

Immunonkologische Highlights des Jahres 2019 & Ausblick auf 2020

Österreichische Gesellschaft für Krankenhauspharmazie
Herbstmeeting 2019

Mag. Markus Krenn
Disease Area Specialist Immuno-Oncology

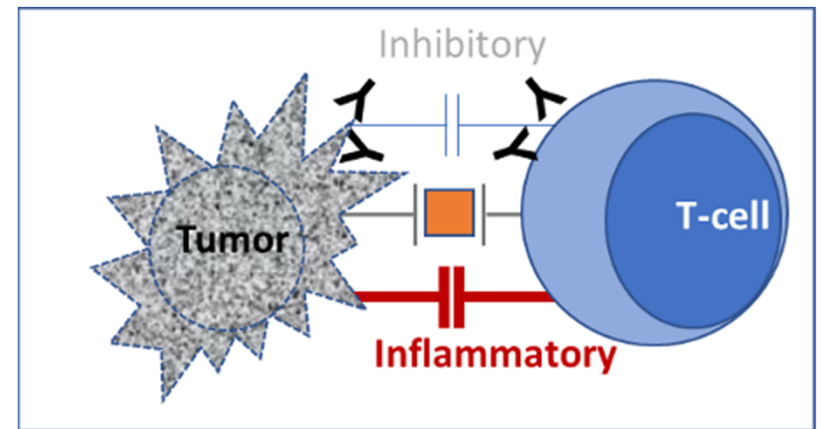


Bristol-Myers Squibb

Was sind Immunonkologische Highlights & Ausblick?

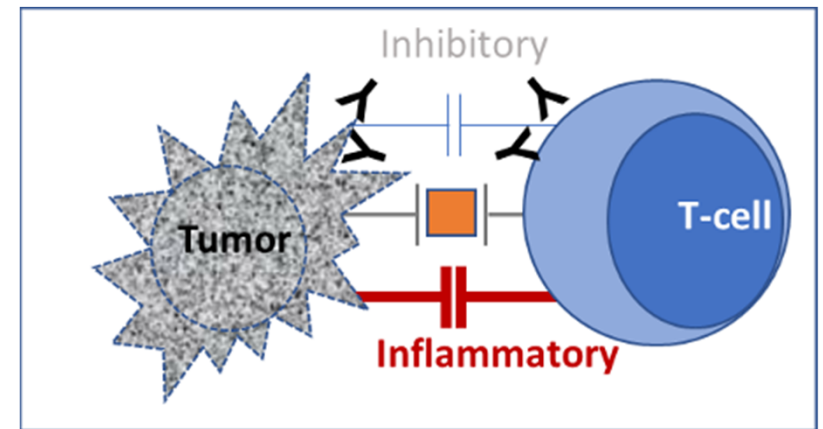
Was sind Immunonkologische Highlights & Ausblick?

- Beschränkung auf Checkpoint-Inhibitoren



Was sind Immunonkologische Highlights & Ausblick?

- Beschränkung auf Checkpoint-Inhibitoren
- EMA Zulassungen 2019



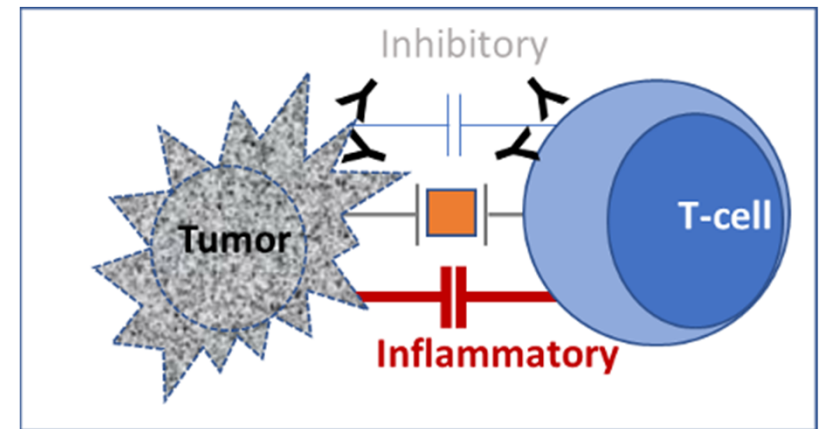
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Was sind Immunonkologische Highlights & Ausblick?

- Beschränkung auf Checkpoint-Inhibitoren
- EMA Zulassungen 2019
- Positive Phase III Studien 2019 ›
Potenzielle EMA Zulassungen 2020

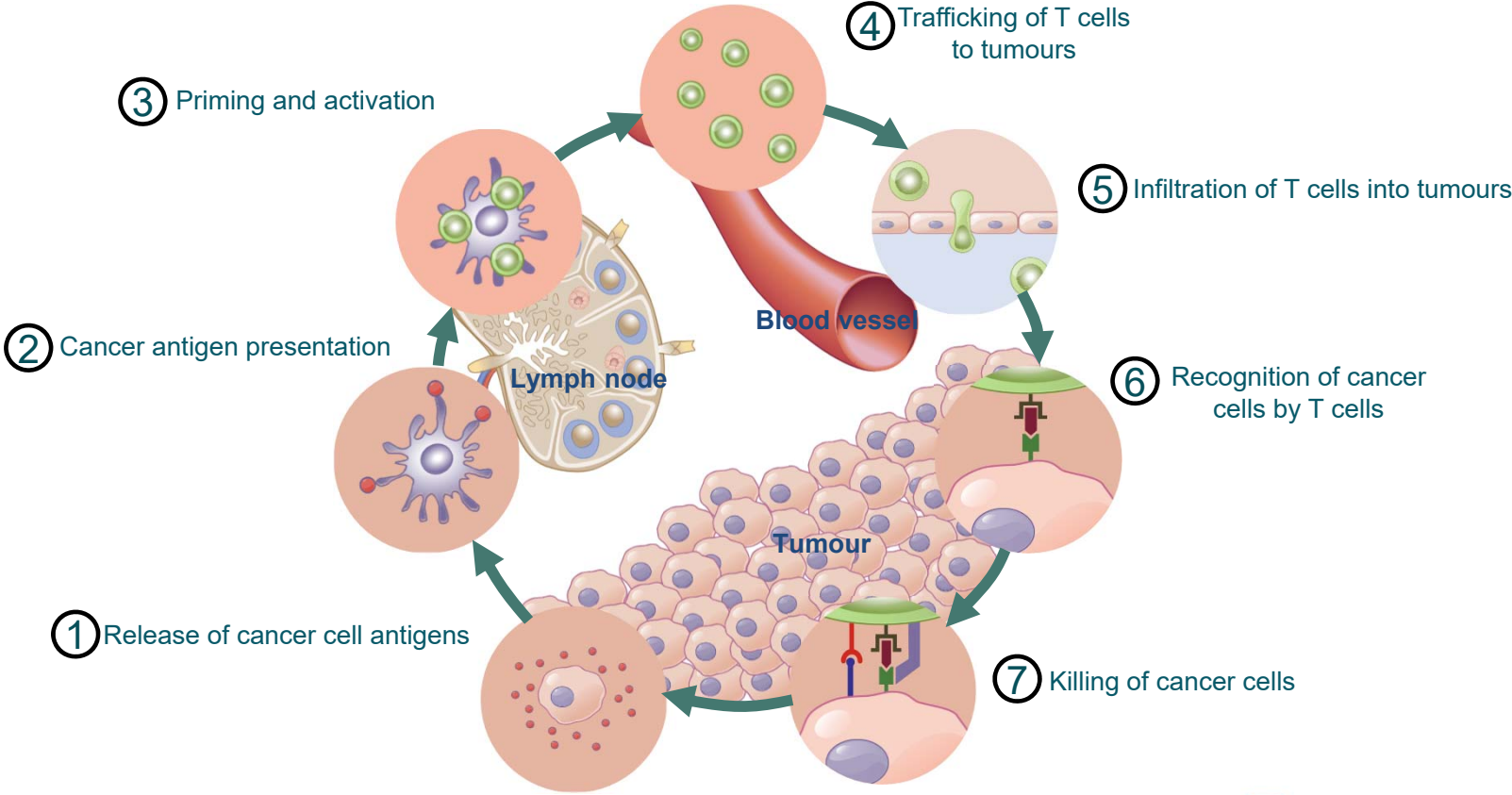


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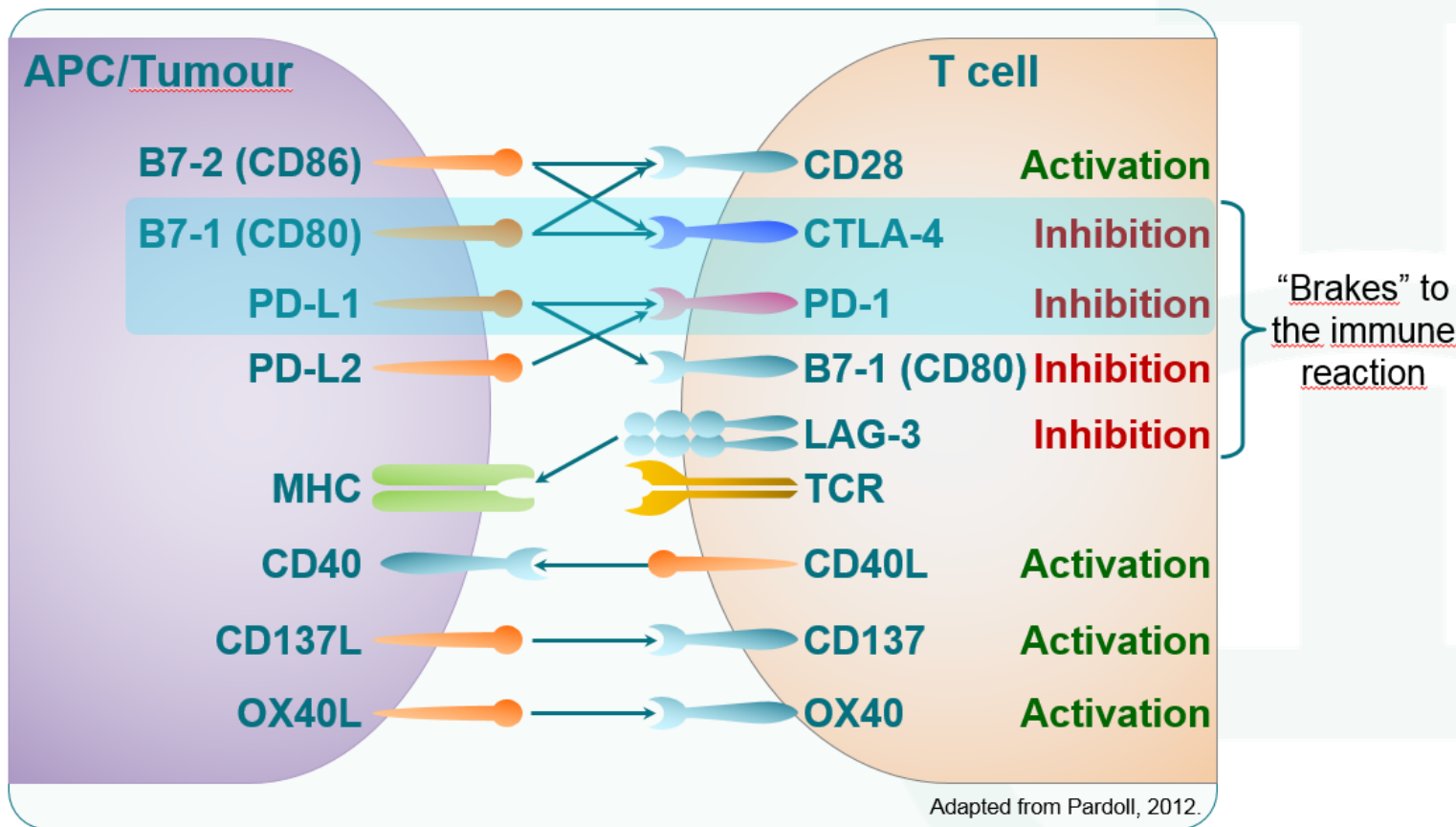


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Immunonkologie: Tumor-Immunogenität



Immunonkologie: Checkpoint Pathways



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L, programmed death ligand; TCR, T-cell receptor.
 Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264.



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EMA Zulassungsstatus Checkpoint-Inhibitoren

Wirkung	Substanz	Indikation(en)
CTLA-4	Ipilimumab (Yervoy®)	<ul style="list-style-type: none"> • Malignes Melanom (nicht resektabel) +/- Nivolumab und adjuvant • Fortgeschrittenes Nierenzellkarzinom + Nivolumab (intermediäres oder ungünstiges Risikoprofil, 1. Linie)
PD-1	Nivolumab (Opdivo®)	<ul style="list-style-type: none"> • Malignes Melanom Stadium III (N+) oder Stadium IV +/- Ipilimumab • NSCLC (nicht resektabel, nach CHT) • RCC (nicht resektabel, 2. Linie) +/- Ipilimumab (nicht resektabel, 2. Linie Monotherapie oder (intermediäres oder ungünstiges Risikoprofil, 1. Linie Kombinationstherapie) • Morbus Hodgkin (nach ABSCT + Brentuximab) • Plattenepithel-Ca bei Kopf-Hals-Tumoren nach Cisplatin • Urothelkarzinom nach platinhaltiger CHT
PD-1	Pembrolizumab (Keytruda®)	<ul style="list-style-type: none"> • Malignes Melanom (nicht resektabel) und adjuvant • NSCLC (nicht resektabel; 1. Linie: PD-L1 >50% oder CHT-Kombinationstherapie; 2. Linie nach CHT) • RCC (nicht resektabel: 1. Linie mit Axitinib) • Morbus Hodgkin (nach ABSCT + Brentuximab) • Plattenepithel-Ca bei Kopf-Hals-Tumoren nach Cisplatin (PD-L1 >50%) • Urothelkarzinom nach platin-hältiger CHT oder nicht geeignet für Platin
PD-L1	Atezolizumab (Tencentriq®)	<ul style="list-style-type: none"> • NSCLC (nicht resektabel; 2. Linie nach CHT; 1. Linie nsq mit CHT +/- Bevacizumab) • ES-SCLC (nicht resektabel; 1. Linie mit CHT) • TNBC (nicht resektabel, 1. Linie mit CHT bei PD-L1 ≥ 1%) • Urothelkarzinom nach platinhaltiger CHT oder nicht geeignet für Platin bei PD-L1 ≥ 5%
PD-L1	Avelumab (Bavencio®)	<ul style="list-style-type: none"> • Metastasiertes Merkelzellkarzinom nach CT
PD-L1	Durvalumab (Imfinzi®)	<ul style="list-style-type: none"> • NSCLC (nicht resektabel Stadium III nach RCT; PD-L1 >20%)
PD-1	Cemiplimab (Libtayo®)	<ul style="list-style-type: none"> • Fortgeschrittenes kutanes Plattenzellkarzinom

I-O Highlights 2019 betreffen Vielzahl Tumorentitäten

- Melanom
- Bronchuskarzinom
- Nierenzellkarzinom
- Urothelkarzinom
- Kopf-Hals-Tumoren
- Brustkrebs
- Magenkrebs
- Speiseröhrenkrebs
- Hepatozelluläres Karzinom
- Kutanes Plattenzellkarzinom

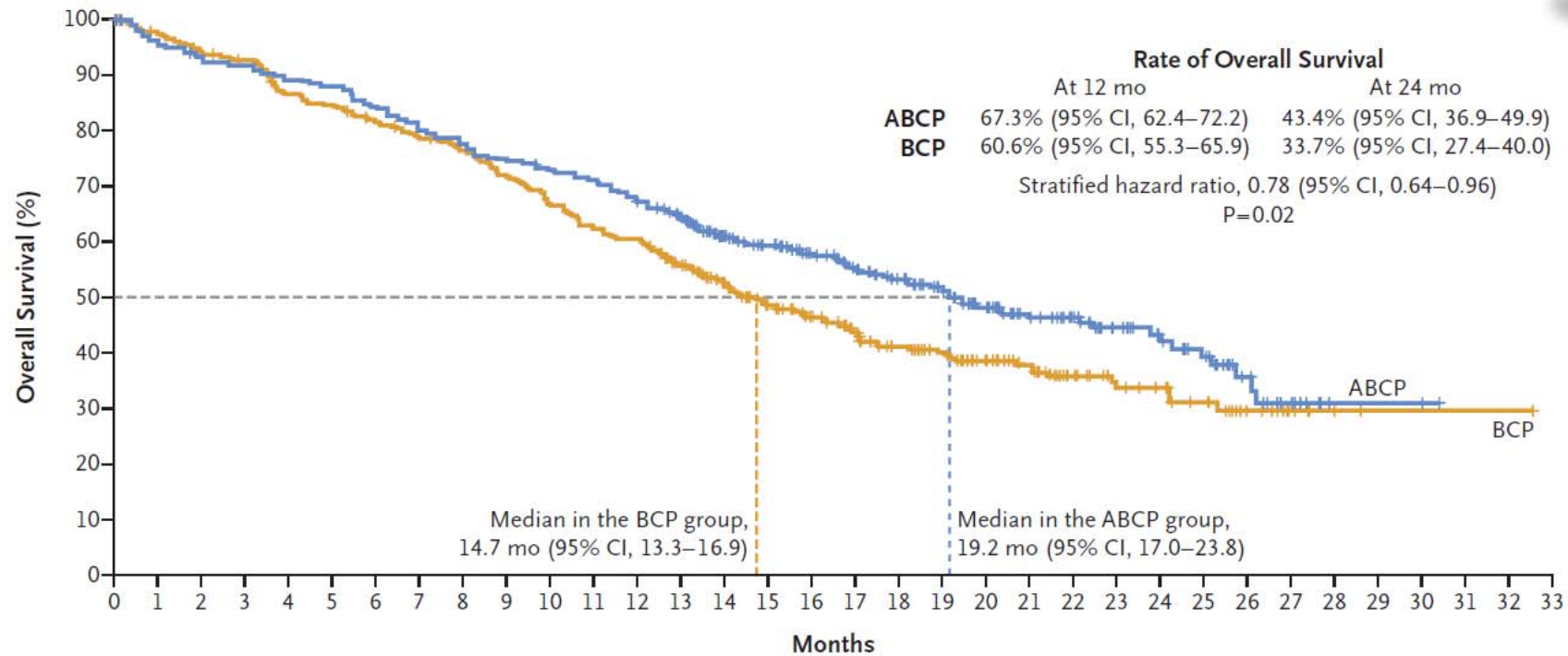
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Bronchuskarzinom
NSCLC



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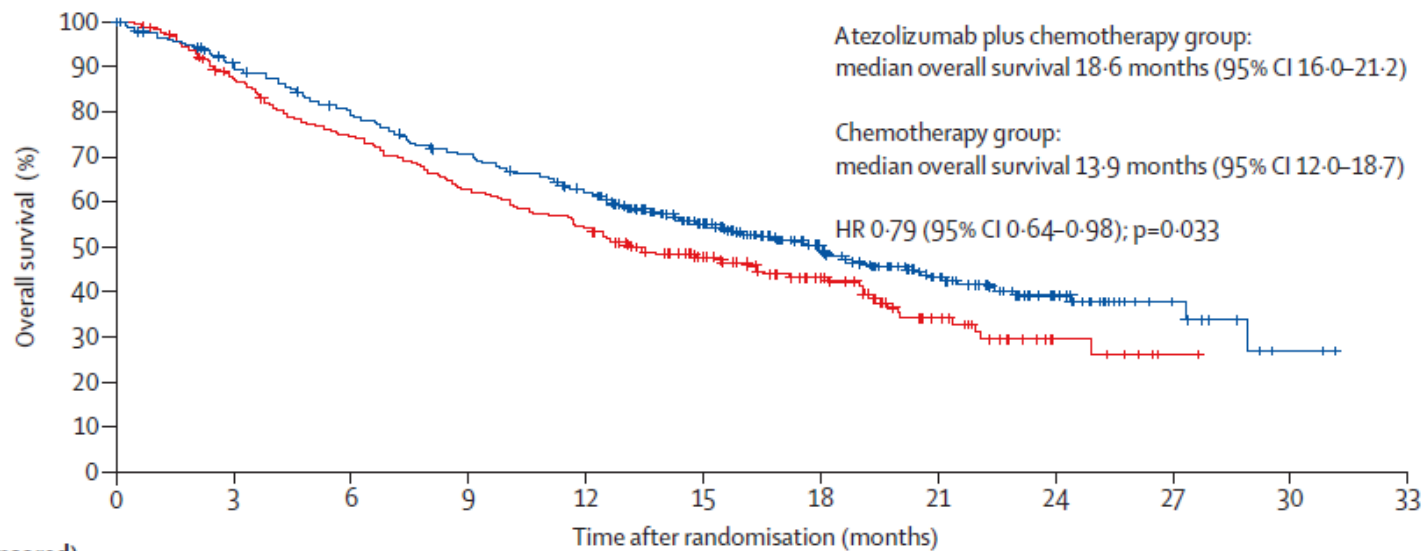
IL NSCLC, Adenokarzinom, Impower-150, Overall Survival



No. at Risk

ABCP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2	
BCP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1

IL NSCLC, Adenokarzinom, Impower-130, Overall Survival



Number at risk (number censored)		0	3	6	9	12	15	18	21	24	27	30	33
Atezolizumab plus chemotherapy group		451 (0)	400 (10)	351 (15)	305 (18)	268 (22)	194 (68)	129 (120)	75 (161)	40 (188)	12 (215)	4 (221)	
Chemotherapy group		228 (0)	190 (12)	161 (13)	136 (13)	119 (13)	90 (28)	58 (52)	31 (70)	13 (85)	3 (94)	0 (0)	

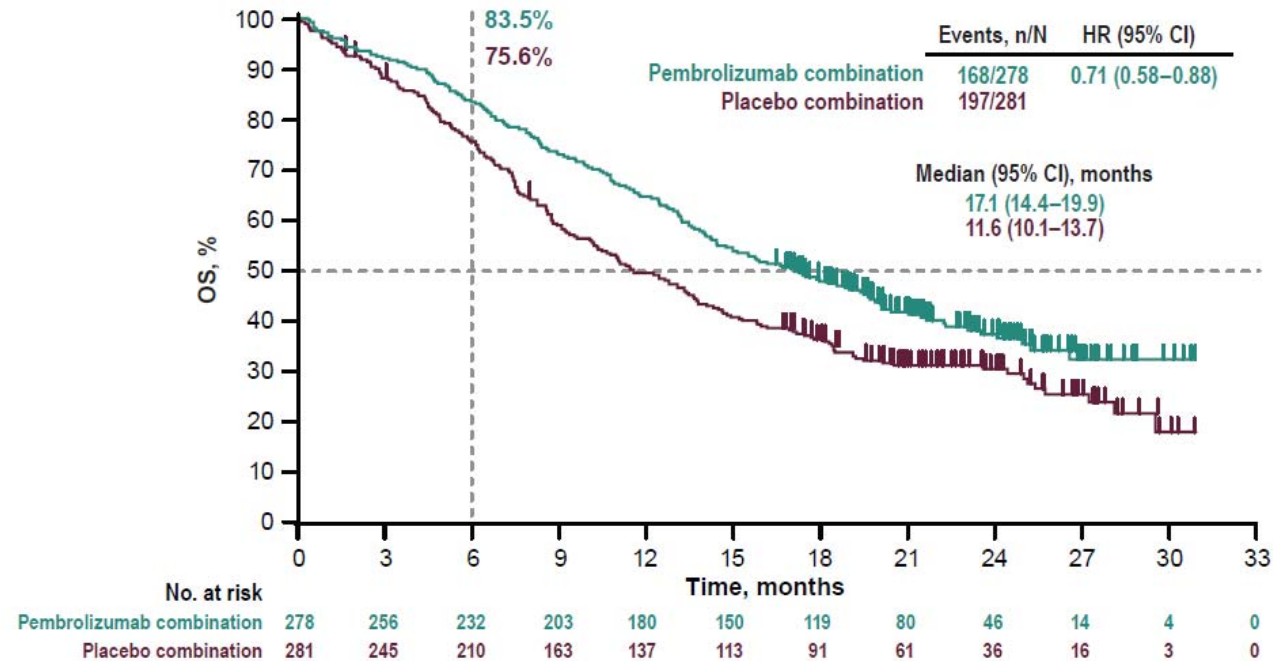
carboplatin plus nab-paclitaxel



IL NSCLC, Plattenzellkarzinom, Keynote-407, Overall Survival



Figure 3. Kaplan-Meier Estimates of OS in the Total Population (ITT)

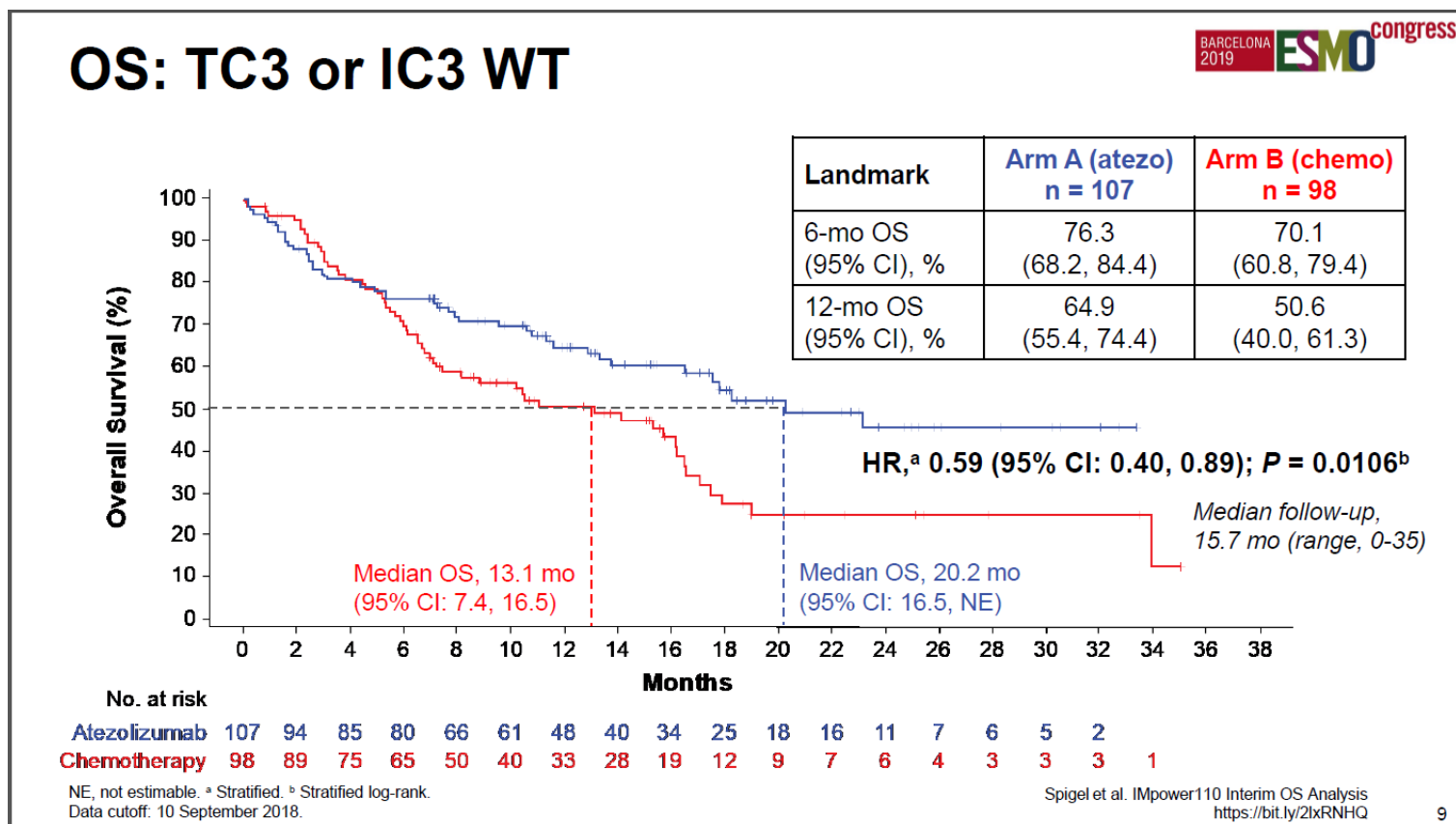


n, number of patients who died; N, number of patients in the group; NR, not reached.

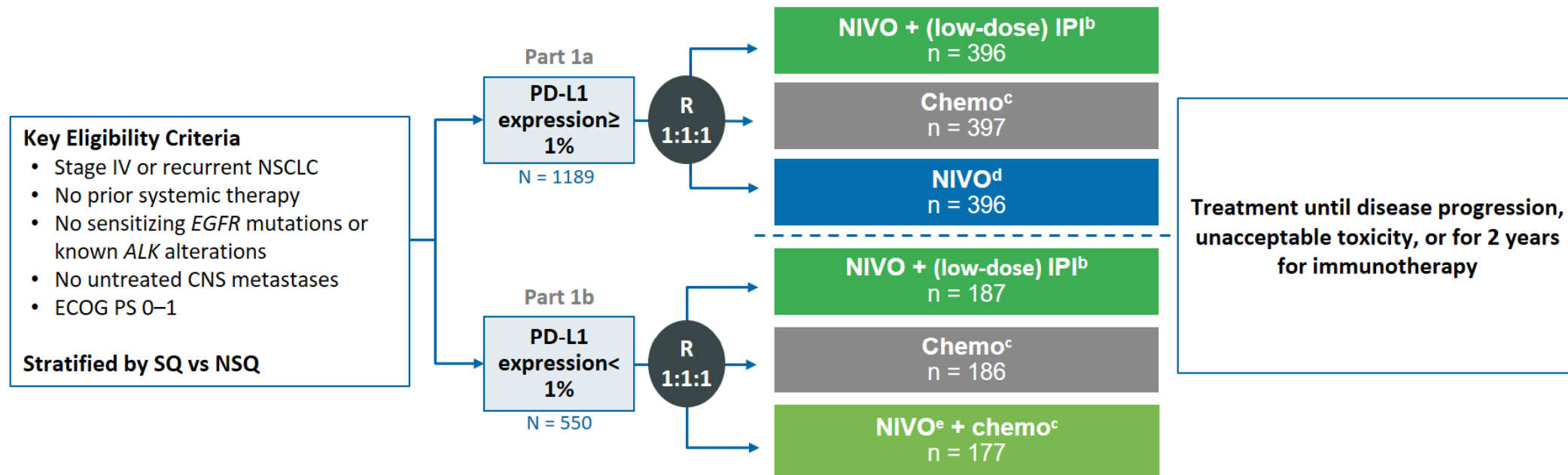
carboplatin and paclitaxel/nab-paclitaxel



1L NSCLC, Impower-110, Overall Survival, TC3 or IC3



IL NSCLC, CheckMate-227, study design



Independent co-primary endpoints: NIVO + IPI vs chemo

- PFS in high TMB (≥ 10 mut/Mb) population^f
- OS in PD-L1 $\geq 1\%$ population^g

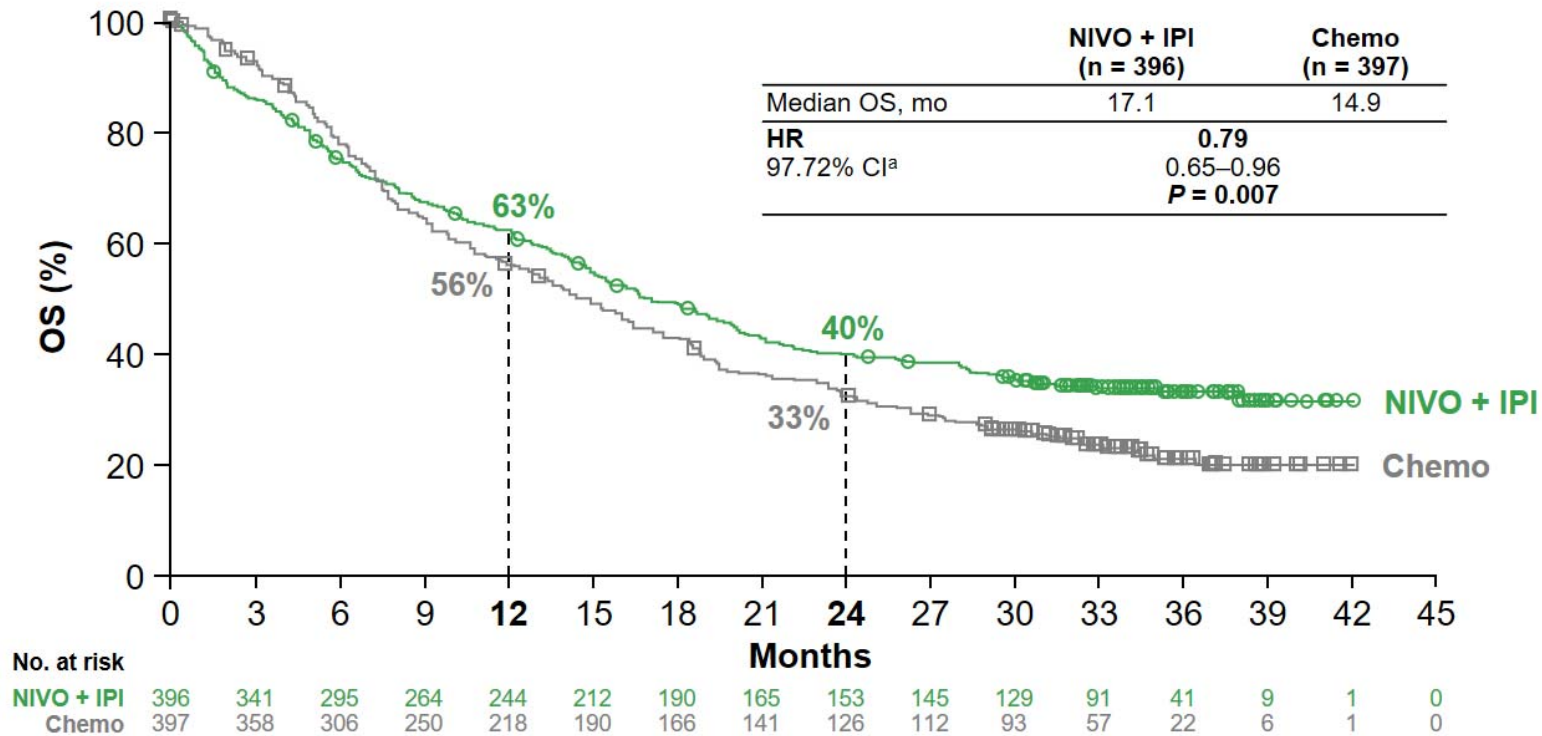
Secondary endpoints (PD-L1 hierarchy):

- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 $\geq 50\%$

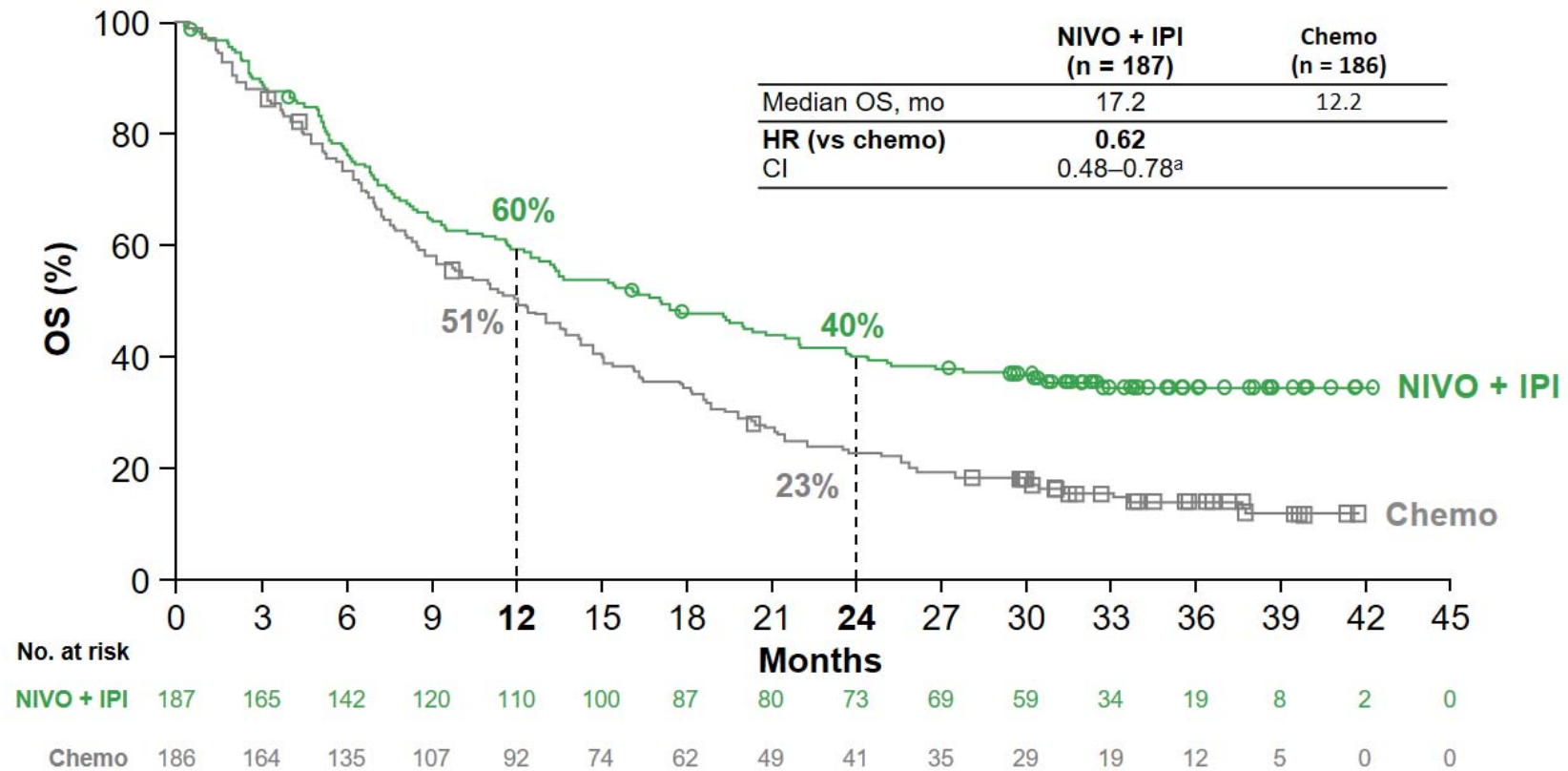
Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

Peters et al. ESMO 2019

IL NSCLC, CheckMate-227, Overall Survival, PD-LI $\geq 1\%$

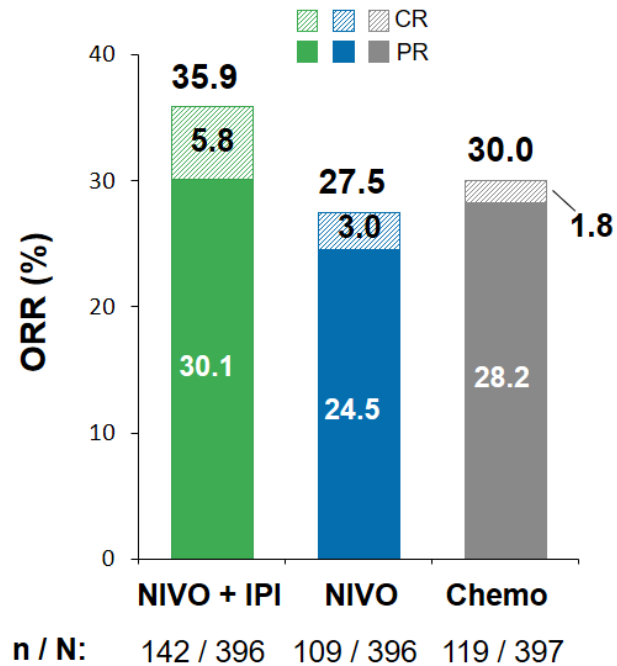


IL NSCLC, CheckMate-227, Overall Survival, < 1%

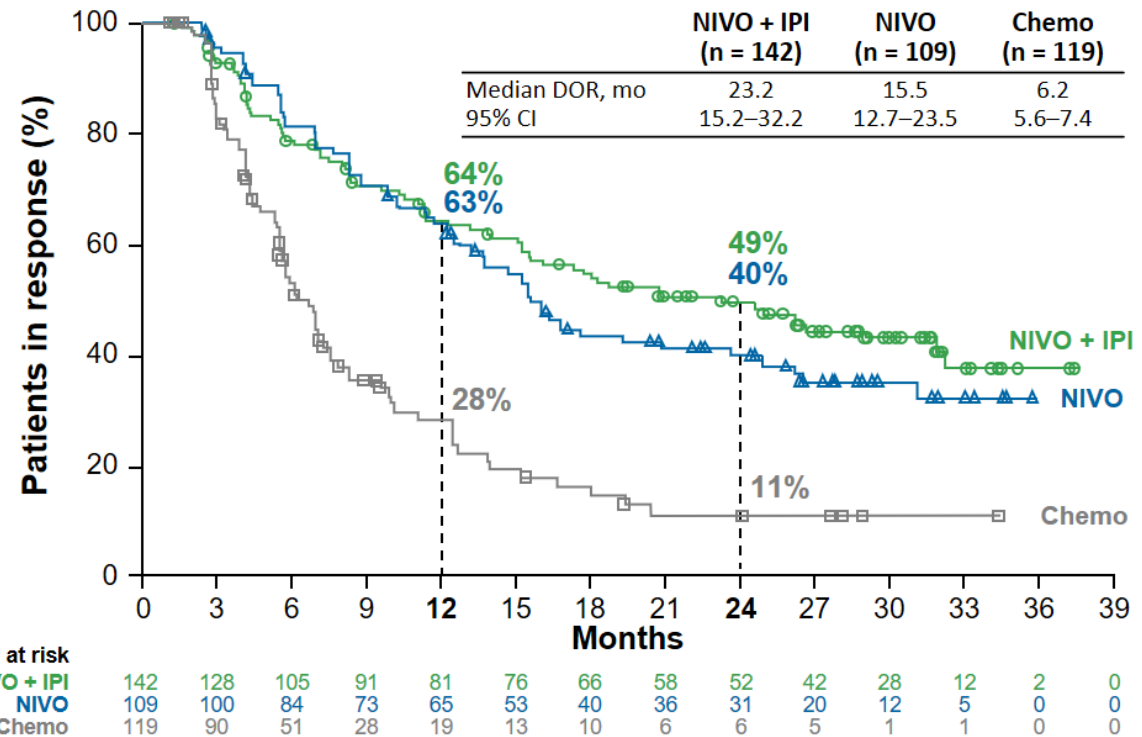


IL NSCLC, CheckMate-227, ORR & DOR, PD-LI ≥ 1%

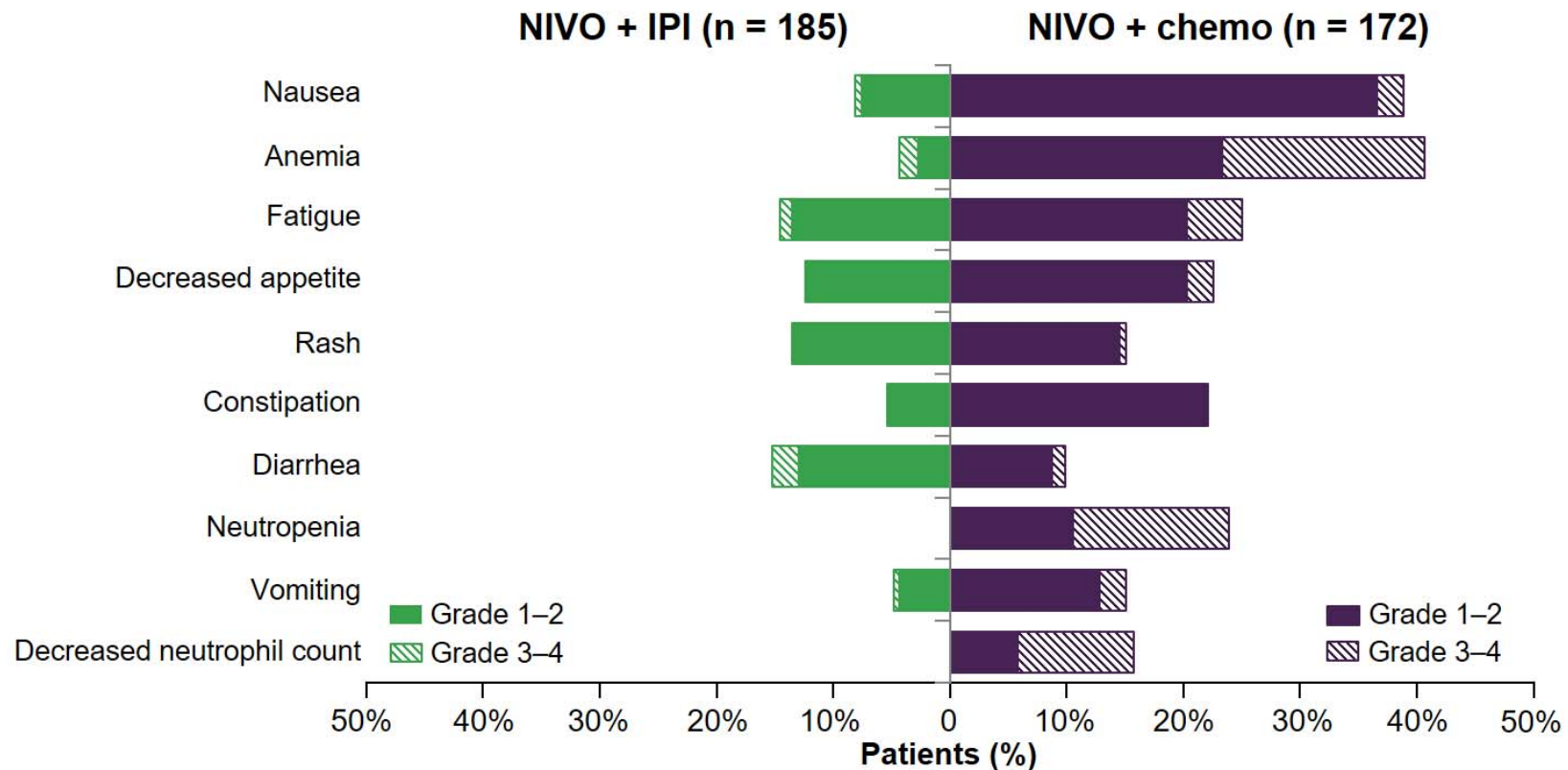
ORR by BICR



DOR by BICR^a

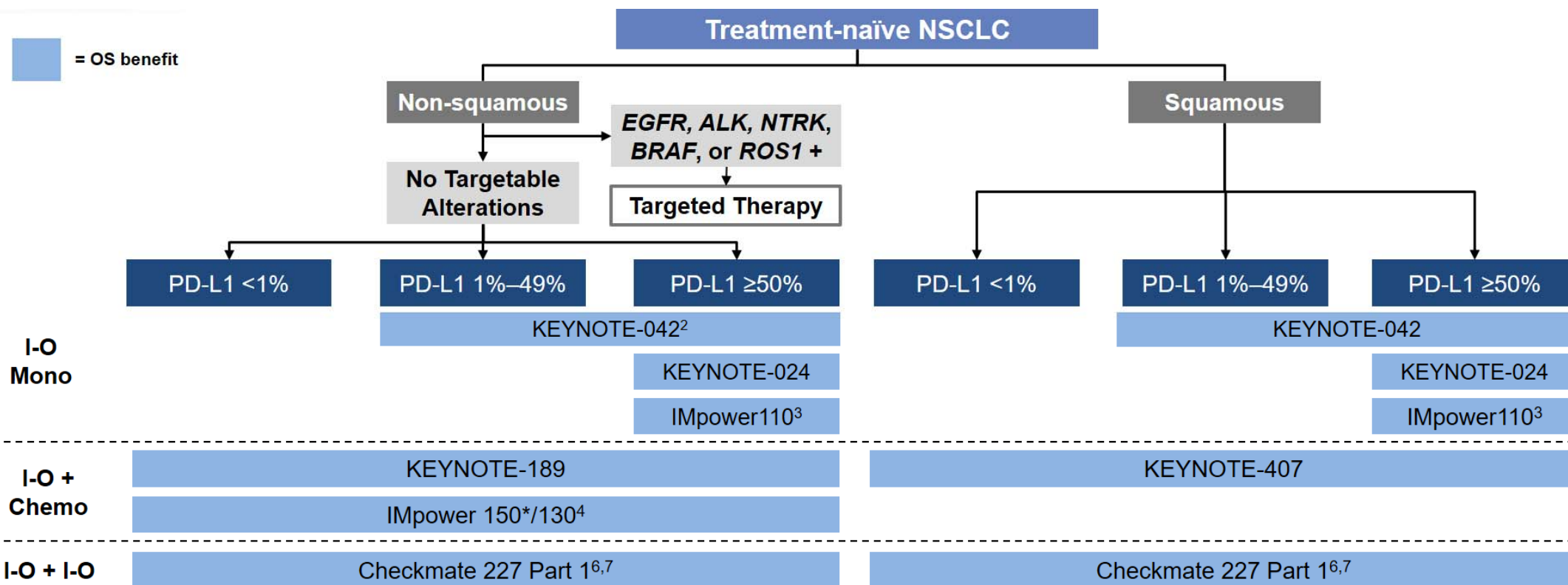


IL NSCLC, CheckMate-227, häufigsten therapieassoziierte AEs



Aktueller und potenziell künftiger 1L NSCLC Behandlungsalgorithmus

Phase 3 research with I-O + I-O¹⁻⁴



This diagram is intended for educational purposes only. It reflects the views of the presenter and not the current treatment landscape in NSCLC.

6. 2019. 5. Barlesi F et al. Oral presentation at ESMO 2018. LBA54. 6. Hellmann MD et al. N Engl J Med. 2018;378(22):2093-2104. 7. Bristol-Myers Squibb [press release]. July 24, 2019. *In patients with EGFR-mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated in the EU after failure of appropriate targeted therapies.11. European Medicines Agency. ema.europa.eu. Accessed September 24, 2019. 2. Mok TSK et al. Oral presentation at ELCC 2019. 102O. 3. Spigel D et al. Oral presentation at ESMO 2019. LBA78. 4. Roche [press release]. September



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Immunonkologische Highlights des Jahres 2019 & Ausblick auf 2020

Bronchuskarzinom
SCLC



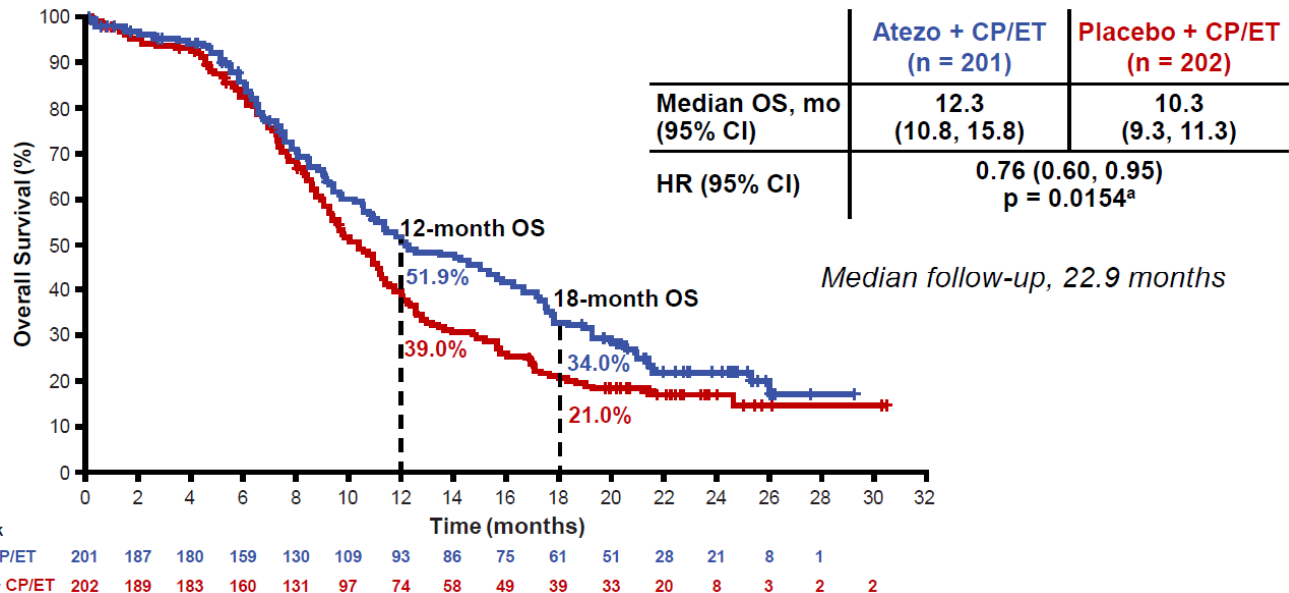
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IL ES-SCLC, Impower-133, Overall Survival



BARCELONA 2019 ESMO congress

Updated OS in ITT



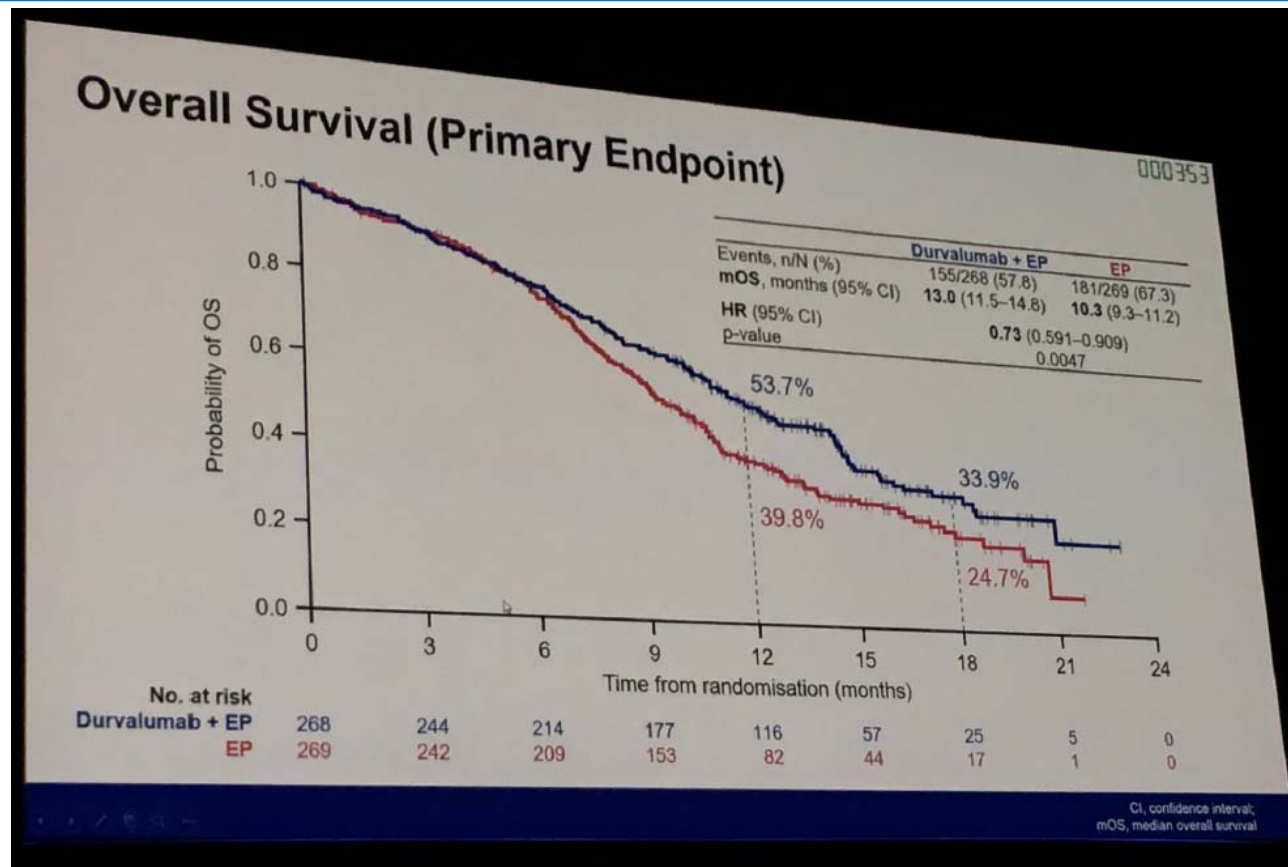
^ap-value is provided for descriptive purpose.
CCOD 24 January 2019

Impower133 Updated OS Analysis: presented by Dr Martin Reck

<http://bit.ly/2Z32WhW>



IL ES-SCLC, CASPIAN, Overall Survival



Cisplatin or carboplatin and etoposid



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Brustkrebs

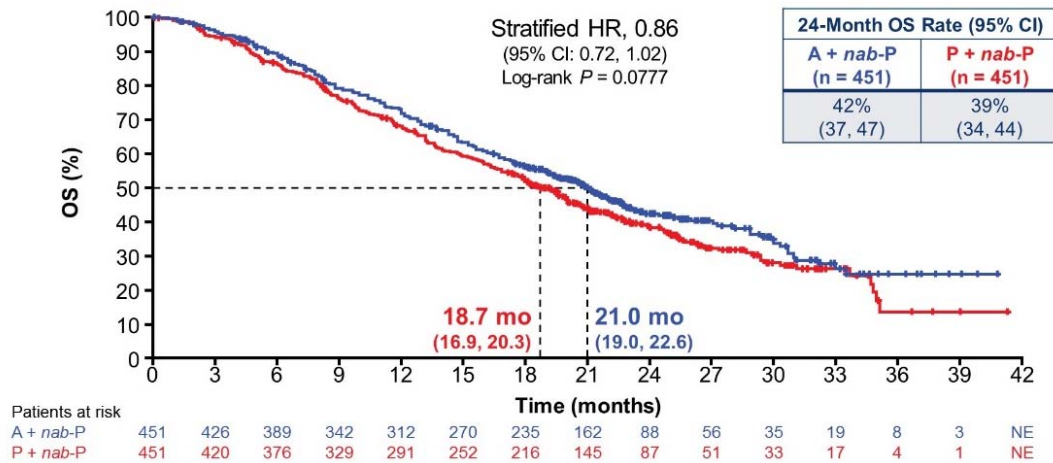


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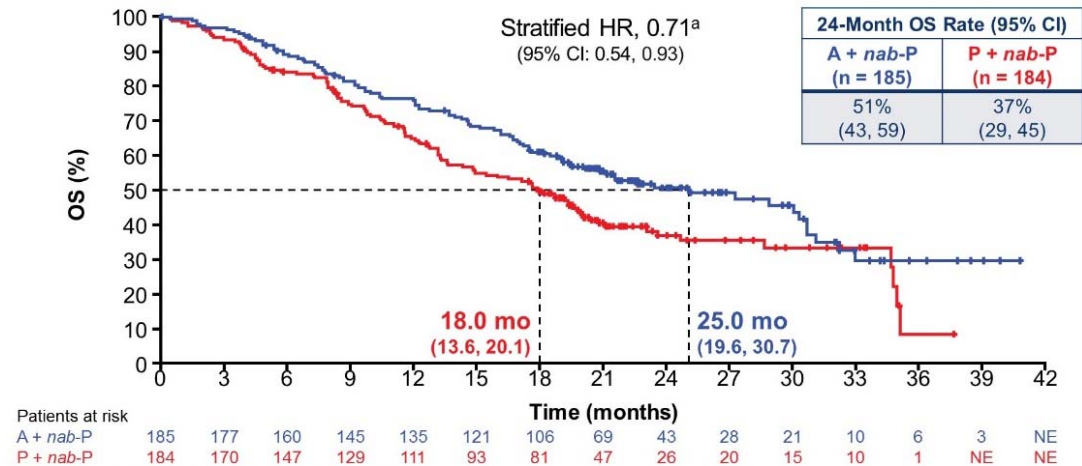
IL mTNBC, Impassion-130, Overall Survival, PD-L1 <1%



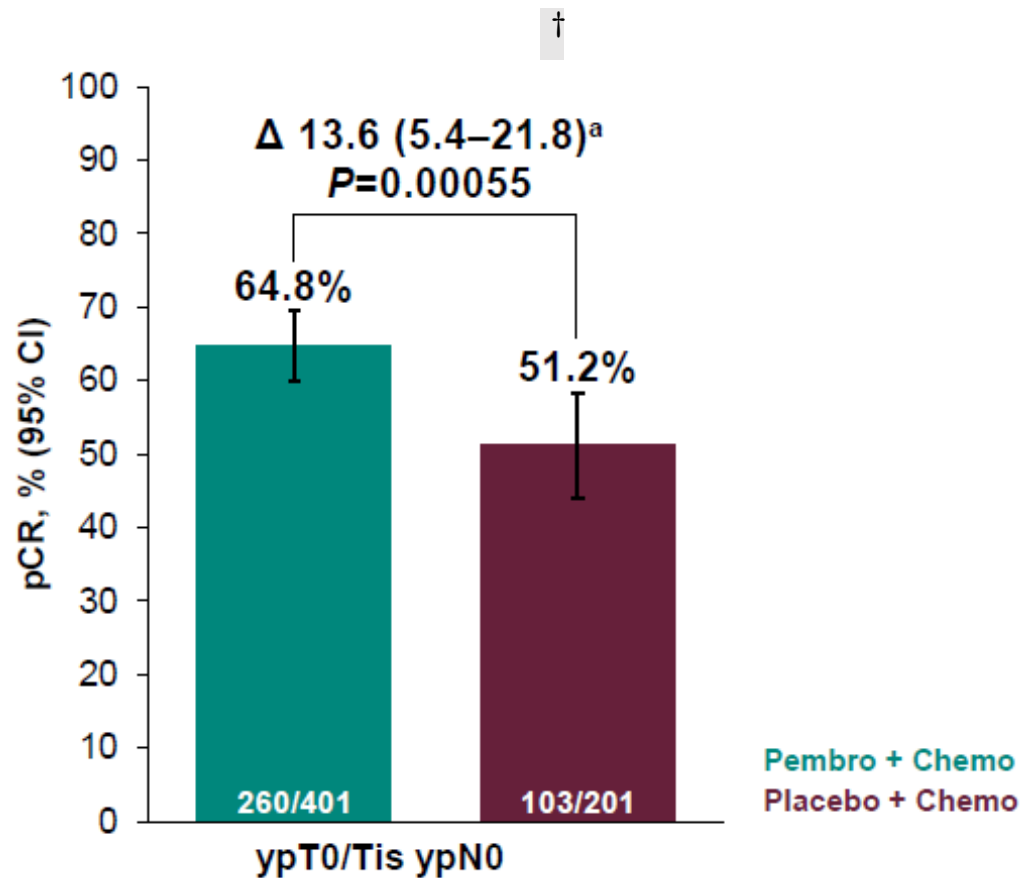
OS in ITT Population



OS in PD-L1+ Population



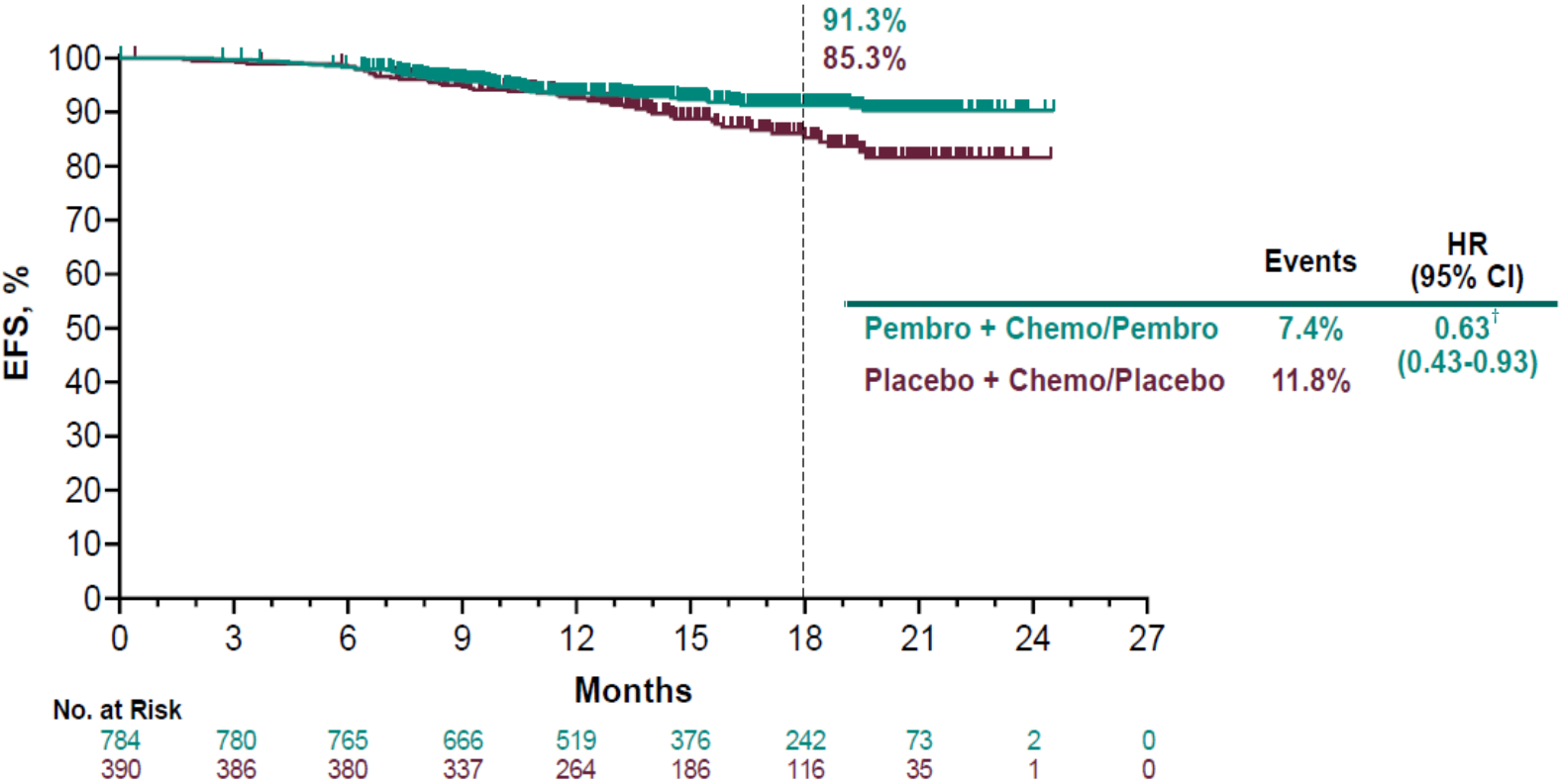
Peri-operativ, TNBC, Keynote-522, pathological Complete Response



Results

- Addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy resulted in a statistically significant and clinically meaningful increase in pCR (ypT0/Tis ypN0) of 13.6 percentage points ($P=0.00055$)
- Consistent benefit is seen with other pCR definitions (ypT0 ypN0 and ypT0/Tis; data not shown)

Peri-operativ, TNBC, Keynote-522, Event Free Survival



At this early timepoint, there was a favorable trend for EFS in the pembrolizumab arm (HR=0.63)



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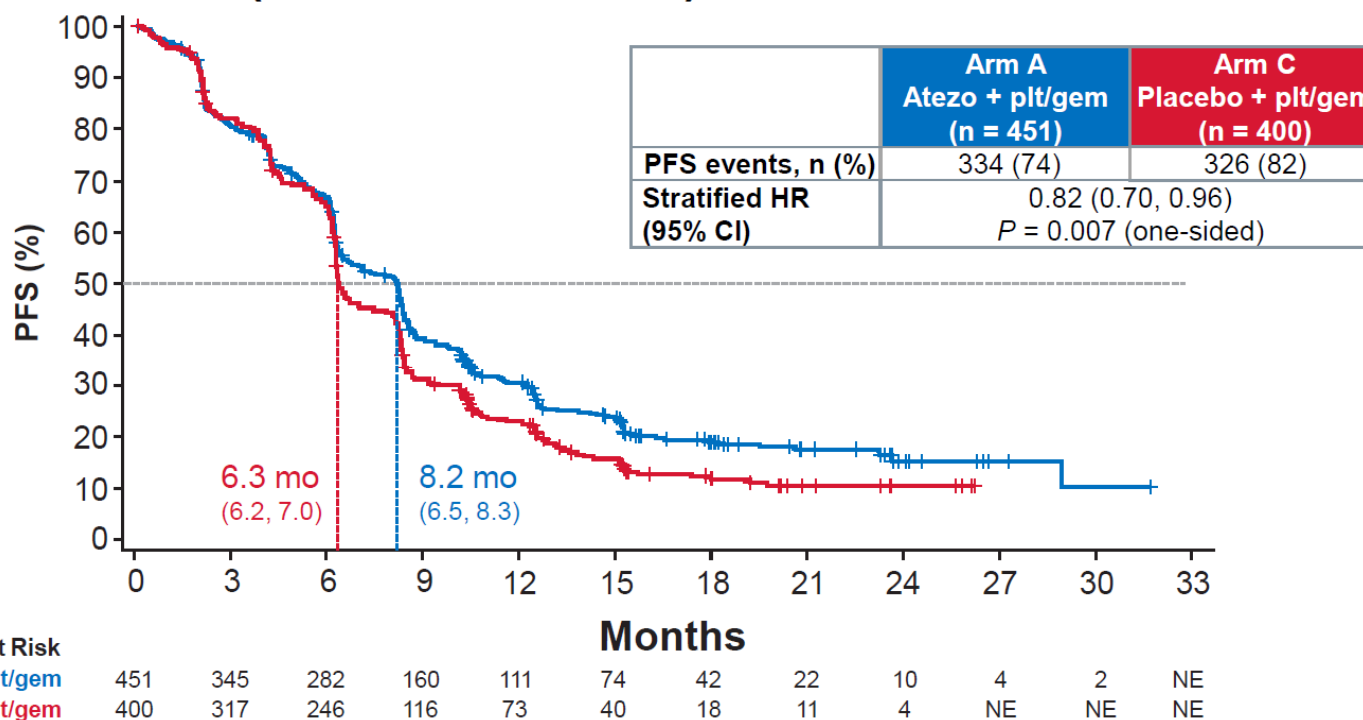
Urothelkarzinom



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IL mUC, Imvigor-130, Progression Free Survival

Final PFS: ITT (Arm A vs Arm C)



NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

IMvigor130—ESMO 2019 (LBA14); presented by Dr Enrique Grande

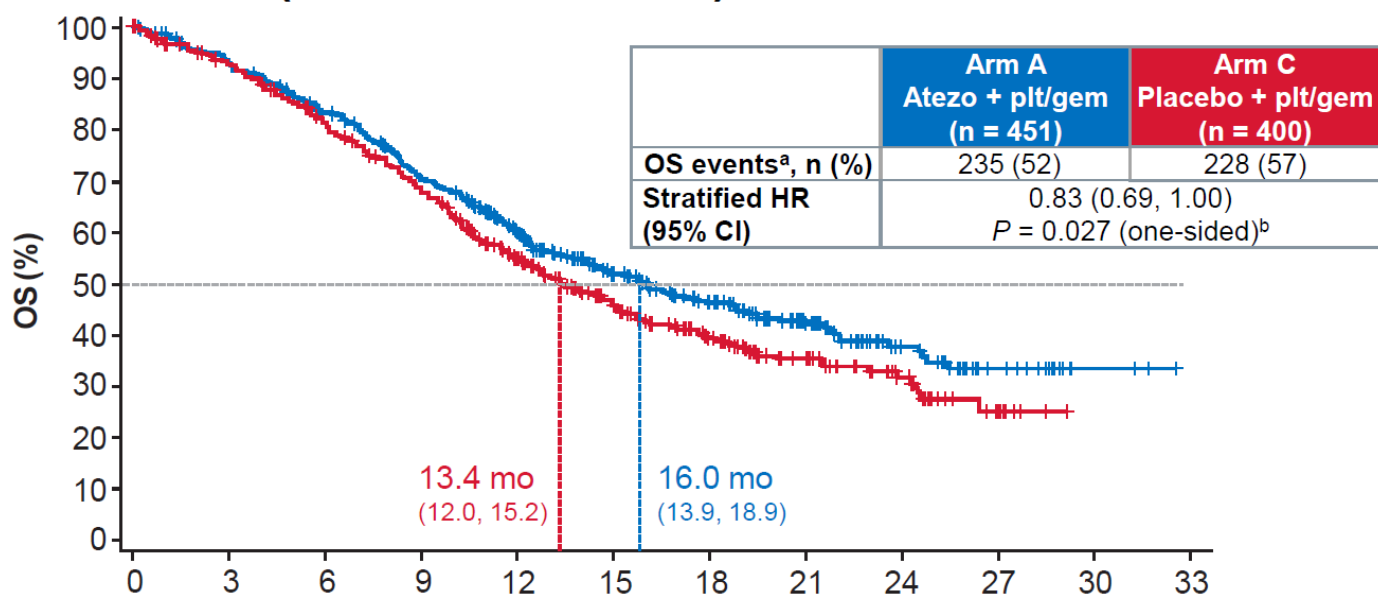
<http://bit.ly/2Z1bPbD>



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IL mUC, Invigor-130, Overall Survival

Interim OS: ITT (Arm A vs Arm C)



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). ^a 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. ^b Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

IMvigor130—ESMO 2019 (LBA14); presented by Dr Enrique Grande

<http://bit.ly/2Z1bPbD>



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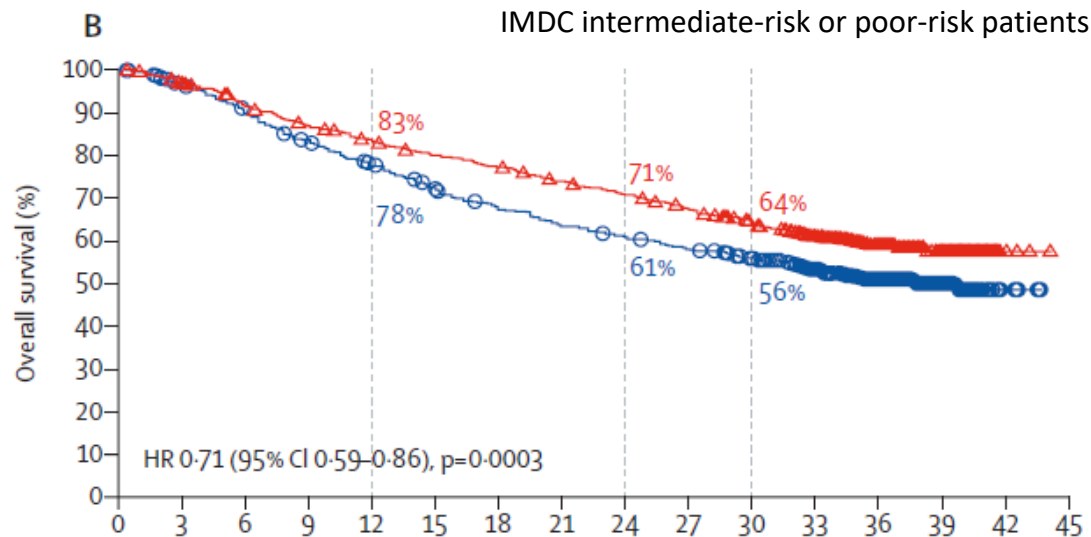
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Nierenzellkarzinom



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IL RCC, CheckMate-214, Overall Survival



Number at risk (number censored)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Nivolumab plus ipilimumab	550 (0)	523 (8)	492 (11)	464 (13)	443 (16)	425 (18)	410 (18)	389 (21)	371 (22)	351 (25)	327 (33)	271 (76)	161 (178)	58 (278)	4 (332)	0 (336)
Sunitinib	546 (0)	507 (16)	472 (17)	435 (20)	404 (23)	367 (28)	345 (29)	325 (29)	310 (30)	295 (31)	275 (41)	232 (71)	145 (150)	55 (238)	5 (287)	0 (292)

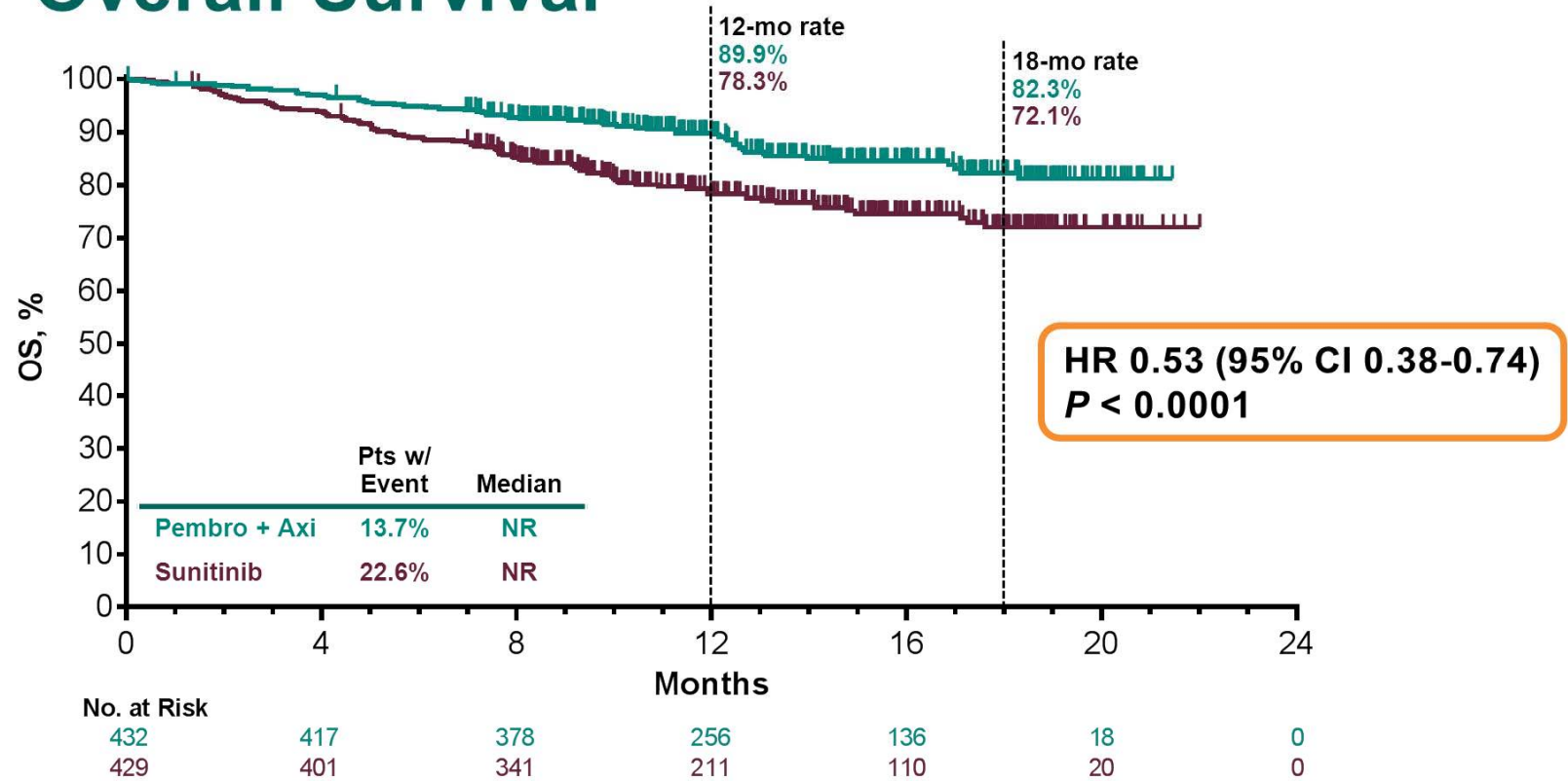
	IMDC intermediate-risk or poor-risk patients		
	Nivolumab plus ipilimumab (n=425)	Sunitinib (n=422)	p value
Proportion of patients with confirmed objective responses, % (95% CI)	42% (37-47)	29% (25-34)	0.0001
Best overall response			
Complete response	48 (11%)	5 (1%)	..
Partial response	130 (31%)	119 (28%)	..
Stable disease	110 (26%)	174 (41%)	..
Progressive disease	106 (25%)	80 (19%)	..
Unable to determine or not reported	31 (7%)	44 (10%)	..
Median time to confirmed objective response (IQR), months*	n=176; 2.8 (2.7-3.1)	n=124; 4.0 (2.8-5.5)	..
Median time to confirmed complete response (IQR), months	n=48; 5.8 (2.9-10.5)	Not calculated	..
Patients with duration of response ≥18 months*	92/176 (52%)	35/124 (28%)	..
Patients with ongoing response*	104/176 (59%)	43/124 (35%)	..
Patients with ongoing complete response	42/48 (88%)	4/5 (80%)	..



IL RCC, Keynote-426, Overall Survival



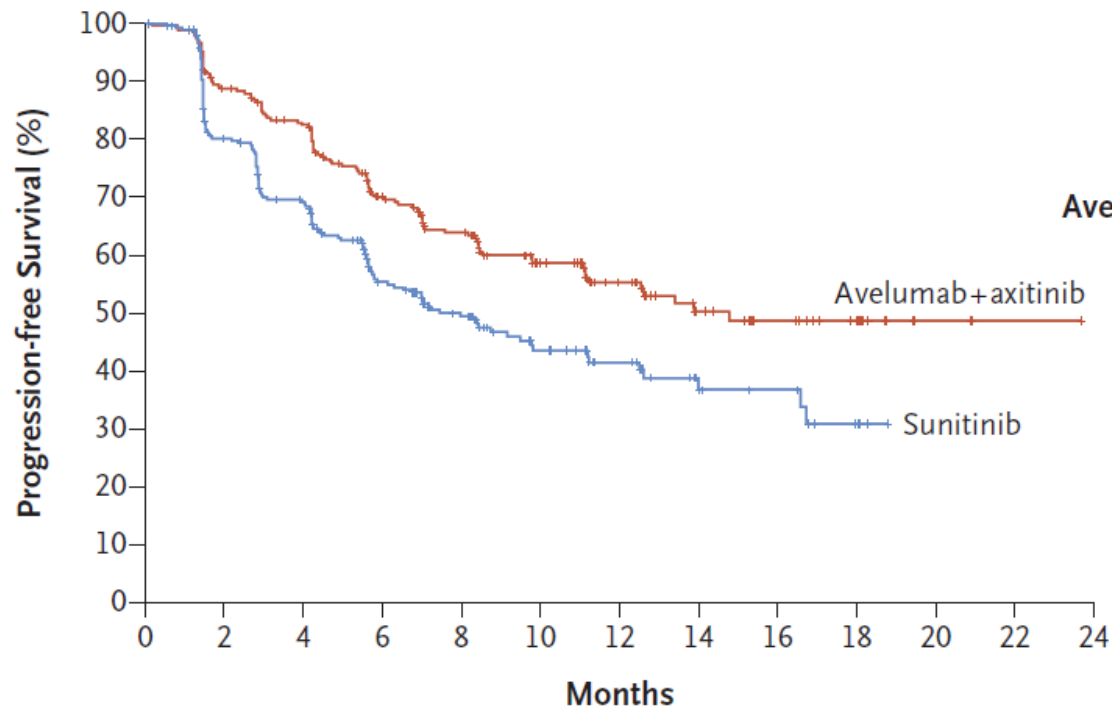
Overall Survival



**HR 0.53 (95% CI 0.38-0.74)
P < 0.0001**

IL RCC, JAVELIN Renal 101, Progression Free Survival, PD-L1 ≥ 1

A Patients with PD-L1-Positive Tumors



	Median Progression-free Survival (95% CI) <i>mo</i>
Avelumab+Axitinib	13.8 (11.1–NE)
Sunitinib	7.2 (5.7–9.7)

Stratified hazard ratio for disease progression or death, 0.61 (95% CI, 0.47–0.79)
P<0.001

Primary endpoints:

- PFS PD-L1 ≥ 1 ✓
- OS PD-L1 ≥ 1

No. at Risk

Avelumab+axitinib	270	227	205	154	120	76	53	32	23	13	3	1	0
Sunitinib	290	210	174	119	85	49	35	16	13	5	0		

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Melanom

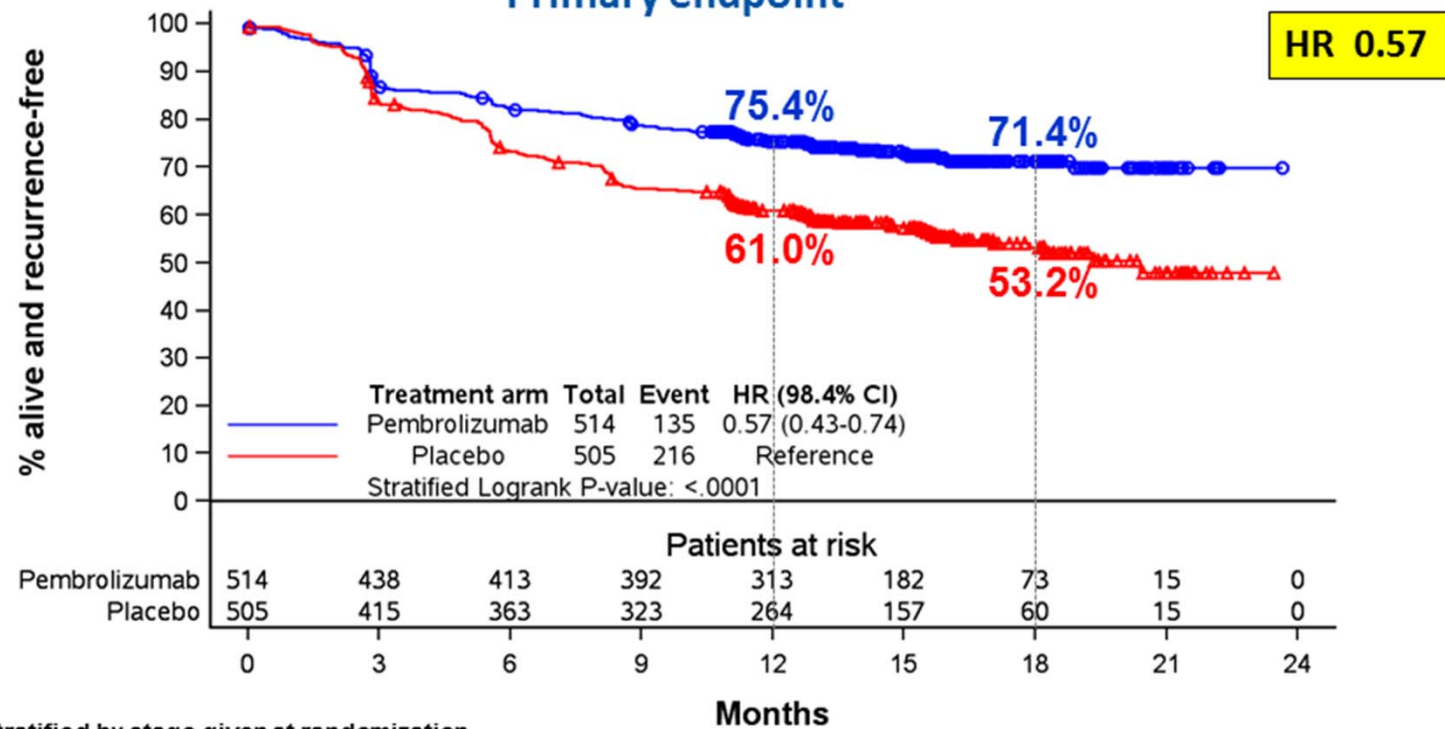


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Adj MEL, Keynote-054, Event Free Survival



Recurrence-Free Survival in the ITT Population Primary endpoint

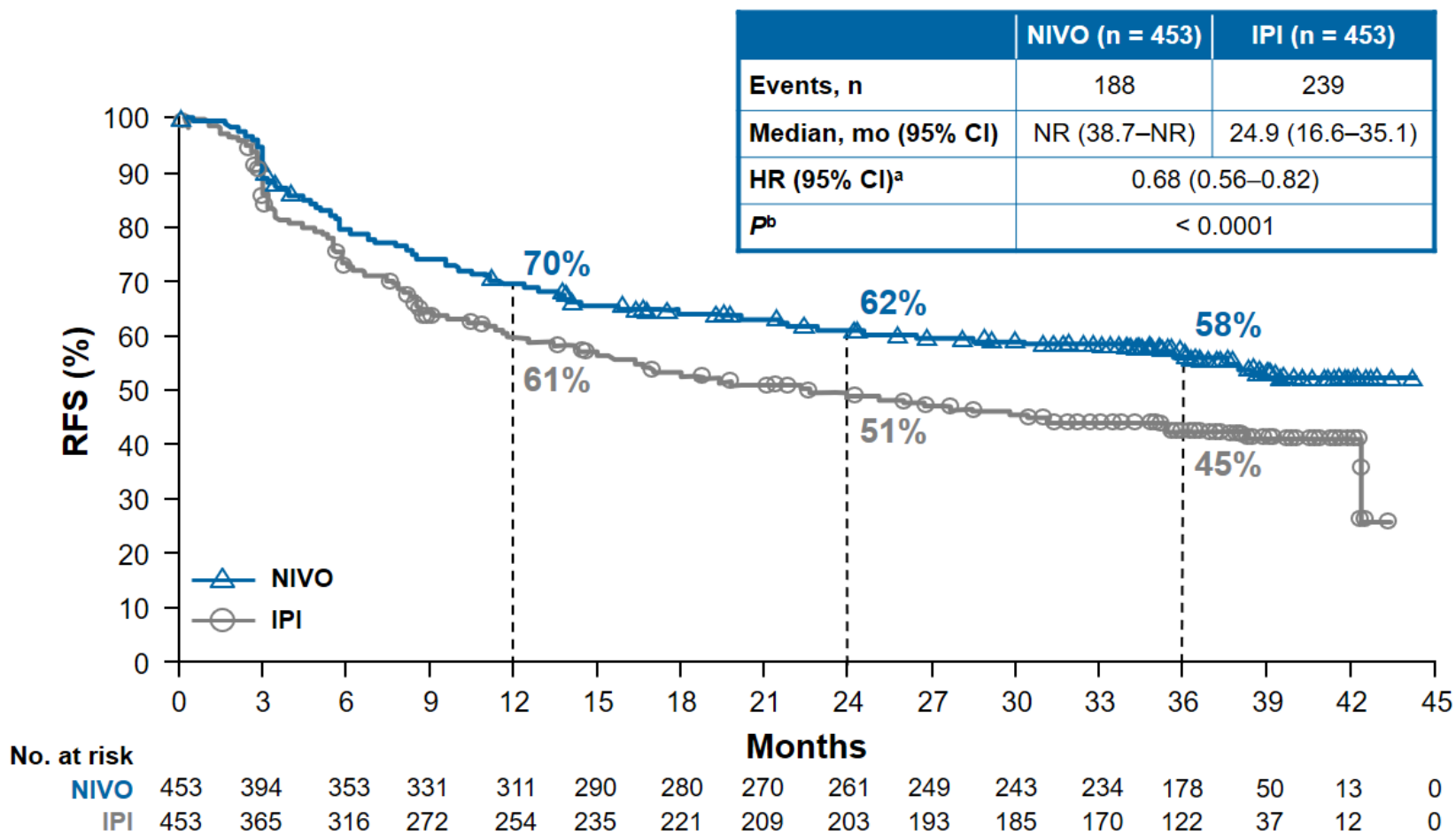


*Stratified by stage given at randomization



The future of cancer therapy

Adj MEL, CheckMate-238, Event Free Survival



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Kutanes Plattenzellkarzinom

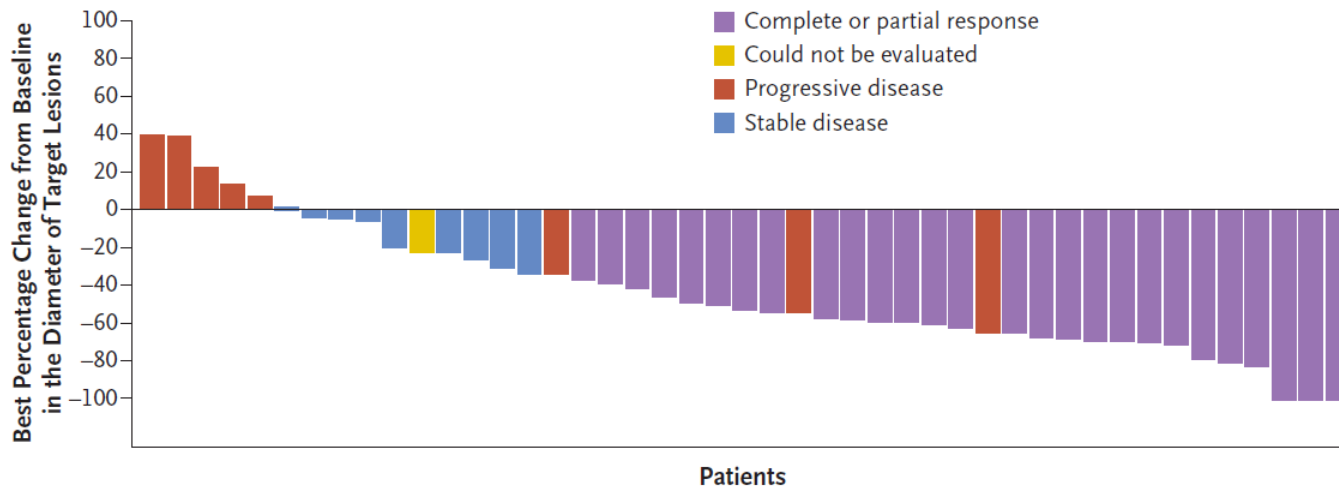


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IL CSCC, Impower CSCC I, Overall Response Rate



Best Tumor Response for 45 Patients in the Phase 2 Study



Cemiplimab

Outcome	Expansion Cohorts of the Phase 1 Study (N = 26)	Metastatic-Disease Cohort of the Phase 2 Study (N = 59)
Best overall response — no. (%) [†]		
Complete response	0	4 (7)
Partial response	13 (50)	24 (41)
Stable disease	6 (23)	9 (15)
Progressive disease	3 (12)	11 (19)
Could not be evaluated [‡]	3 (12)	7 (12)
Nontarget lesions only [§]	1 (4)	4 (7)

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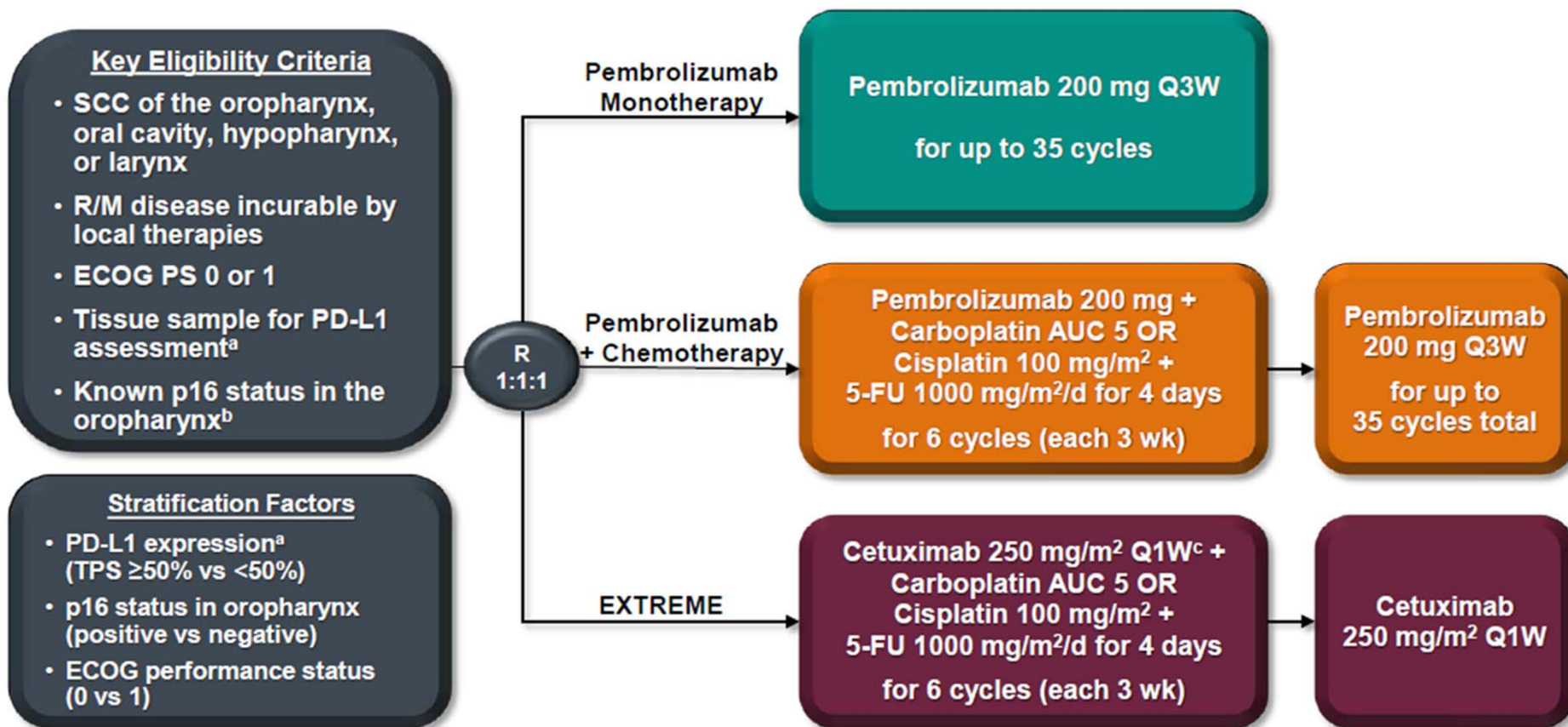
Kopf-Hals-Tumoren



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IL H&N, Keynote-048, study design

- Primary endpoints:
- OS and PFS
 - CPS ≥ 20
 - CPS ≥ 1
 - ITT



IL H&N, Keynote-048, Overall Survival Pembro + Chemo

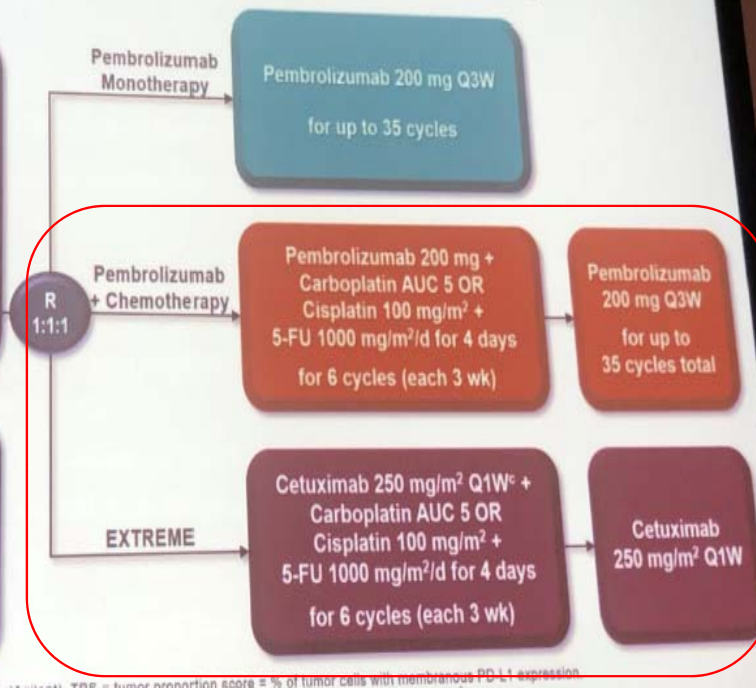
KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

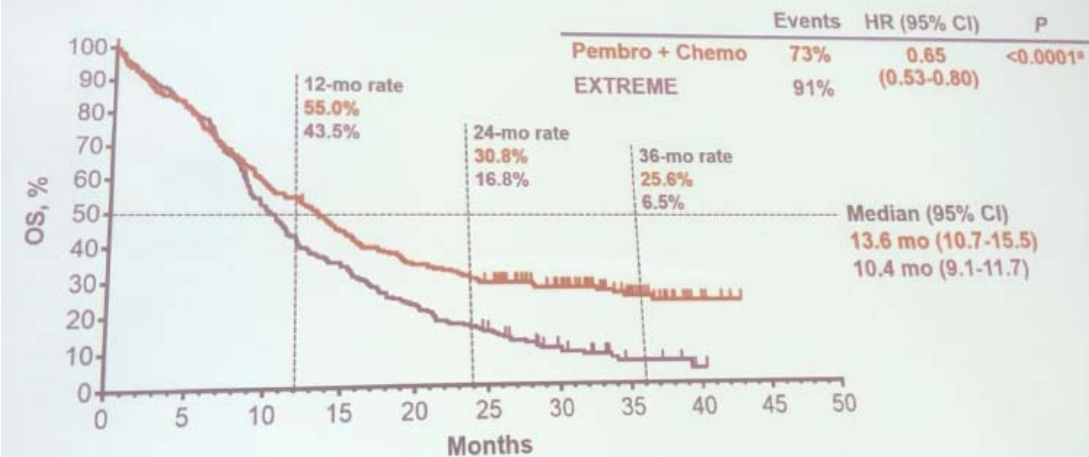
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment^a
- Known p16 status in the oropharynx^b

Stratification Factors

- PD-L1 expression^a (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)



OS, P+C vs E, CPS ≥1 Population



OS benefit in

- CPS ≥ 20 (HR=0.60)
- CPS ≥ 1 (HR=0.65)
- ITT (HR=0.72)

IL H&N, Keynote-048, Overall Survival Pembro mono

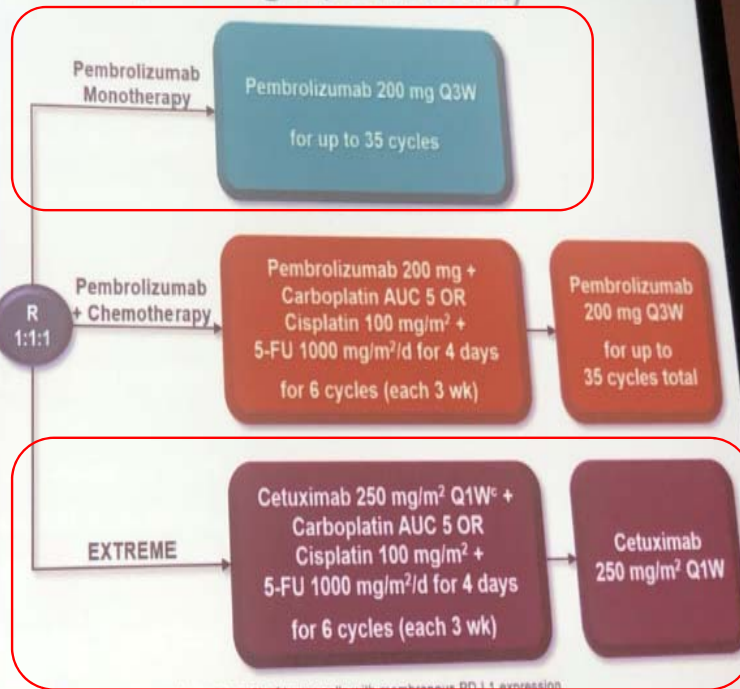
KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment^a
- Known p16 status in the oropharynx^b

Stratification Factors

- PD-L1 expression^a (TPS $\geq 50\%$ vs $< 50\%$)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)



OS, P vs E, CPS ≥ 20 Population



OS benefit in

- CPS ≥ 20 (HR=0.58)
- CPS ≥ 1 (HR=0.74)

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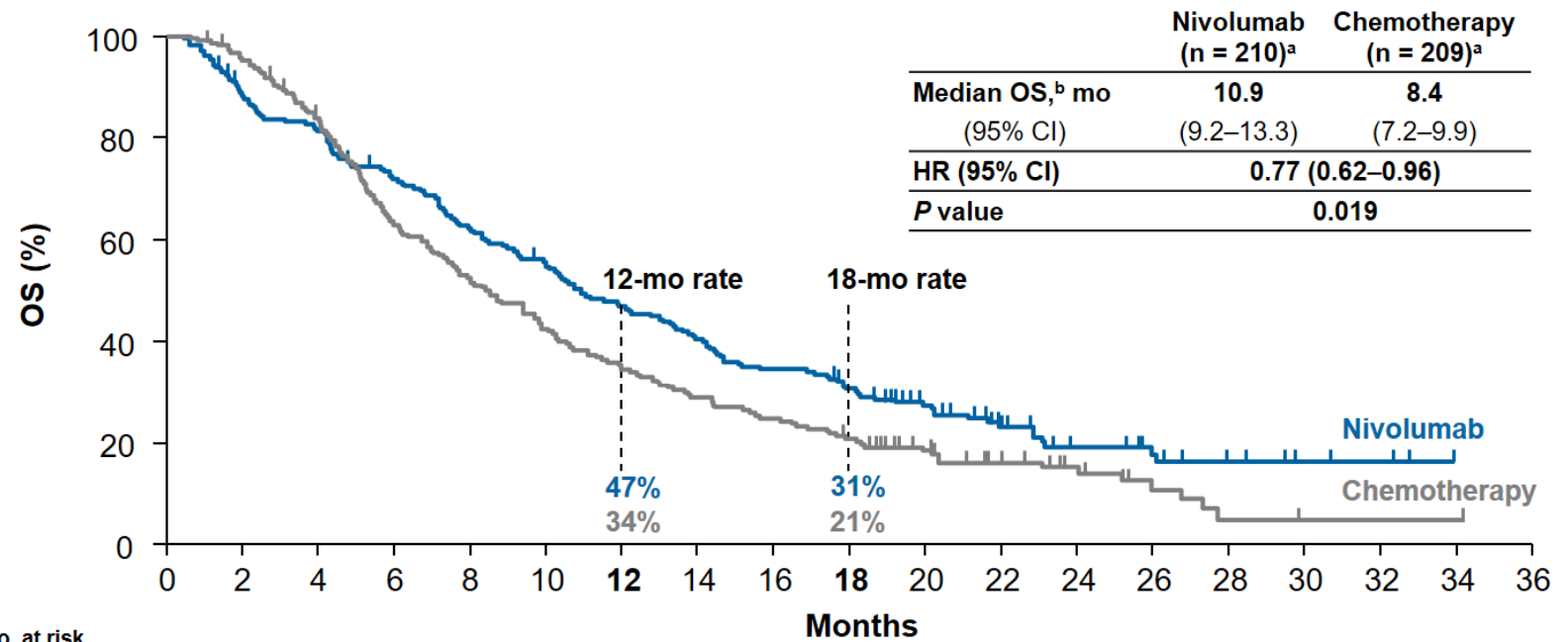
Speiseröhrenkrebs



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2L ESCC, ATTRACTION-3, Overall Survival

Overall Survival

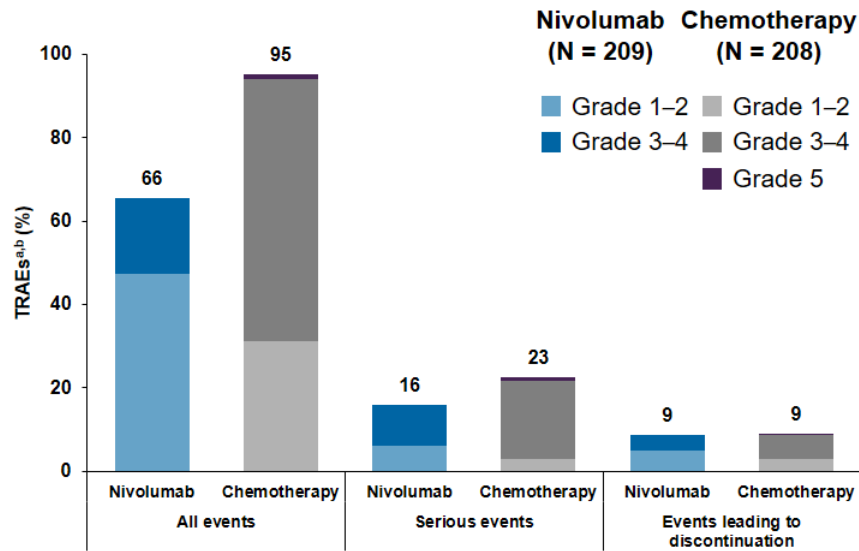


	No. at risk																		
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	210	182	167	147	126	11	95	82	70	60	43	25	17	13	7	4	3	0	0
docetaxel or paclitaxel Chemotherapy	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

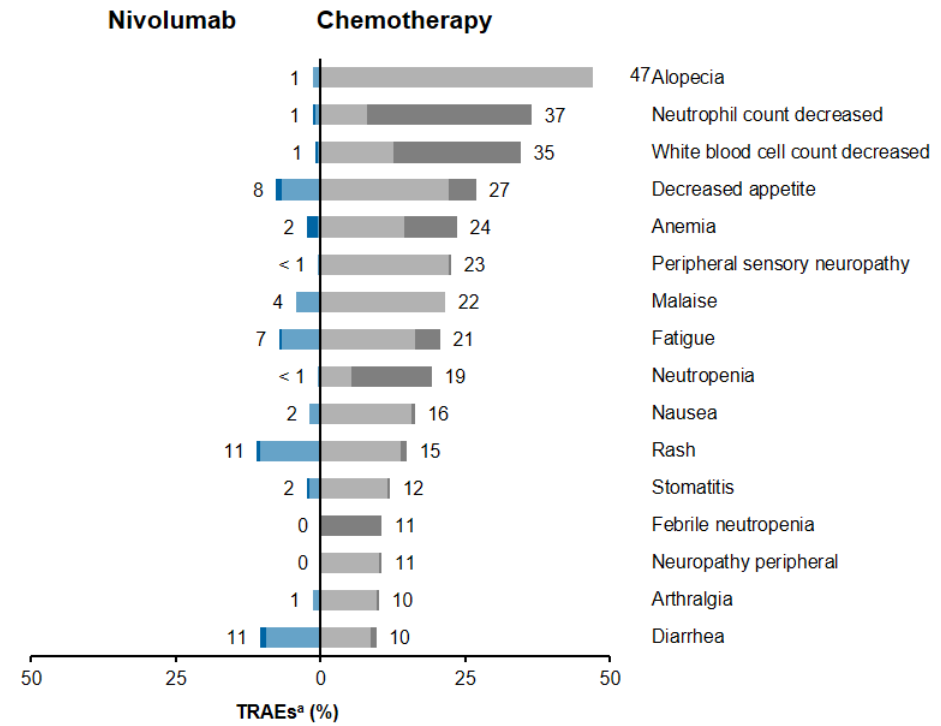
- Nivolumab provided superior OS, with a 23% reduction in the risk of death and a 2.5-month improvement in median OS, versus chemotherapy

2L ESCC, ATTRACTION-3, Verträglichkeit

Summary of TRAEs



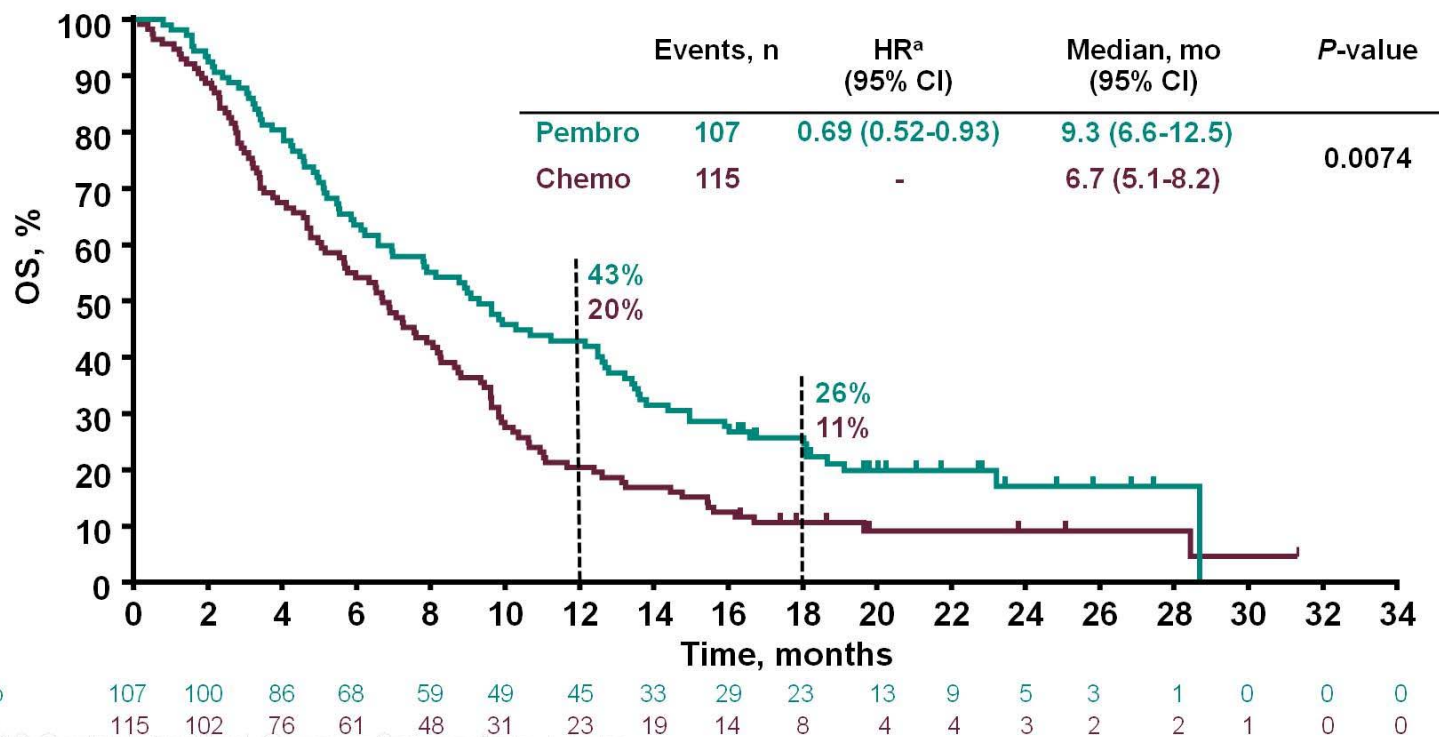
TRAEs in ≥ 10% of patients



Chul Cho et al. ESMO 2019 Fewer TRAEs were reported with nivolumab versus chemotherapy

2L ESCC & EAC, Keynote-181, Overall Survival

Overall Survival (PD-L1 CPS ≥ 10)



Overall survival in

1. Patients with PD-L1 CPS ≥ 10 ✓
2. Patients with SCC
3. All patients (ITT)

^aBased on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

docetaxel or paclitaxel or irinotecan

2L ESCC & EAC, Keynote-181, AEs

Summary of Adverse Events

Event	Pembrolizumab N = 314		Chemotherapy N = 296	
	All grade	Grade 3-5	All grade	Grade 3-5
Any treatment-related, n (%)	202 (64.3)		255 (86.1)	
Grade 3-5	57 (18.2)		121 (40.9)	
Led to discontinuation	19 (6.1)		19 (6.4)	
Led to death ^a	5 (1.5)		5 (1.7)	
Immune-mediated and infusion reactions	73 (23.2)		22 (7.4)	
≥20% treatment-related events any group, n (%)	All grade	Grade 3-5	All grade	Grade 3-5
Fatigue	37 (11.8)	2 (0.6)	61 (20.6)	1 (0.3)
Nausea	22 (7.0)	0	64 (21.6)	7 (2.4)
Diarrhea	17 (5.4)	2 (0.6)	60 (20.3)	9 (3.0)
Anemia	8 (2.5)	4 (1.3)	85 (28.7)	23 (7.8)

^aMyocarditis, death, decreased white blood cell count (n=1 each) and pneumonitis (n=2) in the pembrolizumab group and pneumonia, pneumonia aspiration, sepsis, decreased neutrophil count, and hemorrhagic shock (n=1 each) in chemotherapy group.
Data cutoff: October 15, 2018. © 2018 AstraZeneca. All rights reserved. Permission required for reuse.

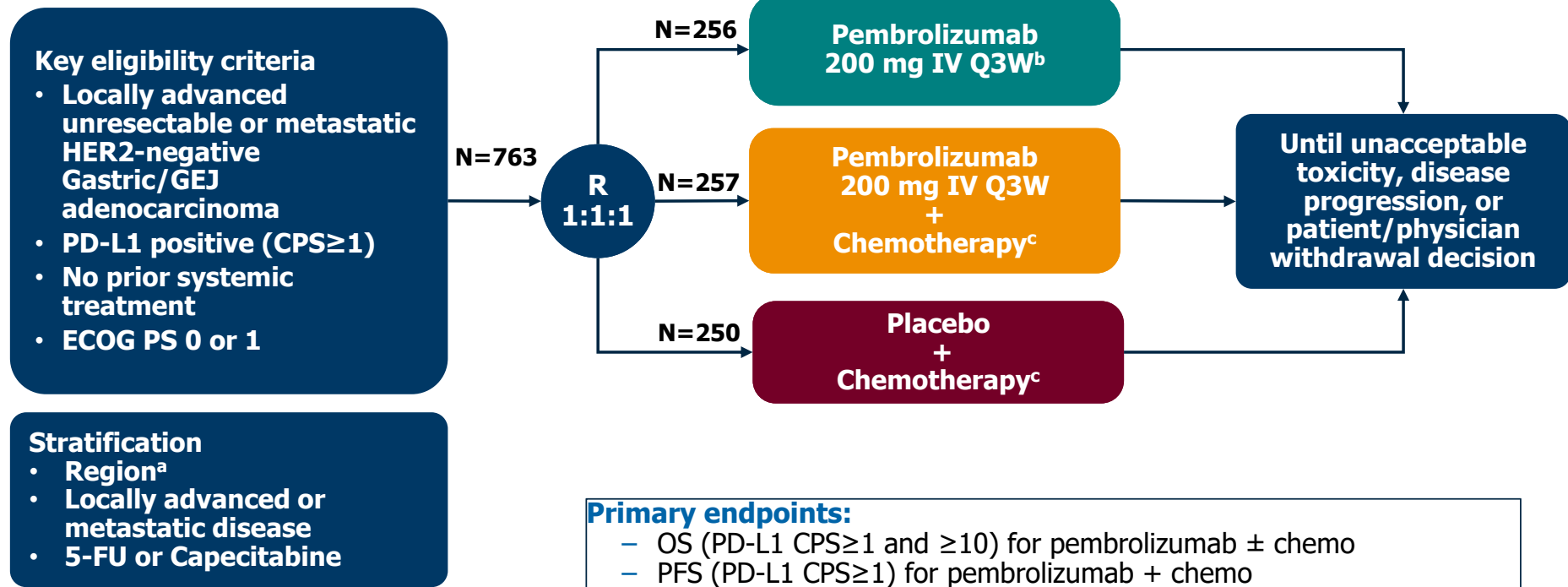
Immunonkologische Highlights des Jahres 2019 & Ausblick auf 2020

Magenkrebs



Bristol-Myers Squibb

IL GC/GEJ, Keynote-062, CPS ≥ 1 , study design

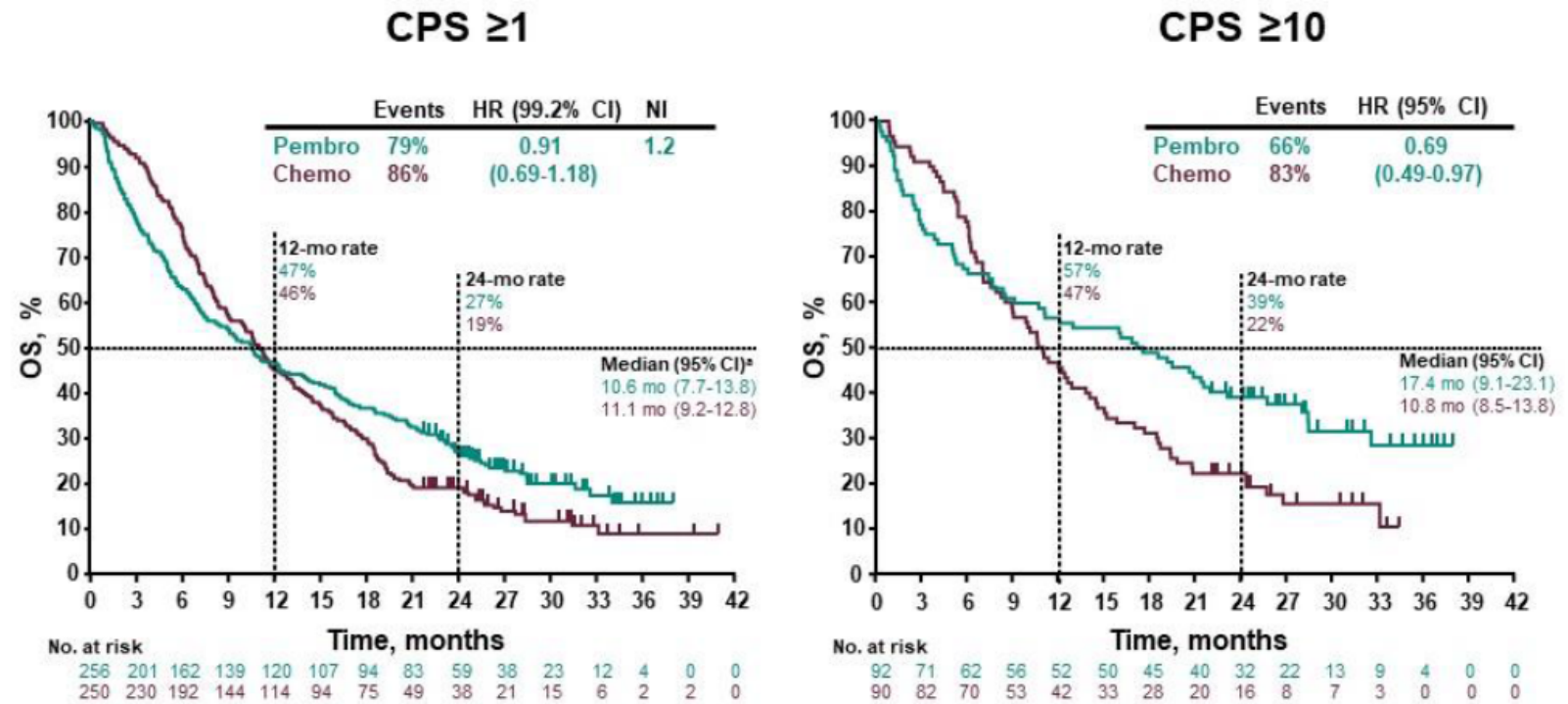


IL GC/GEJ, Keynote-062, OS Pembro Mono

Pembro vs Chemo: OS

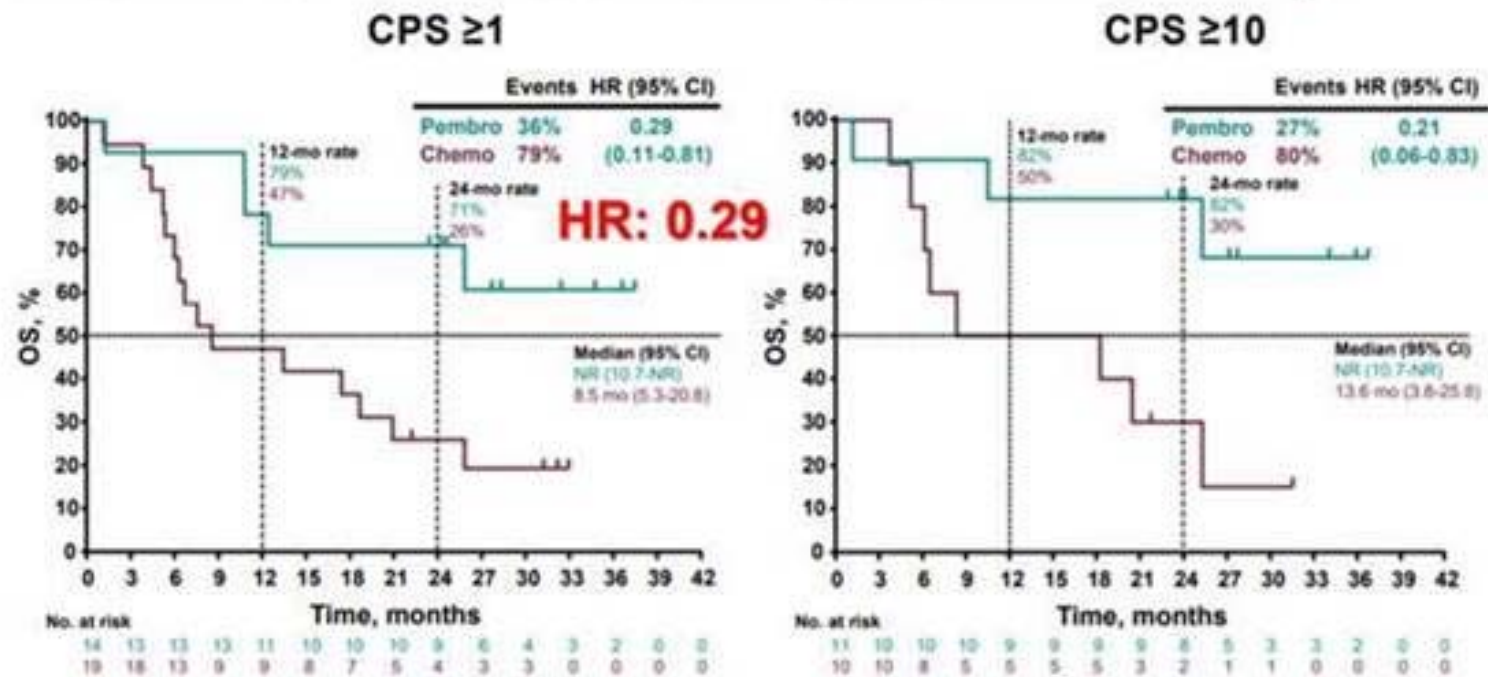
Pembro mono:

- Non-inferior in CPS ≥ 1
- Superior in CPS ≥ 10



IL GC/GEJ Keynote-062, OS Pembro Mono, MSI-H

Pembro vs Chemo: OS in MSI-H Group

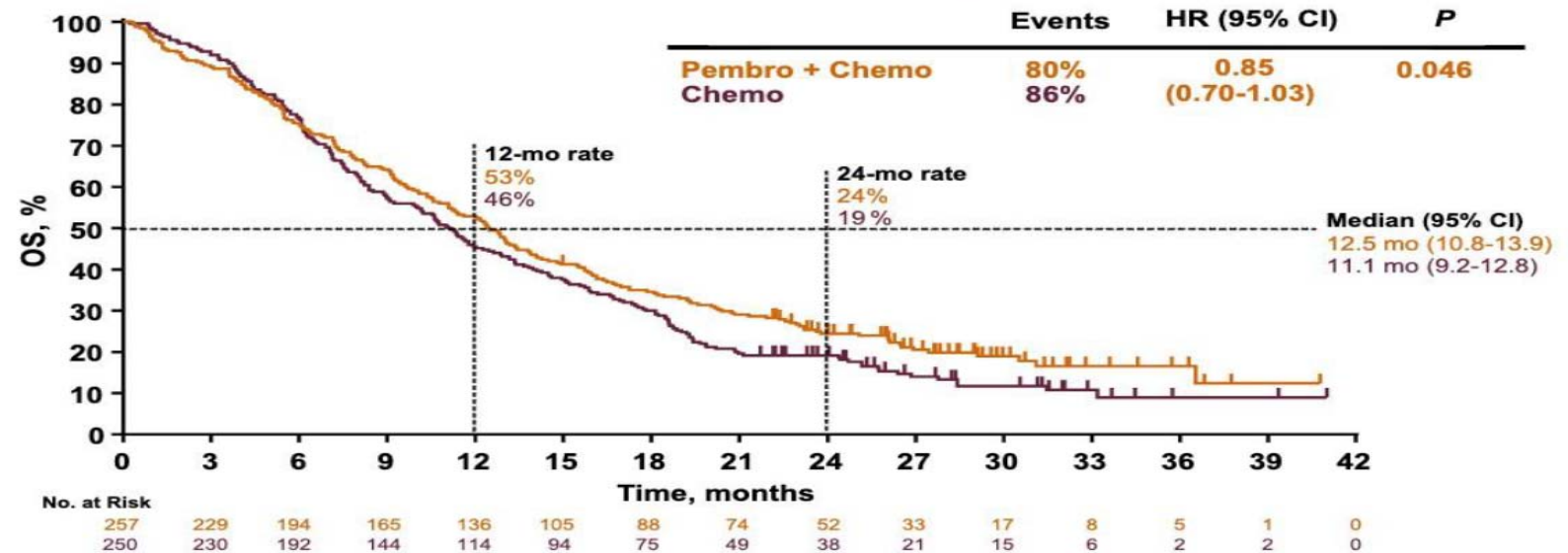


Shitara K, et al. ESMO 2019



IL GC/GEJ Keynote-062, OS Pembro + Chemo

Overall Survival: P+C vs C (CPS ≥ 1)



Pembro + Chemo:

- Non-superior in CPS ≥ 1
- Non-superior in CPS ≥ 10

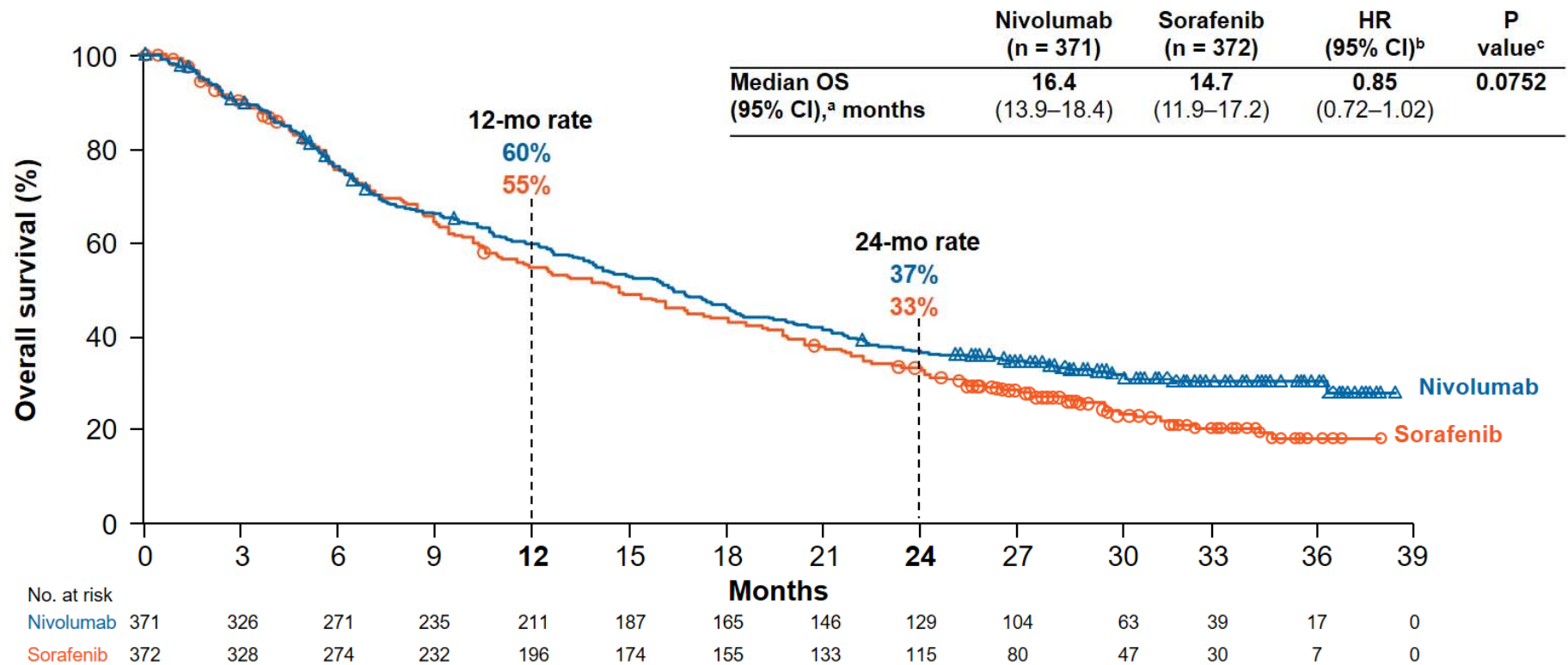
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Hepatozelluläres Karzinom



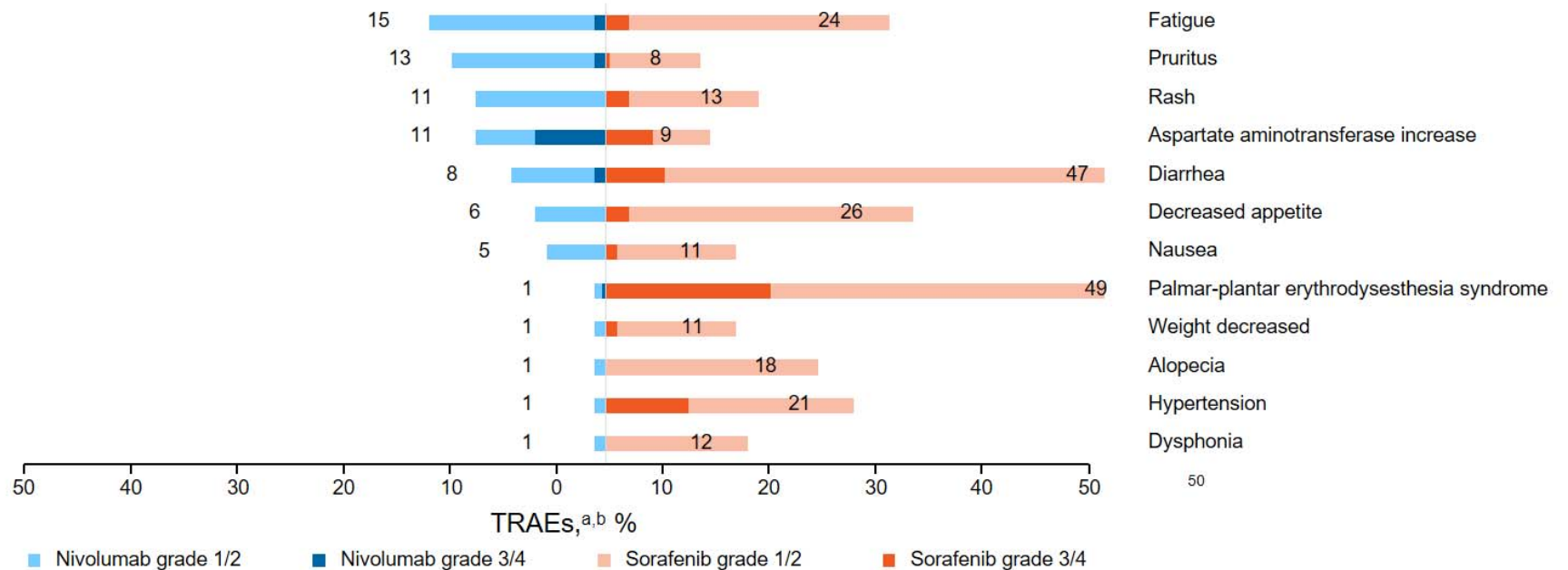
Bristol-Myers Squibb

IL, HCC, CheckMate-459, Overall Survival



- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit

IL, HCC, CheckMate-459, Nebenwirkungsprofil



- Nivolumab demonstrated an improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation versus sorafenib
 - Grade 3/4 TRAEs were reported in 81 patients (22%) in the nivolumab arm and 179 patients (49%) in the sorafenib arm

Zusammenfassung und Ausblick

Trends in I-O

- 1. Welle der Monotherapien am Auslaufen (LC, EC, HCC)
- 2. Welle der 1L Kombinationstherapien am Etablieren (LC, TNBC, UC, H&N, GC, RCC)
- 3. Welle der (neo)adjuvanten Therapien am Entstehen (MEL)

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Nicht alles Gold was glänzt!

- Negative Ph III Studien (LC, TNBC, GBM, GI)
- Wo bleibt die personalisierte I-O Therapie?

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Ausblick

- Vielzahl an Ph III Studien und Zulassungen in den nächsten Jahren
- Biomarker, Sequenzierung, Resistenz, Mikrobiom, next generation I-O

Immunonkologische Highlights des Jahres 2019 & Ausblick auf 2020

Österreichische Gesellschaft für Krankenhauspharmazie
Herbstmeeting 2019

Mag. Markus Krenn
Disease Area Specialist Immuno-Oncology



Bristol-Myers Squibb