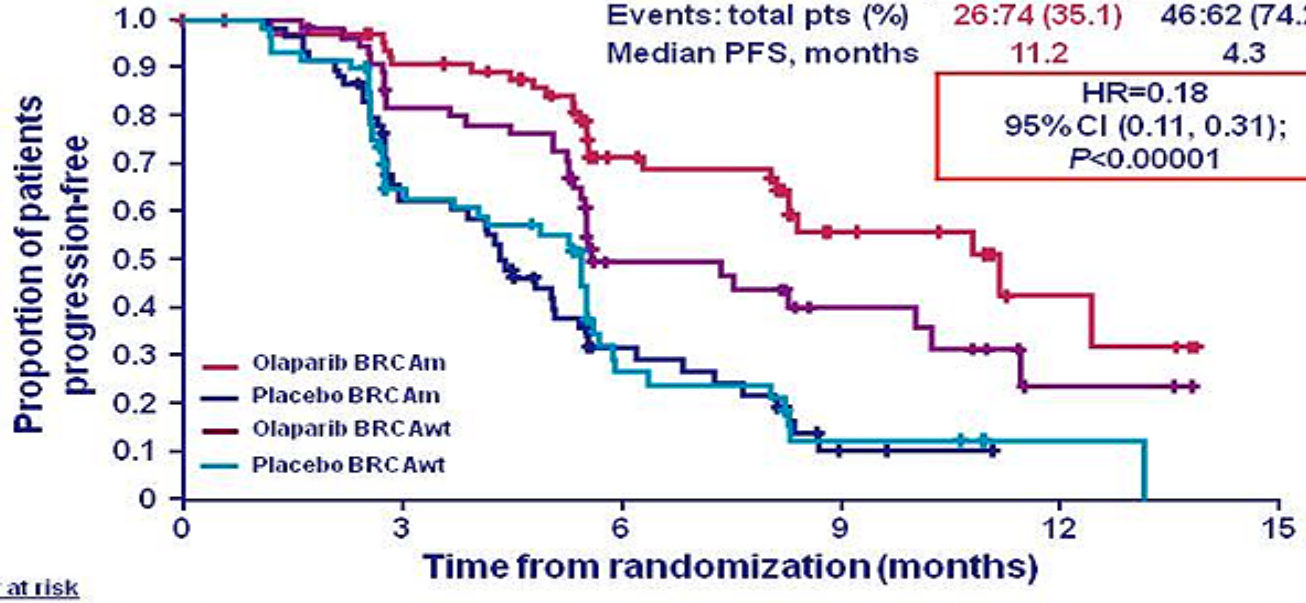
- Interim OS analysis (38% maturity): HR=0.94; 95% CI, 0.63–1.39; *P*=0.75

*Patients were treated until disease progression

Ledermann J *et al*. *N Engl J Med* 2012;366:1382–1392

PFS by BRCAm status

	BRCAm (n=136)		BRCAwt (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Events: total pts (%)	26:74 (35.1)	46:62 (74.2)	32:57 (56.1)	44:61 (72.1)
Median PFS, months	11.2	4.3	5.6	5.5
	HR=0.18 95% CI (0.11, 0.31); *P*<0.00001		HR=0.53 95% CI (0.33, 0.84); *P*=0.007	



Number at risk						
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0
Olaparib BRCAwt	57	44	17	9	2	0
Placebo BRCAwt	61	35	10	4	1	0

BRCAwt, wild type (includes patients with no known BRCAm or a mutation of unknown significance)

Ist die Wirksamkeit der PARP-Inhibitoren beim Ovarialkarzinom von Dauer ?

Study 19: Olaparib maintenance monotherapy leads to a meaningful clinical benefit in ovarian cancer patients

PFS ↑

Statistically significant improvement in progression-free survival with olaparib[1,2]

Overall population:
Median PFS (olaparib vs placebo): 8.4 months vs 4.8 months
HR=0.35, *P*<0.0001

***BRCA*m subgroup:**
Median PFS (olaparib vs placebo): 11.2 months vs 4.3 months
HR=0.18, *P*<0.0001

TFST ↑

Time to first subsequent therapy or death significantly improved with olaparib[2]

Represents the time women are **free from next line** of chemotherapy

TSST ↑

Time to second subsequent therapy or death significantly improved with olaparib[2]

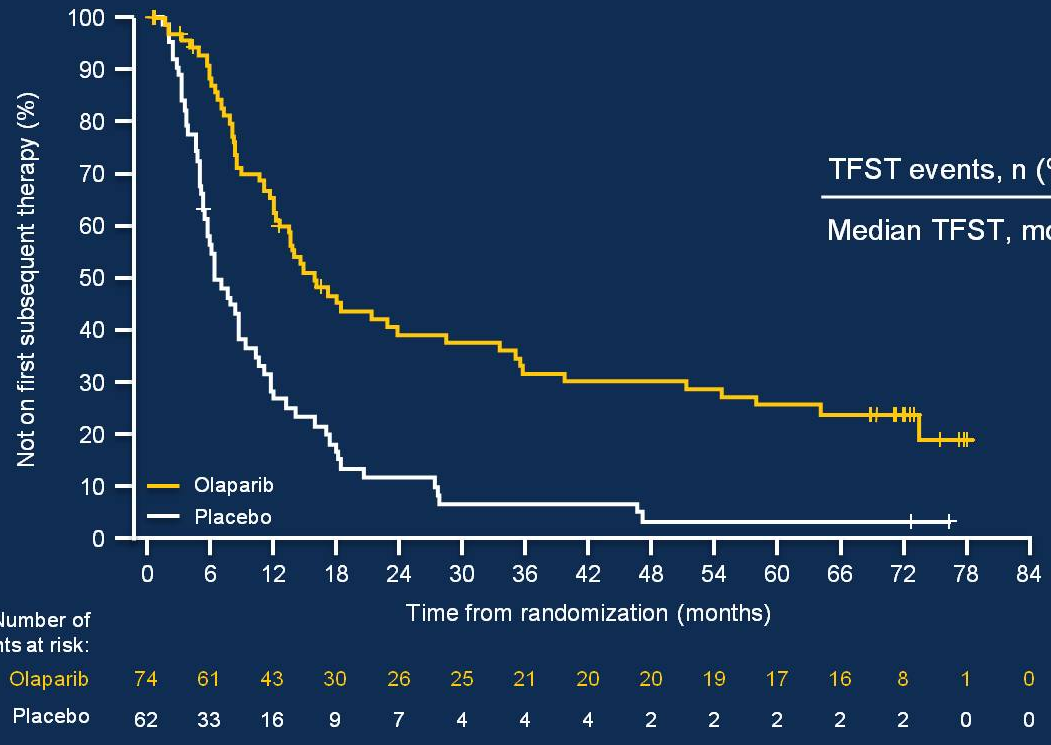
Can demonstrate benefit **beyond the next line** of chemotherapy; helps **address the confounding impact of crossover**

- Patients with a ***BRCA*m** received the greatest benefit from maintenance olaparib[2]
- TFST and TSST are clinically meaningful exploratory endpoints

HR, hazard ratio

1. Ledermann J *et al. New Engl J Med* 2012;366:1382–1392; 2. Ledermann J *et al. Lancet Oncol* 2014;15:852–861

Study 19: *BRCA*m patients – maintenance olaparib TFST



Number of patients at risk:															
Olaparib	74	61	43	30	26	25	21	20	20	19	17	16	8	1	0
Placebo	62	33	16	9	7	4	4	4	2	2	2	2	2	0	0

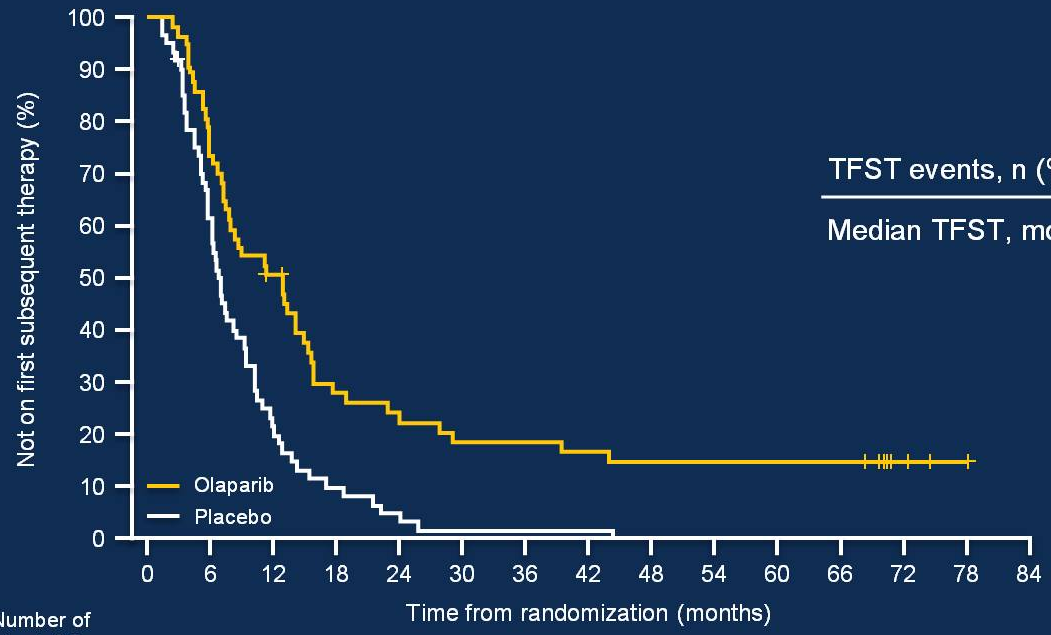
	*BRCA*m subgroup (n=136)	
	Olaparib (n=74)	Placebo (n=62)
TFST events, n (%)	53 (72)	59 (95)
Median TFST, months	15.6	6.2

HR=0.32
95% CI 0.22–0.48
***P*<0.00001**

Maturity: 82%

Updated exploratory analysis

Study 19: *BRCA*wt patients – maintenance olaparib TFST



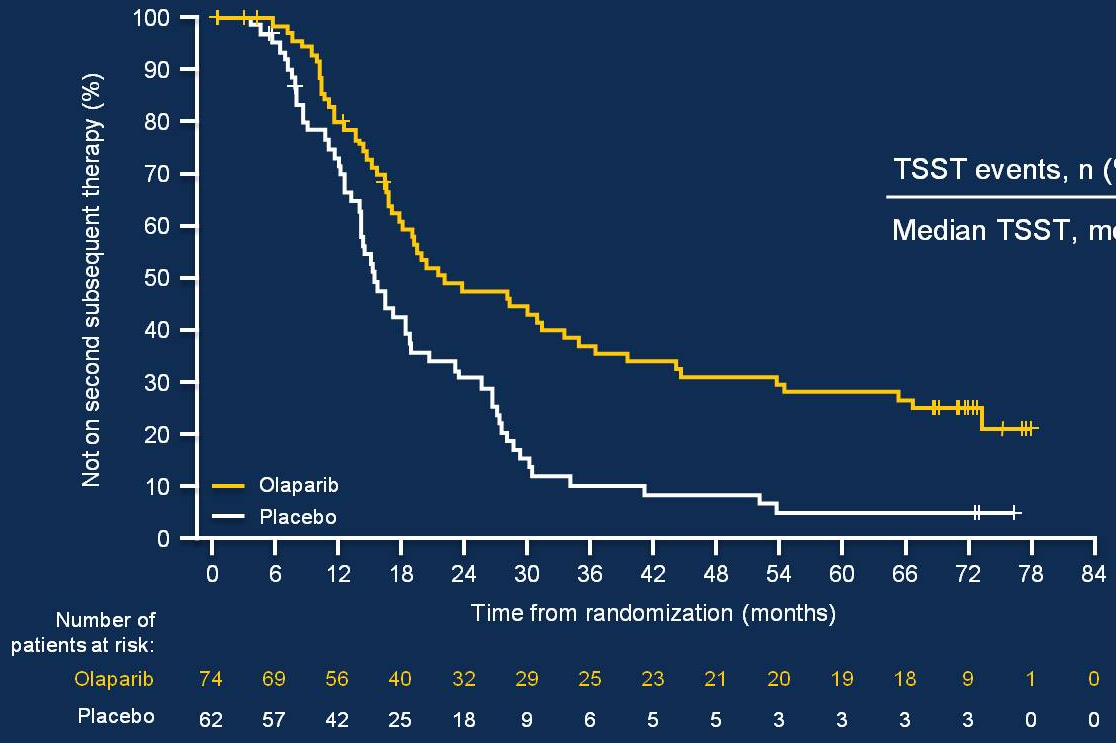
	*BRCA*wt subgroup (n=118)	
	Olaparib (n=57)	Placebo (n=61)
TFST events, n (%)	47 (82)	60 (98)
Median TFST, months	12.9	6.9

HR=0.45
95% CI 0.30–0.66
***P*=0.00006**

Maturity: 91%

Updated exploratory analysis

Study 19: *BRCA*m patients – maintenance olaparib TSST



	*BRCA*m subgroup (n=136)	
	Olaparib (n=74)	Placebo (n=62)
TSST events, n (%)	52 (70)	56 (90)
Median TSST, months	22.0	15.3

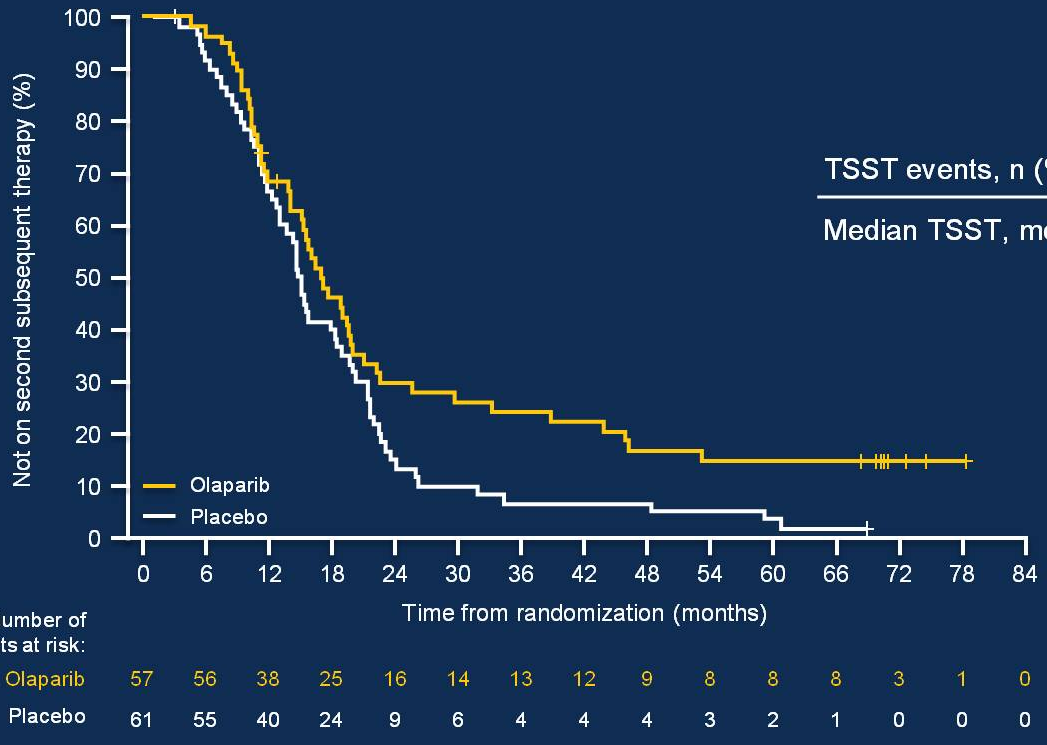
HR=0.41
95% CI 0.28–0.62
***P*=0.00001**

Maturity: 79%

14 patients (23%) from the placebo arm received post-discontinuation PARP inhibitor treatment

Updated exploratory analysis

Study 19: *BRCA*wt patients – maintenance olaparib TSST



	*BRCA*wt subgroup (n=118)	
	Olaparib (n=57)	Placebo (n=61)
TSST events, n (%)	47 (82)	59 (97)
Median TSST, months	17.0	14.7

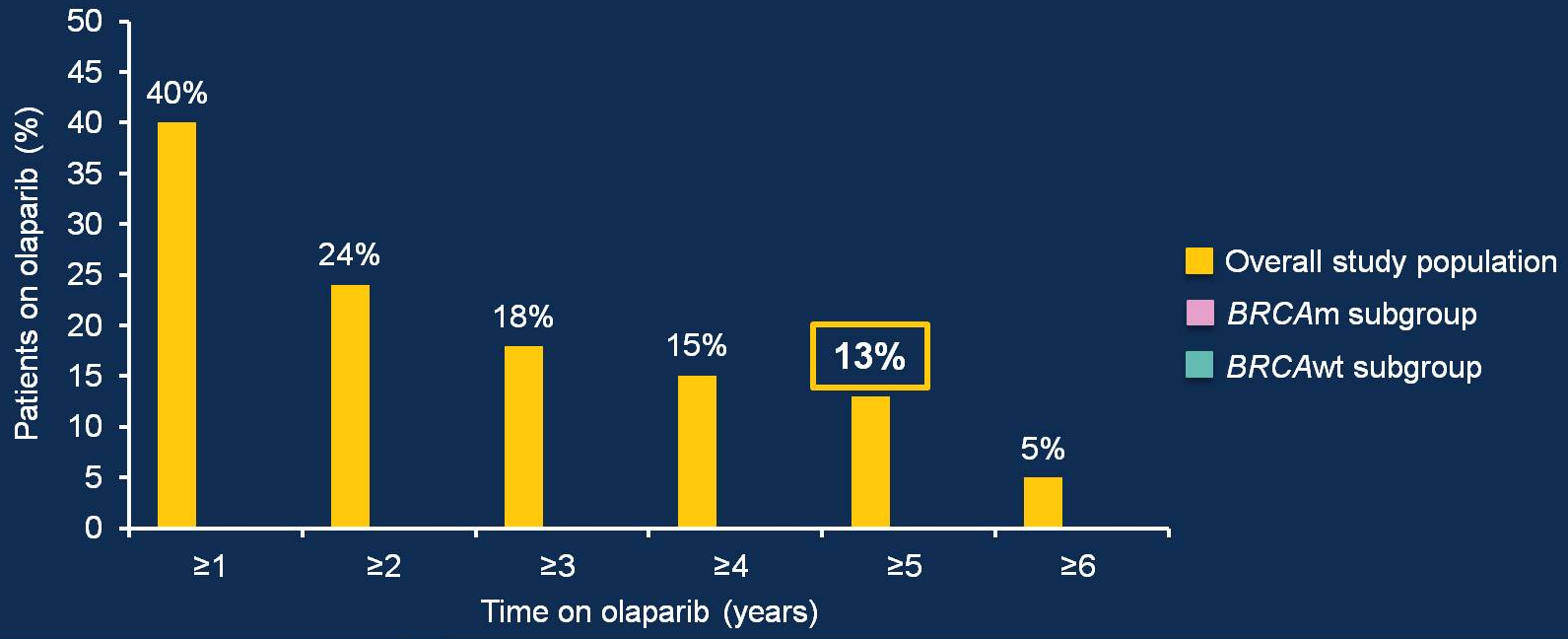
HR=0.63
95% CI 0.43–0.94
***P*=0.02263**

Maturity: 90%

Updated exploratory analysis

Long-term exposure to treatment

- Median follow-up of 5.9 years: **15 patients (11%)** still receiving **olaparib** (**8 *BRCA*m**, 7 *BRCA*wt); one patient (<1%) still receiving placebo (*BRCA*m)



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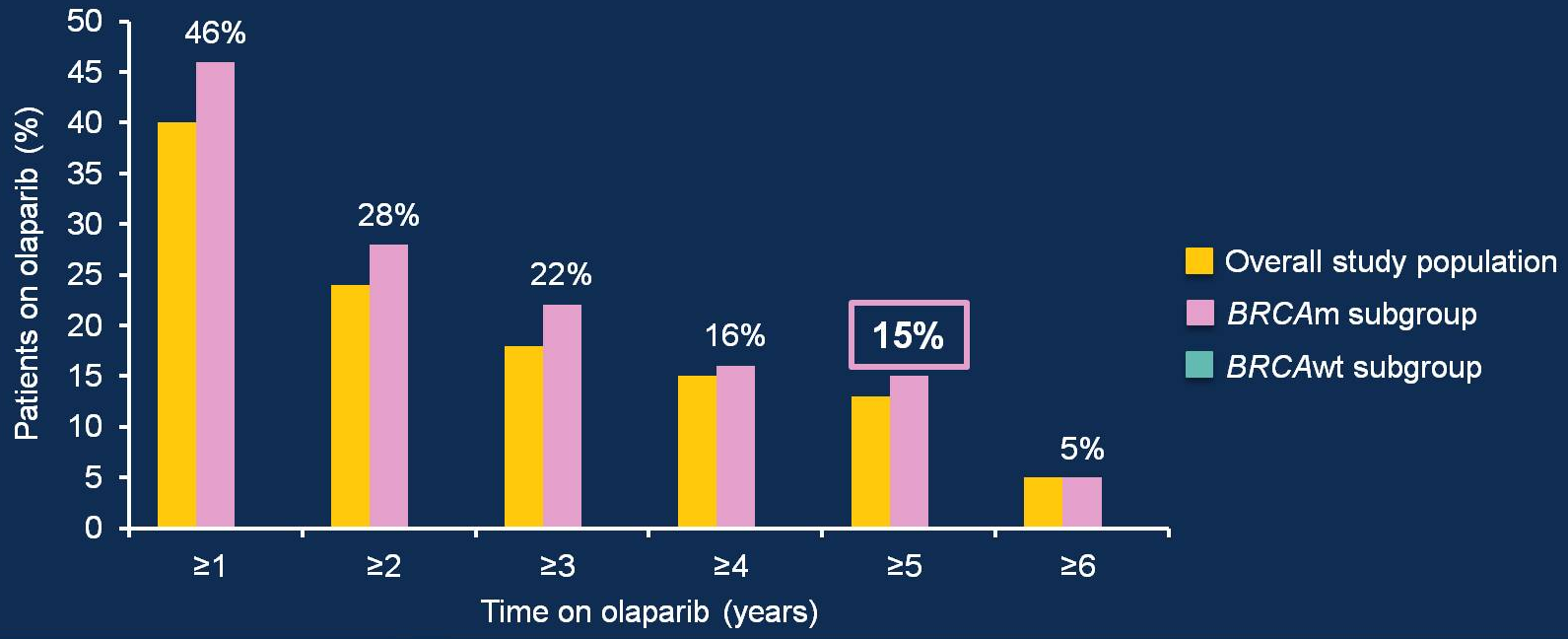

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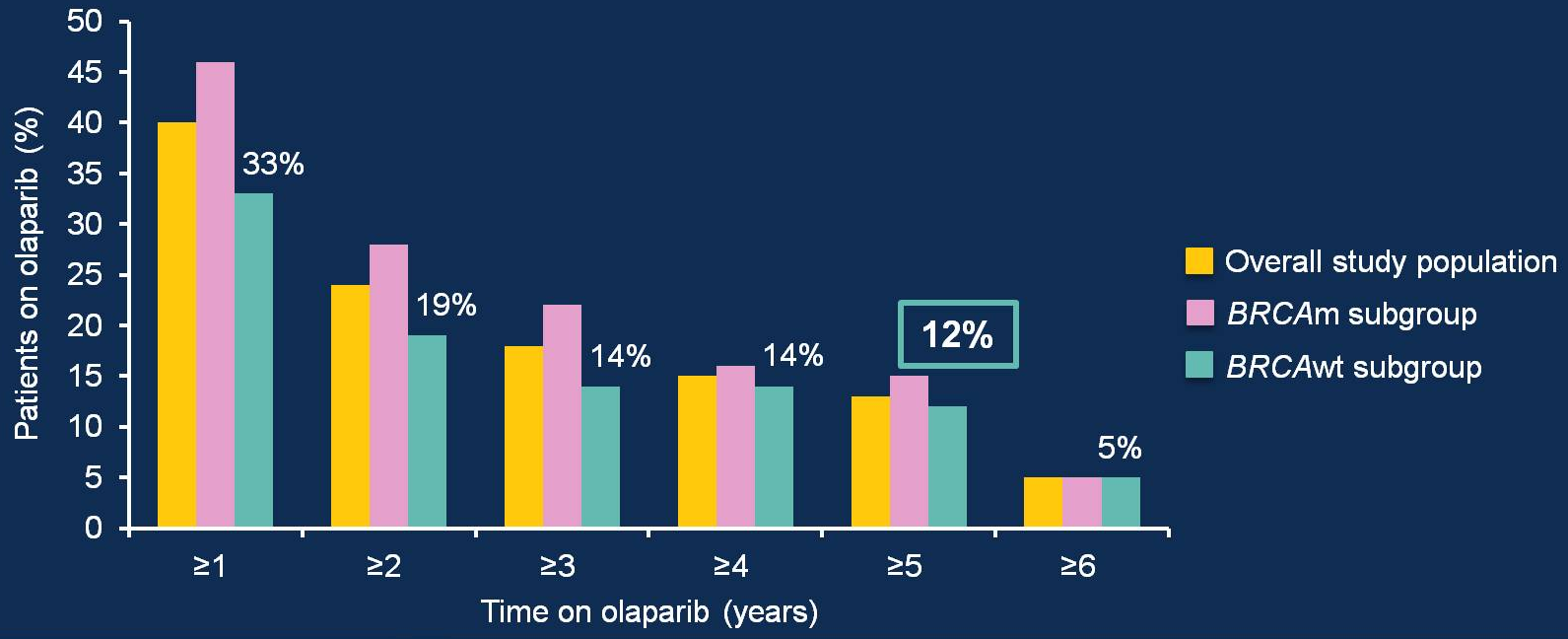


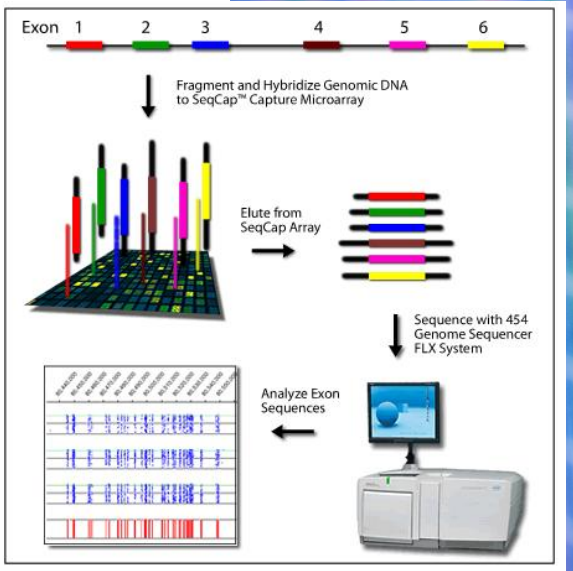
Empfehlungen der AGO AUSTRIA

- Eine genetische Testung und Bestimmung einer BRCA-1/2 Keimbahnmutation soll *allen Patientinnen mit Ovarialkarzinom* angeboten werden.
- Patientinnen mit Borderline-Ovarialtumoren oder nicht-epithelialen Ovarialtumoren haben außerhalb der Kriterien für familiäres Brust- und Ovarialkarzinom durch eine Testung keinen Nutzen zu erwarten.
- Formelle genetische Beratung
- Qualitätsgesicherte *Testung von Tumormaterial (BRCA1-2 + einem erweiterten Gen-Panel)* angestrebt werden.
- Bei BRCA Mutation im Tumorgewebe soll eine Keimbahn-mutations-Analyse für Patientin und deren Familienmitglieder angeboten werden.

Marth et al., WiKliWo 2015

Next Generation Sequencing (NGS)

New High-Throughput Technologies



„Druggability“ von genetischen Veränderungen?

druggable

FAZIT

- Therapie laut Zulassung (4.Juni 2015):
  high grade Karzinome mit platinsensiblen Rezidiv mit BRCA Mutation

- Studien zur first-line Therapie laufen

- Studien zur Identifikation des Ansprechens bei nicht-BRCA-mutierten (wildtype) Tumoren sind gefordert

IMMUNTHERAPIEN

RENAISSANCE DER IMMUNTHERAPIEN

DURCH

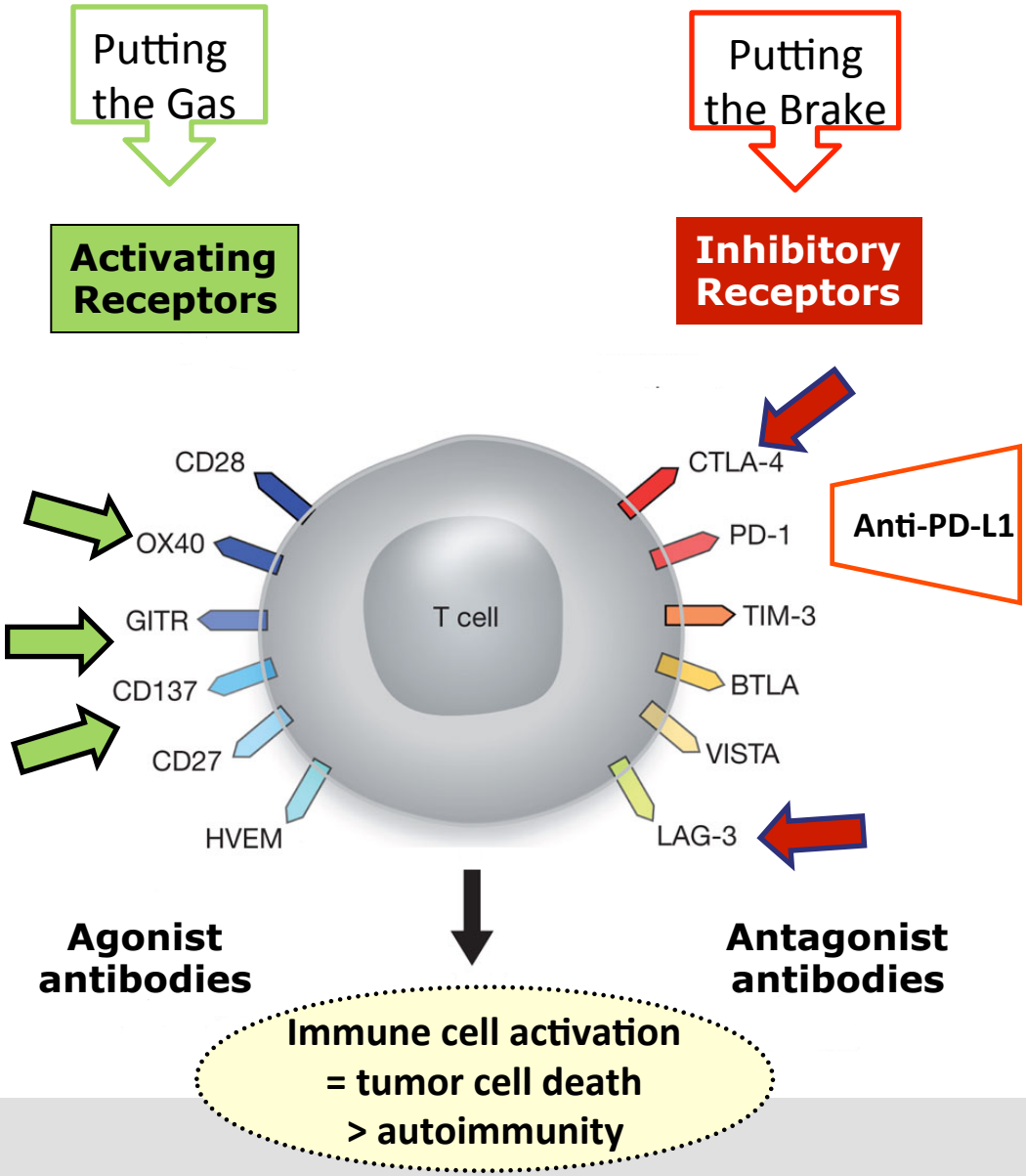
CHECKPOINT-INHIBITOREN

Cell-based Immunotherapy

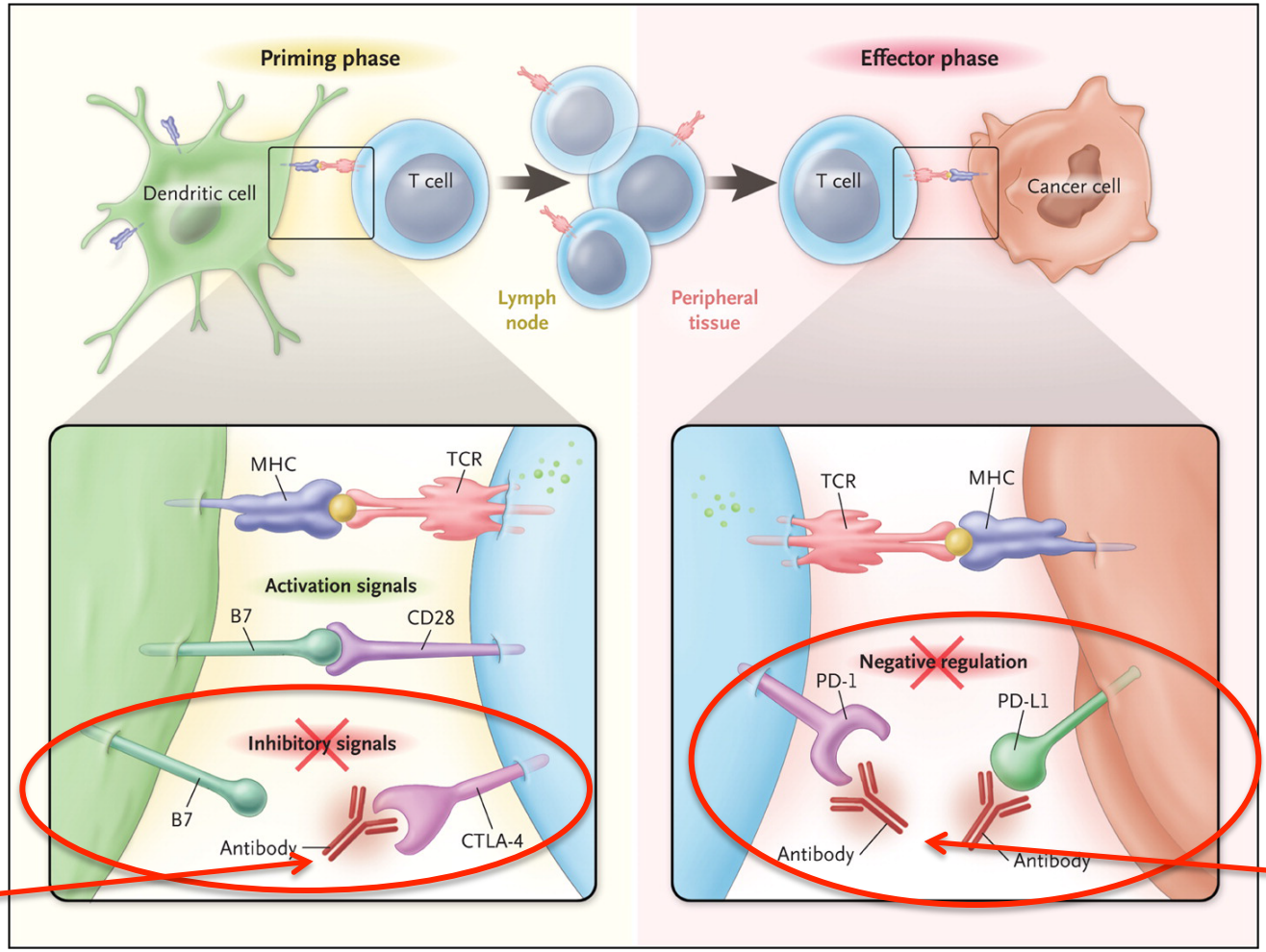
1. Dendritic cell therapy
2. Adoptive T Cell transfer using tumor-infiltrating lymphocytes or CAR-T cells
   (Chimeric Antigen-Receptor engineered)
3. Tumor cell vaccines

Ambivalenz des Immunsystems

→ *„Immun-Escape“* von Tumoren



CTLA-4 and PD-1/L1 Checkpoint Blockade

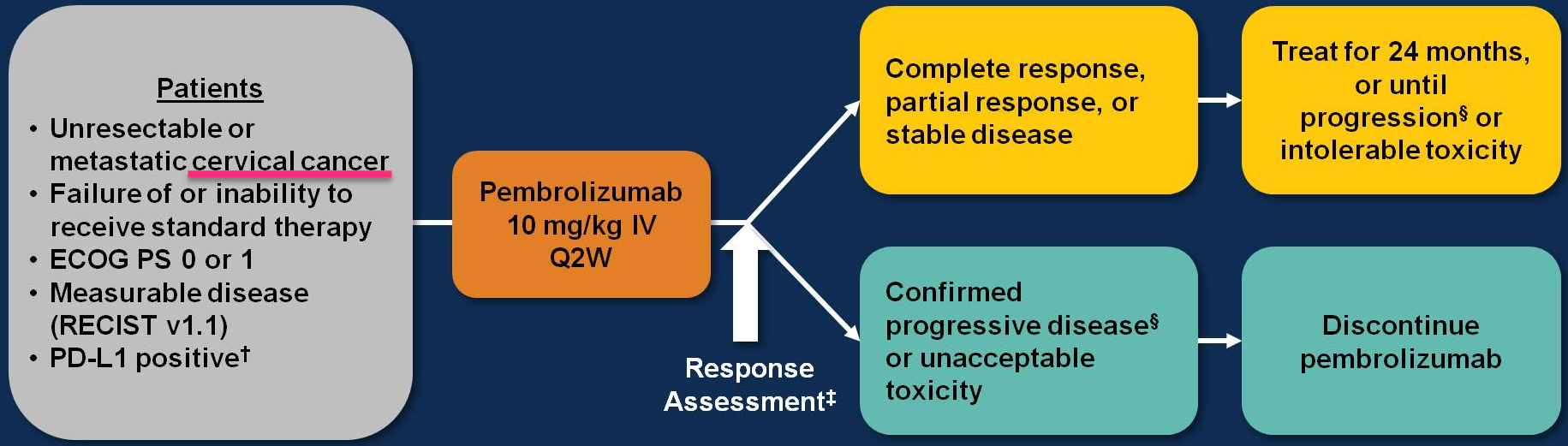


Anti-CTLA-4

Anti-PD1/ PDL-1

Anti-PD-1 Therapie beim Zervixkarzinom

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors



‡Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

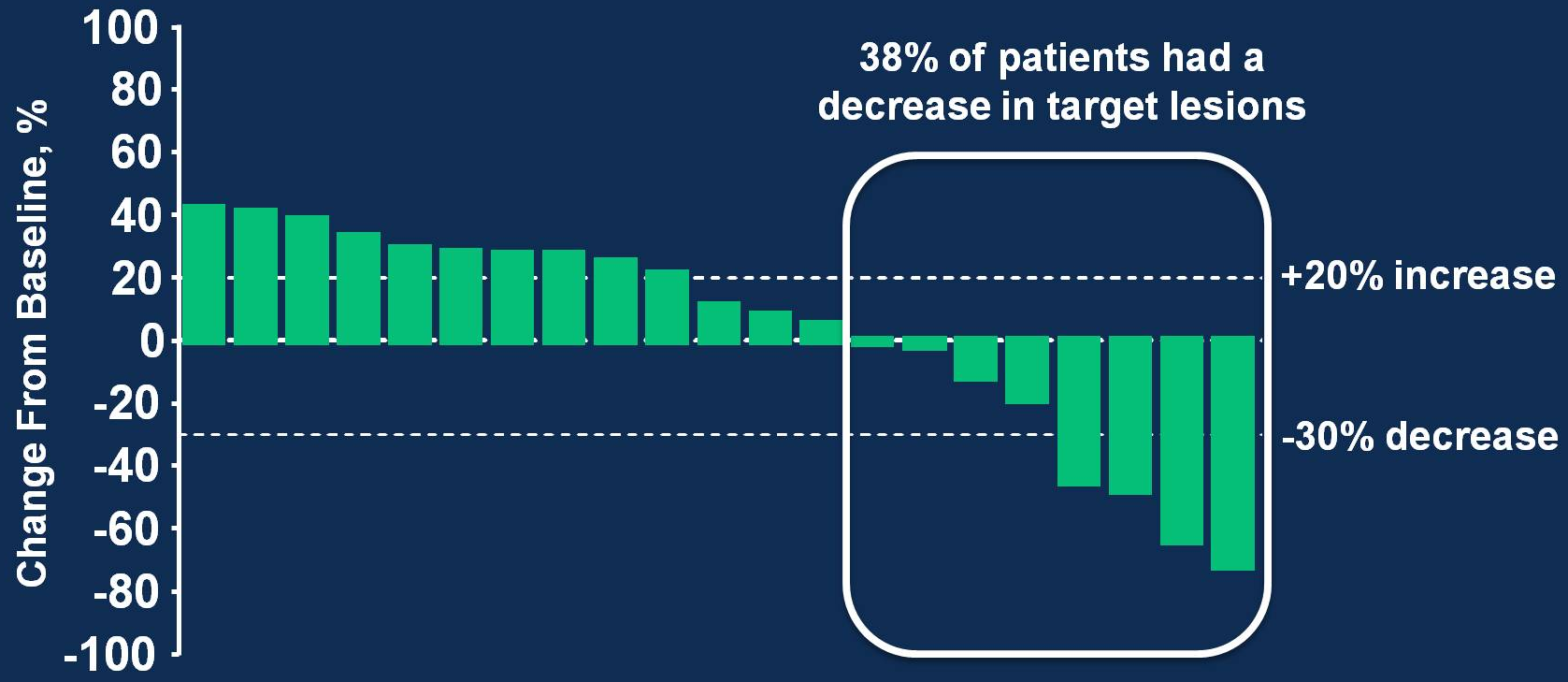
Secondary end points: PFS, OS, duration of response

†Membranous PD-L1 expression in ≥1% of tumor or stromal cells using a prototype immunohistochemistry assay and 22C3 antibody (Merck). §Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

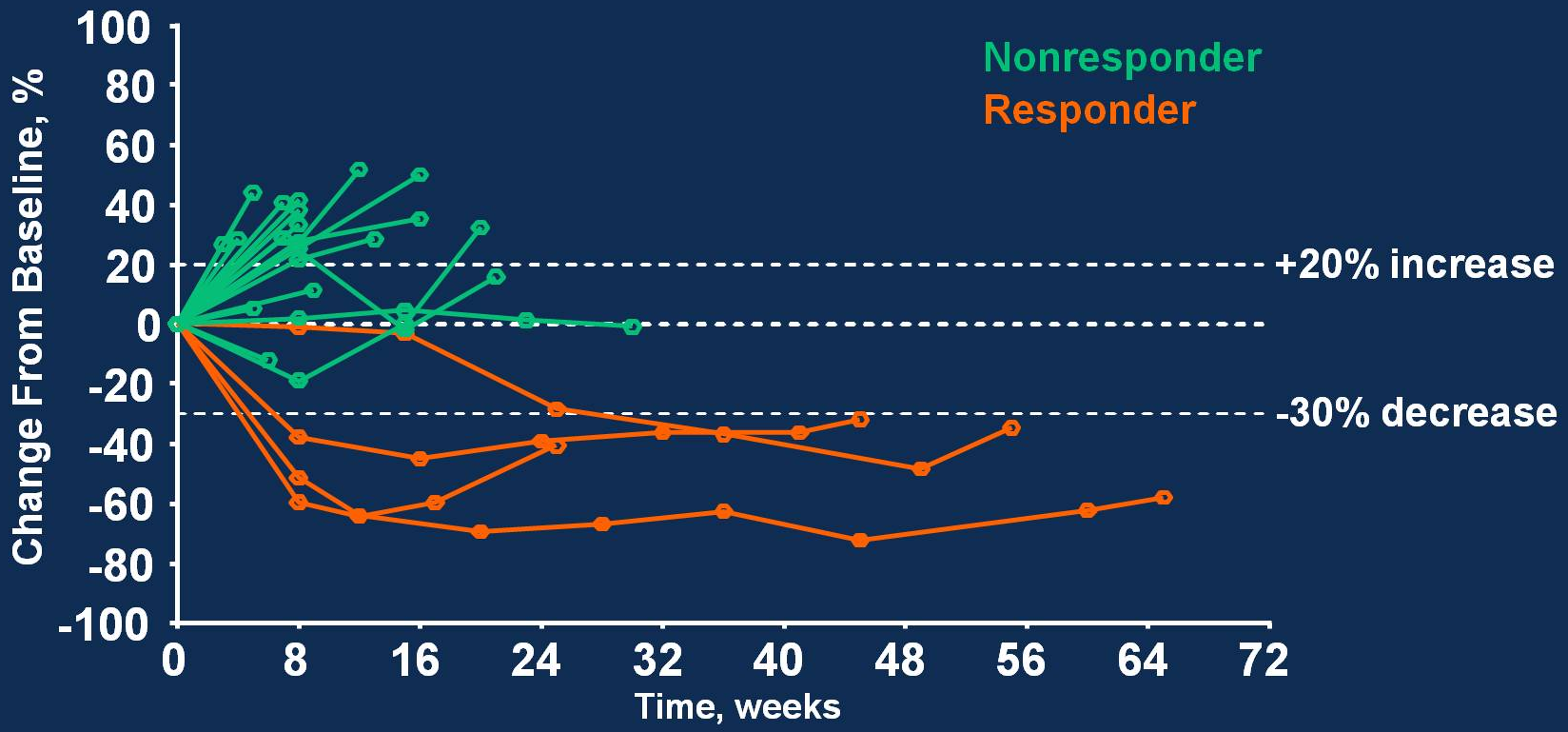
Best Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



Data cutoff date: Feb 17, 2016.
Patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a post-baseline assessment are included (n = 21).

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)

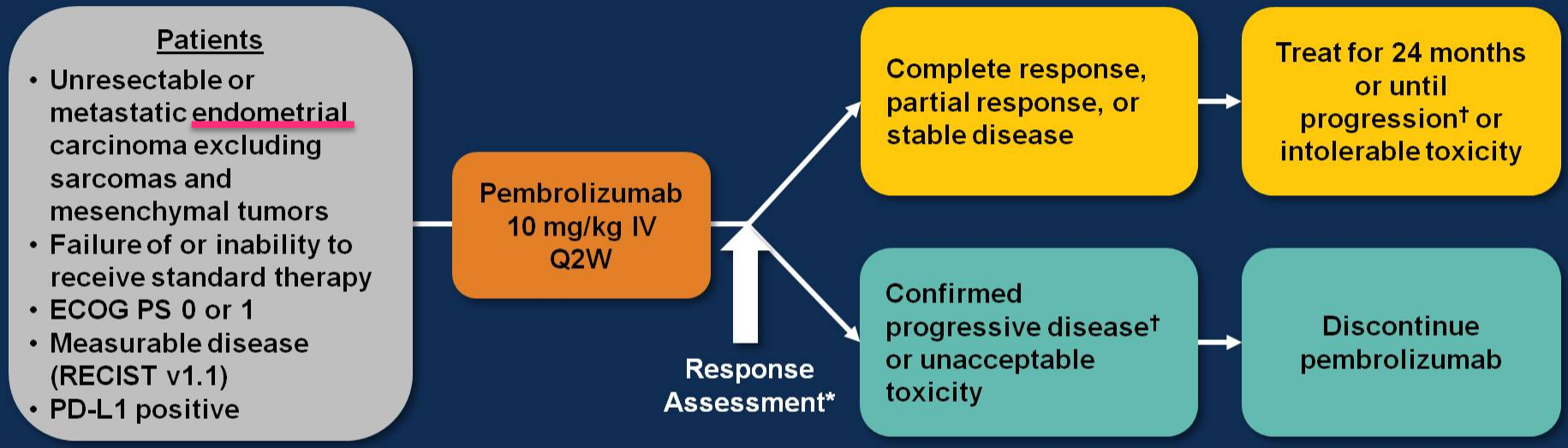


Data cutoff date: Feb 17, 2016. Patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a post-baseline assessment are included (n = 20). One patient was excluded due to 2 scans for the same assessment out of window.

Presented By Jean-Sebastien Frenel at 2016 ASCO Annual Meeting

Anti-PD-1 Therapie beim Endometriumkarzinom

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors



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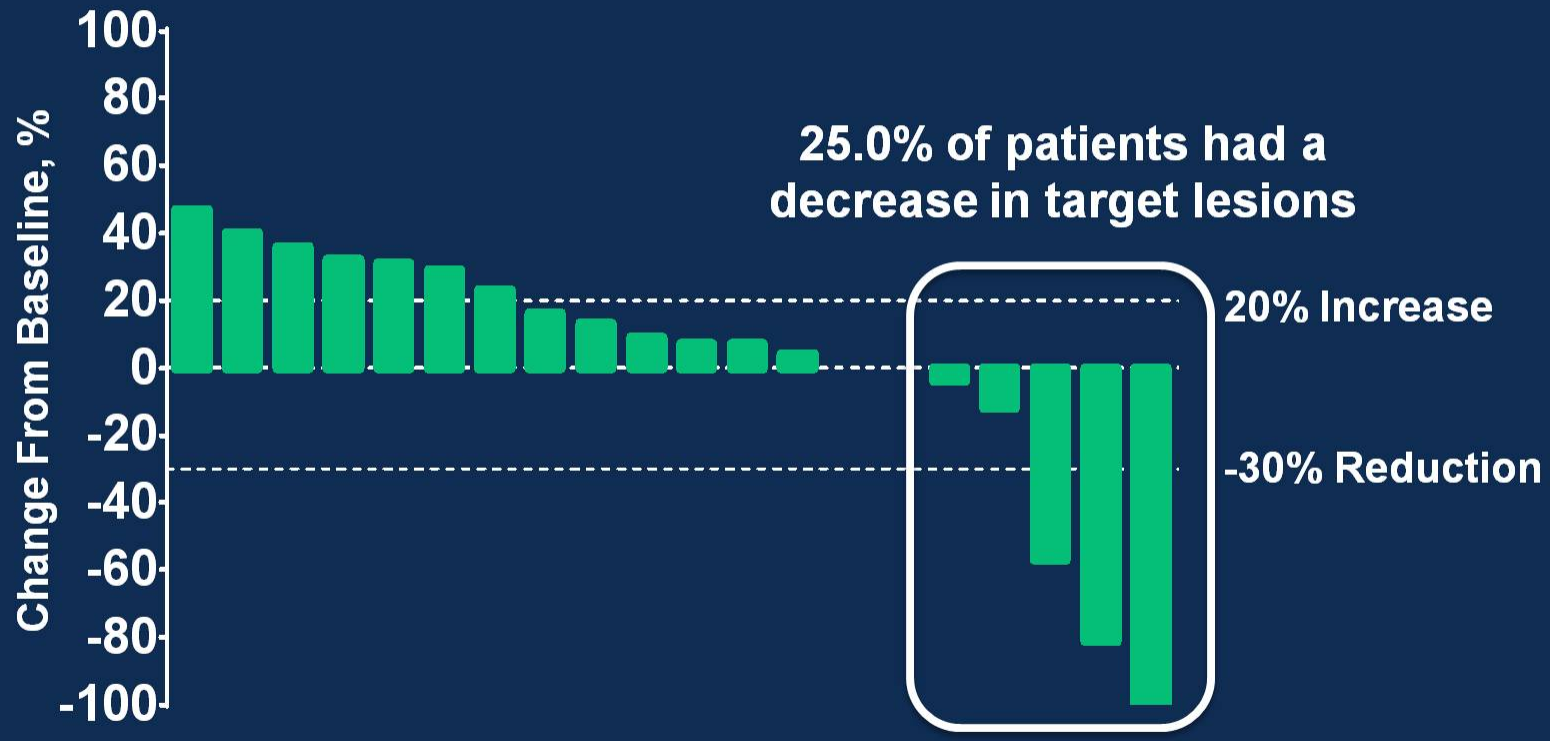
†Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

Best Percentage Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



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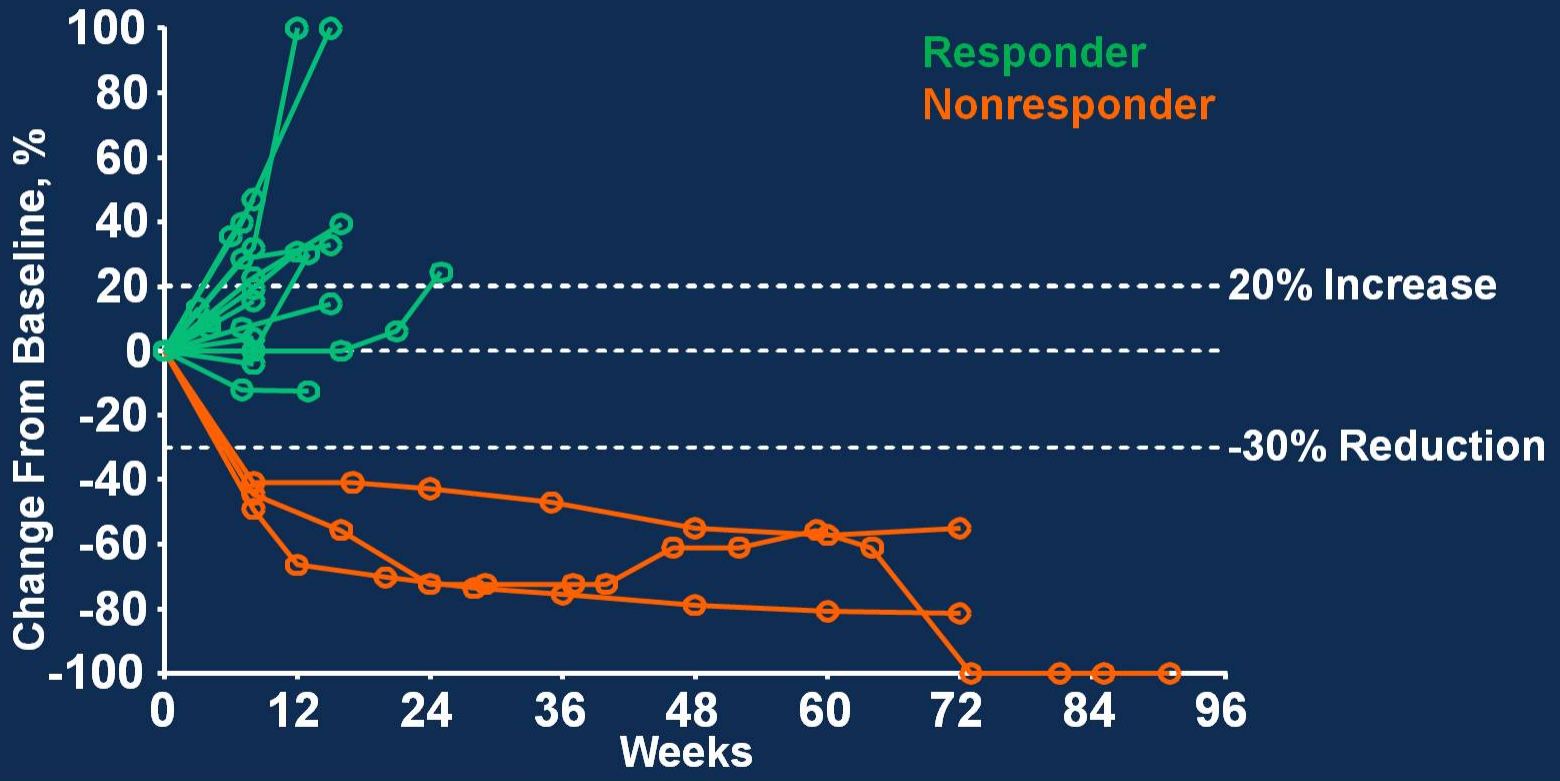
Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



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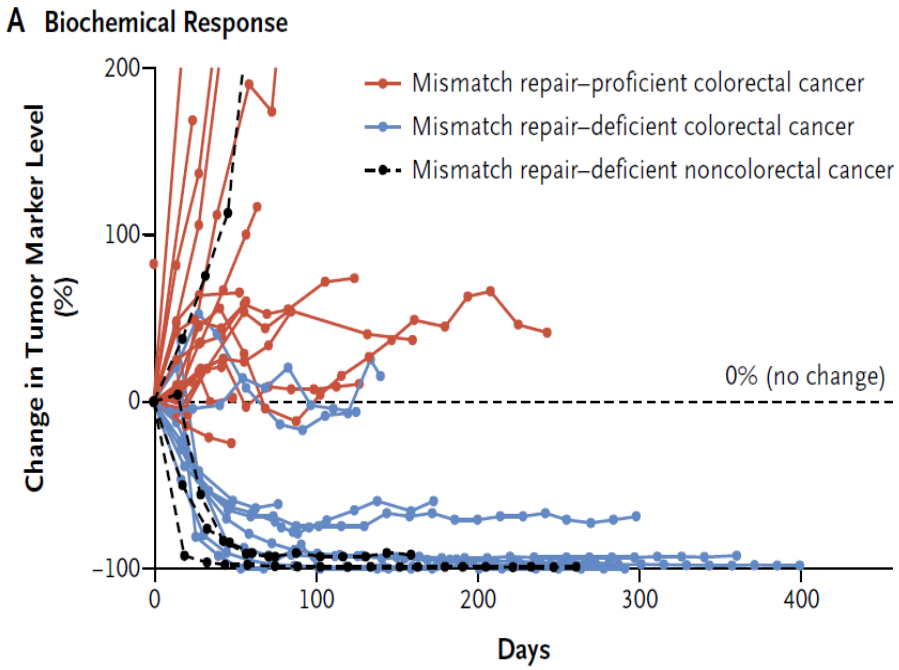
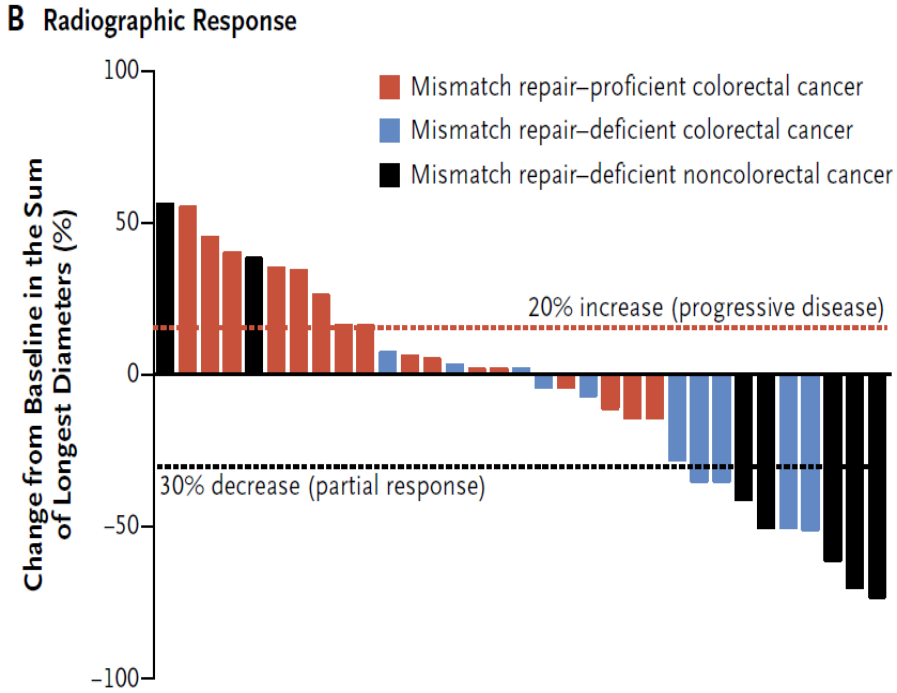
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency





D.T. Le , et al., NEJM 372;26 june 25, 2015

FAZIT

- Prädiktoren des Ansprechens (TILs ?; PD1 bzw. PDL1 IHC im Tumor ?; BRCA ?; MSI ?)
- Response-Evaluierung (Pseudo-Progression)
- Kombination mit Chemotherapeutika
- Kombination Adaptive Immunstimulation (CAR-T -cells *plus* Check-point Blockade
- NW: Autoimmun Effekte (-itis)

Danke für Ihre Aufmerksamkeit