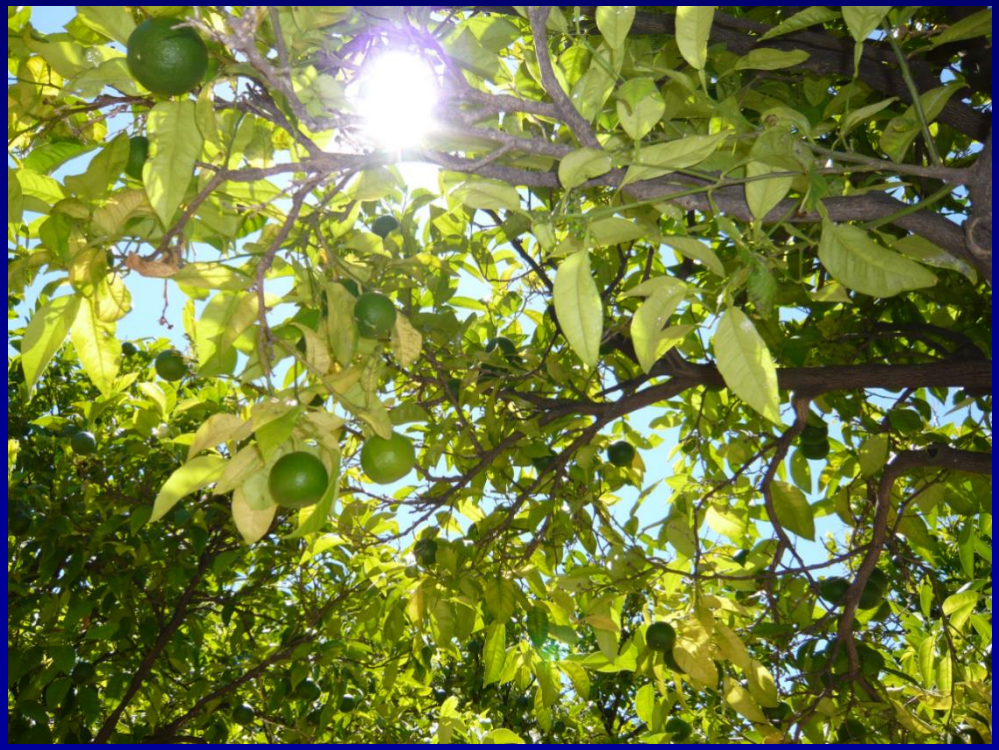
Hämato-Onkologie Hamburg
Prof. Laack und Partner

„Update ESMO/WCLC“



Nicht-kleinzelliges Lungenkarzinom (NSCLC)

Immuntherapie
- First line -
IO-Mono

IASLC
2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
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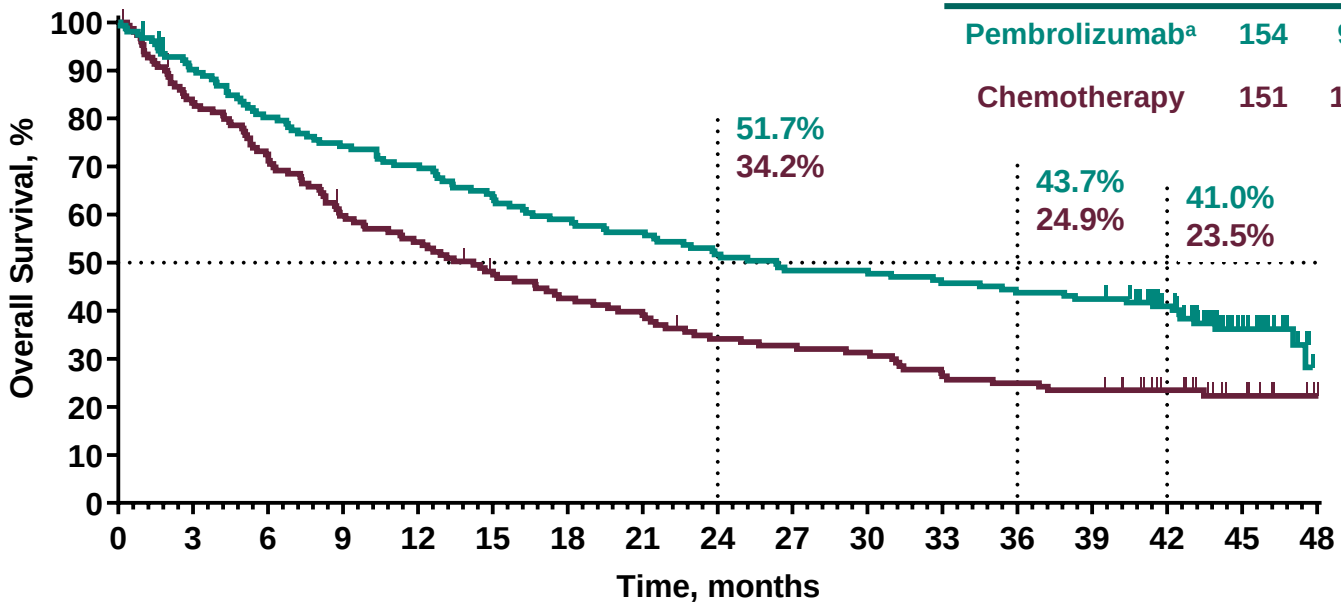
Conquering Thoracic Cancers Worldwide

KEYNOTE-024 3-Year Survival Update: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced NSCLC

Martin Reck,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Tara Garay,[14] Erin Jensen,[14] Victoria Ebiana,[14] Julie R. Brahmer[15]

[1]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Soroka Cancer Center, Ben Gurion University, Beer Sheva, Israel; [9]Wollongong Private Hospital and University of Wollongong, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, Sutton, Surrey, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Overall Survival: Updated Analysis



	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86) *P* = 0.001[b]
Chemotherapy	151	113 (75)	

Median (95% CI)
26.3 mo (18.3–40.4 mo)
14.2 mo (9.8–18.3 mo)

No. at risk																	
Pembrolizumab	154	136	121	112	106	96	89	85	78	73	73	69	66	64	50	24	5
Chemotherapy	151	124	108	88	80	69	61	56	48	46	44	37	35	33	24	14	6

[a]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 64.9% (98 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). [b]Nominal *P* value.
Data cutoff: February 15, 2019.

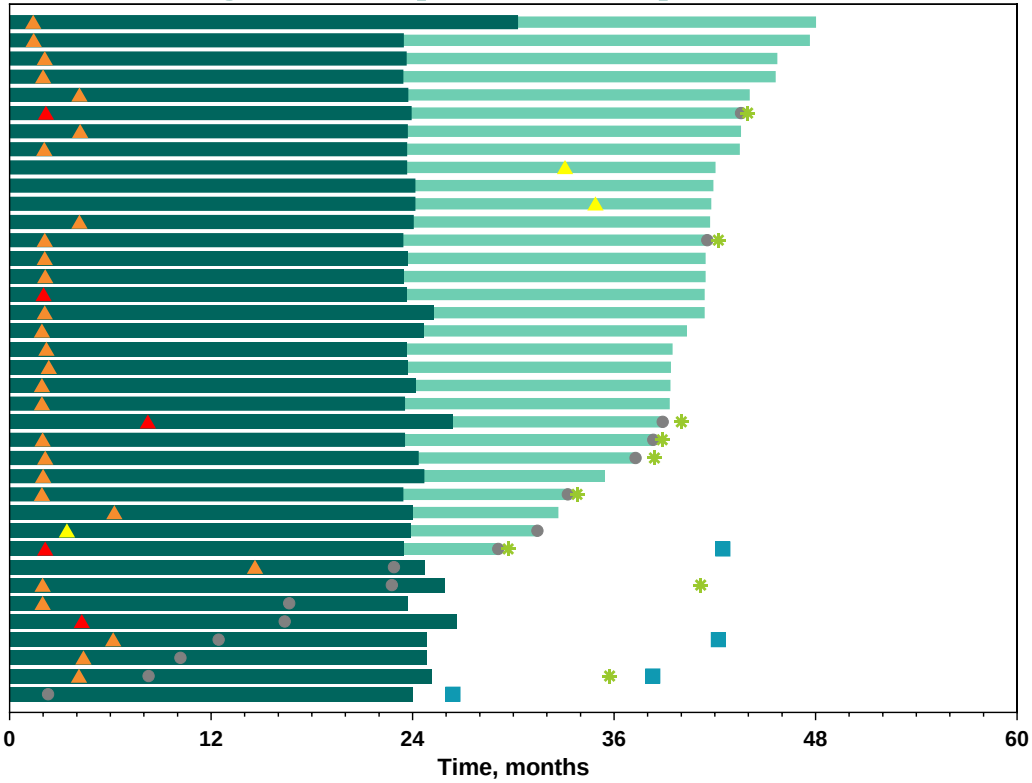
Objective Response[a]
35 Cycles (2 Years) of Pembrolizumab Completed

	35 Cycles (2 Years) of Pembrolizumab N = 38
Objective response, n (%)	31 (82)
Complete response	3 (8)
Partial response	28 (74)
Time to response, median (range), mo	2.1 (1.4–14.6)
DOR, median (range) mo	NR (4.2–46.7+)
Alive at data cutoff, n (%)	34 (89)

"+", indicates response duration is censored; DOR, duration of response; NR, not reached. [a]Response assessed by RECIST v1.1 per investigator review.
Data cutoff: February 15, 2019.

Treatment Duration and Time to Response

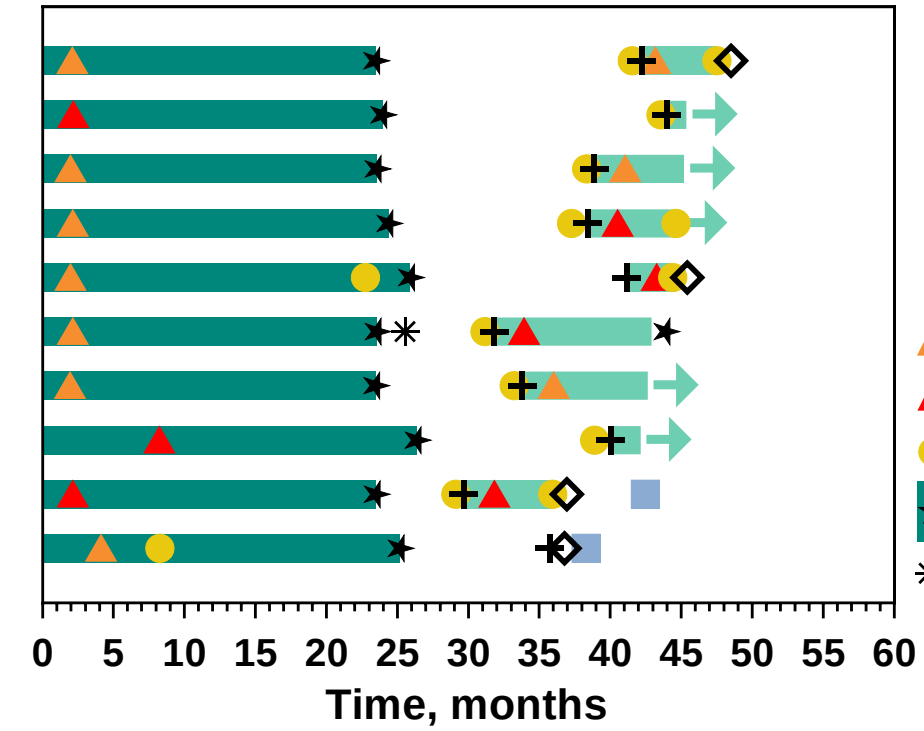
35 Cycles (2 Years) of Pembrolizumab Completed[a]



- 31 of 38 patients (82%) had CR or PR as best response per RECIST version 1.1 by investigator review
  - 27 patients (87.1%) had DOR lasting ≥12 mo; 25 (80.6%) had DOR ≥24 mo[b]
  - 22 patients (58%) had ongoing response at data cutoff
- OS rate 12 months after completing pembrolizumab treatment was 97.4% (95% CI, 82.8–99.6)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. [a]Dark green bars indicate treatment duration and light green bars indicate first course follow-up duration. Follow-up was defined as the time to progression or last non-progression assessment by investigator. [b]From Kaplan-Meier method for censored data.
Data cutoff: February 15, 2019.

Treatment Duration and Time to Response
Patients Who Received Second-Course Treatment[a]



- 7 of 10 patients (70%) who received second course had PR or SD as best response per RECIST v1.1 by investigator review
- 8 patients remained alive and 5 were continuing on pembrolizumab treatment at data cutoff

PR
SD
PD
End of First Course
Completed 34 Cycles

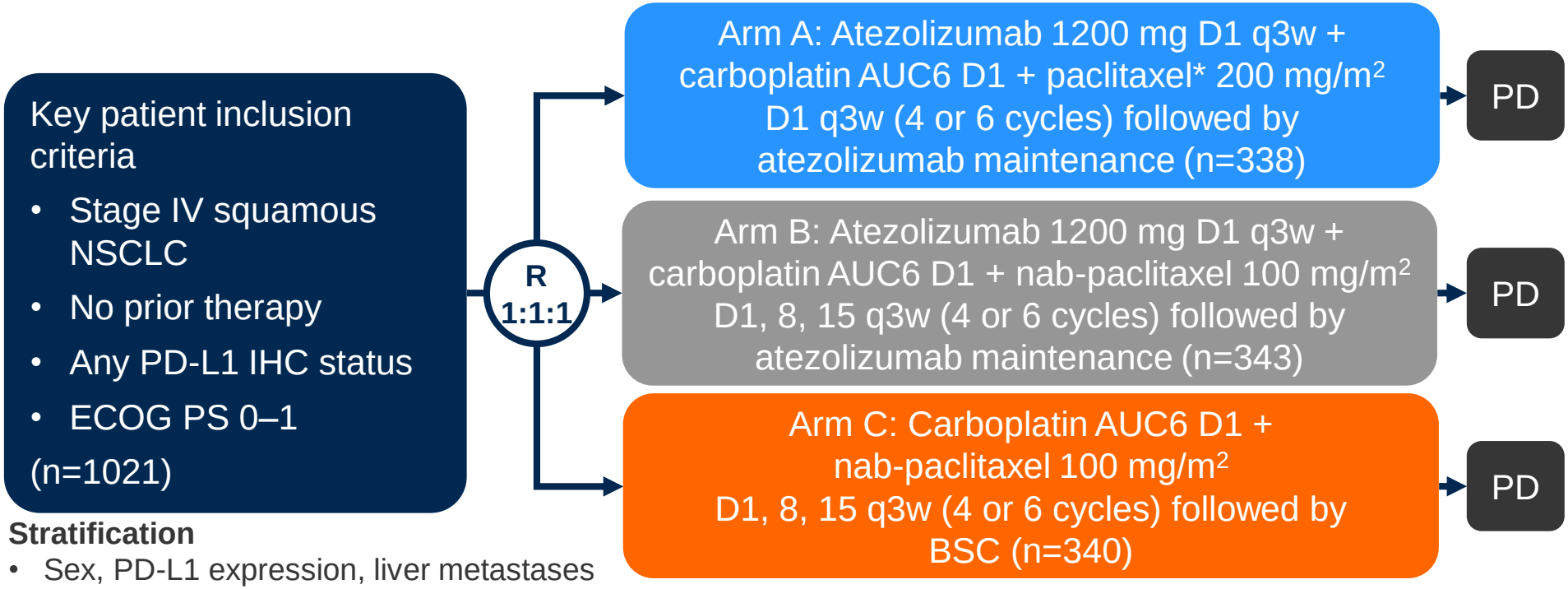
Start of Second Course
Completed Second Course
Discontinued Second Course
Second Course Ongoing
Death

[a]Dark green bars indicate the first course treatment period and light green bars indicate the second-course duration of follow-up. Follow-up was defined as the time to progression or last non-progression assessment by investigator. Response was assessed per RECIST v1.1 by investigator review.
Data cutoff: February 15, 2019.

Immuntherapie
- First line -
squamous
IO + Chemo

OA14.02: IMpower131: Final OS Results of Carboplatin + Nab-Paclitaxel ± Atezolizumab in Advanced Squamous NSCLC – Cappuzzo F, et al

- **Study objective**
  - To investigate the efficacy and safety of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel in patients with stage IV squamous NSCLC



Stratification

- Sex, PD-L1 expression, liver metastases

Primary endpoints

- PFS (RECIST v1.1), OS

Secondary endpoints

- ORR, DoR, safety

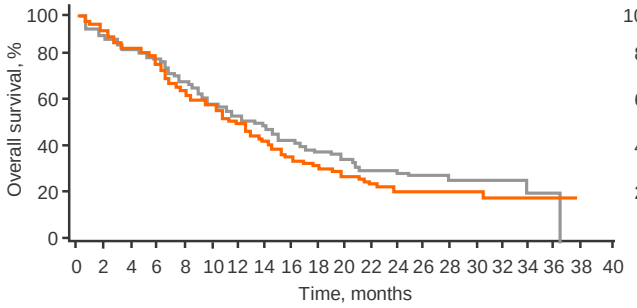
*Asian patients paclitaxel 175 mg/m^2

Cappuzzo F, et al. J Thorac Oncol 2019;14(suppl):Abstr OA14.02

OA14.02: IMpower131: Final OS Results of Carboplatin + Nab-Paclitaxel ± Atezolizumab in Advanced Squamous NSCLC – Cappuzzo F, et al

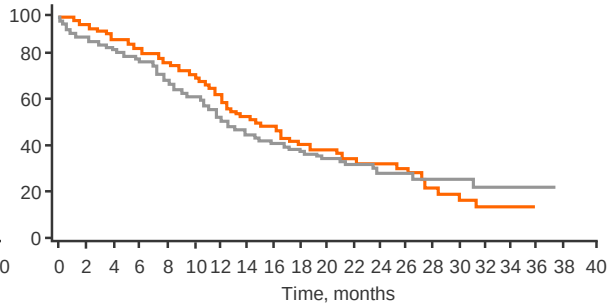
- **Key results**
  - The final mOS was 14.2 vs. 13.5 months for atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel (HR 0.88 [95%CI 0.73, 1.05]; p=0.1581)

PD-L1 negative TC0 and IC0



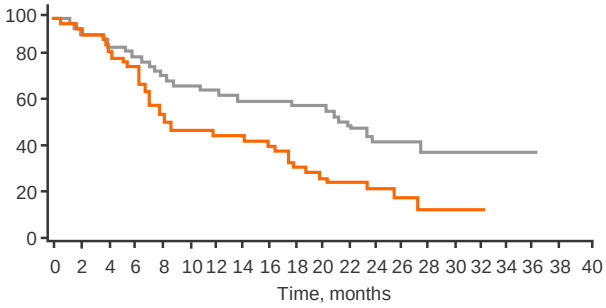
	Arm B: Atezo + CnP (n=160)	Arm C: CnP (n=171)
Median OS, mo (95%CI)	14.0 (11.2, 16.7)	12.5 (10.6, 14.3)
HR (95%CI)	0.87 (0.67, 1.13)	

PD-L1 low TC1/2 and IC1/2



	Arm B: Atezo + CnP (n=136)	Arm C: CnP (n=125)
Median OS, mo (95%CI)	12.8 (11.2, 16.7)	15.5 (12.7, 18.1)
HR (95%CI)	1.08 (0.81, 1.45)	

PD-L1 high TC3 and IC3



	Arm B: Atezo + CnP (n=47)	Arm C: CnP (n=44)
Median OS, mo (95%CI)	23.4 (17.8, NE)	10.2 (7.1, 17.5)
HR (95%CI)	0.48 (0.29, 0.81)	

Atezolizumab + carboplatin + nab-paclitaxel (Atezo + CnP)
Carboplatin + nab-paclitaxel (CnP)

Cappuzzo F, et al. J Thorac Oncol 2019;14(suppl):Abstr OA14.02

Immuntherapie
- First line -
IO + IO

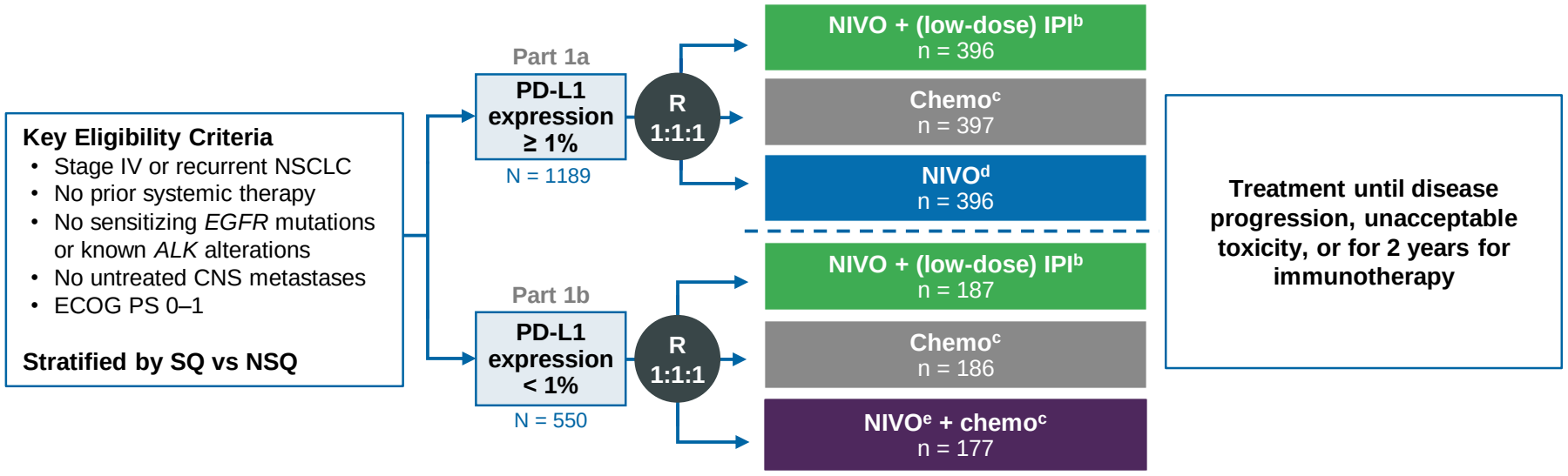
BARCELONA 2019 ESMO congress

Nivolumab + Low-Dose Ipilimumab Versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: CheckMate 227 Part 1 Final Analysis

Solange Peters,[1] Suresh Ramalingam,[2] Luis Paz-Ares,[3] Reyes Bernabe Caro,[4] Bogdan Zurawski,[5] Sang-We Kim,[6] Aurelia Alexandru,[7] Lorena Lupinacci,[8] Emmanuel de la Mora Jimenez,[9] Hiroshi Sakai,[10] István Albert,[11] Alain Vergnenegre,[12] Martin Reck,[13] Hossein Borghaei,[14] Julie R. Brahmer,[15] Kenneth O'Byrne,[16] William J. Geese,[17] Prabhu Bhagavatheeswaran,[17] Faith E. Nathan,[17] Matthew D. Hellmann[18]

[1]Centre hospitalier universitaire Vaudois (CHUV), Lausanne University, Lausanne, Switzerland; [2]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [3]Hospital Universitario Doce de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain; [4]Hospital Universitario Virgen Del Rocio, Seville, Spain; [5]Ambulatorium Chemioterapii, Bydgoszcz, Poland; [6]Asan Medical Center, Seoul, Republic of Korea; [7]Institute Of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucha, Bucharest, Romania; [8]Hospital Italiano De Buenos Aires, Buenos Aires, Argentina; [9]Instituto Jalisciense De Cancerología, Guadalajara, Jalisco, Mexico; [10]Saitama Cancer Center, Saitama, Japan; [11]Matrai Gyogyintezet, Matrahaza, Hungary; [12]Limoges University Hospital, Limoges, France; [13]Lung Clinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; [14]Fox Chase Cancer Center, Philadelphia, PA, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]Princess Alexandra Hospital, Brisbane, Queensland, Australia; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

CheckMate 227 Part 1 Study Design[a]



Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

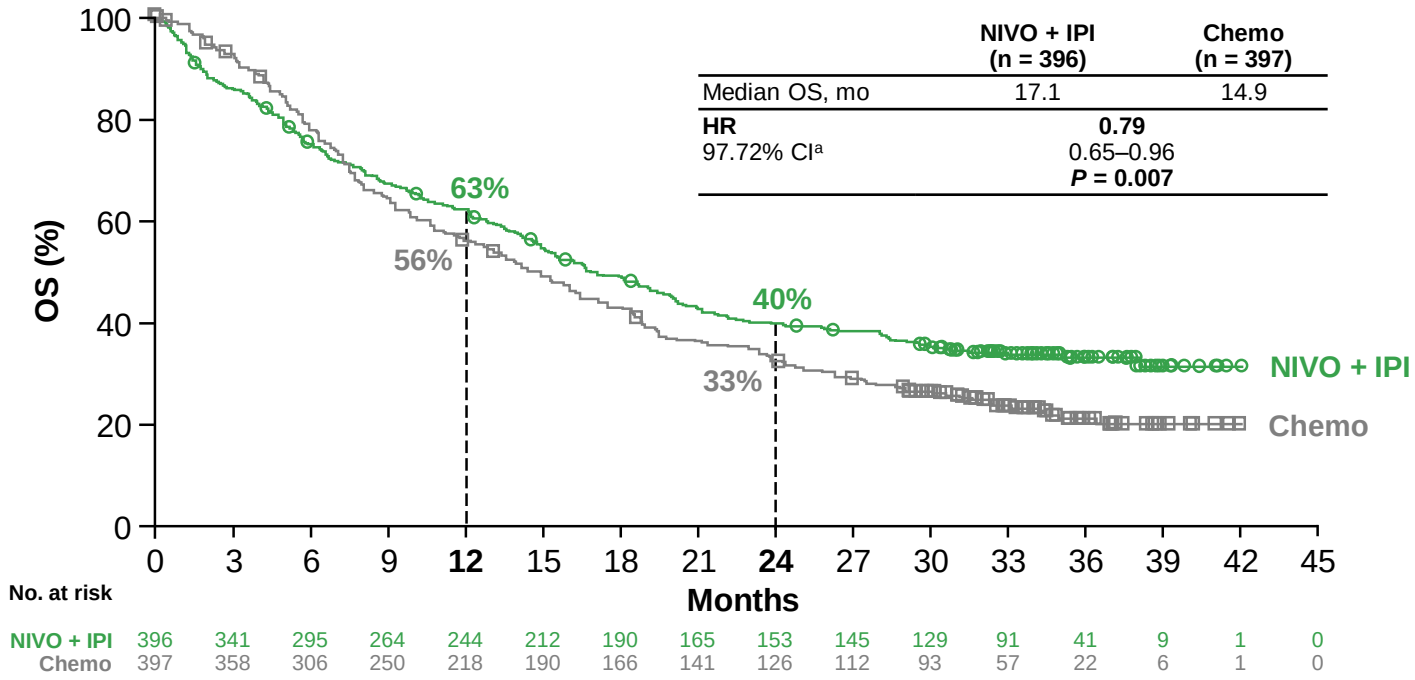
Secondary endpoints (PD-L1 hierarchy):
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

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

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO



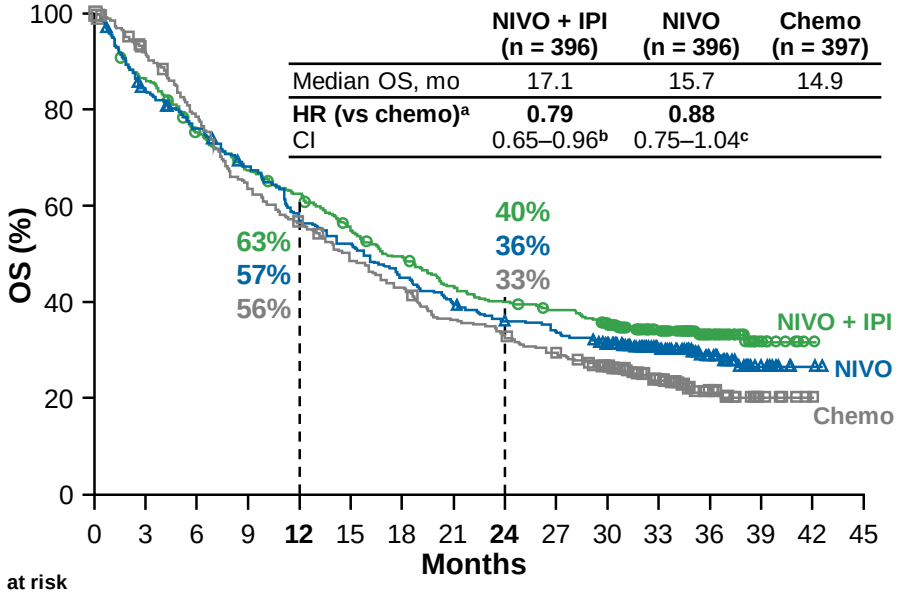
	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR	**0.79**	
97.72% CI[a]	0.65–0.96	
	***P* = 0.007**	

Minimum follow-up for primary endpoint: 29.3 months.
NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 43%, respectively.
[a]95% CI, 0.67–0.94.

OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

OS

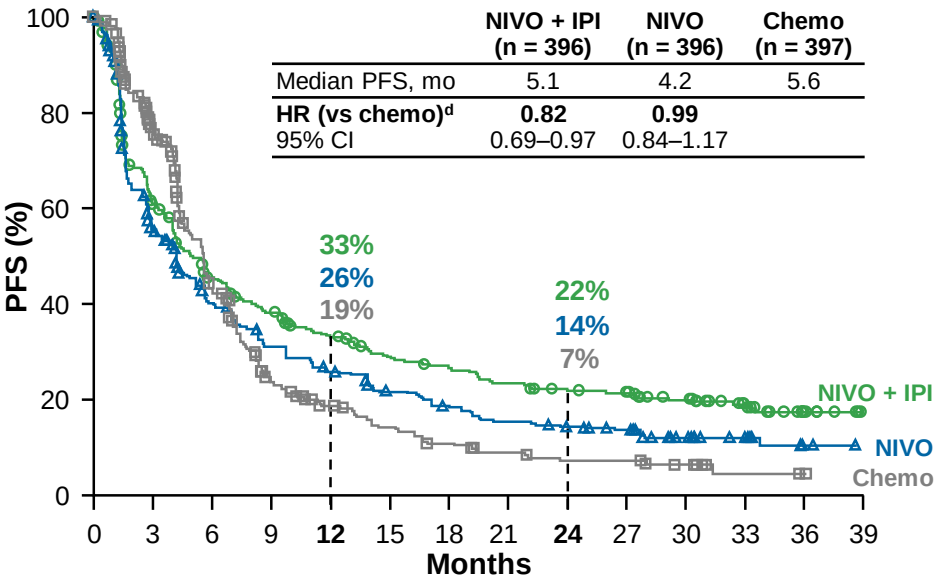


	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo)[a]	**0.79**	**0.88**	
CI	0.65–0.96[b]	0.75–1.04[c]	

No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
NIVO	396	330	299	265	220	201	176	153	139	129	115	70	36	10	2	0
Chemo	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PFS by BICR



	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo)[d]	**0.82**	**0.99**	
95% CI	0.69–0.97	0.84–1.17	

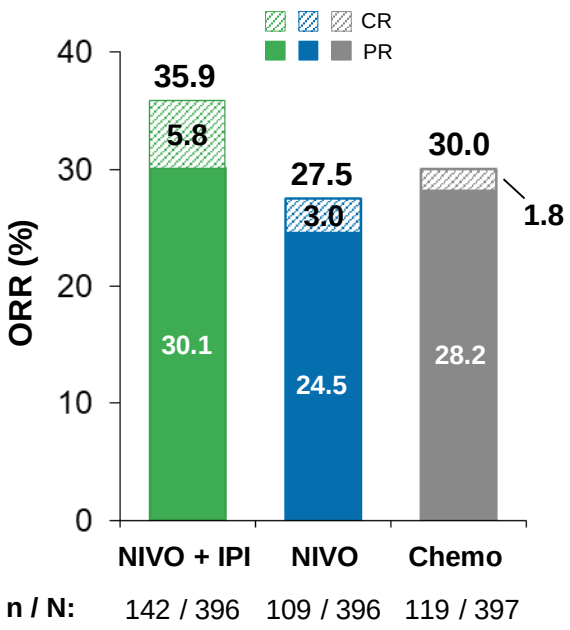
396	221	158	130	108	91	83	73	65	62	47	31	7	0
396	199	136	104	85	68	56	47	42	37	24	15	3	0
397	253	130	63	44	32	23	17	12	12	8	2	1	0

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm, 44% of patients in the NIVO arm, and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6%, 8%, and 43%, respectively.
[a]HR (95% CI) for NIVO + IPI vs NIVO, 0.90 (0.76–1.07); [b]97.72% CI; [c]95% CI; [d]HR (95% CI) for NIVO + IPI vs NIVO, 0.83 (0.71–0.97).

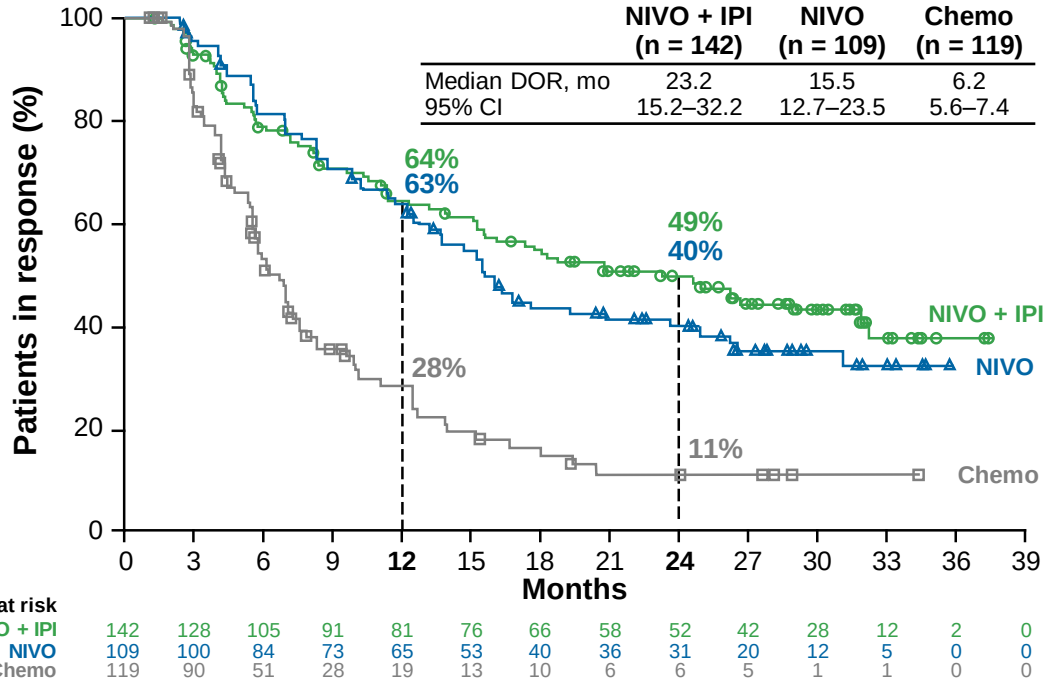
ORR and DOR for NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



DOR by BICR[a]

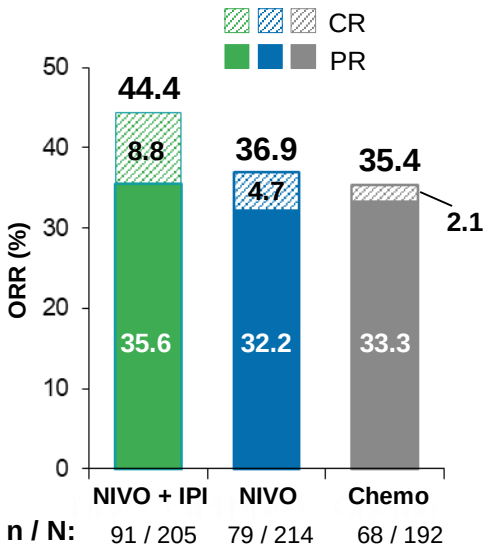


Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W); minimum follow-up for ORR was 28.3 months.
[a]Median time to response was 2.0 mo with NIVO + IPI, 2.7 mo with NIVO, and 1.6 mo with chemo.

Efficacy With NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 50%

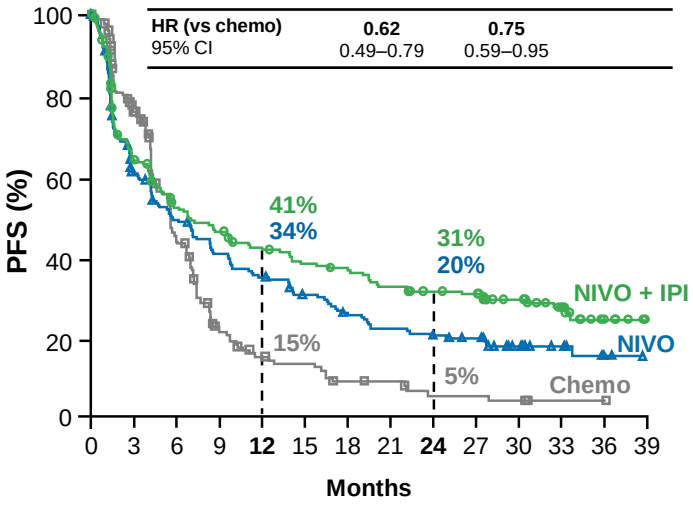
Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



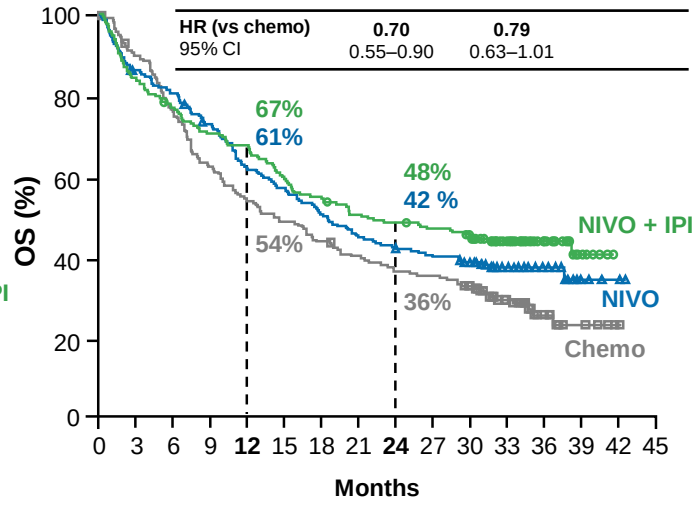
PFS by BICR

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median PFS, mo 95% CI	6.7 4.5–11.0	5.6 4.2–8.3	5.6 4.6–6.6
HR (vs chemo) 95% CI	**0.62** 0.49–0.79	**0.75** 0.59–0.95	



OS

	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	**0.70** 0.55–0.90	**0.79** 0.63–1.01	

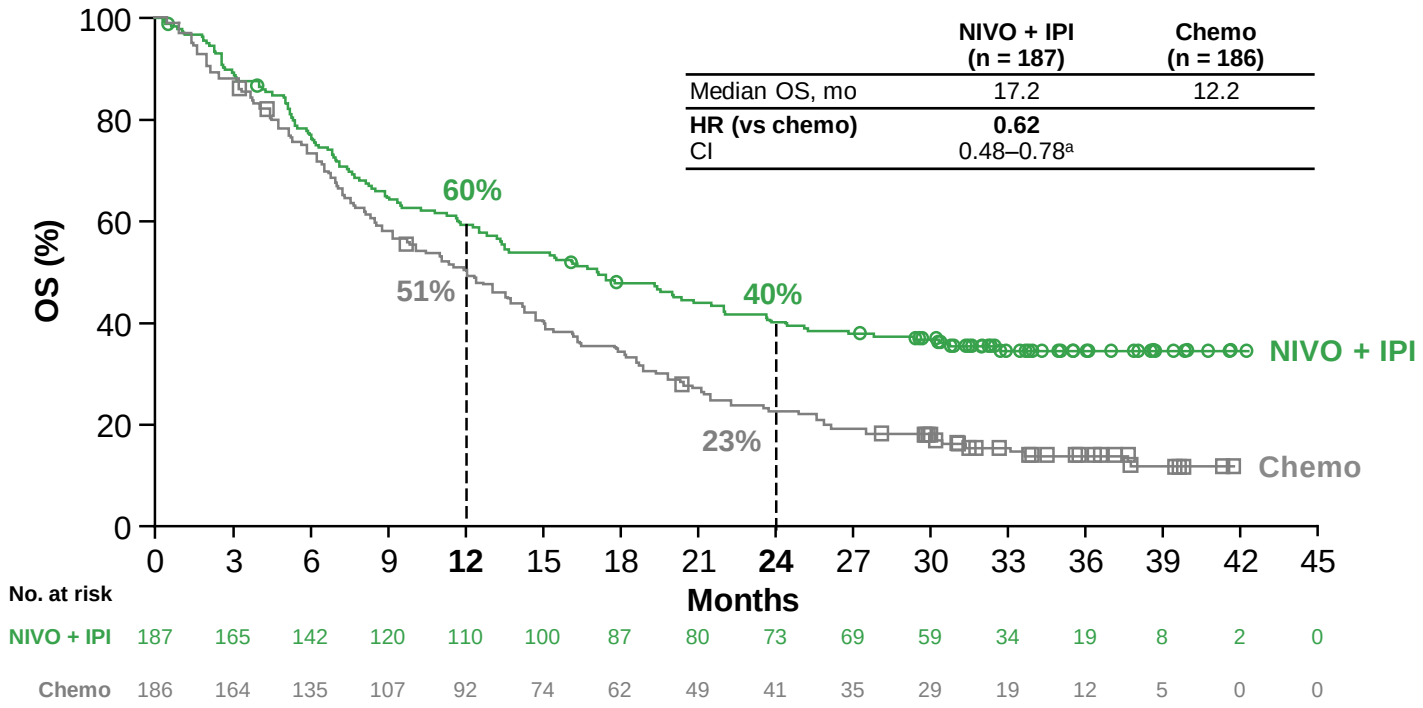


- Median DOR with NIVO + IPI, NIVO and chemo was 31.8, 17.5 and 5.8 months, respectively

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo.

OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b
NIVO + IPI
Chemo
NIVO + chemo

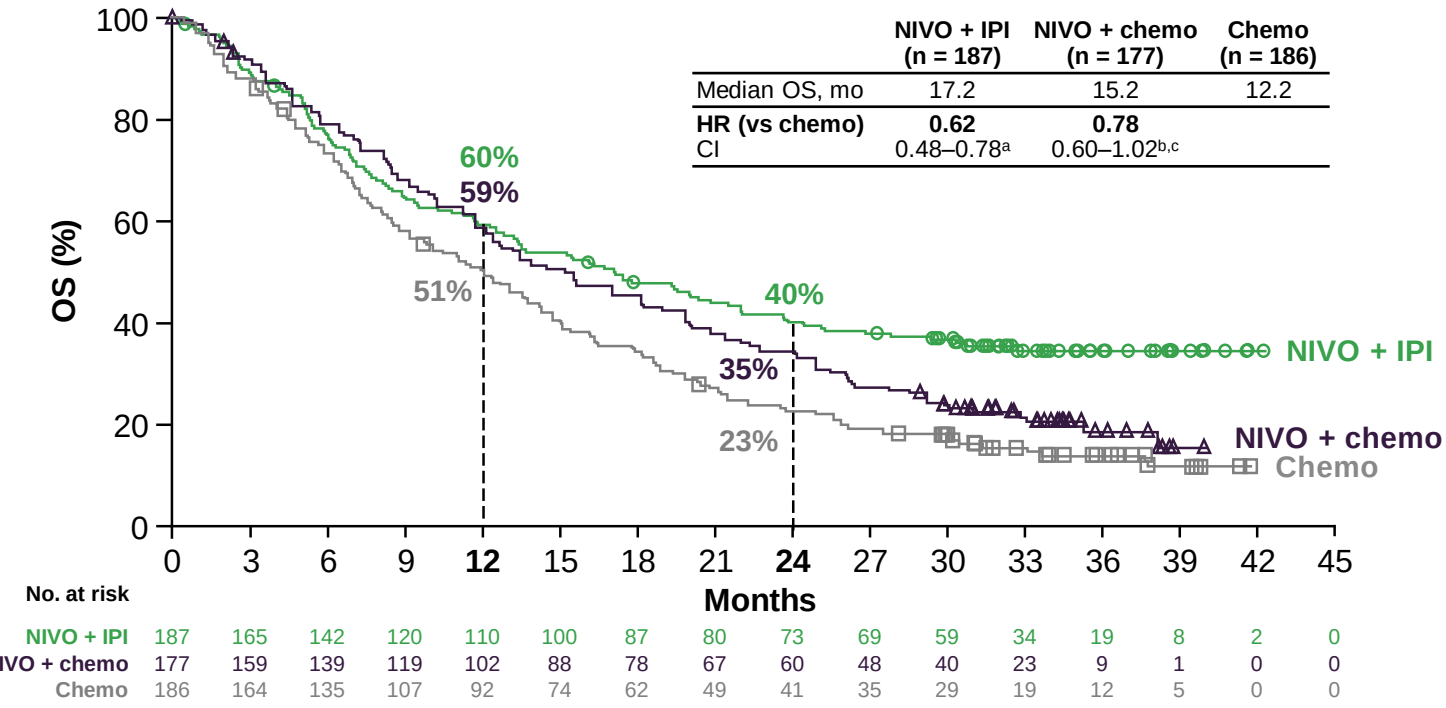


	NIVO + IPI (n = 187)	Chemo (n = 186)
Median OS, mo	17.2	12.2
HR (vs chemo)	**0.62**	
CI	0.48–0.78[a]	

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI.

OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b
NIVO + IPI
Chemo
NIVO + chemo



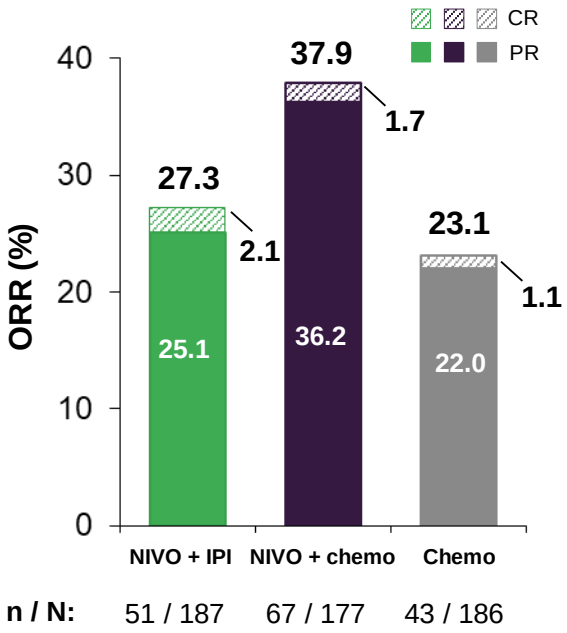
	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.2	15.2	12.2
HR (vs chemo)	**0.62**	**0.78**	
CI	0.48–0.78[a]	0.60–1.02[b,c]	

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI; [b]97.72% CI; [c]*P* = 0.0352.

ORR and DOR for NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

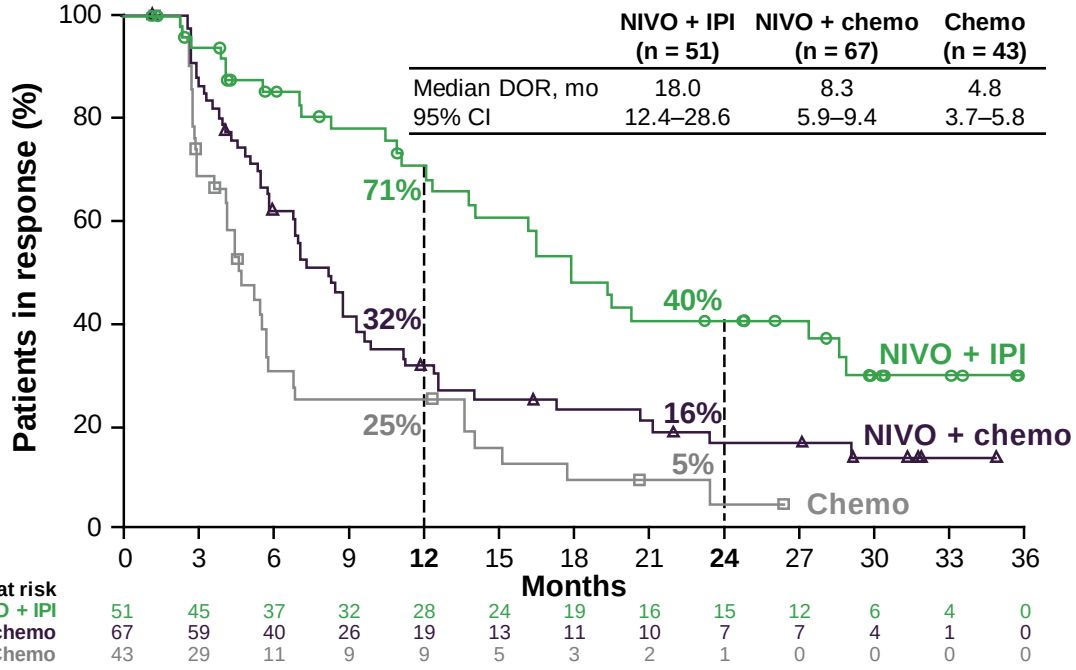
Part 1b
NIVO + IPI
Chemo
NIVO + chemo

ORR by BICR



n / N:	NIVO + IPI	NIVO + chemo	Chemo
	51 / 187	67 / 177	43 / 186

DOR by BICR[a]



	NIVO + IPI (n = 51)	NIVO + chemo (n = 67)	Chemo (n = 43)
Median DOR, mo	18.0	8.3	4.8
95% CI	12.4–28.6	5.9–9.4	3.7–5.8

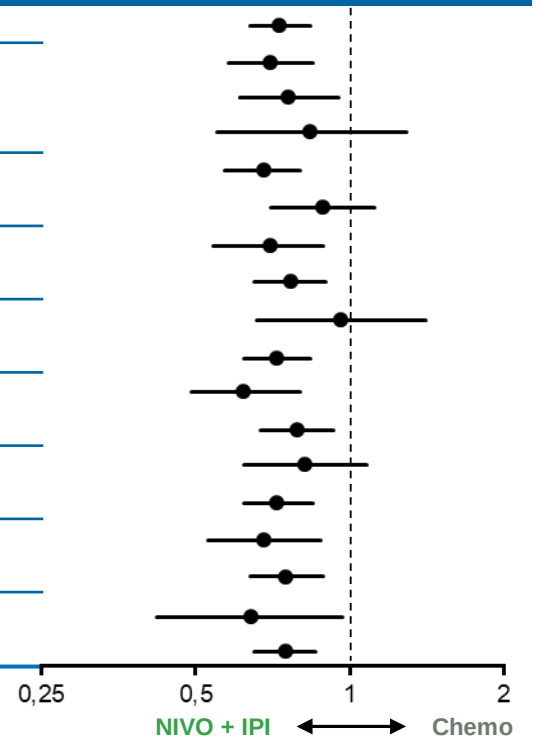
No. at risk													
NIVO + IPI	51	45	37	32	28	24	19	16	15	12	6	4	0
NIVO + chemo	67	59	40	26	19	13	11	10	7	7	4	1	0
Chemo	43	29	11	9	9	5	3	2	1	0	0	0	0

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo.
[a]Median time to response was 2.8 mo with NIVO + IPI, 1.7 mo with NIVO + chemo, and 1.5 mo with chemo.

OS Subgroup Analysis With NIVO + IPI vs Chemo in All Randomized Patients

Part 1 (1a and 1b)
NIVO + IPI
Chemo

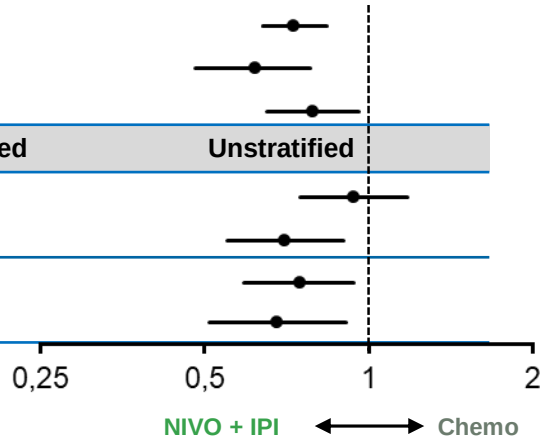
Subgroup	Median OS, months: NIVO + IPI n = 583	Chemo n = 583	Unstratified HR
All randomized (N = 1166)	17.1	13.9	0.73[a]
< 65 years (n = 611)	16.6	14.2	0.70
65 to < 75 years (n = 442)	18.7	13.0	0.76
≥ 75 years (n = 113)	15.1	12.4	0.84
Male (n = 778)	18.7	13.2	0.68
Female (n = 388)	16.1	15.4	0.89
ECOG PS 0 (n = 395)	24.4	18.8	0.70
ECOG PS 1 (n = 763)	14.8	11.3	0.77
Never smoker (n = 157)	15.3	16.1	0.96
Smoker (n = 996)	17.4	13.5	0.72
Squamous[b] (n = 328)	15.0	9.2	0.62
Non-squamous[b] (n = 838)	19.2	15.3	0.79
Liver metastases (n = 252)	10.3	10.4	0.82
No liver metastases (n = 914)	19.4	15.1	0.72
Bone metastases (n = 316)	12.2	8.8	0.68
No bone metastases (n = 850)	19.2	16.0	0.75
CNS metastases (n = 115)	16.8	13.4	0.64
No CNS metastases (n = 1051)	17.2	14.0	0.75



NIVO + IPI dosage was NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W).
HR not computed for subgroups (except age, race, region, and sex) with fewer than 10 patients per treatment group.
[a]Stratified HR; unstratified HR was 0.74 (95% CI, 0.64–0.85); [b]Determined by IVRS.

OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		Median OS, months NIVO + IPI n = 583	Chemo n = 583	HR	HR (95% CI)
Randomized groups				**Stratified**	**Stratified**
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[d] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



- No consistent correlation was observed between survival outcomes with NIVO + IPI vs chemo and PD-L1 or TMB alone or in combination

[a]Stratified HR (97.72% CI); [b]Patients were not stratified by TMB or PD-L1 ≥ or < 50% – subgroup analyses therefore may be impacted by imbalances and should be interpreted with caution; [c]Not controlled by randomization; [d]Unstratified HR for NIVO + IPI vs chemo in TMB-evaluable (n = 679) and non-evaluable (n = 487) patients was 0.74 (95% CI, 0.61–0.88) and 0.74 (95% CI, 0.60–0.92), respectively.

Immuntherapie
- Second line -
IO-Mono

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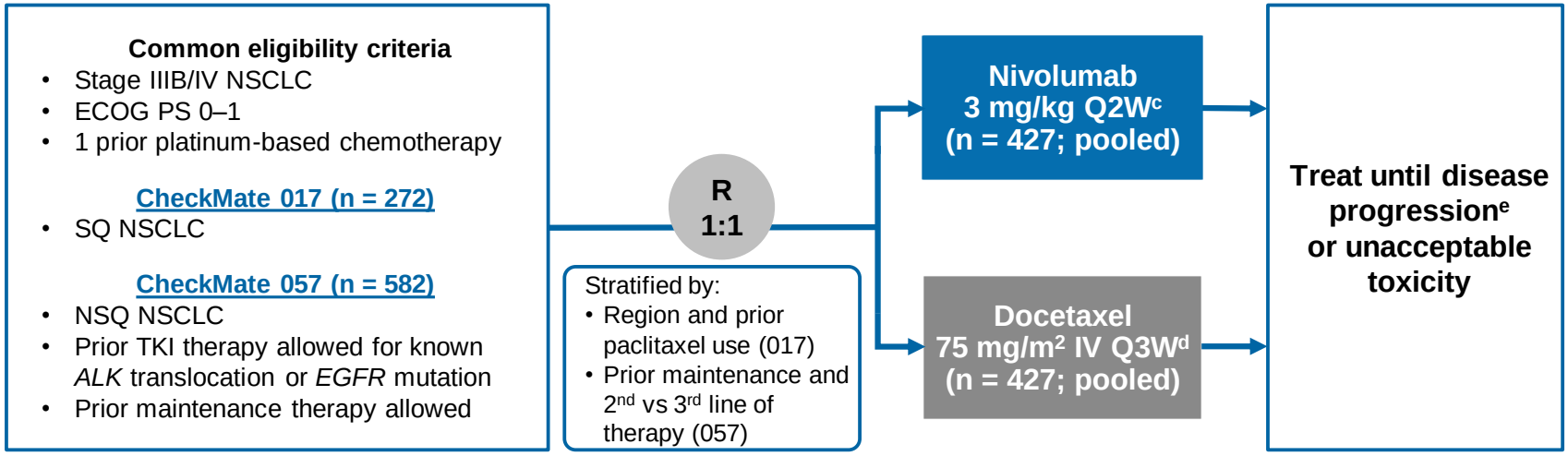
Five-Year Outcomes From the Randomized, Phase 3 Trials CheckMate 017/057: Nivolumab vs Docetaxel in Previously Treated NSCLC

Scott Gettinger,[1] Hossein Borghaei,[2] Julie Brahmer,[3] Laura Q.M. Chow,[4] Marco Angelo Burgio,[5] Javier de Castro Carpeno,[6] Adam Pluzanski,[7] Oscar Arrieta,[8] Osvaldo Arén Frontera,[9] Rita Chiari,[10] Charles Butts,[11] Joanna Wójcik-Tomaszewska,[12] Bruno Coudert,[13] Marina Chiara Garassino,[14] Neal Ready,[15] Enriqueta Felip,[16] Miriam Alonso Garcia,[17] David Waterhouse,[18] Manuel Domine,[19] Fabrice Barlesi,[20] Scott Antonia,[21] Markus Wohlleber,[22] David E. Gerber,[23] Grzegorz Czyżewicz,[24] David R. Spigel,[25] Lucio Crino,[5] Wilfried Ernst Erich Eberhardt,[26] Ang Li,[27] Sathiya Marimuthu,[27] Everett E. Vokes[28]

[1]Yale Comprehensive Cancer Center, New Haven, CT, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [4]University of Washington, Seattle Cancer Care Alliance, Seattle, WA, USA; [5]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [6]Hospital De Madrid, Norte Sanchinarro, CIOCC, Madrid, Spain; [7]Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland; [8]Instituto Nacional De Cancerología, Mexico City, Mexico; [9]Centro de Investigación Clínica Bradford Hill and Centro Internacional de Estudios Clinicos, Santiago, Chile; [10]Ospedale S. Maria Della Misericordia, Perugia, Italy; [11]Cross Cancer Institute, Edmonton, AB, Canada; [12]Provincial Center of Oncology in Gdańsk, Gdańsk, Poland; [13]Centre Georges-François Leclerc, Dijon, France; [14]Instituto Nazionale per lo Studio e la Cura, Milano, Italy; [15]Duke University Medical Center, Durham, NC, USA; [16]Hospital General Universitari Vall D'Hebron, Barcelona, Spain; [17]Hospital Universitario Virgen Del Rocio, Sevilla, Spain; [18]Oncology Hematology Care, Inc., Cincinnati, OH, USA; [19]Hospital Universitario Fundación Jiménez Díaz, IIS-FJD, Madrid, Spain; [20]Aix Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France; [21]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [22]Robert Bosch Cancer Center, Gerlingen, Germany; [23]UT Southwestern Medical Center, Dallas, TX, USA; [24]John Paul II Hospital, Kraków, Poland; [25]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [26]Universitaetsmedizin Essen und Ruhrlandklinik, Essen, Germany; [27]Bristol-Myers Squibb, Princeton, NJ, USA; [28]University of Chicago Medicine and Biologic Sciences Division, Chicago, IL, USA

CheckMate 017[a] and 057[b] Study Design

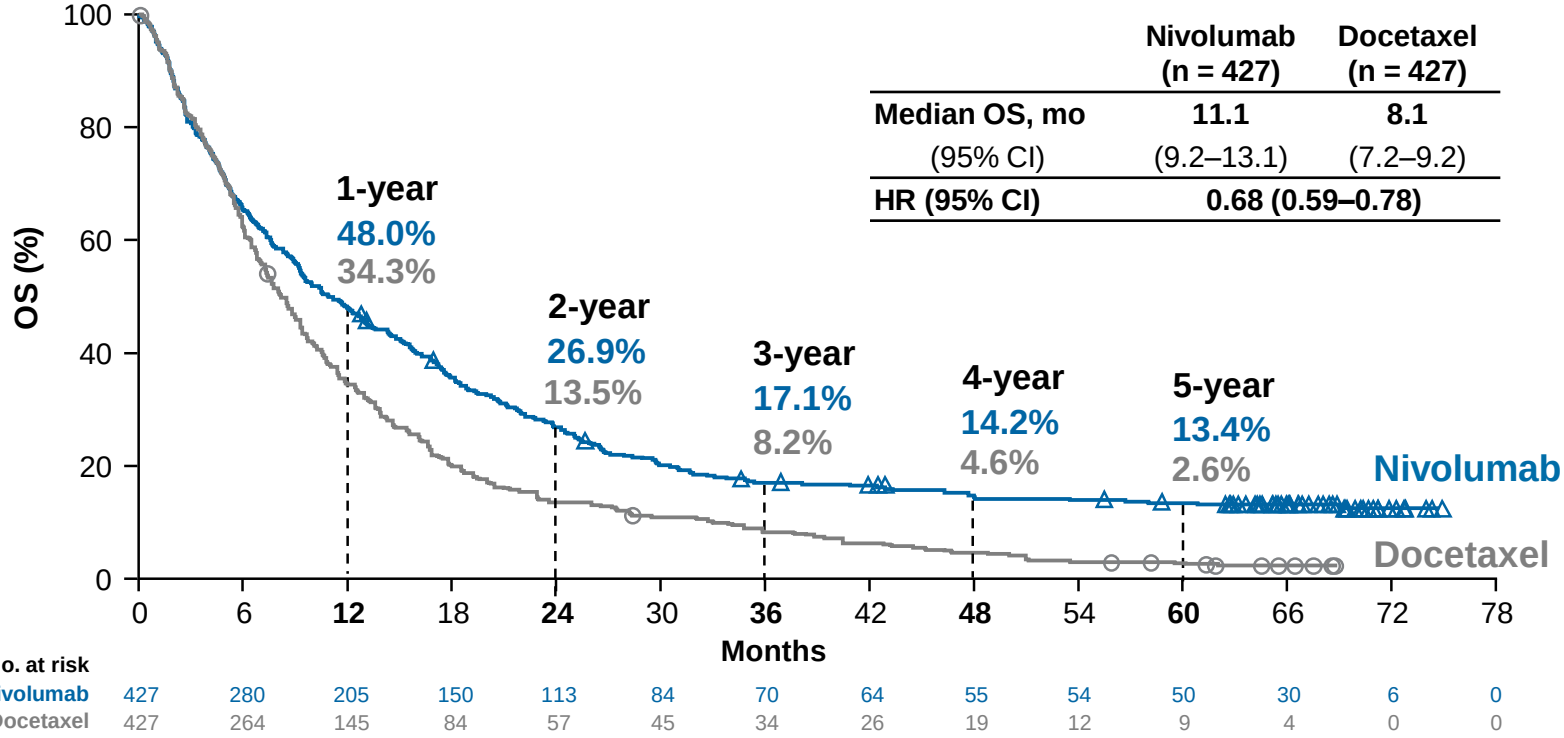


Primary endpoint: OS

Additional endpoints: PFS,[f] ORR,[f] efficacy by tumor PD-L1 expression, safety, PROs

[a]NCT01642004; database lock: May 8, 2019; minimum follow-up for OS, 62.6 months; [b]NCT01673867; database lock: May 16, 2019; minimum follow-up for OS, 62.7 months; [c]Optional switch to nivolumab 480 mg Q4W allowed as per protocol amendment in September 2016; [d]After completion of the primary analyses, patients in the docetaxel arms who ended treatment at any time during the studies were allowed to cross over to nivolumab; [e]Defined by RECIST 1.1; patients receiving nivolumab may be treated beyond progression under protocol-defined circumstances; [f]As assessed by investigator.

5-Year Pooled OS: Nivolumab vs Docetaxel[a]



	Nivolumab (n = 427)	Docetaxel (n = 427)
Median OS, mo	**11.1**	**8.1**
(95% CI)	(9.2–13.1)	(7.2–9.2)
HR (95% CI)	**0.68 (0.59–0.78)**	

- 5-year OS rate (nivolumab vs docetaxel): 12.3% vs 3.6% (CheckMate 017; SQ); 14.0% vs 2.1% (CheckMate 057; NSQ)

[a]Minimum follow-up for OS: 62.6 months (CheckMate 017), 62.7 months (CheckMate 057).

Zielgerichtete Therapie

Flaura trial

BARCELONA 2019 ESMO congress

OSIMERTINIB VS COMPARATOR EGFR-TKI AS FIRST-LINE TREATMENT FOR EGFRm ADVANCED NSCLC (FLAURA): FINAL OVERALL SURVIVAL ANALYSIS

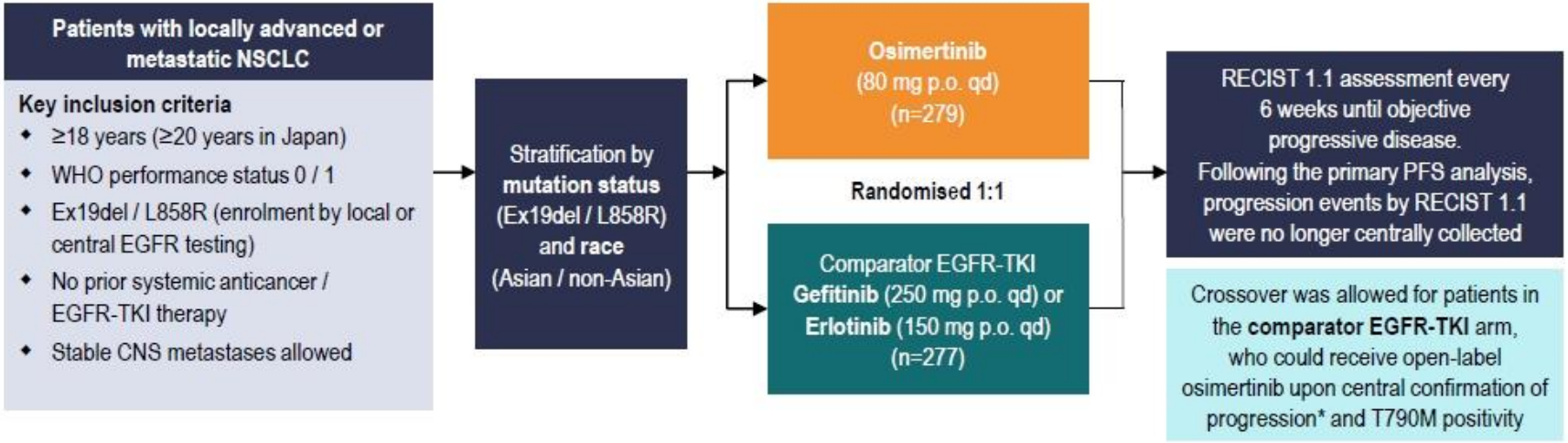
Suresh S Ramalingam[1], Jhanelle E Gray[2], Yuichiro Ohe[3], Byoung Chul Cho[4], Johan Vansteenkiste[5], Caicun Zhou[6], Thanyanan Reungwetwattana[7], Ying Cheng[8], Busayamas Chewaskulyong[9], Riyaz Shah[10], Ki Hyeong Lee[11], Parneet Cheema[12], Marcello Tiseo[13], Thomas John[14], Meng-Chih Lin[15], Fumio Imamura[16], Rachel Hodge[17], Yuri Rukazenkov[17], Jean-Charles Soria[18,19], David Planchard[19]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [3]Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; [4]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]University Hospital KU Leuven, Leuven, Belgium; [6]Pulmonary Hospital of Tongji University, Shanghai, China; [7]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [8]Jilin Provincial Cancer Hospital, Changchun, China; [9]Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; [10]Kent Oncology Centre, Maidstone Hospital, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK; [11]Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, Korea; [12]William Osler Health System, University of Toronto, Toronto, ON, Canada; [13]Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [14]Department of Medical Oncology, Austin Health, Melbourne, Australia; [15]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [16]Department of Thoracic Oncology, Osaka International Cancer Institute, Chuo-ku, Osaka, Japan; [17]Global Medicines Development, AstraZeneca, Cambridge, UK; [18]Early Oncology Research & Development, AstraZeneca, Gaithersburg, Maryland / Université Paris-Sud, Orsay, France; [19]Department of Medical Oncology, Gustave Roussy, Villejuif, France

esmo.org

Flaura trial

FLAURA DOUBLE-BLIND STUDY DESIGN



OS was a key secondary endpoint

- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment

Data cut-off: 25 June 2019

Soria et al. N Engl J Med 2018;378:113-25

*By investigator assessment if disease progression occurred after the primary analysis data cut-off

p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

Flaura trial

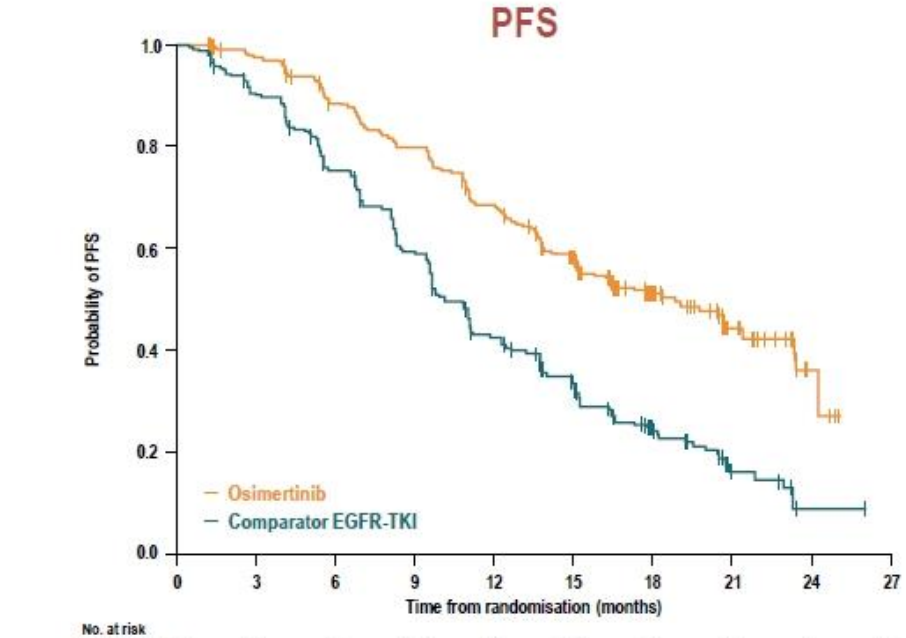
BASELINE CHARACTERISTICS

Characteristic, %	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Sex: male / female	36 / 64	38 / 62
Age, median (range), years	64 (26–85)	64 (35–93)
Race: Asian / non-Asian	62 / 38	62 / 38
Smoking status: never / ever	65 / 35	63 / 37
CNS metastases at study entry	19	23
WHO performance status: 0 / 1	40 / 60	42 / 58
Overall disease classification: metastatic / advanced	95 / 5	95 / 5
Histology: adenocarcinoma / other	99 / 1	98 / 2
EGFR mutation at randomisation: Ex19del / L858R	63 / 37	63 / 37

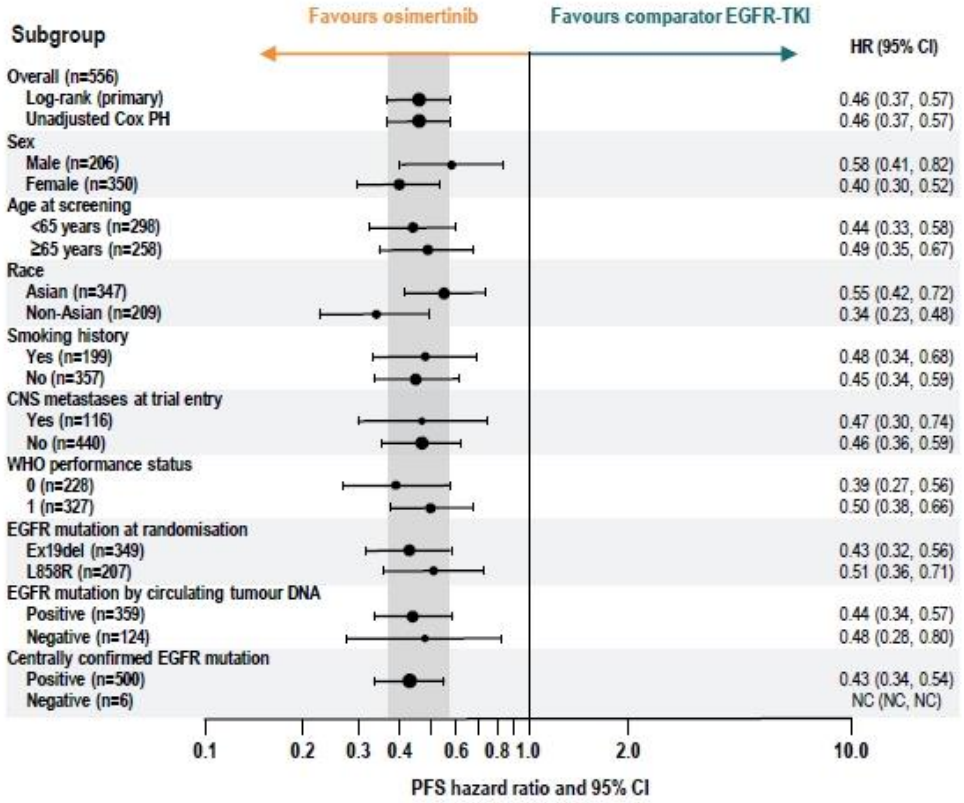
Data cut-off: 12 June 2017
Soria et al. N Engl J Med 2018;378:113-25

Flaura trial

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



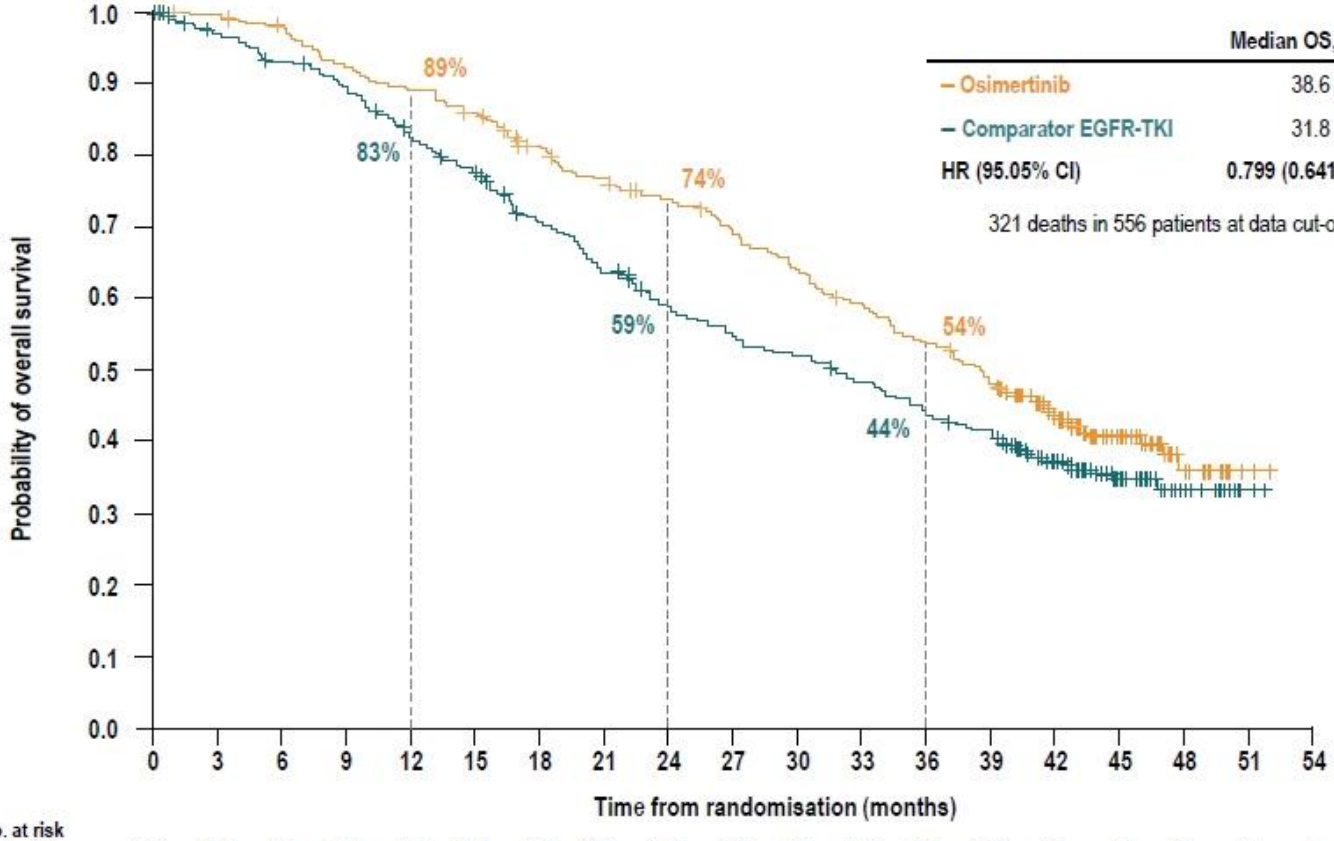
Data cut-off: 12 June 2017

Soria et al. N Engl J Med 2018;378:113-25

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

Flaura trial

FINAL ANALYSIS: OVERALL SURVIVAL



No. at risk																		
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

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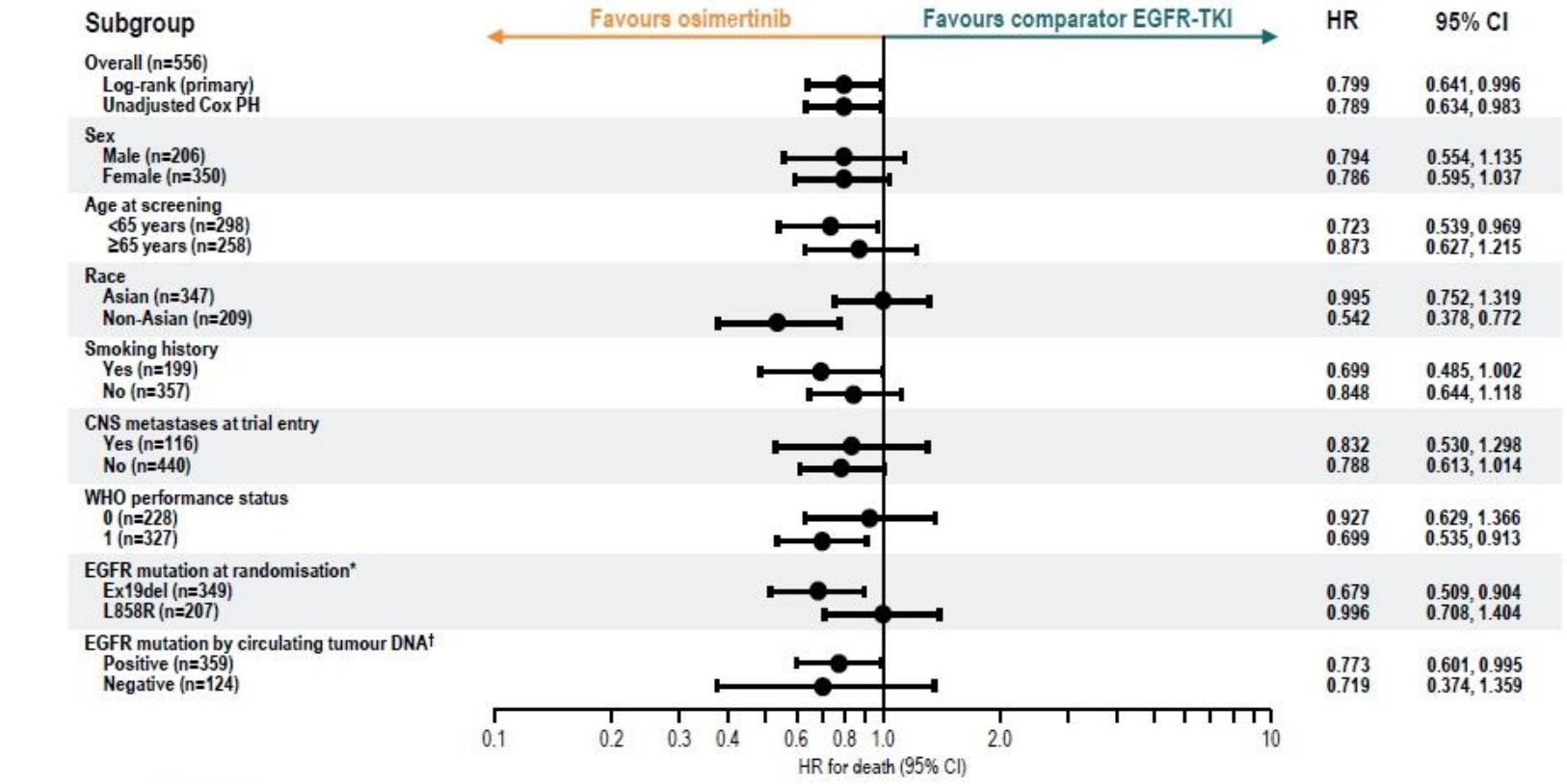
Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

Flaura trial

OVERALL SURVIVAL ACROSS SUBGROUPS



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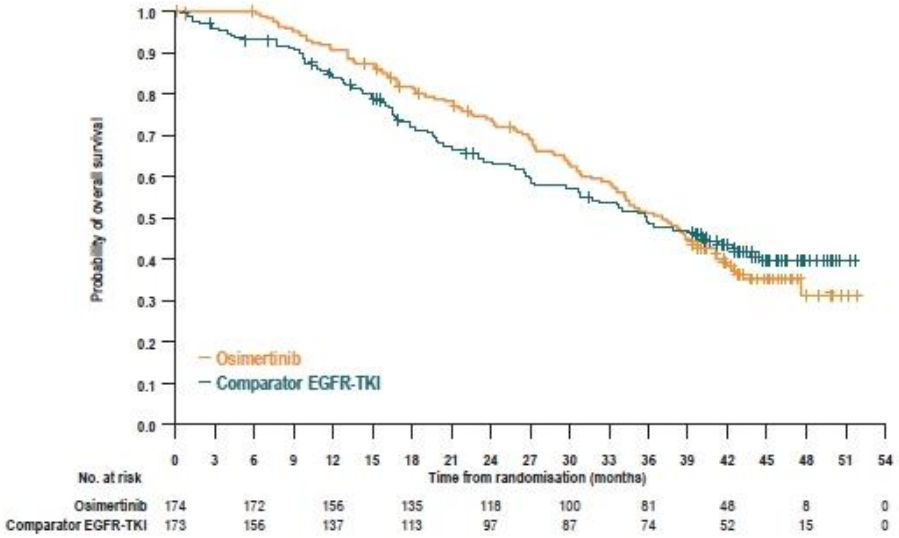
Data cut-off: 25 June 2019
Hazard ratio <1 implies a lower risk of death on osimertinib
*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

Flaura trial

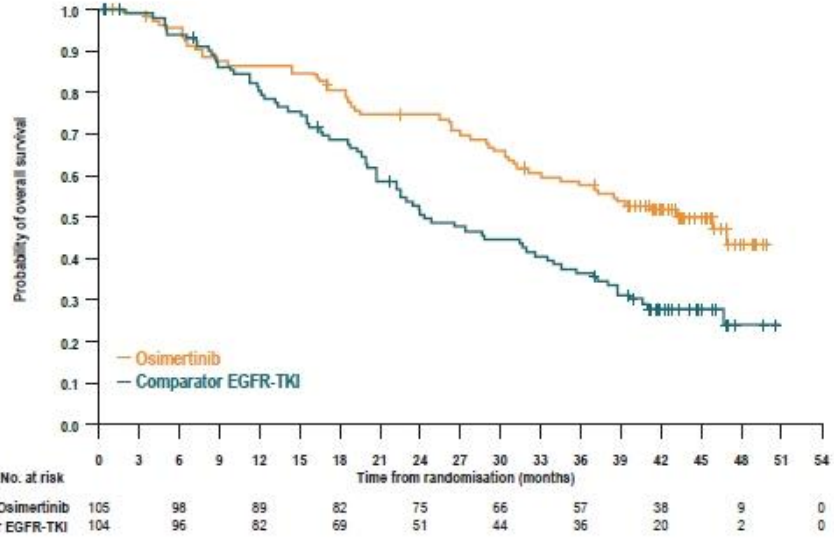
OVERALL SURVIVAL IN ASIAN AND NON-ASIAN PATIENTS

Asian patients



No. at risk										
Osimertinib	174	172	156	135	118	100	81	48	8	0
Comparator EGFR-TKI	173	156	137	113	97	87	74	52	15	0

Non-Asian patients



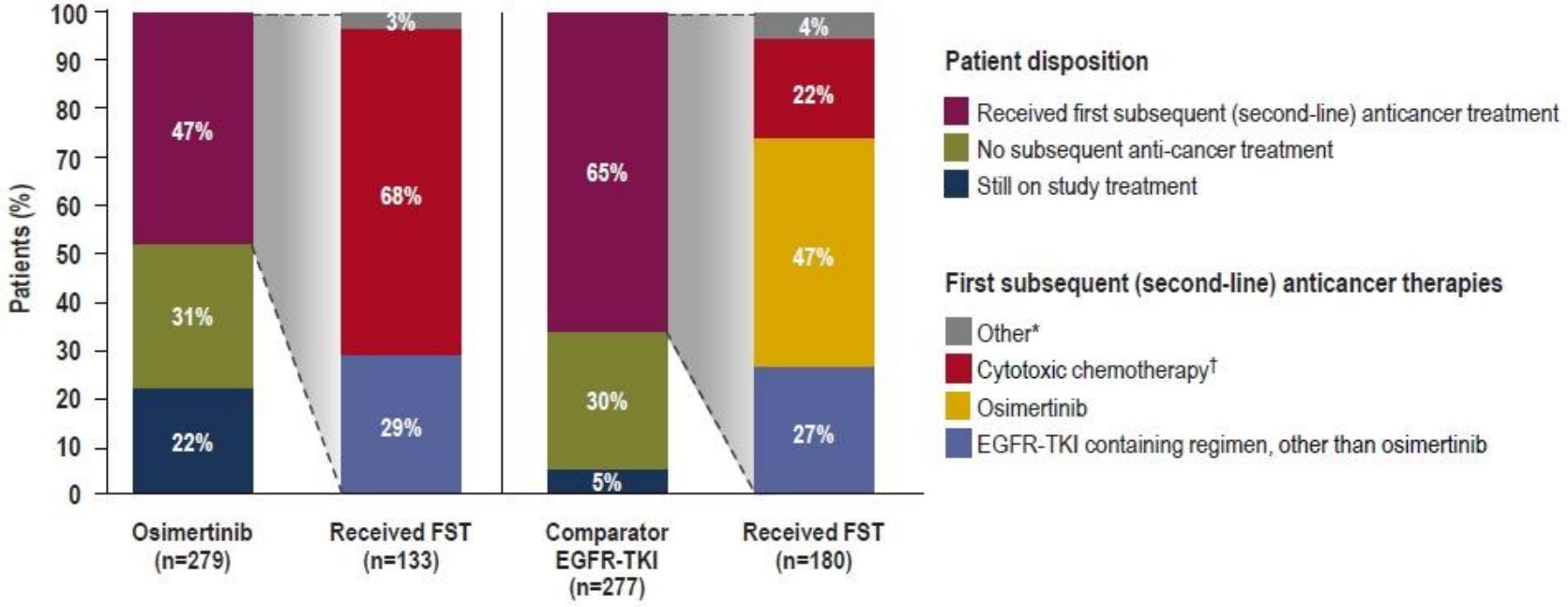
No. at risk										
Osimertinib	105	98	89	82	75	66	57	38	9	0
Comparator EGFR-TKI	104	96	82	69	51	44	36	20	2	0

Data cut-off: 25 June 2019

Flaura trial

SECOND-LINE TREATMENT FOLLOWING PROGRESSION

- Of the 180 patients in the comparator EGFR-TKI arm who received a first subsequent treatment, **85 patients (47%) crossed over to osimertinib** (31% of all patients randomised from the comparator EGFR-TKI arm)



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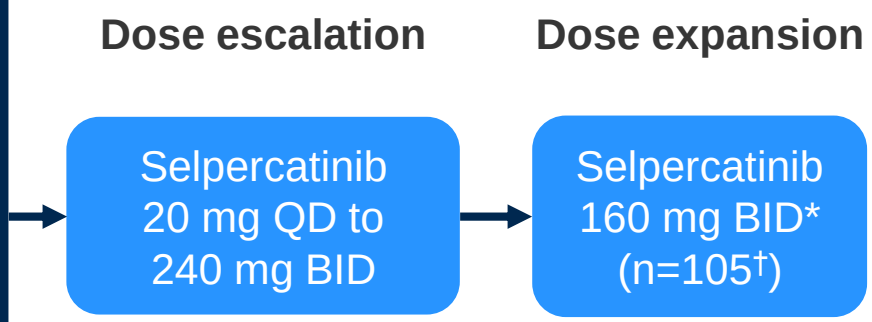
Data cut-off: 25 June 2019

*Refers to those patients who did not receive either chemotherapy or an EGFR-TKI; †The majority of patients who received cytotoxic chemotherapy received a platinum-based chemotherapy regimen
FST, first subsequent treatment

PL02.08: Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of LOXO-292 in Patients with RET Fusion-Positive Lung Cancers – Drilon A, et al

- **Study objective**
  - To investigate the efficacy and safety of selpercatinib (LOXO-292) in patients with RET fusion-positive lung cancers

Key patient inclusion criteria (n=531)
- RET fusion-positive NSCLC (n=253)
  - Prior platinum chemotherapy (n=184)
  - Prior non-platinum chemotherapy (n=16)
  - Treatment naïve (n=39)
  - Non-measurable disease (n=14)
- RET-mutant medullary thyroid cancer (n=226)
- RET fusion-positive thyroid cancer (n=27)
- Other (n=25)



Primary endpoint
- ORR (RECIST v1.1)

Secondary endpoints
- DoR, PFS, safety

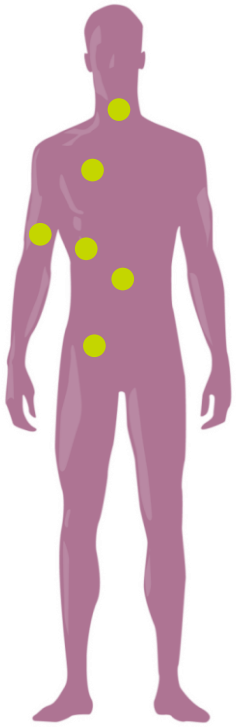
*Treatment beyond progression permitted with continued benefit; †primary analysis set – patients with RET fusion-positive NSCLC who had received prior platinum chemotherapy

Drilon A, et al. J Thorac Oncol 2019;14(suppl):Abstr PL02.08

LIBRETTO-001

Hintergrund

***RET*-Fusionen**



Nicht-kleinzelliges Lungenkarzinom (2%)

Schilddrüsenkarzinom (10-20%)

Pankreaskarzinom (<1%)

Speicheldrüsenkarzinom (<1%)

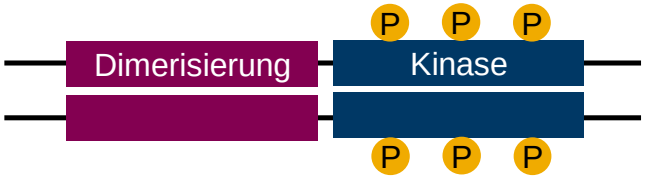
Spitz-Tumore (<1%)

Kolonkarzinom (<1%)

Ovarialkarzinom (<1%)

Myeloproliferative Erkrankungen (<1%)

Viele andere (<1%)



KIF5B (am häufigsten bei Lungenkarzinomen)
CCDC6 oder ***NCOA4*** (am häufigsten bei Schilddrüsenkarzinomen)

- ***RET*-Fusionen sind maßgebliche Treiber von Lungenkarzinomen**
  - Schließen andere Treibermutationen aus[1,2]
  - Veränderlich und messbar *in vitro* und *in vivo*[3,4]
  - Bis zu 50% der Patienten mit fortgeschrittener Erkrankung haben Gehirnmetastasen[5]
- **Bis heute wurde kein RET-Inhibitor für die Behandlung von RET-abhängigen Karzinomen zugelassen**
  - Multikinase-Inhibitoren
    - Mäßiger klinischer Nutzen
    - Signifikante Toxizität (Nicht-RET-Kinase-Inhibitor[6])
  - Immuntherapien (PD-1-/PD-L1-Inhibitoren)
    - Können bei Treiber-positivem NSCLC, einschließlich *RET*-Fusionen, weniger wirksam sein[7,8]

1. Drilon et al., Nat Rev Clin Oncol 2018;15(3):151-67; 2. Wang et al., J Clin Oncol 2012;30(35):4352-9; 3. Saito et al., Carcinogenesis 2014;35(11):2452-6; 4. Takahashi et al., Cell 1985;42(2):581-8; 5. Drilon et al., J Clin Oncol 2017;35:15_suppl:9069; 6. Ferrara et al., J Thorac Oncol 2018;13(1):27-45; 7. Sabari et al., J Clin Oncol 2018;36(15 suppl; abstr 9034); 8. Mazieres et al., J Clin Oncol 2018;35(15 suppl; abstr 9010)

PL02.08: Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of LOXO-292 in Patients with RET Fusion-Positive Lung Cancers – Drilon A, et al

- **Key results**

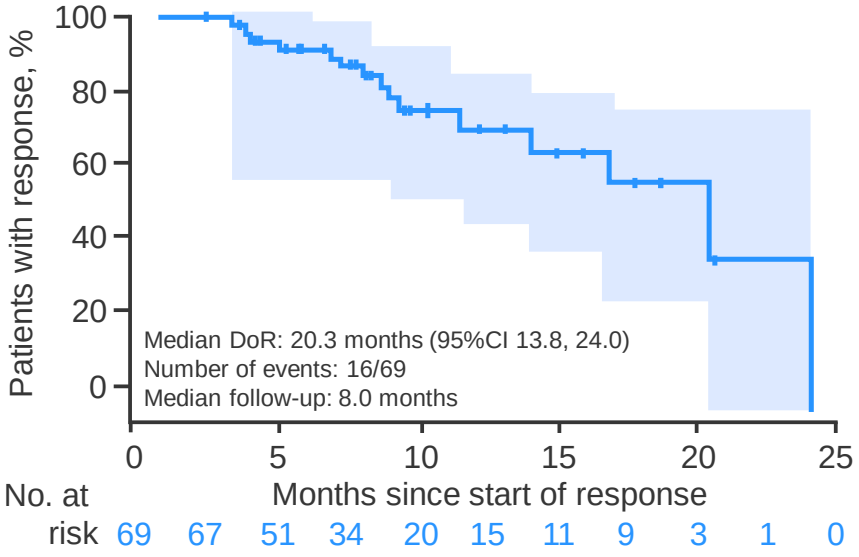
	RET fusion-positive received prior platinum chemotherapy		RET fusion-positive treatment naïve
Response	**Overall (n=105)**	**CNS (n=11)**	**(n=34)**
ORR, % (95%CI)	68 (58, 76)	91 (59, 100)	85 (69, 95)
CR, %	2	18	3
PR, %	66	73	82
SD, %	26	9	9
PD, %	2	-	3
NE, %	5	-	3

Drilon A, et al. J Thorac Oncol 2019;14(suppl):Abstr PL02.08

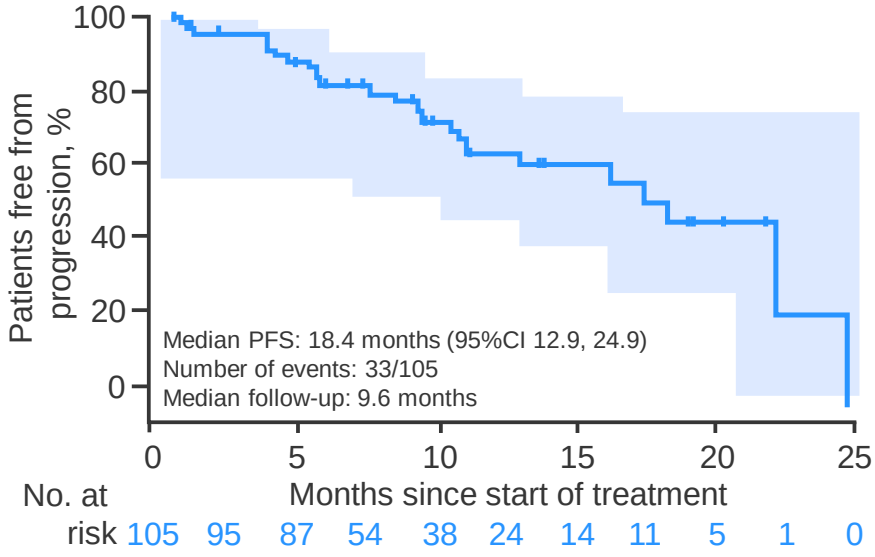
PL02.08: Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of LOXO-292 in Patients with RET Fusion-Positive Lung Cancers – Drilon A, et al

- **Key results (cont.)** **Primary analysis set**
  - Treatment beyond progression was continued in 23 of 28 who had progressed

DoR



PFS



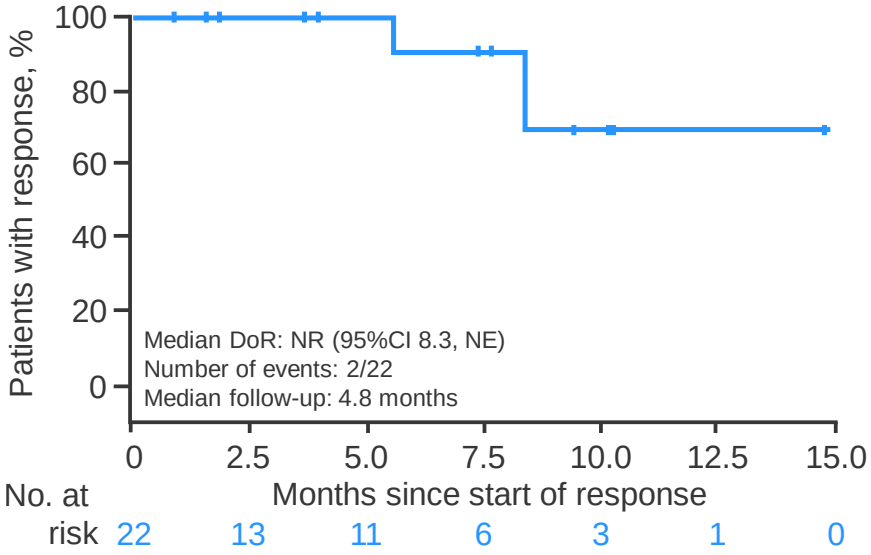
Drilon A, et al. J Thorac Oncol 2019;14(suppl):Abstr PL02.08

PL02.08: Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of LOXO-292 in Patients with RET Fusion-Positive Lung Cancers – Drilon A, et al

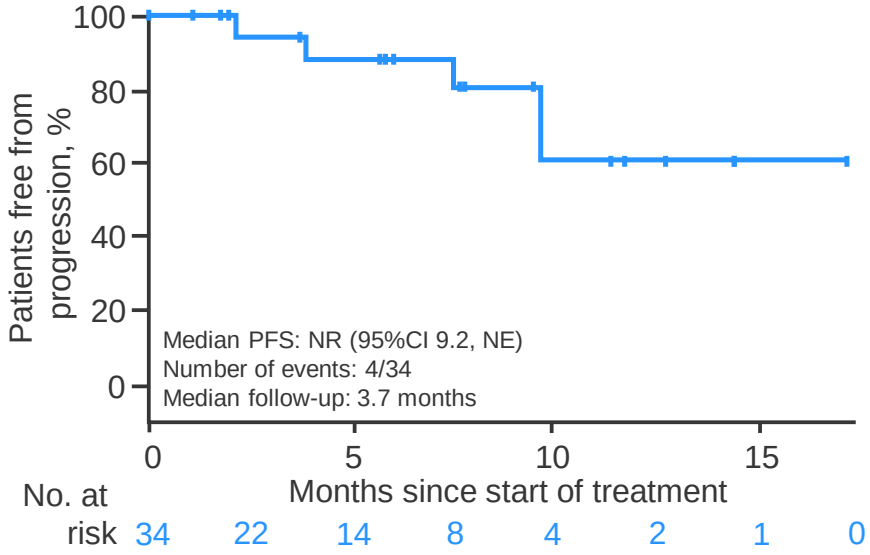
- **Key results (cont.)**

Treatment naïve population

DoR



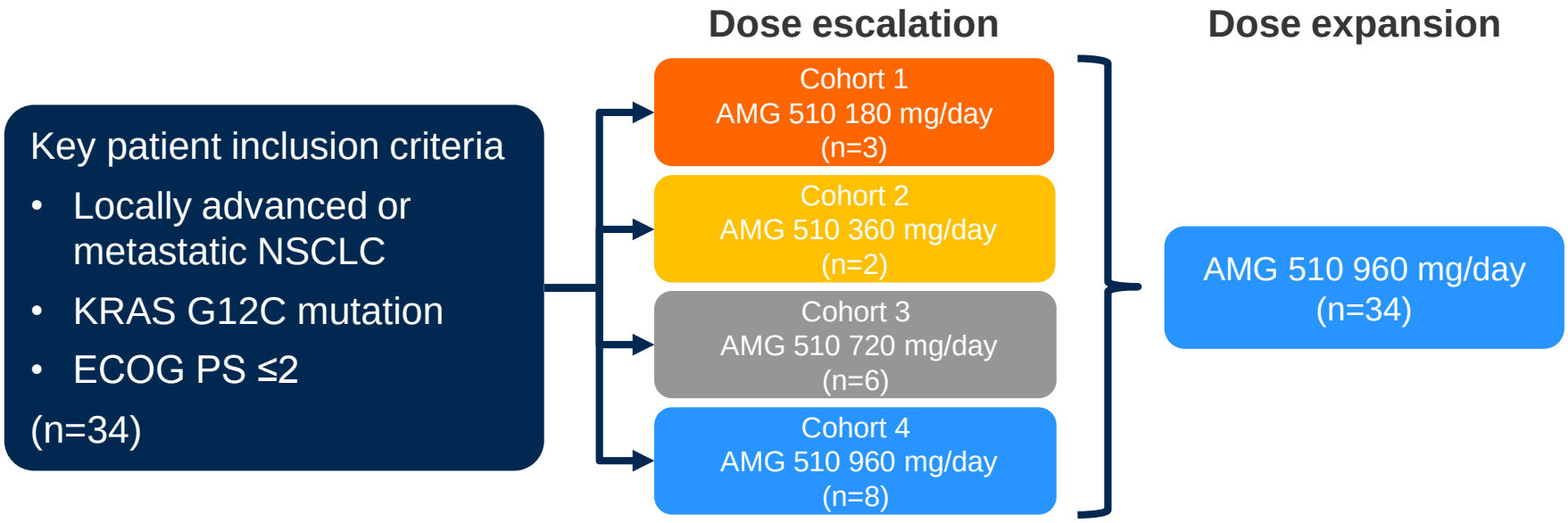
PFS



Drilon A, et al. J Thorac Oncol 2019;14(suppl):Abstr PL02.08

OA02.02: Phase 1 Study of Safety, Tolerability, PK and Efficacy of AMG 510, a Novel KRAS^{G12C} Inhibitor, Evaluated in NSCLC – Govindan R, et al

- **Study objective**
  - To investigate the efficacy and safety of AMG 510, a KRAS^{G12C} inhibitor, in patients with advanced NSCLC and a KRAS G12C mutation



Primary endpoint

- Safety

Secondary endpoints

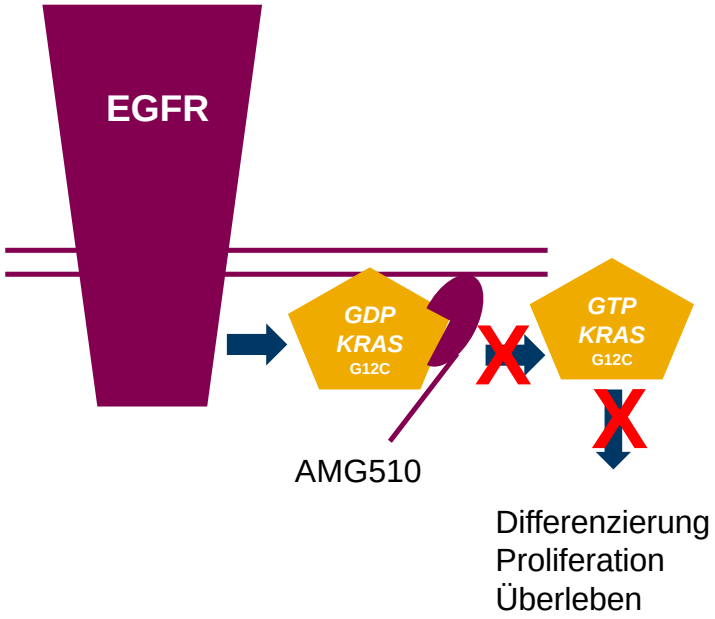
- ORR, DoR, DCR, PFS, PK

Govindan R, et al. J Thorac Oncol 2019;14(suppl):Abstr OA02.02

KRAS^{G12C}-Inhibitor AMG 510: Phase-I-Studie

Einführung

- AMG 510 ist der erste KRAS^{G12C}-Inhibitor seiner Klasse
- *KRAS^{G12C}*-Mutationen wurden bei ca. 13% der Lungenkarzinome[1], 3% der kolorektalen[2] und Appendixkarzinome sowie 1–3% aller anderen soliden Tumoren[3] festgestellt
- Aktuell gibt es keine zielgerichtete, zugelassene Therapie für diese Mutation
- AMG 510 ist ein neuartiges, kleines Molekül – das erste seiner Klasse – das KRAS^{G12C} spezifisch und irreversibel blockiert, indem es das Protein dauerhaft in seiner inaktiven GDP-gebundenen Form fixiert



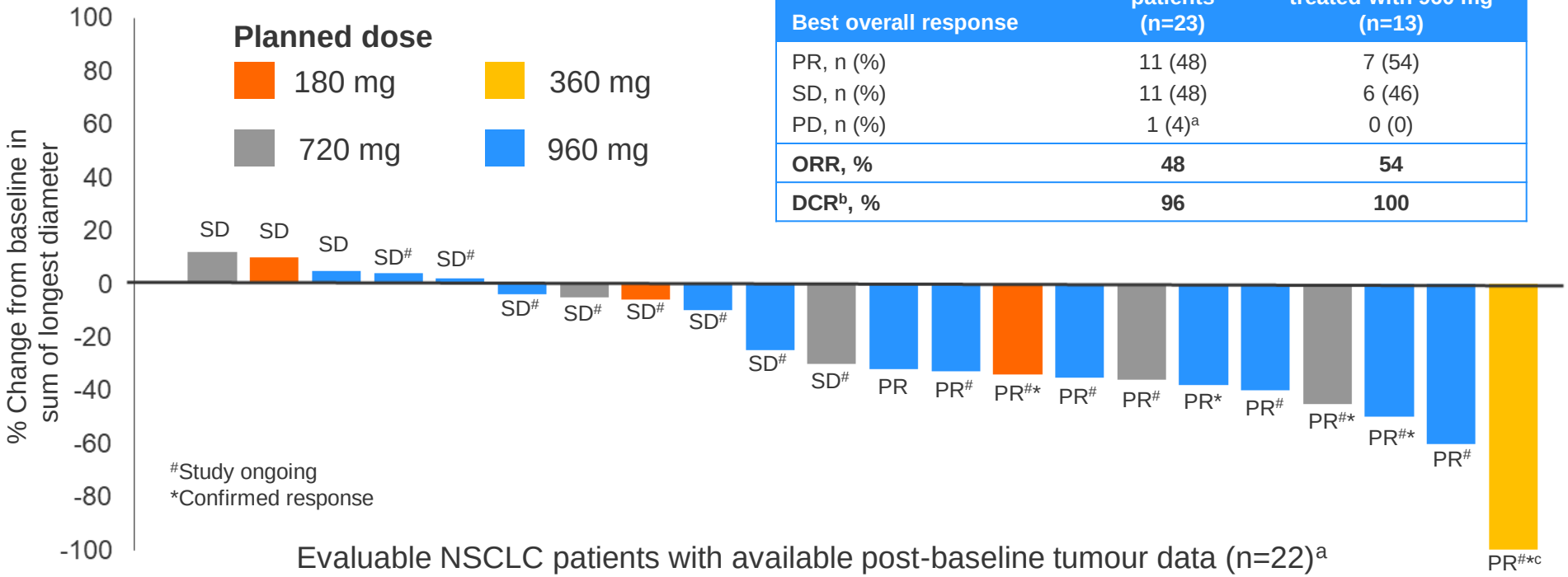
GDP: Guanosindiphosphat
GTP: Guanosintriphosphat
KRAS: „Kirsten rat sarcoma viral ongogene homolog“
KRAS^{G12C}: KRAS-Protein mit einer G12C-Mutation auf Proteinebene

1. Biernacka et al., Cancer Genet. 2016;209(5):195-198; 2. Neumann et al., Pathol Res Pract. 2009;205(12):858-62; 3. Zhou et al., Med Oncol. 2016;33(4):32

OA02.02: Phase 1 Study of Safety, Tolerability, PK and Efficacy of AMG 510, a Novel KRAS^{G12C} Inhibitor, Evaluated in NSCLC – Govindan R, et al

- **Key results (cont.)**

Best overall response	All evaluable patients (n=23)	Evaluable patients treated with 960 mg (n=13)
PR, n (%)	11 (48)	7 (54)
SD, n (%)	11 (48)	6 (46)
PD, n (%)	1 (4)[a]	0 (0)
ORR, %	**48**	**54**
DCR[b], %	**96**	**100**



Evaluable NSCLC patients with available post-baseline tumour data (n=22)[a]

- **Conclusion**
  - In patients with NSCLC and a KRAS G12C mutation, AMG 510 demonstrated a manageable safety profile and provided encouraging responses

[a]Patient discontinued due to PD prior to first assessment;
[b]PR or SD at week 6; [c]patient had CR

Govindan R, et al. J Thorac Oncol 2019;14(suppl):Abstr OA02.02

Larotrectinib beim Lungenkarzinom mit *TRK*-Fusion

Hintergrund

- ***NTRK*-Genfusionen:**
  - Reorganisationen umfassen entweder die Gene *NTRK1*, *2* oder *3* und verschiedene unabhängige Partner[1]
  - Bilden onkogene Fusionsproteine, die eine TRK-Kinasedomäne enthalten und die Tumorentwicklung steuern[2,3]

- ***TRK*-Fusionen wurden in >20 Tumorarten identifiziert und treten wie folgt auf:**
  - Mit niedriger Frequenz in häufigen Tumorarten (~1% aller Malignome)[2,4]
  - Mit hoher Frequenz in seltenen Tumorarten (~90%)[2]

- **Die geschätzte Frequenz von *NTRK*-Fusionen in NSCLC liegt bei 0,2%[5]**
  - Bei einem Screening von 4.872 NSCLC-Patienten wurden in 0,23%[5] der Fälle *NTRK*-Genfusionen detektiert
  - Die Patienten mit *NTRK*-Genfusionen hatten keine gleichzeitig auftretenden Alterationen in anderen onkogenen Treibern[5]
  - Das Auftreten von *NTRK*-Genfusionen ist unabhängig von den Rauchgewohnheiten, dem Alter und der Tumorhistologie

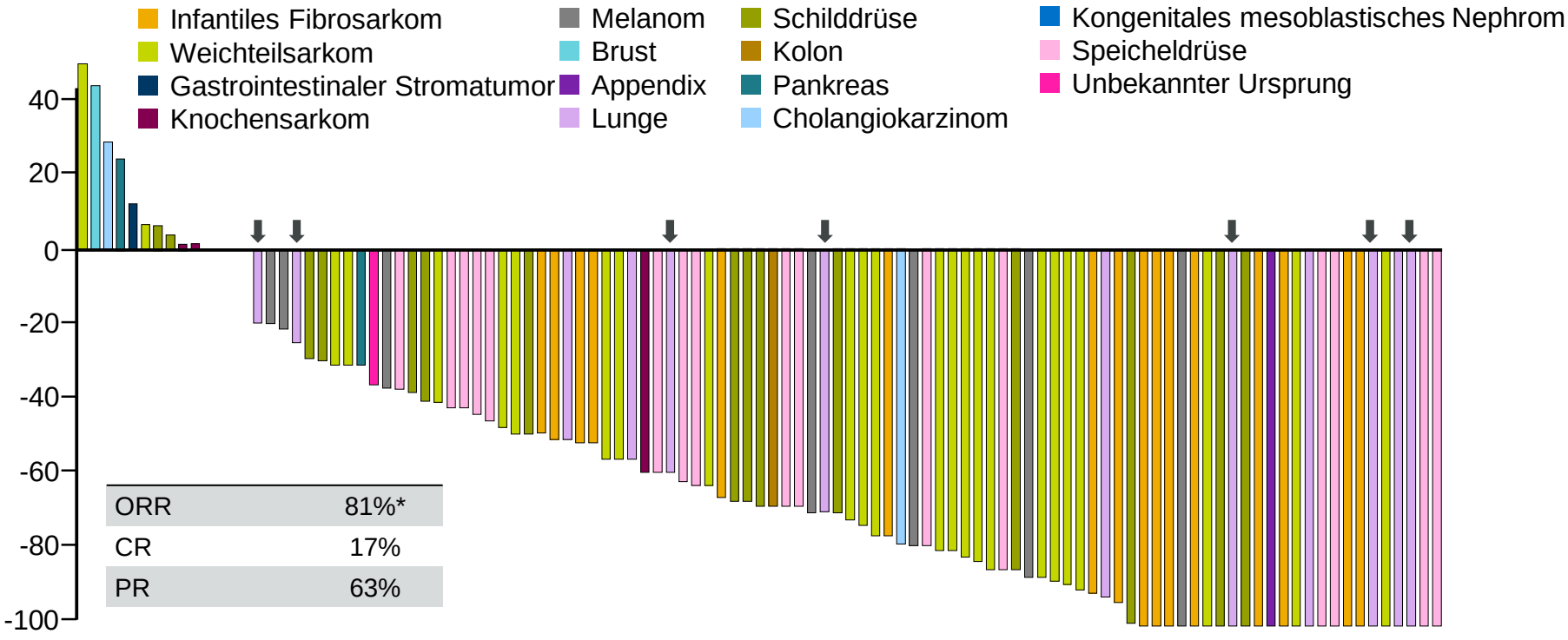
1. Vaishnavi et al. Cancer Discov. 2015;5(1):25-34; 2. Cocco et al. Nat Rev Clin Oncol. 2018; 15(12):731-747;
3. Penault-Llorca et al. J Clin Pathol 2019;72(7):460-467; 4. Drilon et al. N Engl J Med. 2018;378(8):731-739;
5. Farago et al. JCO Precis Oncol. 2018:2;1-12

Farago AF et al., WCLC 2019, Barcelona, Spanien, MA09.07

Larotrectinib beim Lungenkarzinom mit *TRK*-Fusion

Hintergrund

- **Larotrectinib ist ein hochselektiver, „erster-in-seiner-Klasse“ TRK-Inhibitor**
  - Tumoragnostische Wirksamkeit bei Krebspatienten mit TRK-Genfusionen[1,2]



⬇ Patienten mit Lungenkarzinom

Data Cut-Off: 30. Juli 2018; *Beurteilung durch den Prüfarzt (N=109)

1. Drilon et al. N Engl J Med. 2018;378(8):731-739; 2. Lassen et al., ESMO 2018, München, Deutschland

Larotrectinib beim Lungenkarzinom mit *TRK*-Fusion

Methoden

Phase-I-Studie mit erwachsenen Patienten (NCT02122913)

- Alter ≥18 Jahre
- Fortgeschrittener solider Tumor

N=1

Phase-II-Basket-Studie mit jugendlichen/ erwachsenen Patienten (NAVIGATE; NCT02576431)

- Alter ≥12 Jahre
- Fortgeschrittener solider Tumor
- Tumor mit *TRK*-Fusionsgen

N=11

- Data Cut-off: 19. Februar 2019

12 Lungenkarzinompatienten mit *TRK*-Fusionsgen

Patientencharakteristika

Alter (Jahre)	
Median (Bereich)	49,0 (25-76)
Geschlecht, n (%)	
Männlich	6 (50)
Weiblich	6 (50)
***NTRK*-Fusionsgen, n (%)**	
NTRK1	9 (75)
NTRK2	0 (0)
NTRK3	3 (25)
Gehirnmetastasen bei Studienbeginn, n (%)	
Ja	6 (50)
Nein	6 (50)

Dosierung

- Larotrectinib, 2x täglich 100 mg, kontinuierlich
- 28-Tage-Zyklen

Endpunkte

Primärer Endpunkt:

- Beste objektive Ansprechrate (RECIST 1.1)

Sekundärer Endpunkt:

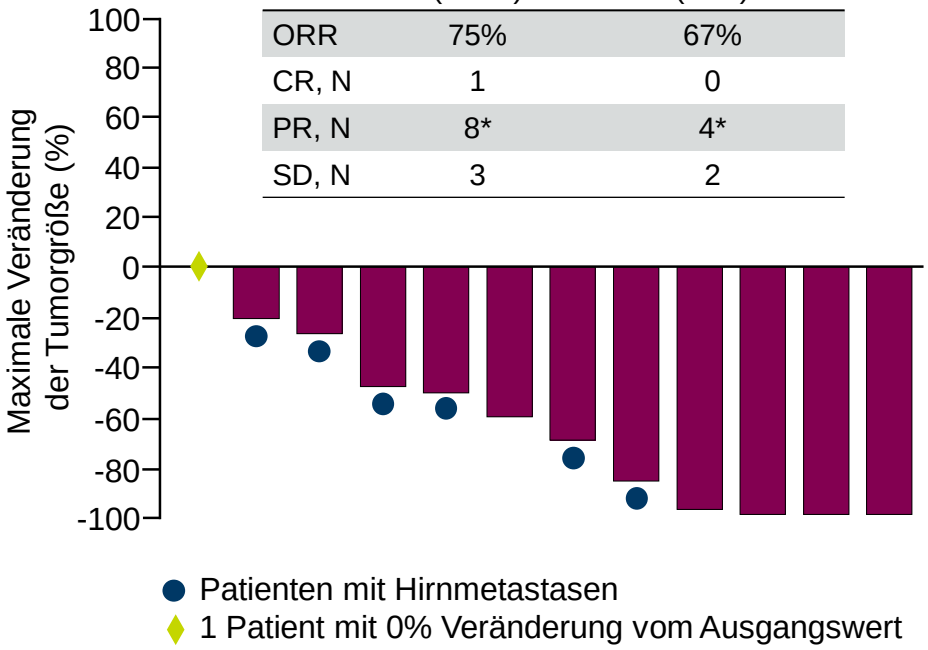
- Ansprechdauer
- Progressionsfreies Überleben
- Gesamtüberleben
- Toxizität

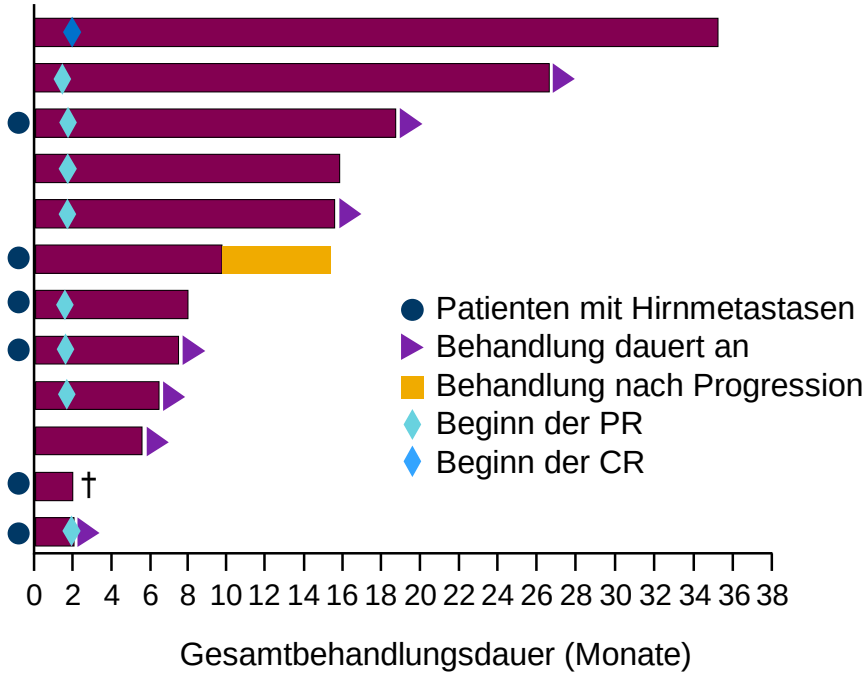
Der Status des *TRK*-Fusiongens wurde mittels lokaler CLIA (oder mithilfe ähnlicher akkreditierter Laboratorien) bestimmt

Larotrectinib beim Lungenkarzinom mit *TRK*-Fusion

Larotrectinib ist wirksam beim Lungenkarzinom mit *TRK*-Fusion

	Alle Patienten (N=12)	Patienten mit Hirnmetastasen (N=6)
ORR	75%	67%
CR, N	1	0
PR, N	8*	4*
SD, N	3	2





Mediane Ansprechdauer nicht erreicht (Bereich 3,9* bis 25,9* Monate) (medianes Follow-Up: 12,8 Monate)

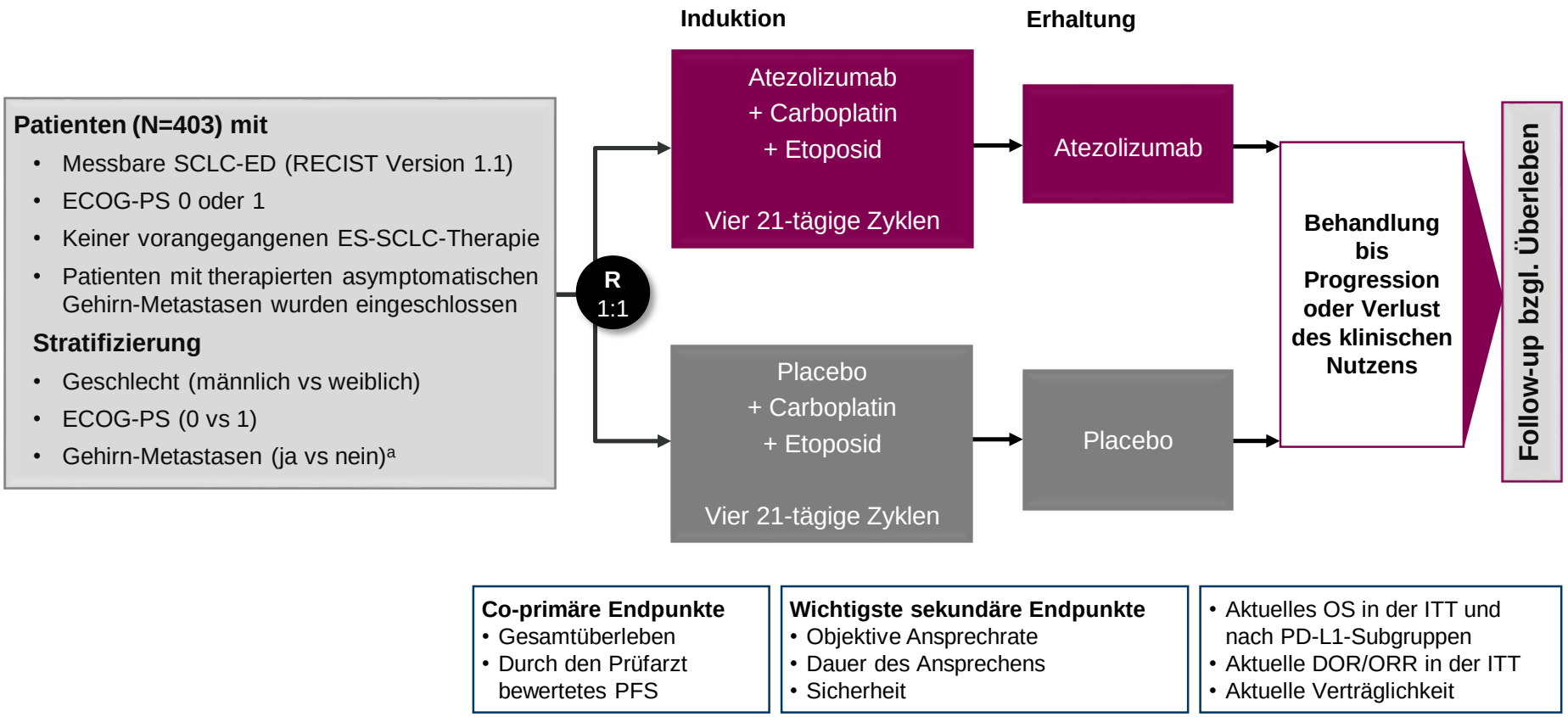
Behandlungsdauer: 1,8* bis 35,2* Monate

*Bestätigung des PR steht bei 1 Patient aus. Bewertung durch den Prüfarzt bis 19. Februar 2019. †Nicht-Ziel PD mit asymptomatischem leptomeningealem Fokus

Kleinzelliges Lungenkarzinom (SCLC)

IMpower133: OS-Update

Studiendesign



Atezolizumab, 1200 mg IV, Tag 1; Carboplatin, AUC 5 mg/ml/min IV, Tag 1; Etoposid, 100 mg/m2 IV, Tage 1-3

[a]Nur Patienten mit behandelten Gehirn-Metastasen wurden eingeschlossen.

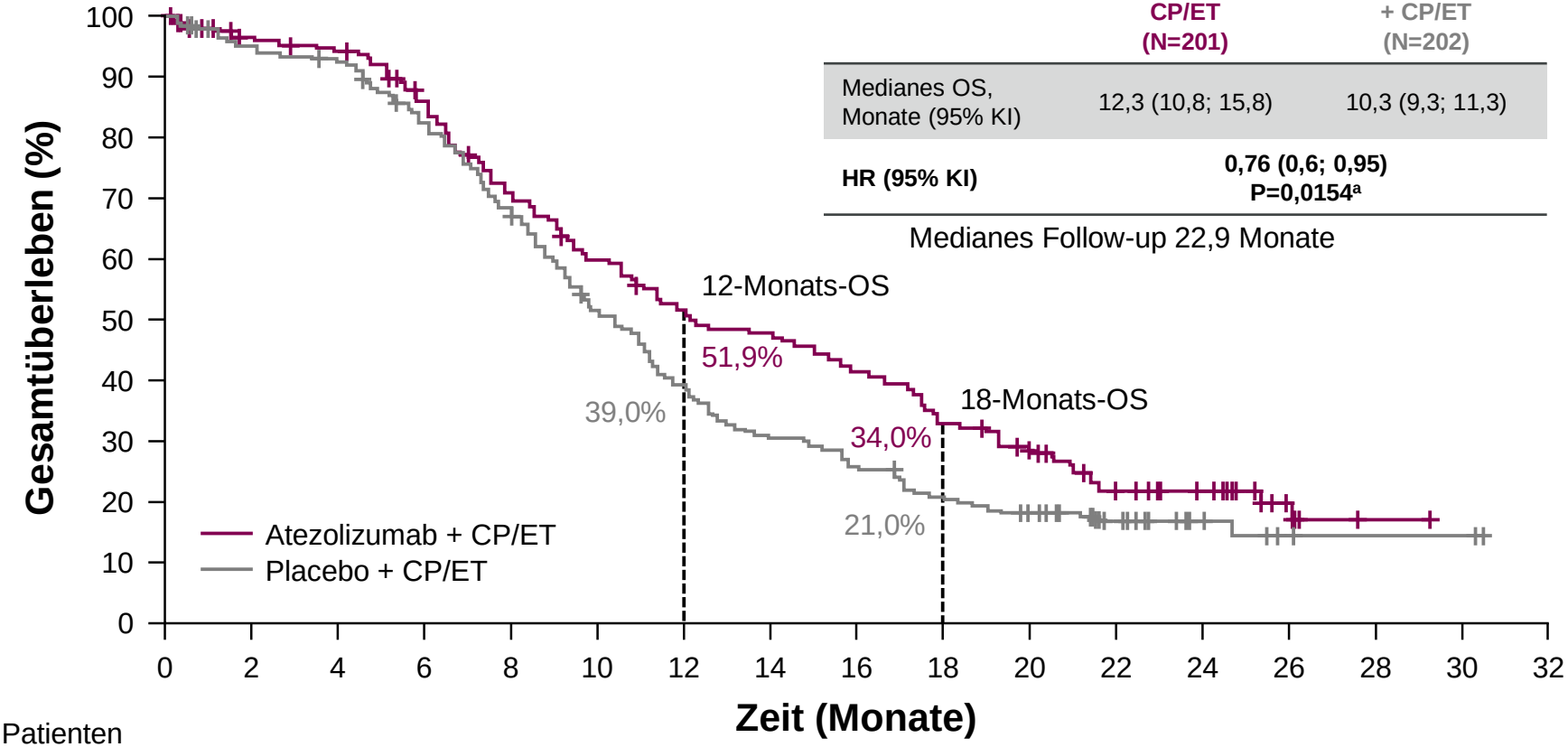
Reck M et al., Annals of Oncology (2019) 30 (suppl_5): v710-v717. 10.1093/annonc/mdz264

IMpower133: OS-Update

Aktualisiertes Gesamtüberleben in der ITT-Population

	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
Medianes OS, Monate (95% KI)	12,3 (10,8; 15,8)	10,3 (9,3; 11,3)
HR (95% KI)	**0,76 (0,6; 0,95) P=0,0154[a]**	

Medianes Follow-up 22,9 Monate



N Patienten

Atezolizumab	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1
Placebo	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

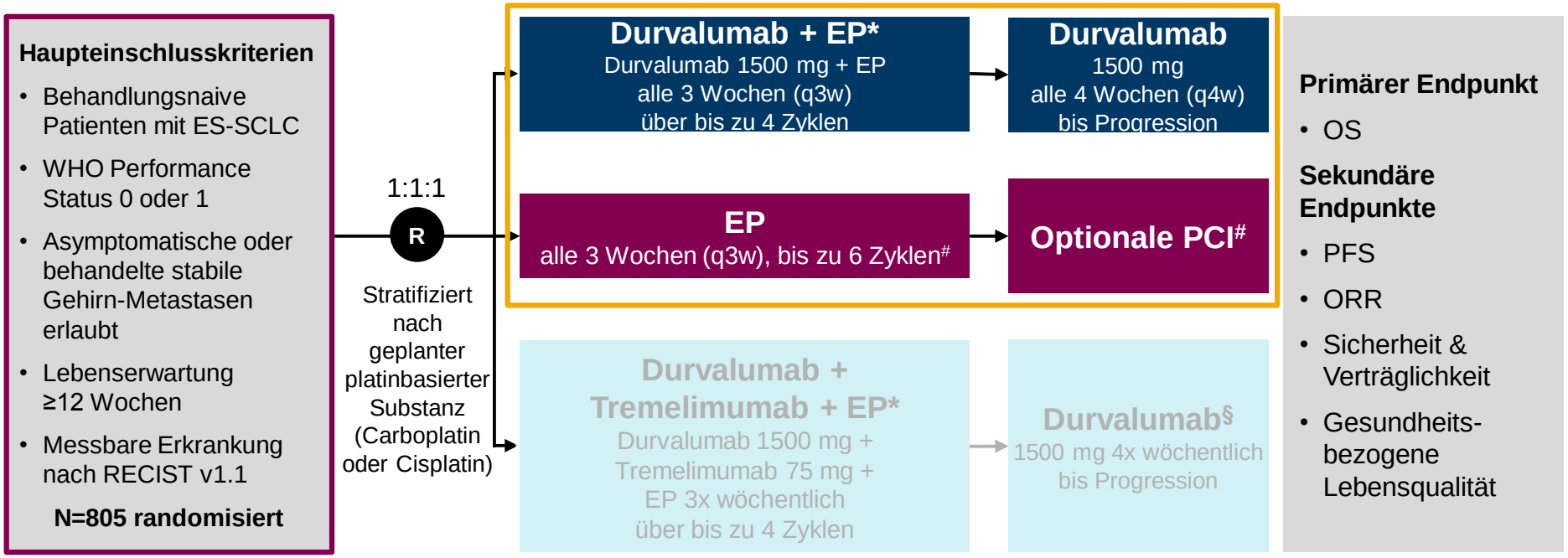
[a]P-Wert wird für deskriptive Zwecke angegeben
CCOD 24. Januar 2019

Reck M et al., Annals of Oncology (2019) 30 (suppl_5): v710-v717. 10.1093/annonc/mdz264

CASPIAN

Studiendesign

Globale, multizentrische, randomisierte, offene, Sponsoren-verblindete Phase-III-Studie



Der Vergleich von Durvalumab + Tremelimumab + EP vs EP wird bis zur finalen Analyse fortgeführt

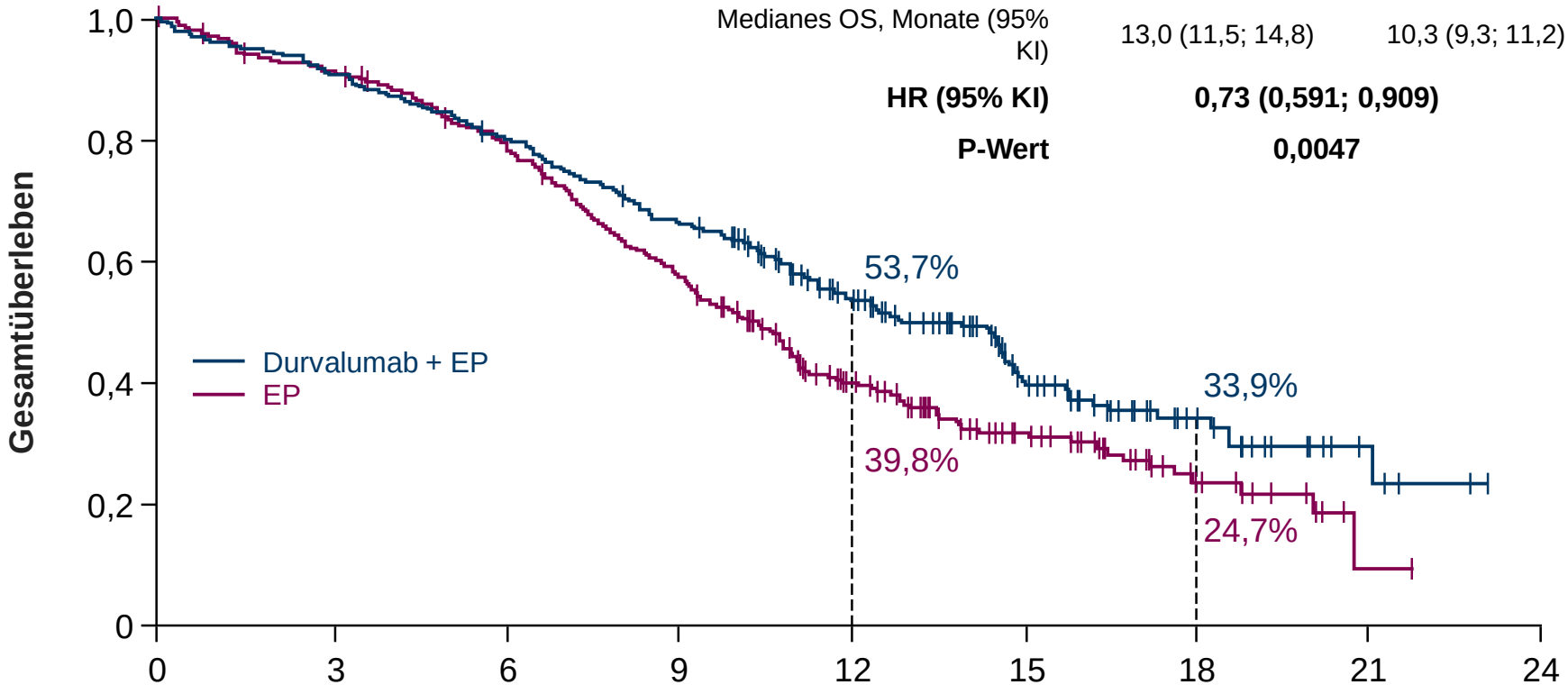
*EP besteht aus Etoposid 80-100 mg/m^2 mit entweder Carboplatin AUC 5-6 oder Cisplatin 75-80 mg/m^2. #Patienten konnten 2 zusätzliche Zyklen erhalten (bis zu 6 Zyklen insgesamt); PCI erfolgte nach Ermessen des behandelnden Arztes. §Patienten erhielten eine zusätzliche Dosis Tremelimumab nach EP

Paz-Ares L et al., WCLC 2019, Barcelona, Spanien, PL02.11

CASPIAN

Primärer Endpunkt: OS

	Durvalumab + EP	EP
Ereignisse, n/N (%)	155/268 (57,8)	181/269 (67,3)
Medianes OS, Monate (95% KI)	13,0 (11,5; 14,8)	10,3 (9,3; 11,2)
HR (95% KI)	**0,73 (0,591; 0,909)**	
P-Wert	**0,0047**	



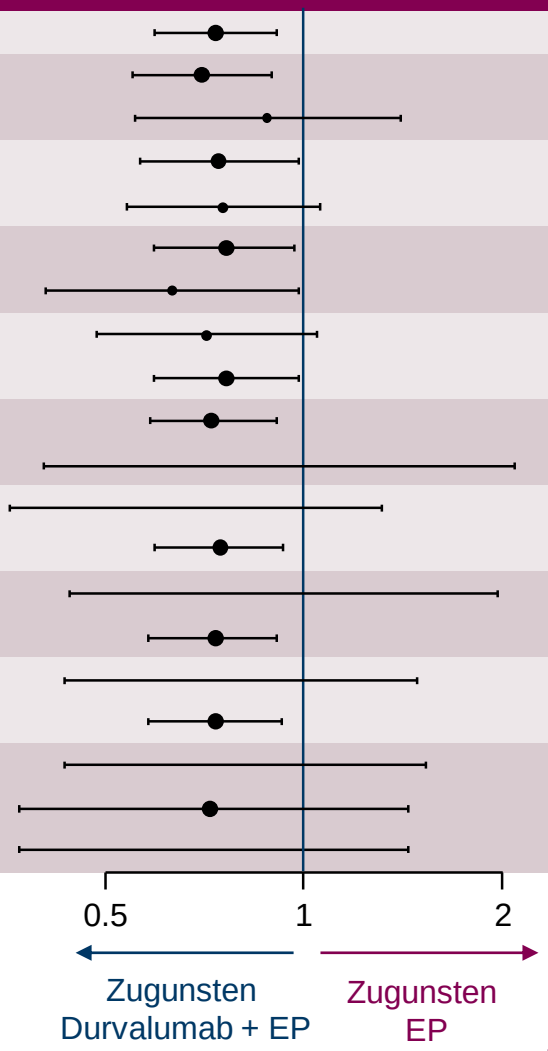
N Patienten									
Durvalumab + EP	268	244	214	177	116	57	25	5	0
EP	269	242	209	153	82	44	17	1	0

Paz-Ares L et al., WCLC 2019, Barcelona, Spanien, PL02.11

CASPIAN

OS – Subgruppenanalyse

Präspezifizierte Subgruppe		HR (95% KI)
Patienten gesamt (N=537)		0,73 (0,591; 0,909)
Geplante Platin-Chemotherapie	Carboplatin (N=402)	0,70 (0,548; 0,890)
	Cisplatin (N=135)	0,88 (0,549; 1,408)
Alter	<65 Jahre (N=324)	0,74 (0,562; 0,982)
	≥65 Jahre (N=213)	0,75 (0,536; 1,058)
Geschlecht	Männlich (N=374)	0,76 (0,590; 0,968)
	Weiblich (N=163)	0,63 (0,402; 0,984)
Performance Status	0 (N=189)	0,71 (0,483; 1,043)
	1 (N=348)	0,76 (0,586; 0,986)
Raucher-Status	Raucher (N=500)	0,72 (0,579; 0,905)
	Nichtraucher (N=37)	0,90 (0,399; 2,107)
Gehirn-Metastasen	Ja (N=55)	0,69 (0,354; 1,312)
	Nein (N=482)	0,74 (0,591; 0,933)
AJCC-Stadium bei Diagnose	Stadium III (N=52)	0,92 (0,439; 1,977)
	Stadium IV (N=485)	0,73 (0,579; 0,908)
Ethnizität	Asiatisch (N=78)	0,81 (0,429; 1,486)
	Nicht-Asiatisch (N=458)	0.73 (0,580; 0,919
Region	Asien (N=76)	0,82 (0,430; 1,536)
	Europa (N=405)	0,72 (0,564; 0,919)
	Amerika (N=56)	0,72 (0,366; 1,438)

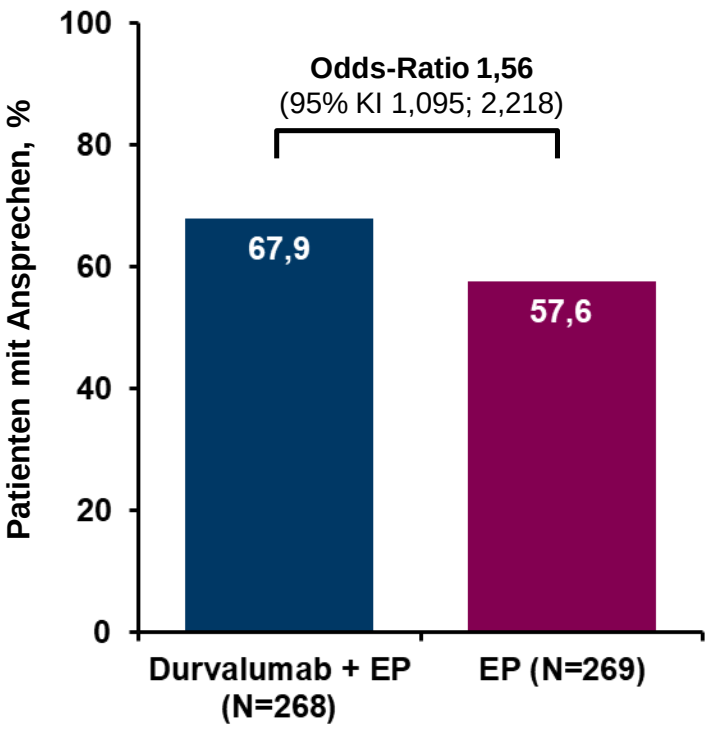


Paz-Ares L et al., WCLC 2019, Barcelona, Spanien, PL02.11

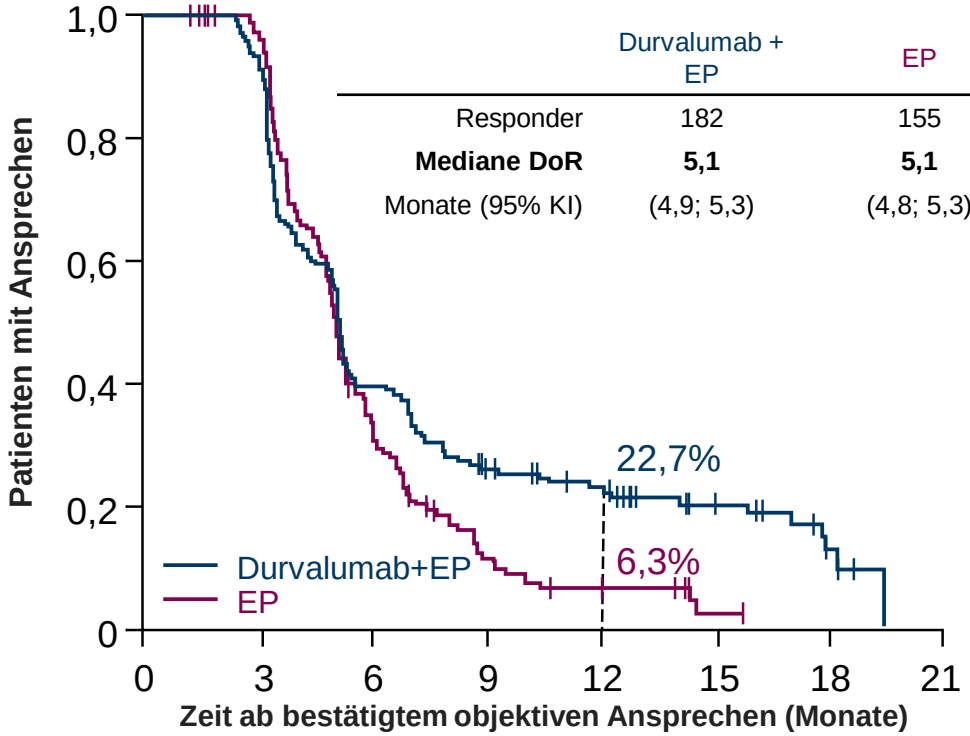
CASPIAN

Bestätigtes objektives Ansprechen

ORR*



Ansprechdauer



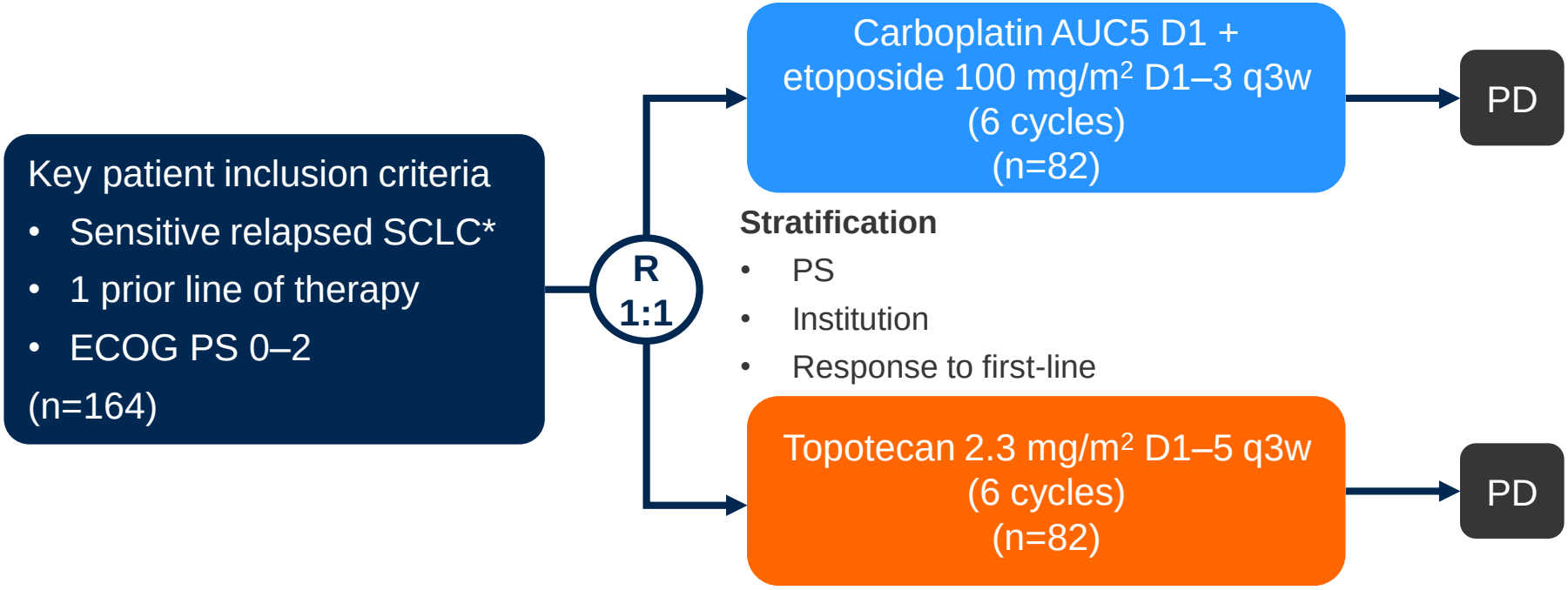
N Patienten								
D + EP	182	170	70	38	28	16	4	0
EP	155	144	48	14	7	1	0	0

*Bewertung durch Prüfarzt nach RECIST v1.1

Paz-Ares L et al., WCLC 2019, Barcelona, Spanien, PL02.11

OA15.02: Carboplatin-Etoposide Versus Topotecan as Second-Line Treatment for Sensitive Relapsed Small-Cell Lung Cancer: Phase 3 Trial – Monnet I, et al

- **Study objective**
  - To investigate the efficacy and safety of carboplatin-etoposide compared with topotecan in previously treated patients with sensitive relapsed SCLC



Primary endpoint

- PFS

Secondary endpoints

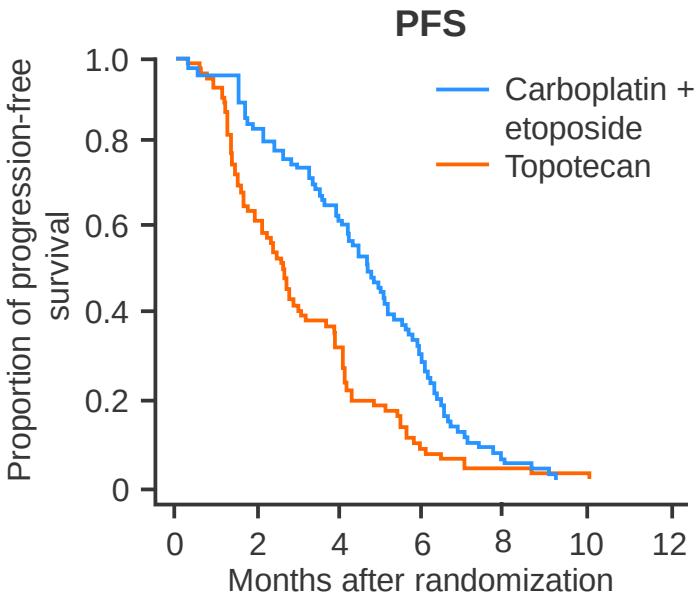
- OS, ORR (RECIST v1.1), QoL, safety

*Defined as SCLC responding to initial chemotherapy and relapsing >3 months after completion of chemotherapy

Monnett I, et al. J Thorac Oncol 2019;14(suppl):Abstr OA15.02

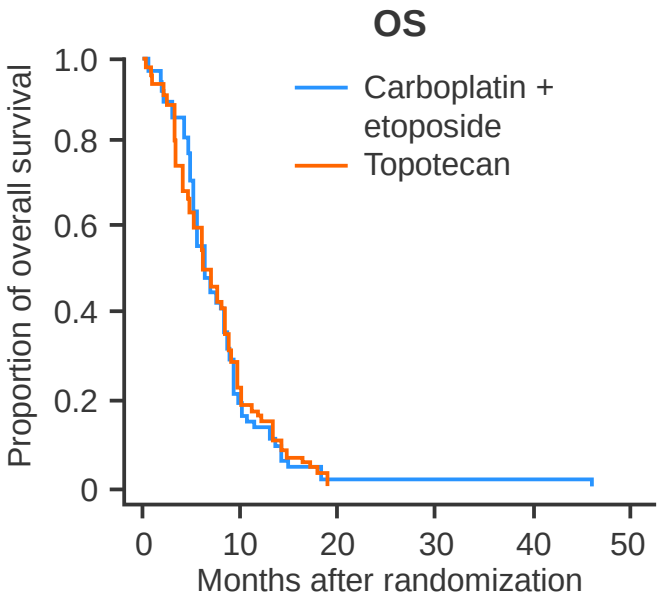
OA15.02: Carboplatin-Etoposide Versus Topotecan as Second-Line Treatment for Sensitive Relapsed Small-Cell Lung Cancer: Phase 3 Trial – Monnet I, et al

- **Key results**



	Carboplatin + etoposide	Topotecan
Events, n	81	81
mPFS, months (95%CI)	4.7 (3.9, 5.5)	2.7 (2.3, 3.2)
One sided p	<0.001 by stratified log-rank test	
HR (95%CI)	0.6 (0.4, 0.8)	

Median follow-up: 16 months



	Carboplatin + etoposide	Topotecan
Events, n	81	81
mOS, months (95%CI)	7.5 (5.4, 9.5)	7.4 (6.0, 8.7)
One sided p	<0.936 by stratified log-rank test	
HR (95%CI)	0.987 (0.7, 1.3)	

Monnett I, et al. J Thorac Oncol 2019;14(suppl):Abstr OA15.02

OA15.02: Carboplatin-Etoposide Versus Topotecan as Second-Line Treatment for Sensitive Relapsed Small-Cell Lung Cancer: Phase 3 Trial – Monnet I, et al

- **Key results (cont.)**

Tumour assessment, %	Carboplatin + etoposide (n=81)	Topotecan (n=81)
CR	14.0	1.2
PR	35.5	24.0
ORR	**49**	**25***
SD	37.4	37.4
PD	21.5	37.4

  - Grade 3–4 neutropenia was observed in 23% vs. 36% (p=0.035) patients in the carboplatin + etoposide vs. topotecan arms, respectively. Treatment-related death occurred in 2 patients in the topotecan arm (both febrile neutropenia)
- **Conclusion**
  - In patients with sensitive relapsed SCLC, carboplatin + etoposide demonstrated significant improvements in PFS and ORR, but not OS, compared with topotecan and had a lower incidence of neutropenia

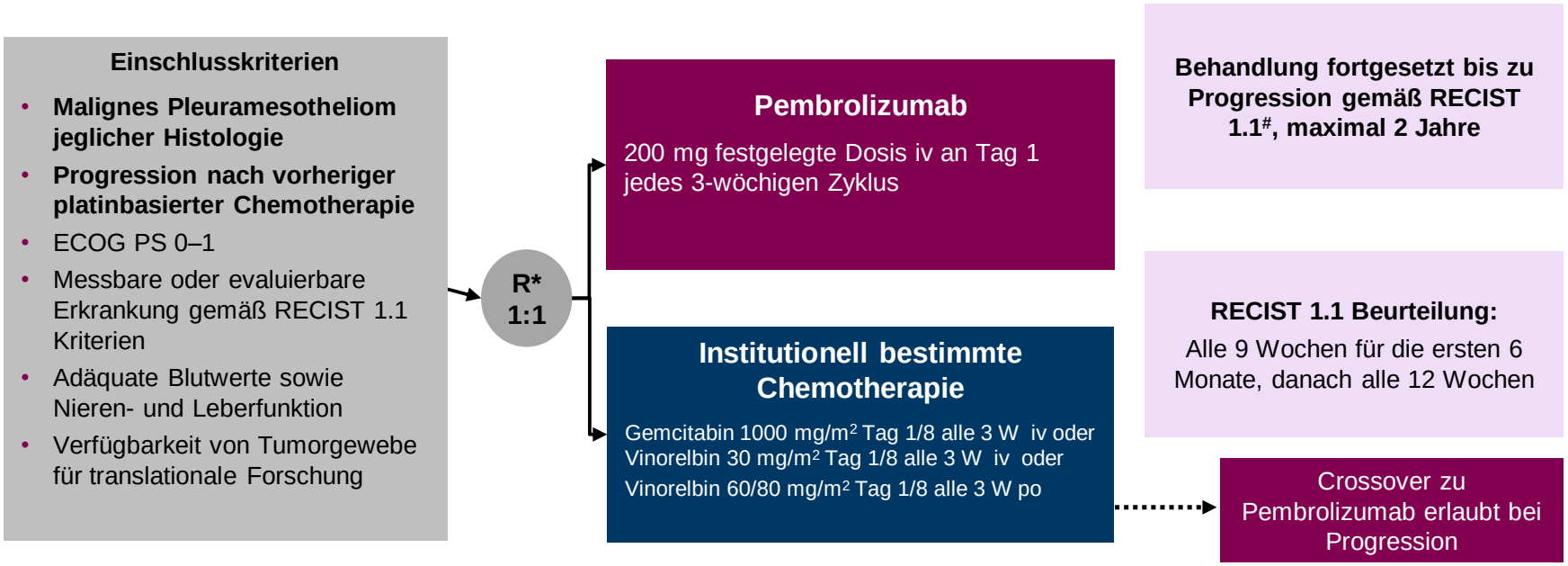
*p=0.002

Monnett I, et al. J Thorac Oncol 2019;14(suppl):Abstr OA15.02

Mesotheliom

ETOP 9-15 PROMISE-meso

Studiendesign und -ziele



Primärer Endpunkt:

- Progressionsfreies Überleben (PFS), beurteilt durch eine verblindete, unabhängige, zentralisierte Beurteilung (BICR)

Sekundärer Endpunkte:

- Objektive Ansprechrate (ORR)
- Zeit bis zum Therapieversagen (TTF)
- Gesamtüberleben (OS)
- Vom Prüfarzt bewertetes PFS
- Unerwünschte Ereignisse

Korrelative Endpunkte:

- Ergebnisse gemäß PD-L1-Status

***Stratifizierungsfaktor:** Histologischer Subtyp: Epitheloid vs Nicht-epitheloid

#Bei klinischem Nutzen war die Fortsetzung über PD hinaus erlaubt

Popat S. et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394

ETOP 9-15 PROMISE-meso

Patientencharakteristika

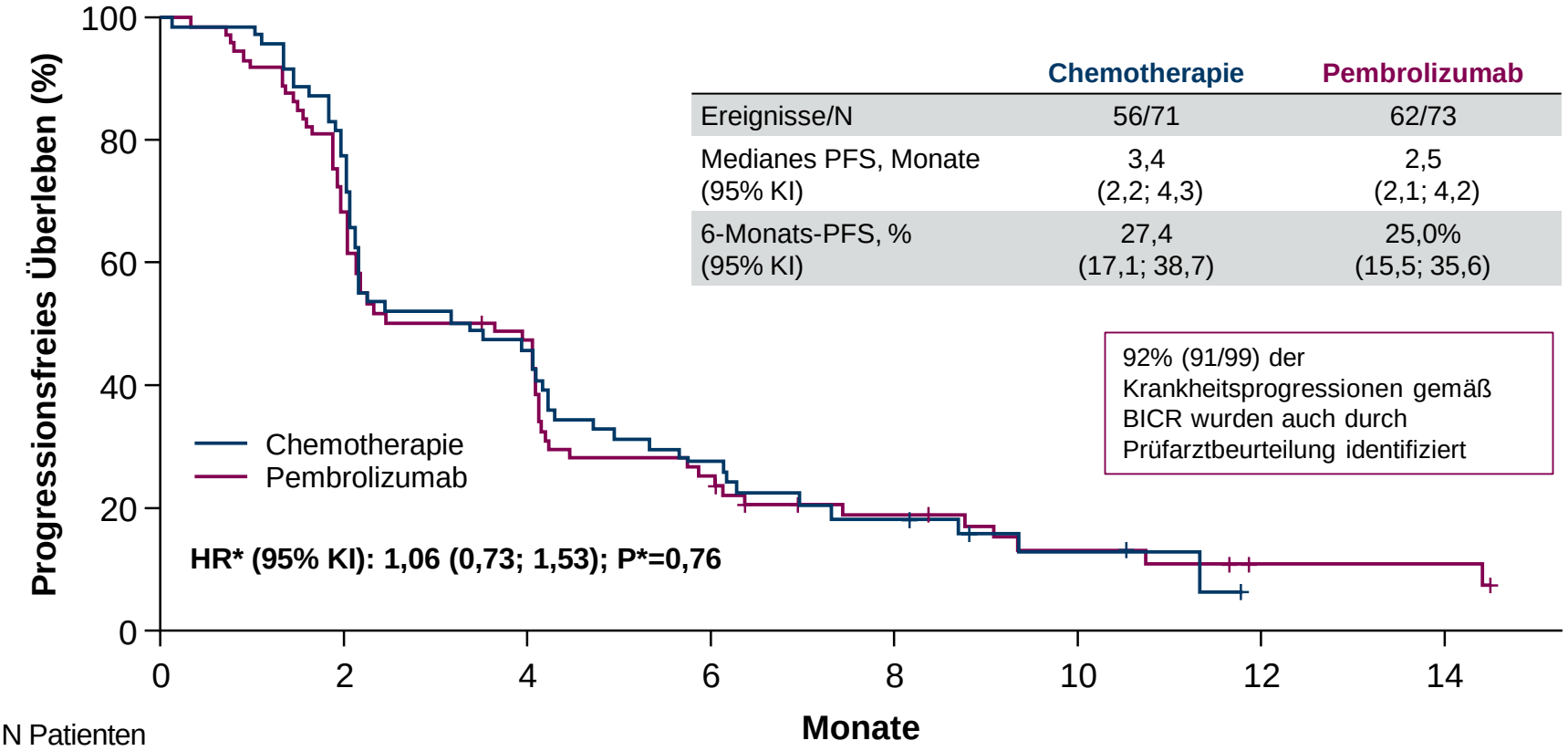
Patientencharakteristika	Pembrolizumab (N=73)	Chemotherapie (N=71)
Medianes Alter, Jahre (Bereich)	69 (52; 83)	71 (53; 83)
Geschlecht, N (%)		
Männlich	58 (79,4)	60 (84,5)
Weiblich	15 (20,6)	11 (15,5)
Rauchen, N (%)		
Gegenwärtig	5 (6,8)	4 (5,6)
Ehemals	34 (46,6)	28 (39,4)
Nie	33 (45,2)	39 (54,9)
Histologie, N (%)		
Epitheloid	66 (90,4)	62 (87,3)
Nicht-epitheloid	7(9,6)	9 (12,7)
ECOG PS, N (%)		
0	21 (28,8)	14 (19,7)
1	51 (69,9)	57 (80,3)
2[#]	1 (1,4)	
EORTC-Score*, N (%)		
Guter prognostischer Score	45 (61,6)	54 (76,1)
Schlechter prognostischer Score	28 (38,4)	17 (23,9)
Vorherige Therapien, N (%)		
Carboplatin/Pemetrexed	27 (37,0)	27 (38,0)
Cisplatin/Pemetrexed	24 (32,9)	22 (31,0)
Platin ± Pemetrexed ± Andere	13 (17,8)	17 (23,9)
Cisplatin/Pemetrexed + Carboplatin/Pemetrexed	7 (9,6)	1 (1,4)
Fehlend	2 (2,7)	4 (5,6)

*Für Klassifizierung als schlechter prognostischer EORTC-Score müssen zumindest 3 der folgenden Kriterien zutreffen:
1. PS≥2, 2. Männlich, 3. Nicht-epitheloid, 4. Unklare Histologie, 5. WBC >8,3x10^9/L; [#]Aufgrund von Beinschienen

Popat S. et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394

ETOP 9-15 PROMISE-meso

Progressionsfreies Überleben gemäß BICR



	Chemotherapie	Pembrolizumab
Ereignisse/N	56/71	62/73
Medianes PFS, Monate (95% KI)	3,4 (2,2; 4,3)	2,5 (2,1; 4,2)
6-Monats-PFS, % (95% KI)	27,4 (17,1; 38,7)	25,0% (15,5; 35,6)

92% (91/99) der Krankheitsprogressionen gemäß BICR wurden auch durch Prüfarztbeurteilung identifiziert

N Patienten								
Chemotherapie	71	55	29	16	9	4	0	0
Pembrolizumab	73	50	33	17	11	6	3	3

*Nach histologischem Subtyp stratifiziert

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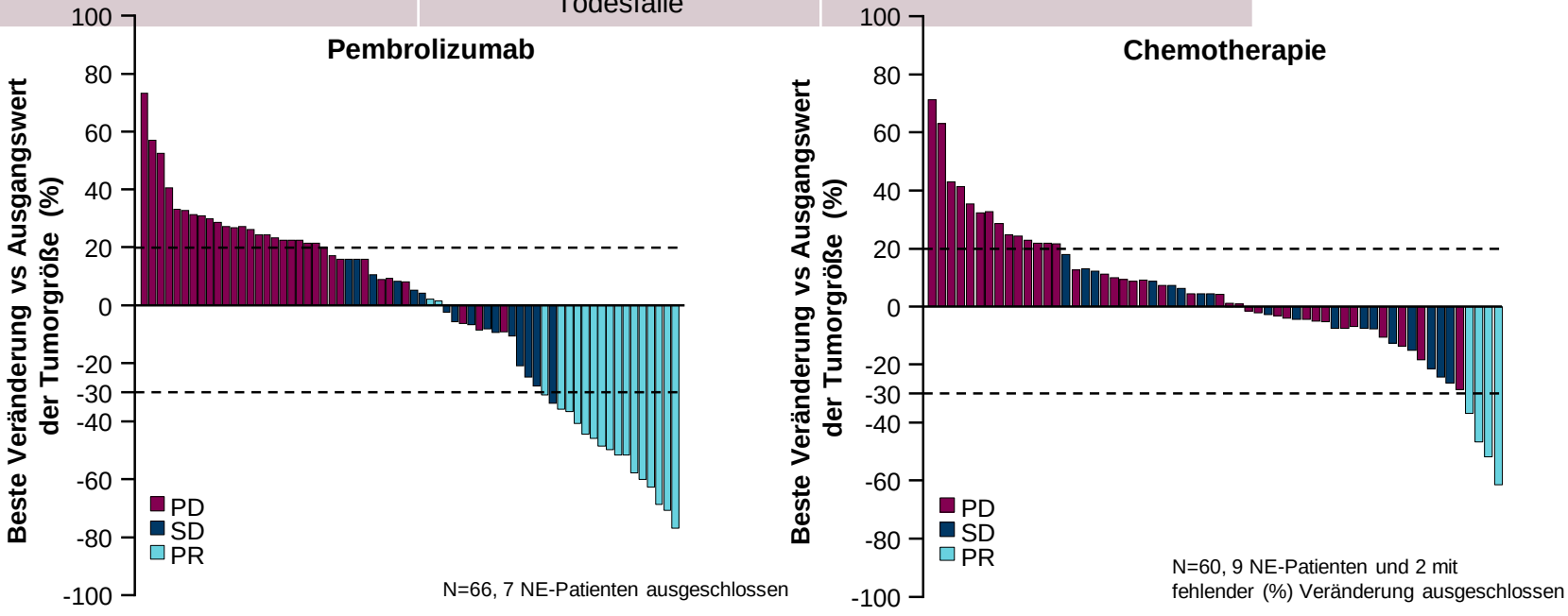
Bestes Gesamtansprechen – Dauer des Ansprechens (DOR) gemäß BICR

	Pembrolizumab, N (%)	Chemotherapie, N (%)
ORR (95% KI)	**22% (13; 33)**	**6% (2; 14)**
Partielle Remission (PR)	16 (21,9)	4 (5,6)
Stabile Erkrankung (SD)	17 (23,3)	23 (32,4)
Krankheitsprogression (PD)	33 (45,2)	35 (49,3)
Nicht evaluierbar (NE)	7 (9,6)	9 (12,7)
Mediane DOR*, Monate (95% KI)	**4,6 (2,2; 10,3)**	**11,2 (6,2; 15,3)**
	16 Patienten mit Ansprechen → 7 Fälle von PD und 4 Todesfälle	4 Patienten mit Ansprechen → 3 Fälle von PD

Stratifiziert P=0,004



*Stand August 2019

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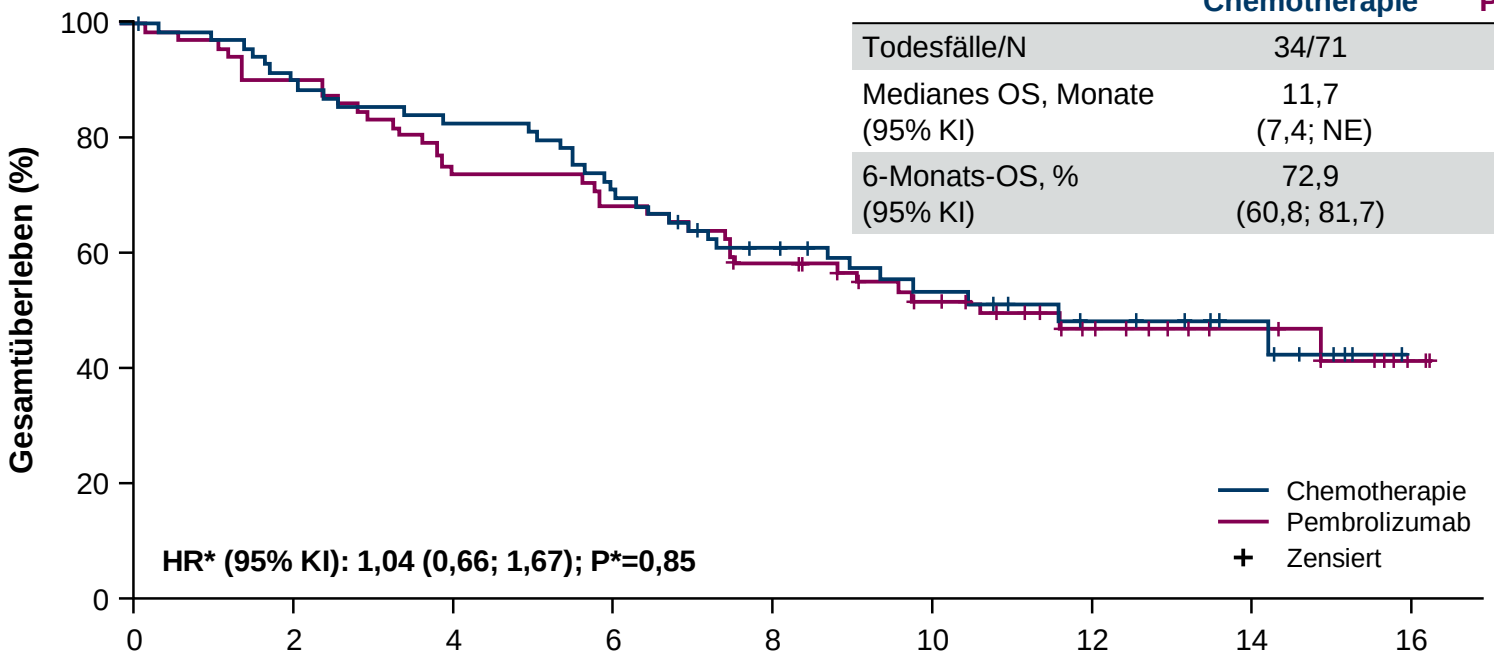
Gesamtüberleben (OS) – ITT-Population

	Chemotherapie	Pembrolizumab
Todesfälle/N	34/71	37/73
Medianes OS, Monate (95% KI)	11,7 (7,4; NE)	10,7 (7,6; NE)
6-Monats-OS, % (95% KI)	72,9 (60,8; 81,7)	68,5 (56,5; 77,8)



N Patienten									
Chemotherapie	71	64	58	51	39	26	15	8	1
Pembrolizumab	73	66	55	50	39	27	17	9	3

Cross-over-Adjustierung

Analyse	HR* (95% KI)	P*
Zensiert	1,44 (0,77; 2,67)	0,25
Gewichtung nach umgekehrter Wahrscheinlichkeit	1,07 (0,67; 1,71)	0,79

*Stratifiziert nach histologischem Subtyp

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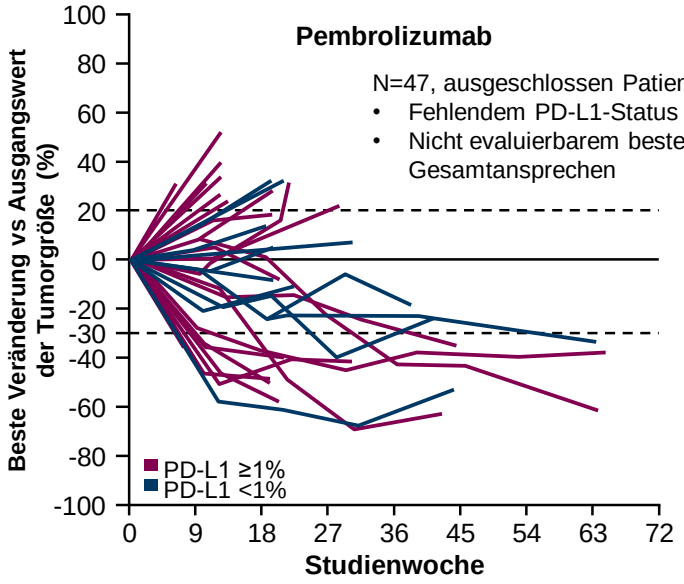
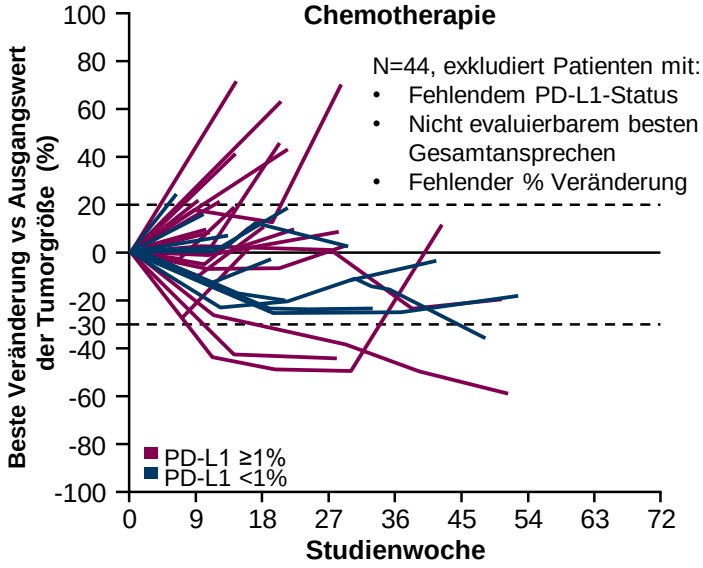
Wirksamkeit gemäß PD-L1-Status

- Der PD-L1-Status wurde mittels IHC unter Verwendung des E1L3N-Klons mit vordefinierten Cut-offs von 0%, 1% und 50% bestimmt

PD-L1-Score	Pembrolizumab (N=73)	Chemotherapie (N=71)
Fälle mit evaluierbarem Ergebnis, N (%)	51 (69,9)	51 (71,8)
TPS <1%	**19 (37,3)**	**17 (33,3)**
TPS ≥1	**32 (62,7)**	**34 (66,7)**
1–49%	31	33
≥50%	1	1
Nicht evaluierbar	22 (30,1)	20 (28,2)

PD-L1-Score	Nicht-epitheloid (N=16)	Epitheloid (N=128)
Fälle mit evaluierbarem Ergebnis, N (%)	12 (75,0)	90 (70,3)
TPS <1%	**3 (25,0)**	**33 (36,7)**
TPS ≥1	**9 (75,0)**	**57 (63,3)**
Nicht evaluierbar	4 (25,0)	38 (29,7)





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