PD-1/PD-L1 Directed Immunotherapy for Advanced NSCLC

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Disclosures

Commercial Interest	Relationship(s)
Advisor:	AbbVie, Amgen, AstraZeneca, Debiopharm, Daiichi Sankyo, EMD Serono, Genentech, Genmab, Lilly, Merck, Novartis, Regeneron, Targeted Oncology, Takeda
Honoraria:	N/A
Research:	AbbVie, Astellas, EMD Serono, Five Prime, Genentech, Lilly, Novartis, Regeneron
Royalty:	UpToDate Author

Pembrolizumab Plus Ipilimumab vs Pembrolizumab Plus Placebo as 1L Therapy For Metastatic NSCLC of PD-L1 TPS ≥50%: KEYNOTE-598

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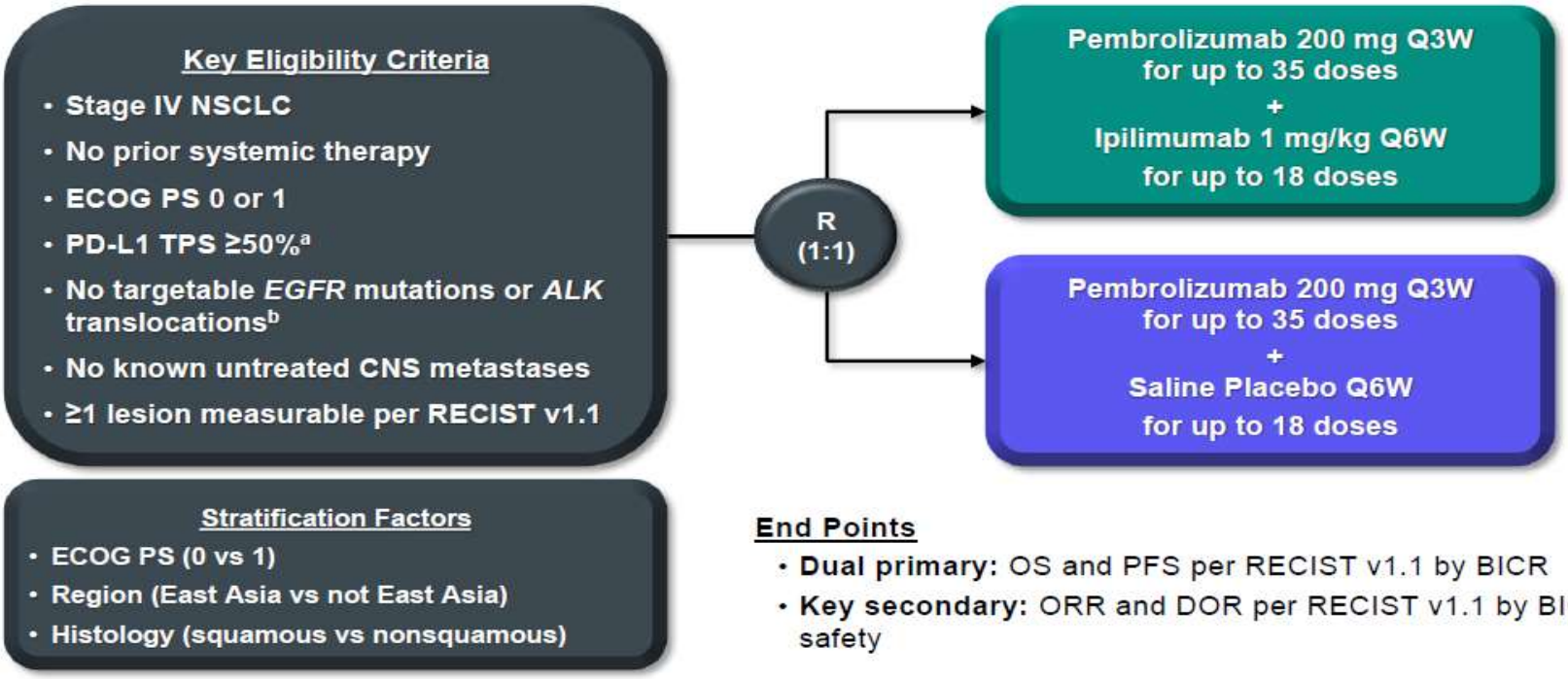
KEYNOTE-598 Study Design



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

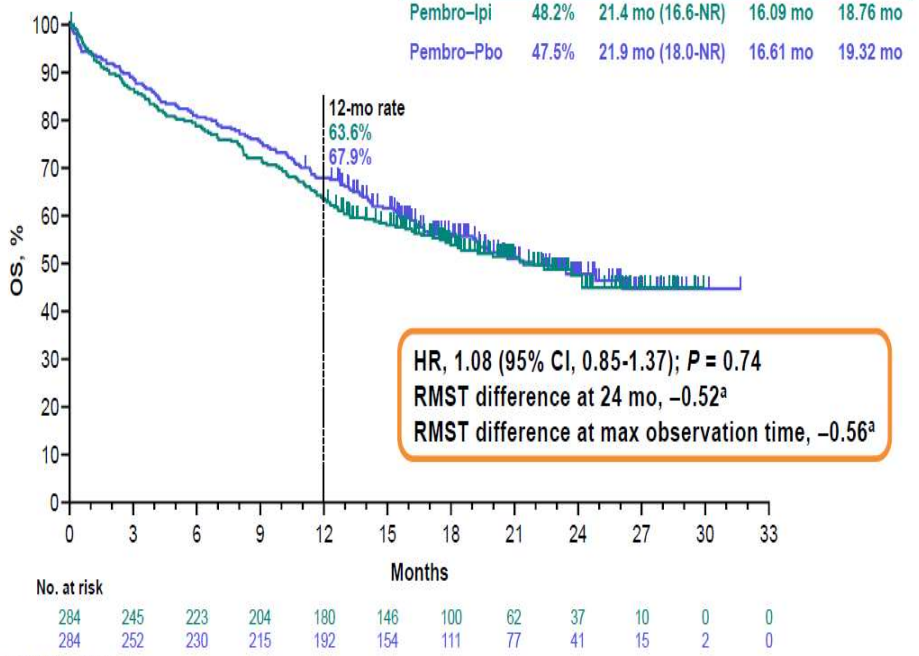
[a]Assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent).
[b]Patients with *ROS1* rearrangement were also excluded if *ROS1* testing and treatment were locally approved and accessible.
KEYNOTE-598 ClinicalTrials.gov identifier, NCT03302234. BICR, blinded independent central review.

Baseline Characteristics

	Pembrolizumab–Ipilimumab (N = 284)	Pembrolizumab–Placebo (N = 284)
Age, median (range), years	64 (35-85)	65 (35-85)
Men	202 (71.1%)	191 (67.3%)
Enrolled in East Asia	32 (11.3%)	31 (10.9%)
ECOG PS 1	183 (64.4%)	180 (63.4%)
Former/current smoker	255 (89.8%)	259 (91.2%)
Histology		
Squamous	77 (27.1%)	81 (28.5%)
Nonsquamous	207 (72.9%)	203 (71.5%)
Brain metastases	31 (10.9%)	29 (10.2%)

Overall Survival

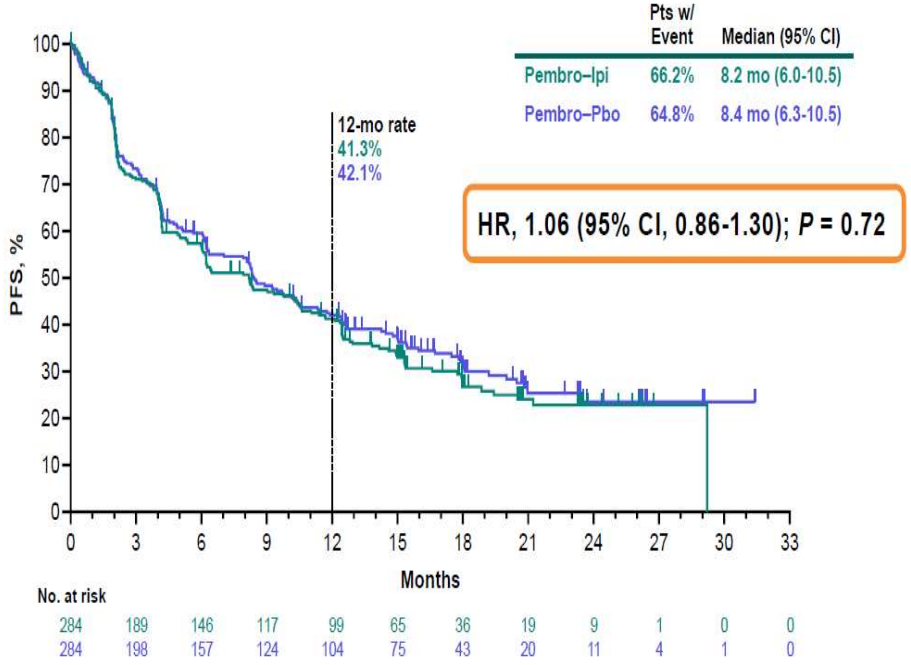
	Pts w/ Event	Median (95% CI)	RMST at 24 mo	RMST at Max Time
Pembro–Ipi	48.2%	21.4 mo (16.6-NR)	16.09 mo	18.76 mo
Pembro–Pbo	47.5%	21.9 mo (18.0-NR)	16.61 mo	19.32 mo



[a]Nonbinding futility criteria met.
Data cutoff date: Sep 1, 2020.

Progression-Free Survival

	Pts w/ Event	Median (95% CI)
Pembro–Ipi	66.2%	8.2 mo (6.0-10.5)
Pembro–Pbo	64.8%	8.4 mo (6.3-10.5)

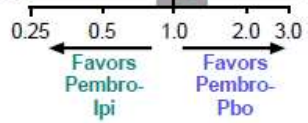


Data cutoff date: Sep 1, 2020.

OS and PFS in Subgroups

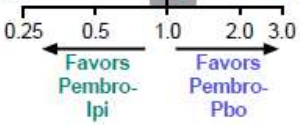
OS

	No. of Deaths/ No. of Participants	Hazard Ratio (95% CI)
Overall	272/568	1.08 (0.85-1.37)
Age		
<65 years	131/281	1.05 (0.74-1.47)
≥65 years	141/287	1.10 (0.79-1.53)
Sex		
Male	190/393	0.97 (0.73-1.29)
Female	82/174	1.29 (0.84-1.99)
ECOG PS		
0	87/205	1.26 (0.83-1.92)
1	185/363	0.98 (0.74-1.31)
Geographic region		
East Asia	27/63	0.60 (0.28-1.30)
Not East Asia	245/505	1.14 (0.89-1.47)
Tumor histologic features		
Squamous	85/158	1.16 (0.76-1.78)
Nonsquamous	187/410	1.04 (0.78-1.38)
Baseline brain metastasis		
Yes	25/60	0.79 (0.36-1.75)
No	247/508	1.10 (0.86-1.42)



PFS

	No. of Events/ No. of Participants	Hazard Ratio (95% CI)
Overall	372/568	1.06 (0.86-1.30)
Age		
<65 years	179/281	1.11 (0.83-1.49)
≥65 years	193/287	1.05 (0.79-1.39)
Sex		
Male	270/393	1.02 (0.80-1.29)
Female	102/174	1.15 (0.78-1.69)
ECOG performance-status score		
0	131/205	1.33 (0.94-1.87)
1	241/363	0.94 (0.73-1.22)
Geographic region		
East Asia	43/63	0.76 (0.42-1.39)
Not East Asia	329/505	1.12 (0.90-1.39)
Tumor histologic features		
Squamous	112/158	0.98 (0.68-1.42)
Nonsquamous	260/410	1.12 (0.88-1.43)
Baseline brain metastasis		
Yes	33/60	0.78 (0.39-1.57)
No	339/508	1.10 (0.89-1.37)



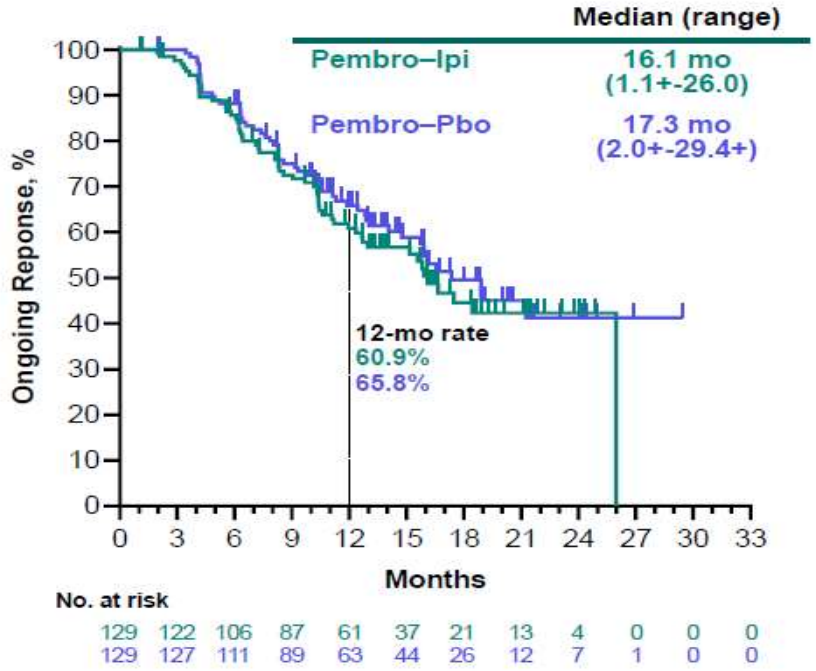
Only those subgroups for that accounted for ≥10% of the overall population are shown. Data cutoff date: Sep 1, 2020.

Summary of Response

	Pembro–Ipi N = 284	Pembro–Pbo N = 284
ORR, % (95% CI)	45.4% (39.5-51.4)	45.4% (39.5-51.4)
Best response, n (%)		
CR	13 (4.6%)	8 (2.8%)
PR	116 (40.8%)	121 (42.6%)
SD	70 (24.6%)	73 (25.7%)
PD	51 (18.0%)	44 (15.5%)
NE[a]	6 (2.1%)	6 (2.1%)
NA[b]	28 (9.9%)	32 (11.3%)

[a]≥1 post-baseline imaging assessment, but none evaluable per RECIST v1.1 by BICR.
[b]No post-baseline imaging assessment.
Data cutoff date: Sep 1, 2020.

Duration of Response



Adverse Events and Exposure

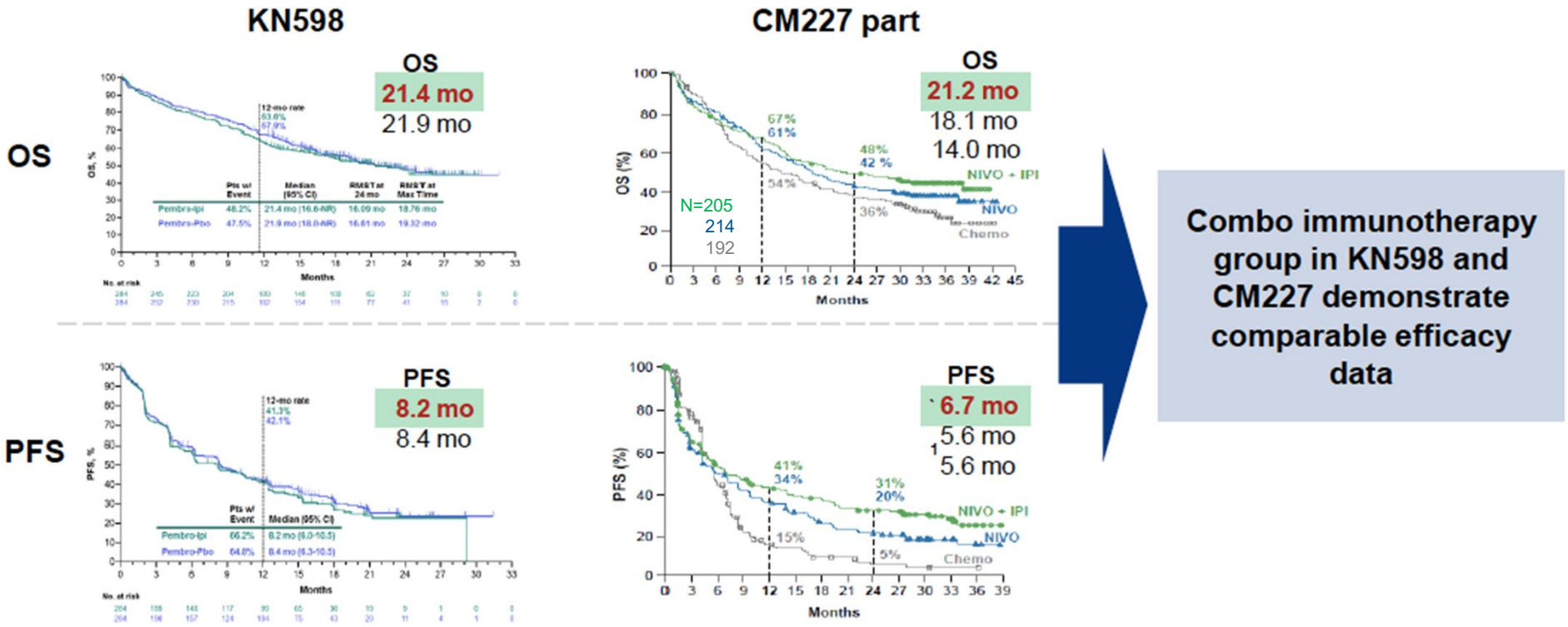
No. of Patients (%)	Treatment-Related AEs		Immune-Mediated AEs and Infusion Reactions[a]	
	Pembro–Ipi (N = 282)	Pembro–Pbo (N = 281)	Pembro–Ipi (N = 282)	Pembro–Pbo (N = 281)
Any grade	215 (76.2%)	192 (68.3%)	126 (44.7%)	91 (32.4%)
Grade 3-5	99 (35.1%)	55 (19.6%)	57 (20.2%)	22 (7.8%)
Serious	78 (27.7%)	39 (13.9%)	54 (19.1%)	20 (7.1%)
Led to death	7 (2.5%)	0	6 (2.1%)	0
Led to discontinuation[b]				
Ipi or placebo only	17 (6.0%)	9 (3.2%)	5 (1.8%)	3 (1.1%)
Both drugs	54 (19.1%)	21 (7.5%)	34 (12.1%)	12 (4.3%)

Median Treatment Exposure, Pembrolizumab–Ipilimumab vs Pembrolizumab–Placebo

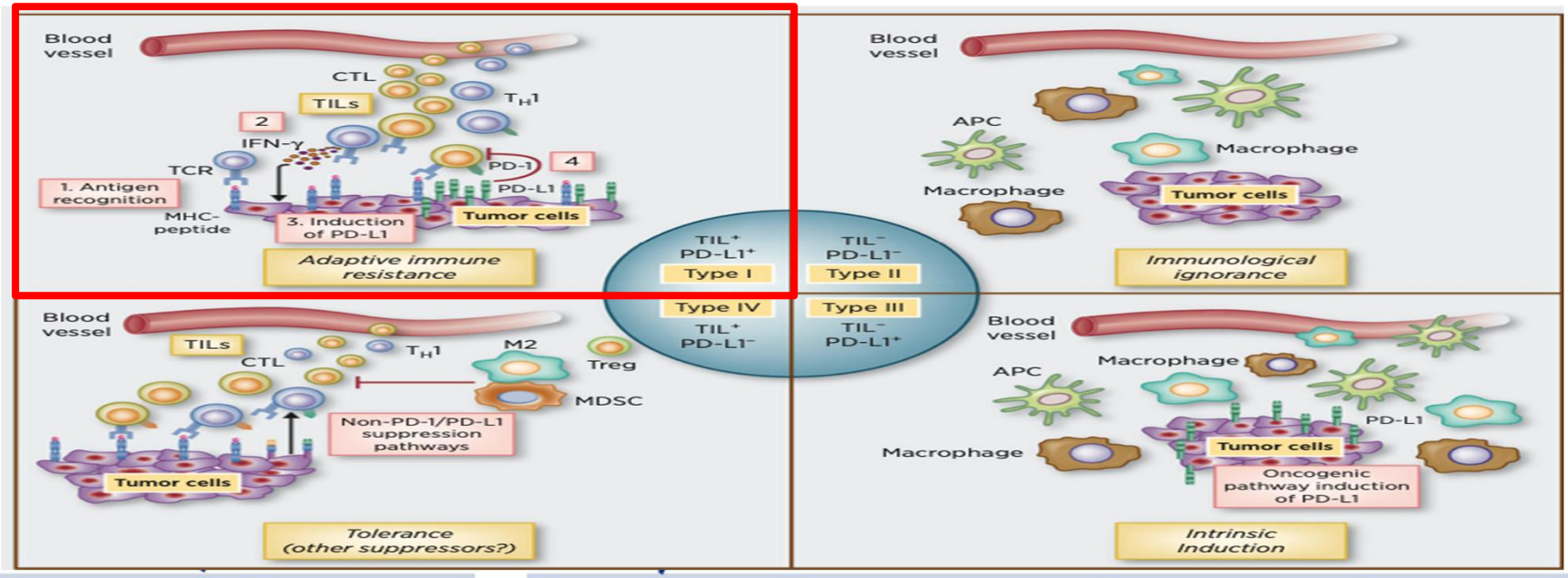
- No. of cycles[c]: 10 vs 15
- Months on ipilimumab or placebo: 5.6 vs 8.8
- Months on pembrolizumab: 6.3 vs 9.7

[a]Events were considered regardless of attribution to treatment by the investigator. [b]Patients could discontinue ipilimumab/placebo and continue pembrolizumab; pembrolizumab discontinuation required ipilimumab/placebo discontinuation. [c]One cycle = 3 weeks. Data cutoff date: Sep 1, 2020.

Efficacy data of Pembro-Ipi and Nivo-Ipi in KN598 and CM227



Potential rationale for the non-beneficial treatment of double blockade in PD-L1≥50% NSCLC population



CTLA-4 blockade allows for activation and proliferation of extra T-cell clones

PD-L1≥50% population presents with high level of pre-actived CD8+T cells already, hence additional CTLA-4 blockade may not bring clinical benefits as expected

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EMPOWER-Lung 1: Clinical benefits of first-line (1L) cemiplimab monotherapy by PD-L1 expression levels in patients with advanced NSCLC

Saadettin Kilickap,[1] Ahmet Sezer,[2] Mahmut Gümüş,[3] Igor Bondarenko,[4] Mustafa Özgüroğlu,[5] Miranda Gogishvili,[6] Haci M Turk,[7] Irfan Cicin,[8] Dmitry Bentsion,[9] Oleg Gladkov,[10] Philip Clingan,[11] Virote Sriuranpong,[12] Naiyer Rizvi,[13] Siyu Li,[14] Sue Lee,[14] Tamta Makharadze,[15] Semra Paydas,[16] Marina Nechaeva,[17] Frank Seebach,[18] David M Weinreich,[18] George D Yancopoulos,[18] Giuseppe Gullo,[18] Israel Lowy,[18] Petra Rietschel[18]

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EMPOWER-Lung 1 Study Design

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Only current/former smokers

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia, or ROW)

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → Optional continuation of cemiplimab + 4 cycles of chemotherapy

Arm B
4–6 cycles of investigator's choice chemotherapy

PD → Optional crossover to cemiplimab monotherapy

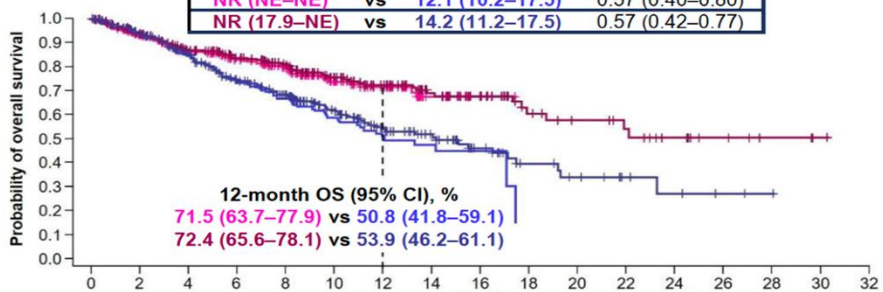
Follow-up

N=710

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL, and safety

OS

Median, months (95% CI)			HR (95% CI)
NR (NE–NE)	vs	12.1 (10.2–17.5)	0.57 (0.40–0.80)
NR (17.9–NE)	vs	14.2 (11.2–17.5)	0.57 (0.42–0.77)



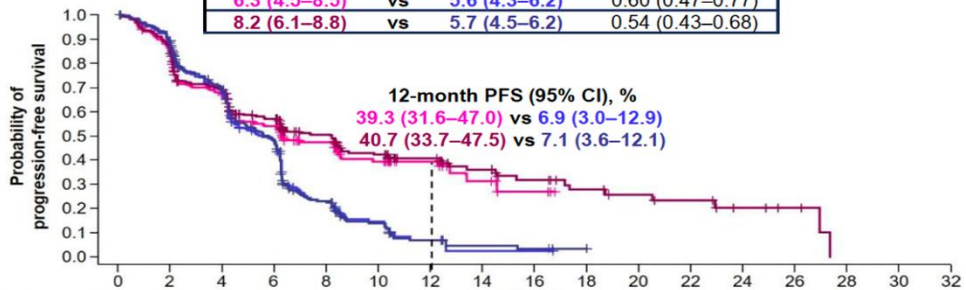
Number of subjects at risk

Cemiplimab	238	200	165	141	120	76	53	26	14	0	0	0	0	0	0	0	0
Chemotherapy	237	200	163	123	98	62	36	20	8	0	0	0	0	0	0	0	0
Cemiplimab	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0
Chemotherapy	280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0

Cemiplimab (N=475)
Cemiplimab (N=563)

PFS

Median, months (95% CI)			HR (95% CI)
6.3 (4.5–8.5)	vs	5.6 (4.3–6.2)	0.60 (0.47–0.77)
8.2 (6.1–8.8)	vs	5.7 (4.5–6.2)	0.54 (0.43–0.68)

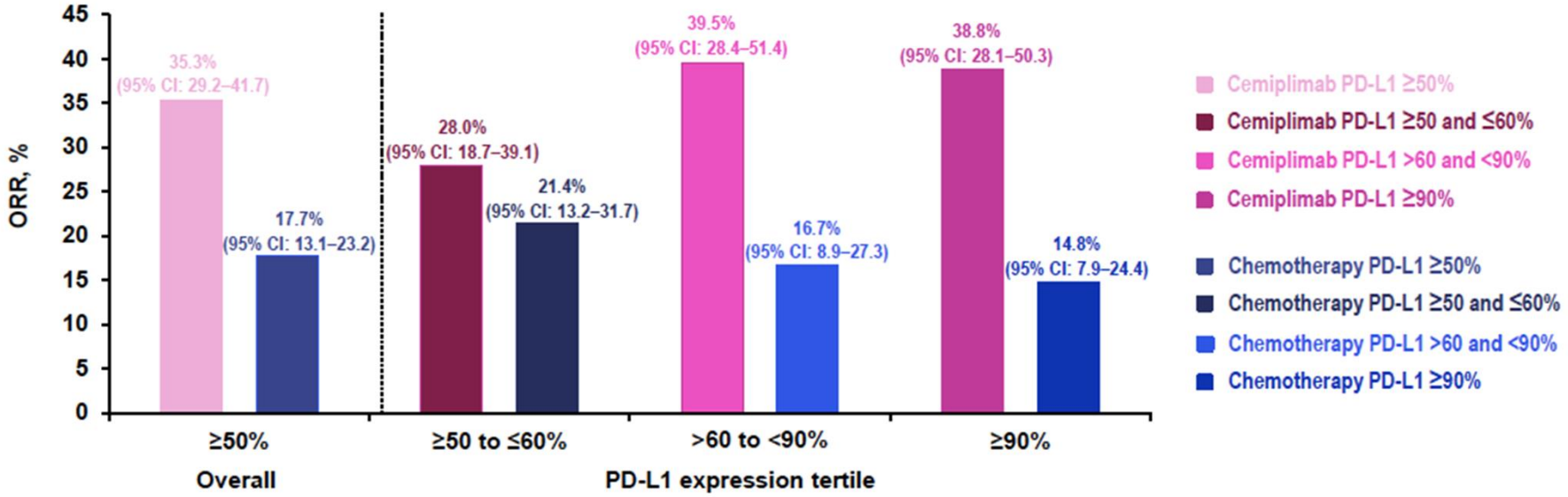


Number of subjects at risk

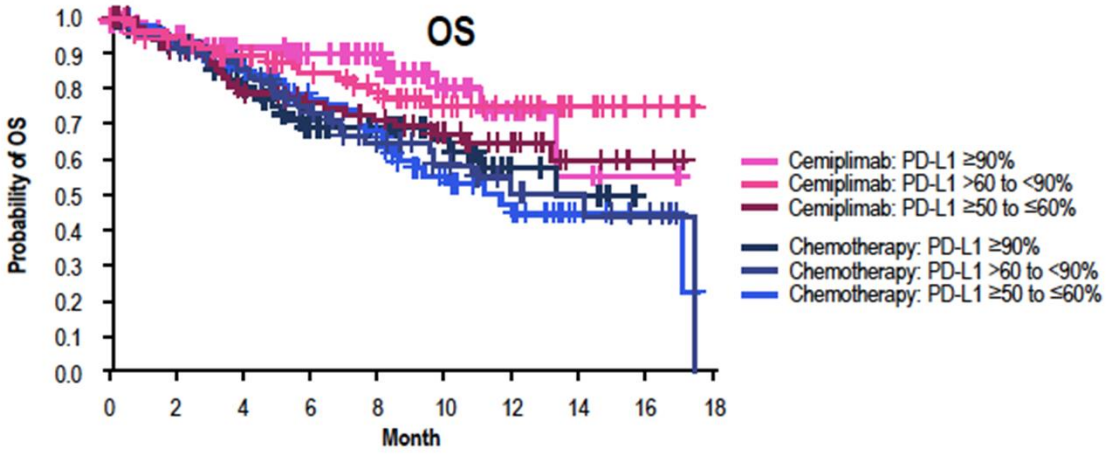
Cemiplimab	238	181	130	93	67	38	24	10	4	0	0	0	0	0	0	0	0
Chemotherapy	237	183	128	84	33	15	5	1	1	0	0	0	0	0	0	0	0
Cemiplimab	283	221	162	123	92	59	43	28	20	14	11	9	5	3	0	0	0
Chemotherapy	280	220	157	104	42	20	8	4	3	0	0	0	0	0	0	0	0

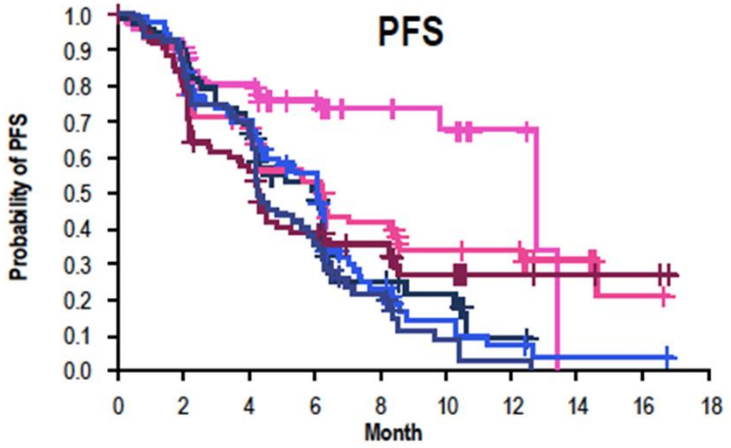
Chemotherapy (N=475)
Chemotherapy (N=563)

PD-L1 Expression Levels Correlate with Objective Response Rate (N=475)



PD-L1 Expression Levels Correlate with OS and PFS (N=475)



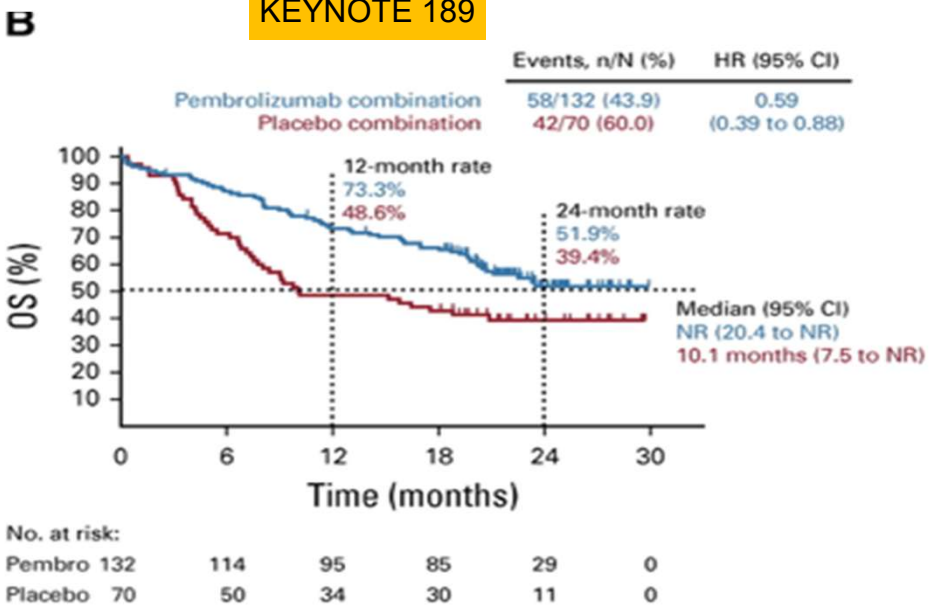


	Median, months (95% CI)			HR (95% CI)
	Cemiplimab (N=238)		Chemotherapy (N=237)	
≥90%	NR (13.4–NE)	vs	13.3 (10.2–NE)	0.54 (0.27–1.10)
>60 to <90%	NR (NE–NE)	vs	14.2 (9.6–17.5)	0.49 (0.26–0.92)
≥50 to ≤60%	NR (13.2–NE)	vs	11.7 (8.3–NE)	0.74 (0.44–1.24)

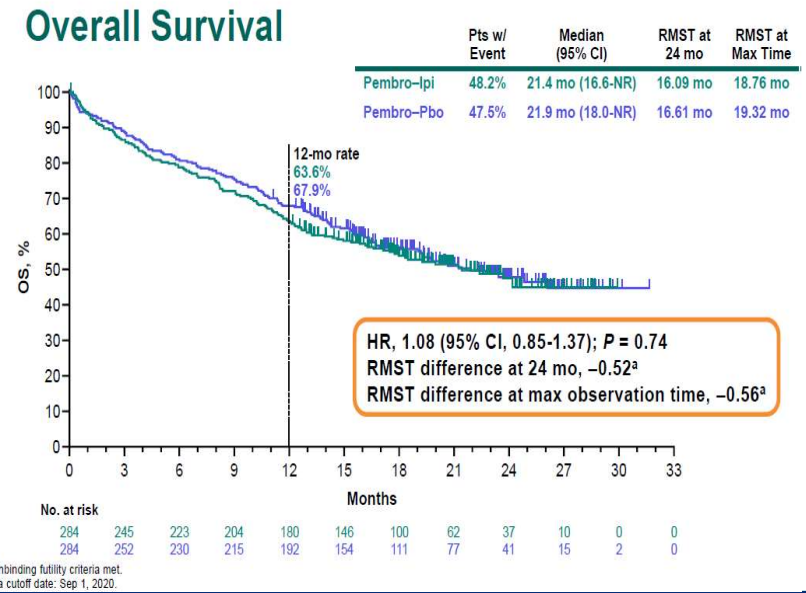
	Median, months (95% CI)			HR (95% CI)
	Cemiplimab (N=238)		Chemotherapy (N=237)	
≥90%	12.7 (9.8–13.4)	vs	6.1 (4.2–6.2)	0.33 (0.19–0.58)
>60 to <90%	6.2 (4.2–8.4)	vs	4.3 (4.1–5.9)	0.57 (0.38–0.85)
≥50 to ≤60%	4.3 (2.8–5.2)	vs	6.0 (4.4–6.2)	0.89 (0.61–1.29)

How do we improve efficacy in patients with tumors expressing PD-L1 ≥ 50%?
Adding chemotherapy to PD-L1 inhibitors

KEYNOTE 189



KEYNOTE 598



What's more for immunotherapy in advanced PD-L1≥50% NSCLC ? (phase I/II study)

Trial	N	Population	Line of treatment	IMP/control	PD-L1 stratum	ORR%	PFS mo	OS mo
CITYSCAPE (Phase 2) 1	135	PD-L1 TPS ≥ 1%	Treatment-naïve	Tiragolumab + Atezolizumab	≥1%	37	5.55	NR
					≥50%	66	NR HR 0.3	NR
				Atezolizumab	≥1%	21	3.88	NR
					≥50%	24	4.11	NR
M7824 (Phase 2) [2]	80	All comer	Second or later	M7824 1200mg	ALL	27.5	4.0	14.5
					≥80%	85.7	NR	NR
WJOG10718L (Phase 2) [3]	39	PD-L1 TPS ≥ 50%	Treatment-naïve	Atezolizumab + Bevacizumab	≥50%	64.1	15.9	NR

Fan Yun MD discussant

What's more for immunotherapy in advanced PD-L1≥50% NSCLC ? (phase I/II study)

Trial	N	Population	Line of treatment	IMP/control	PD-L1 stratum	ORR%	PFS mo	OS mo
CITYSCAPE (Phase 2) 1	135	PD-L1 TPS ≥ 1%	Treatment-naïve	Tiragolumab + Atezolizumab				
				Atezolizumab				
M7824 (Phase 2) [2]	80	All comer	Second or later	M7824 1200mg				
WJOG10718L (Phase 2) [3]	39	PD-L1 TPS ≥ 50%	Treatment-naïve	Atezolizumab + Bevacizumab				

SKYSCRAPER 1

INTR@PID Lung 037 Negative

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HUDSON

An Open-Label, Multi-Drug, Biomarker-Directed, Phase II Platform Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an anti-PD(L)-1 Therapy

Benjamin Besse

Institut Gustave Roussy, Villejuif and Paris-Sud University, Paris, France

On behalf of the HUDSON study group

B. Besse, M. Awad, P. Forde, M. Thomas, K. Park, G. Goss, N. Rizvi, F. Huemer, M. Hochmair, J. Bennouna, J. Cosaert, Z. Szucs, P. Mortimer, R. Hobson, K. Sachsenmeier, E. Dean, H. Ambrose, C. Hayward, M. Dressman, S. Barry, J. Heymach

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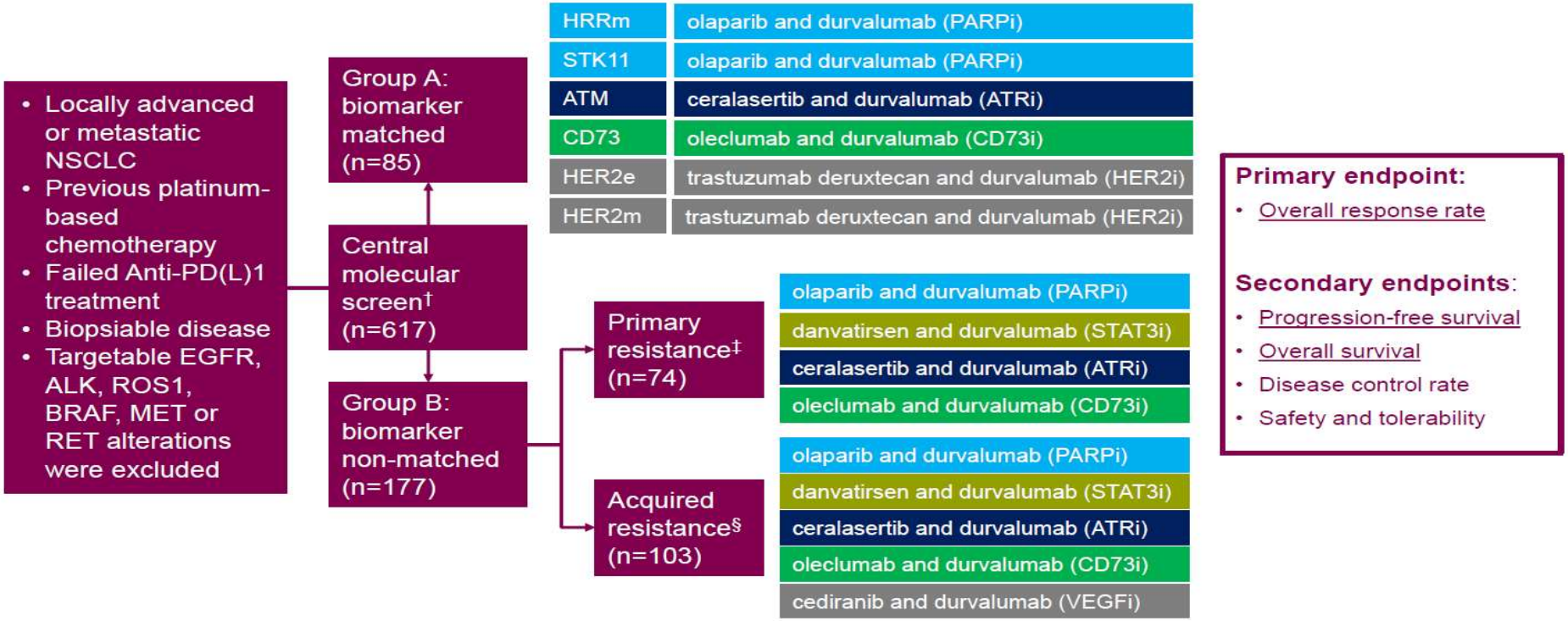
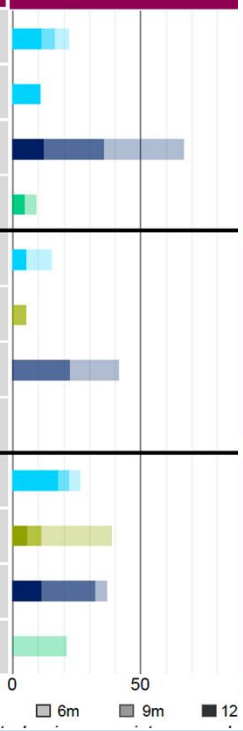
HUDSON study design



†Immunohistochemistry was also performed. ‡PD on ICI within 24 weeks (fresh biopsy or archived tissue); §PD on ICI > 24 weeks (fresh biopsy or archived tissue). ATM, ataxia-telangiectasia mutated; ATRi, ataxia-telangiectasia receptor inhibitor; CD73, cluster of differentiation 73; HER2, human epidermal growth factor receptor 2; HRR, homologous recombination repair; NSCLC, non-small-cell lung cancer; PARPi, poly ADP ribose polymerase inhibitor; PD, progression of disease; STAT3i, Signal transducer and activator of transcription 3 inhibitor; STK11, Serine/threonine kinase 11 (also known as LKB1)

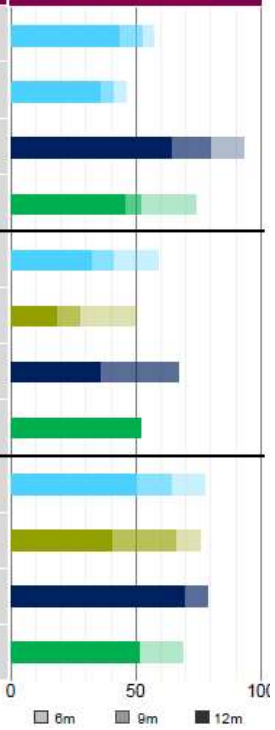
HUDSON – ORR and median PF

	Durvalumab combination	N	mF/U m	ORR n (%)	Median PFS m (80% CI)	PFS rate (%) 6, 9 and 12 m
Biomarker selected	Olaparib HRR	21	2.8	2 (9.5)	2.79 (1.48 – 5.26)	
	Olaparib STK11	21	1.4	1 (4.8)	1.41 (1.38 – 1.81)	
	Ceralasertib ATM	18	*5.0*	*2 (11.1)*	7.43 (3.45 – 9.46)	
	Oleclumab 73H	23	1.5	0 (0)	1.58 (1.41 – 2.76)	
Primary resistance	Olaparib	22	2.8	0 (0)	3.38 (2.10 – 4.93)	
	Danvatirsen	23	1.7	0 (0)	1.68 (1.64 – 2.99)	
	Ceralasertib	20	2.6	2 (10.5)	*4.24 (1.94 – 6.77)*	
	Oleclumab	9	1.4	0 (0)	1.41 (1.35 – 1.81)	
Acquired resistance	Olaparib	23	4.2	1 (4.3)	4.17 (2.69 – 4.37)	
	Danvatirsen	22	2.8	0 (0)	3.09 (2.83 – 6.14)	
	Ceralasertib	24	4.6	2 (8.3)	4.96 (3.55 – 5.98)	
	Oleclumab	25	2.6	1 (4.2)	2.63 (1.64 – 2.79)	



HUDSON – median OS

	Durvalumab combination	N	mF/U m	Median OS m (80% CI)	OS rate (%) 6, 9 and 12 m
Biomarker selected	Olaparib HRR	21	9.6	9.63 (5.26 – 15.97)	
	Olaparib STK11	21	5.6	5.75 (5.29 – 10.84)	
	Ceralasertib ATM	18	*10.5*	*15.80 (11.01 – NC)*	
	Oleclumab 73H	23	7.6	*9.49 (7.49 – NC)*	
Primary resistance	Olaparib	22	7.2	7.16 (4.93 – 10.28)	
	Danvatirsen	23	6.0	6.01 (3.55 – 6.51)	
	Ceralasertib	20	*6.7*	*11.60 (10.45 - NC)*	
	Oleclumab	9	2.8	7.06 (4.90 – 7.06)	
Acquired resistance	Olaparib	23	11.6	15.51 (8.80 – 19.75)	
	Danvatirsen	22	10.8	11.20 (9.72 – 12.55)	
	Ceralasertib	24	*12.7*	*17.38 (14.06 – NC)*	
	Oleclumab	25	6.1	*12.78 (6.14 – 12.78)*	



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Randomised phase 2 study of Nivolumab (N) versus Nivolumab and Ipilimumab (NI) combination in *EGFR* mutant NSCLC

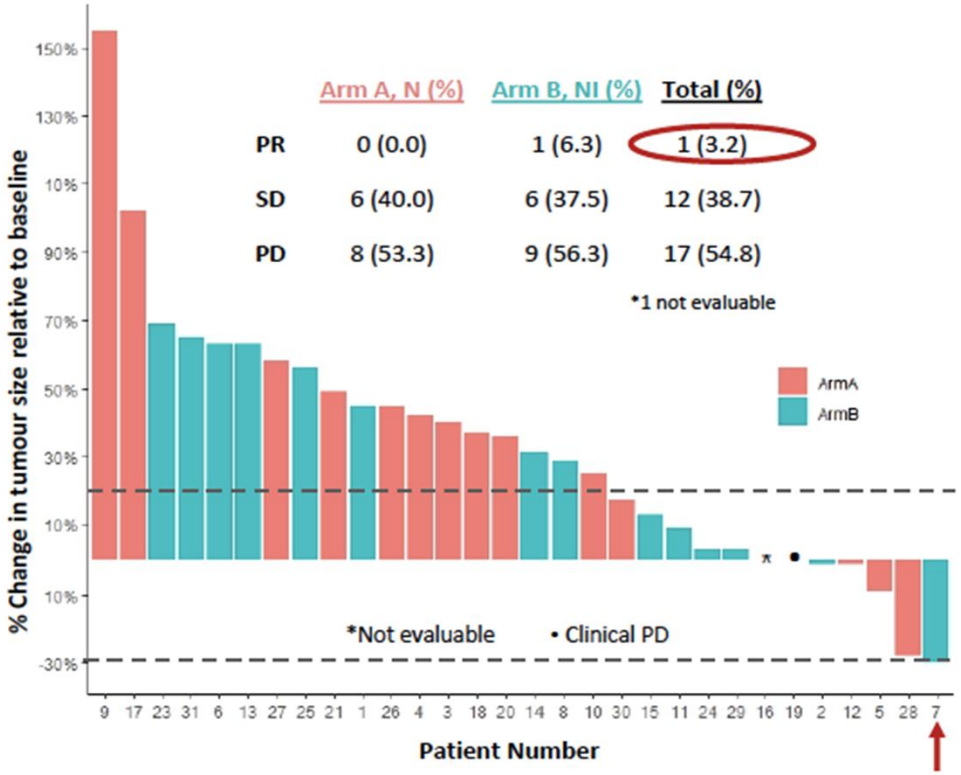
Gillianne G.Y. Lai[1], Jacob J.S. Alvarez[2], Jia Chi Yeo[2], Ngak Leng Sim[2], Aaron C. Tan[1], Siqin Zhou[1], Lisda Suteja[1], Tze Wei Lim[1], Neha Rohatgi[2], Joe P.S. Yeong[3], Angela Takano[3], Kiat Hon Lim[3], Apoorva Gogna[3], Chow Wei Too[3], Kun Da Zhuang[3], Amit Jain[1], Wan Ling Tan[1], Ravindran Kanesvaran[1], Quan Sing Ng[1], Mei Kim Ang[1], Tanujaa Rajasekaran[1], Lanying Wang[1], Chee Keong Toh[1], Wan-Teck Lim[1], Wai Leong Tam[2], Florent Ginhoux[4], Sze Huey Tan[1], Anders M.J. Skanderup[2], Daniel S.W. Tan[1], Eng-Huat Tan[1]

[1]National Cancer Centre Singapore, [2]Genome Institute of Singapore,
[3]Singapore General Hospital, [4]Singapore Immunology Network

Best Overall Response

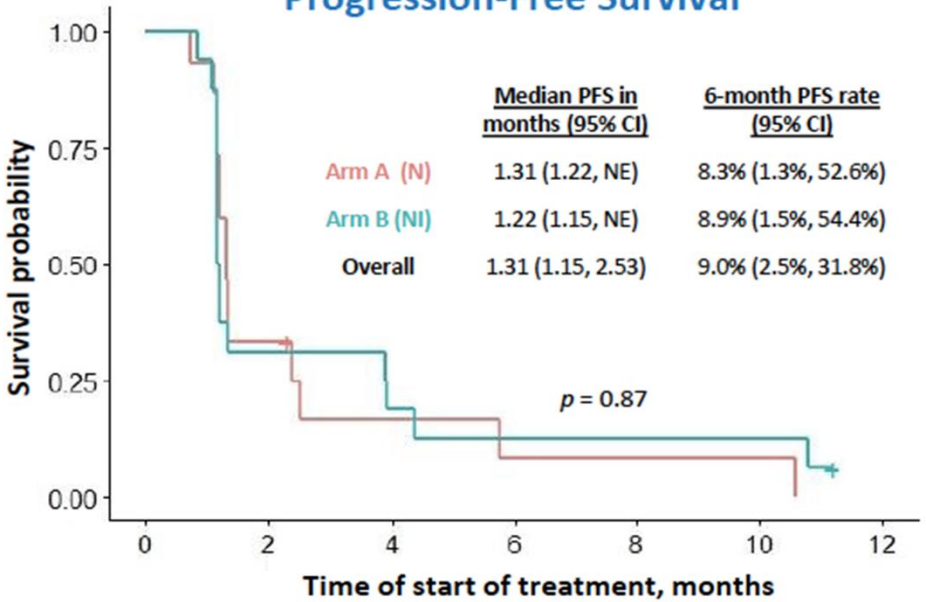
	Arm A, N (%)	Arm B, NI (%)	Total (%)
PR	0 (0.0)	1 (6.3)	1 (3.2)
SD	6 (40.0)	6 (37.5)	12 (38.7)
PD	8 (53.3)	9 (56.3)	17 (54.8)

*1 not evaluable



Progression-Free Survival

	Median PFS in months (95% CI)	6-month PFS rate (95% CI)
Arm A (N)	1.31 (1.22, NE)	8.3% (1.3%, 52.6%)
Arm B (NI)	1.22 (1.15, NE)	8.9% (1.5%, 54.4%)
Overall	1.31 (1.15, 2.53)	9.0% (2.5%, 31.8%)



No. at risk

Arm A	15	5	2	1	1	1	0
Arm B	16	5	3	2	2	2	0
	0	2	4	6	8	10	12

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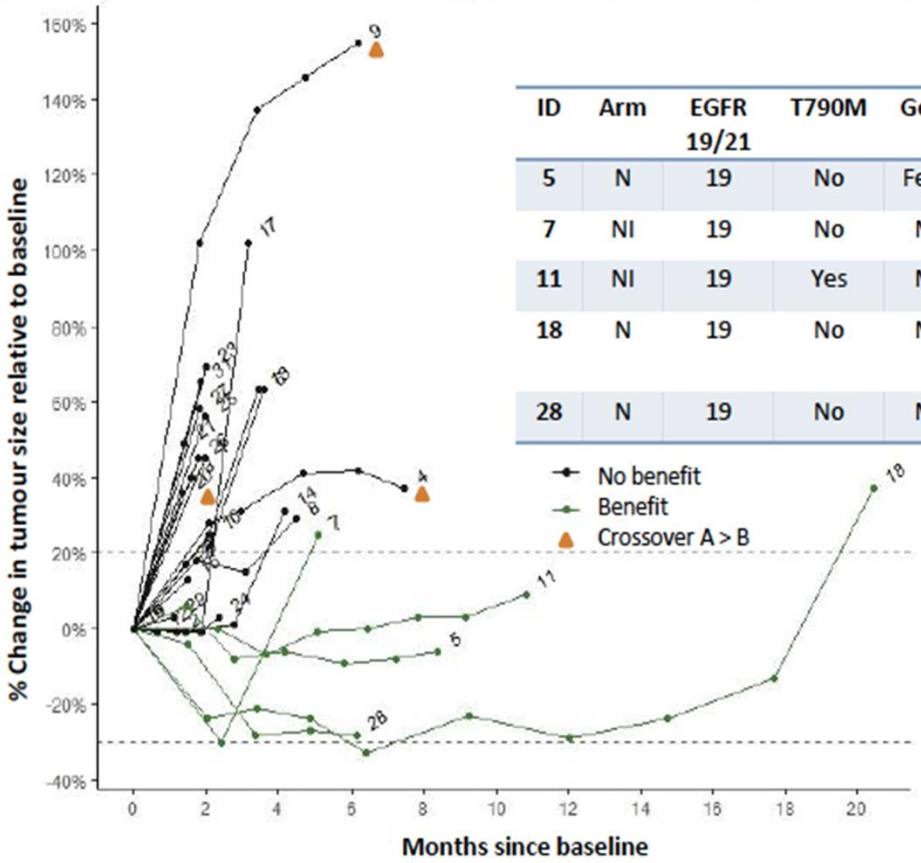
Individual Tumour Response



ID	Arm	EGFR 19/21	T790M	Gender	Smoking Status	PDL1 status	CNS mets	Best Response
5	N	19	No	Female	Non-smoker	5%	No	SD
7	NI	19	No	Male	Non-smoker	0%	No	PR
11	NI	19	Yes	Male	Non-smoker	10%	No	SD
18	N	19	No	Male	Non-smoker	-	No	SD
28	N	19	No	Male	Non-smoker	80%	Yes	SD

**Clinical benefit defined by ongoing PR/SD at 6 months, or best response of PR*

- 5 patients with clinical benefit
- All EGFR exon 19 deletion; 4 of 5 T790M negative
- No association between PDL1 status and response to ICI
- No salvage achieved with crossover from A > B (ID 4, 9, 20)

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Treatment-related adverse events

Adverse Event	Any Grade (n=31) N (%)	Grade 3 N (%)
Any event	23 (74.2)	2 (6.0)
Immune-related		
Skin	11 (35.5)	-
Endocrine	4 (12.9)	1 (3.2)
Gastrointestinal	3 (9.6)	-
Hepatic	3 (9.6)	-
Pulmonary	1 (3.2)	-
Musculoskeletal	-	1 (3.2)

Checkmate 227[1]

Common treatment-related select AE with a potential immunologic cause

	Nivolumab-Ipilimumab	Nivolumab
Skin	34.0%	21.2%
Endocrine	23.8%	13.0%
Gastrointestinal	18.2%	12.8%
Hepatic	15.8%	10.7%
Pulmonary	8.3%	7.7%

[1]Hellmann MD, et al. NEJM 2019

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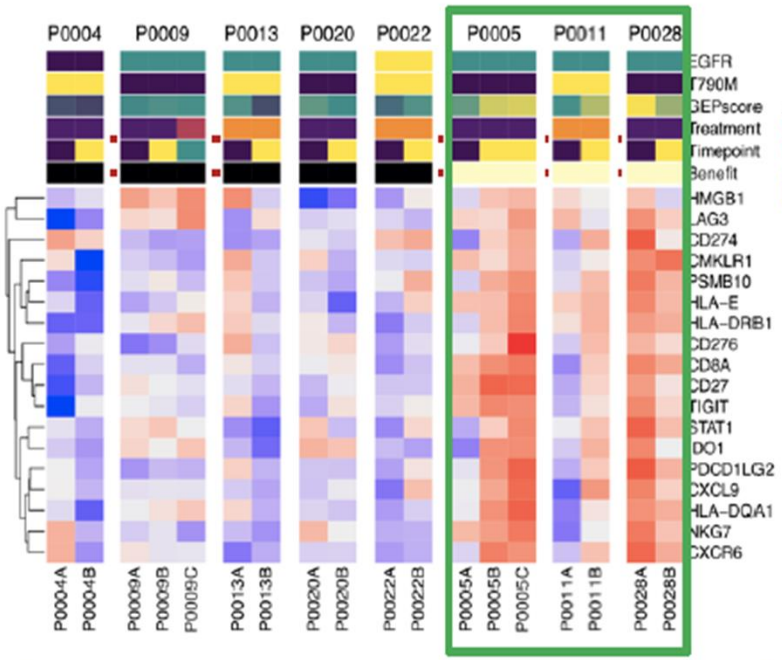
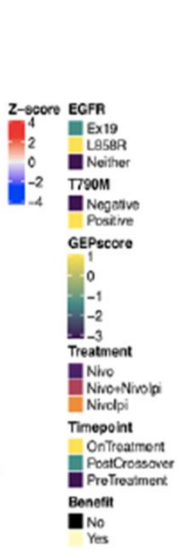
Dynamic changes across paired biopsies (n=8)

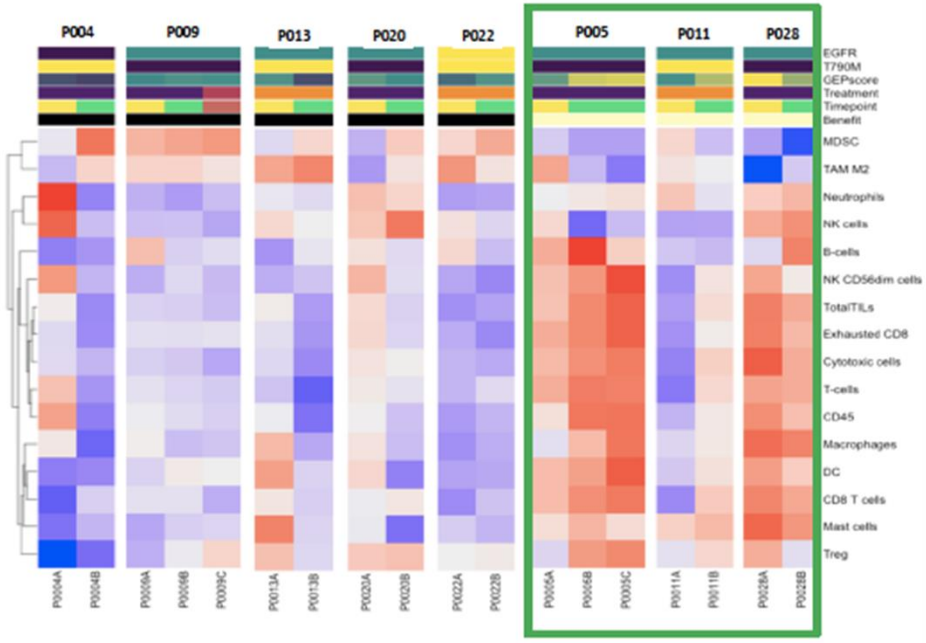
Gene expression profile



Clinical benefit



Immune cell populations

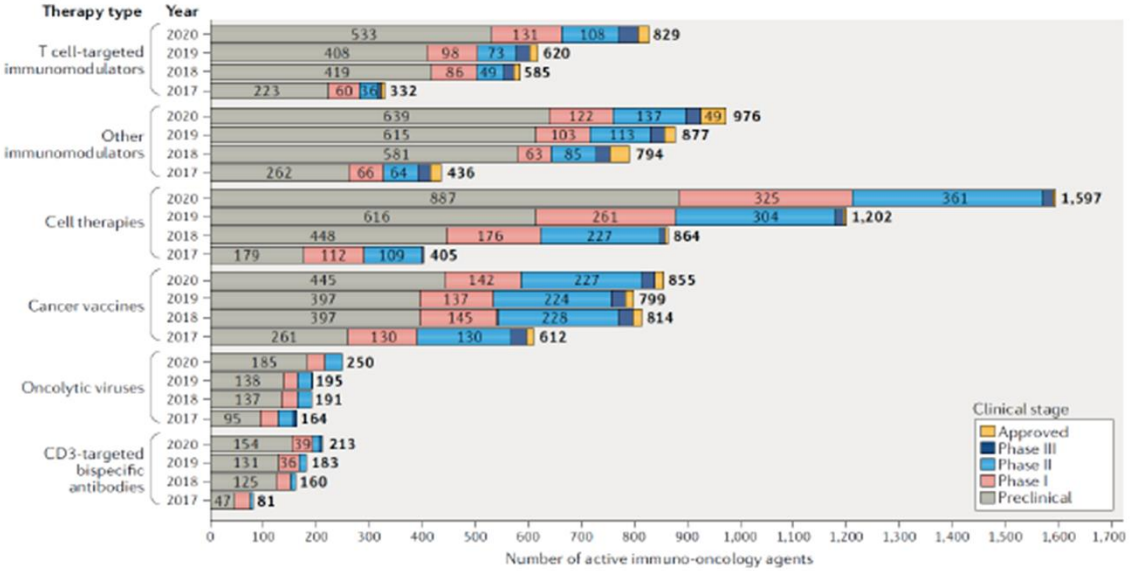


Immune-hot at baseline, or became hot on treatment

Lower numbers of suppressive MDSCs over time

How do we continue to exploit the immune system to increase treatment efficacy?

- Immuno-oncology drug development forges on despite COVID-19



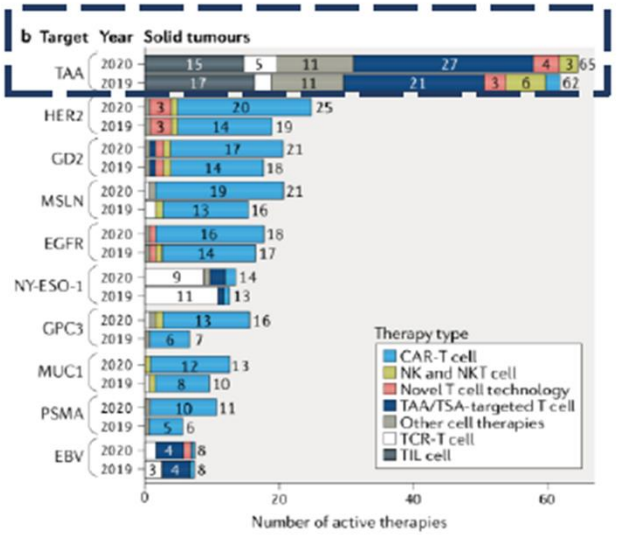


Fig. 1 | **Trends in the immuno-oncology drug development pipeline.** The 4,720 immuno-oncology agents in the current global clinical pipeline are compared with the pipelines from analogous analyses in previous years, based on the therapy type.

TAKE HOME MESSAGE

Vast opportunities to exploit the immune system for therapeutic advances alone and in combinations.

Precision immuno-oncology will require a deeper understanding of the interactions between the tumor, TME and the host.