Metastatic Lung Cancer Immunotherapy: Approach to NSCLC Without Targetable Mutations

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First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC and SQCC:

- Cemiplimab/Chemotherapy [Empower Lung-3]
- Durvalumab +Tremelimumab/Chemotherapy [Poseidon 3]

IO single Agent (NSQCC OR SQCC)

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

EMPOWER

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c[†], IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases[‡]

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Follow-up

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

[†]Patient not a candidate for definitive chemoradiation. [‡]Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). [§]For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

1. Sezer A et al. Lancet 2021;397:592–604.

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EMPOWER

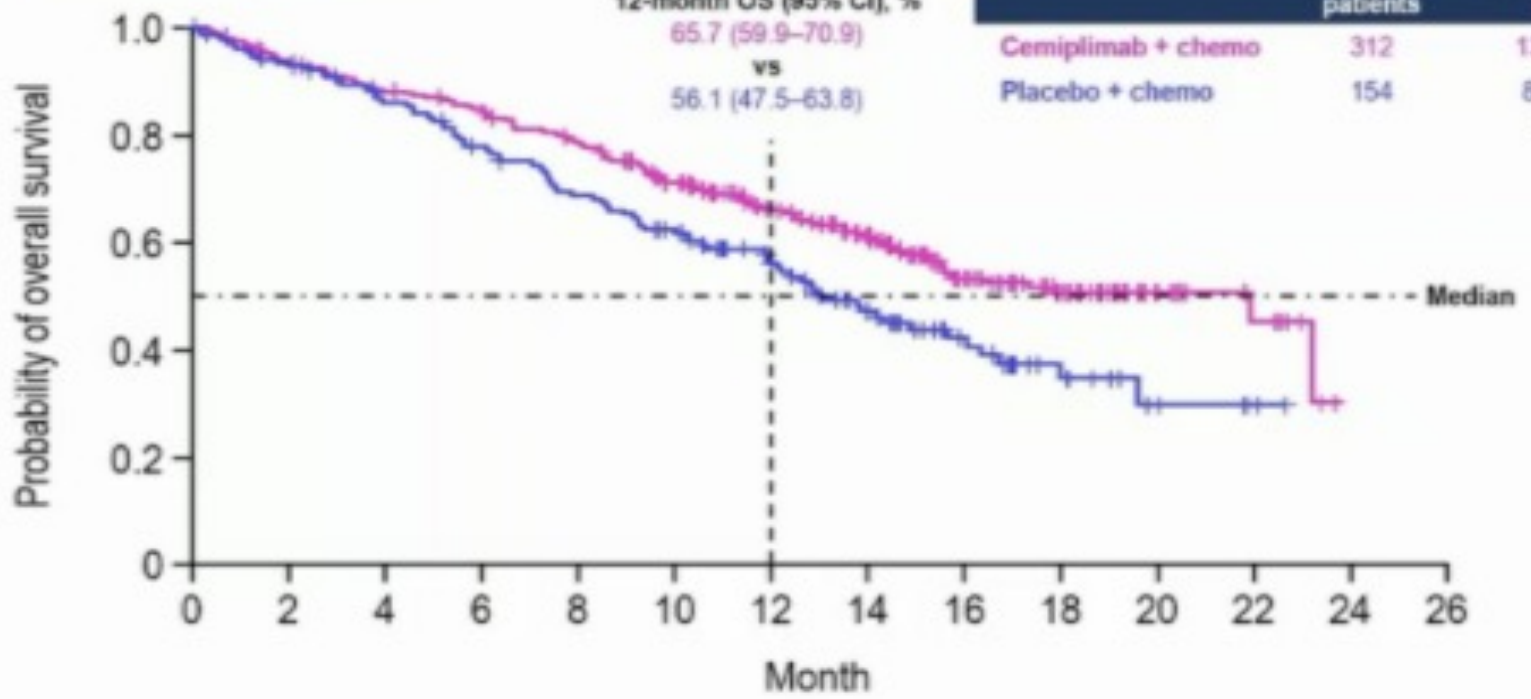
Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014

12-month OS (95% CI), %
65.7 (59.9–70.9)
vs
56.1 (47.5–63.8)



No. at risk:

Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

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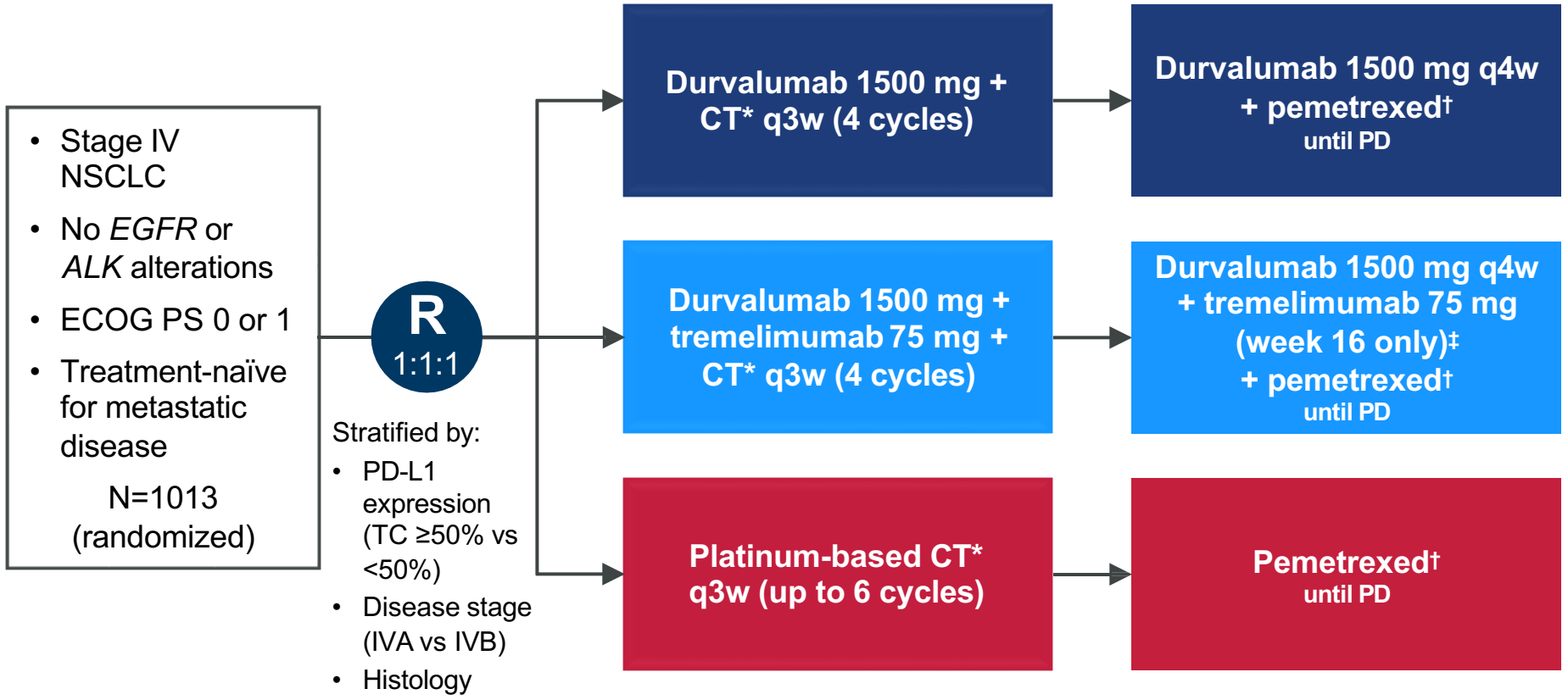
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off date:
14 June 2021

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study



Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

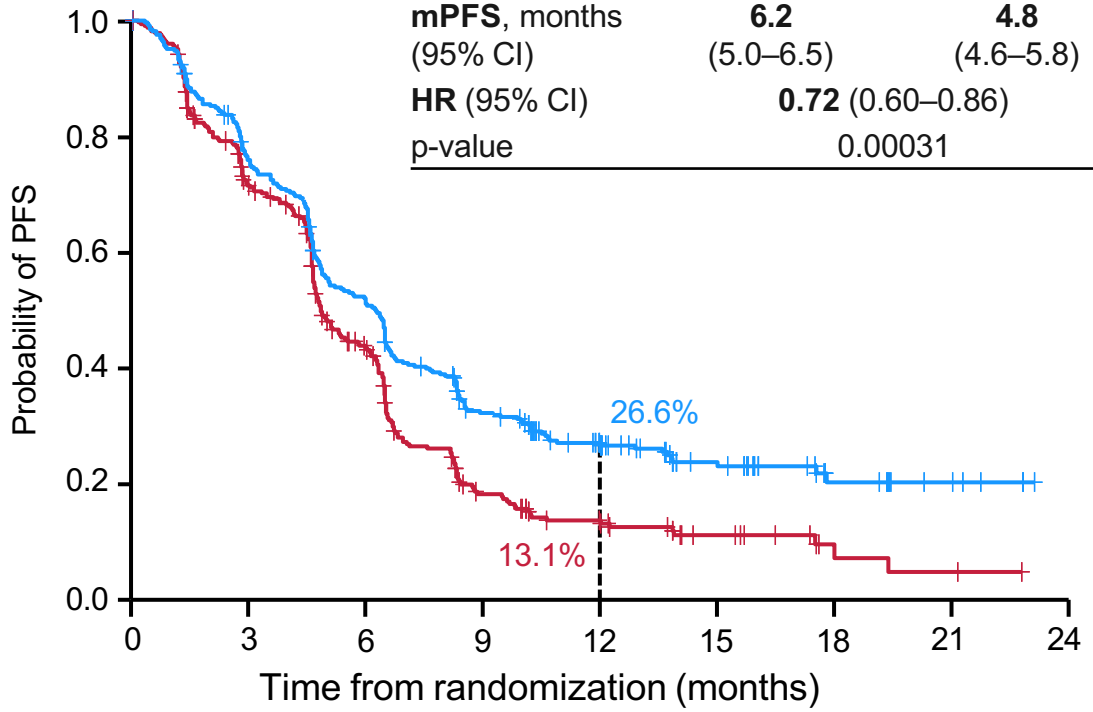
*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

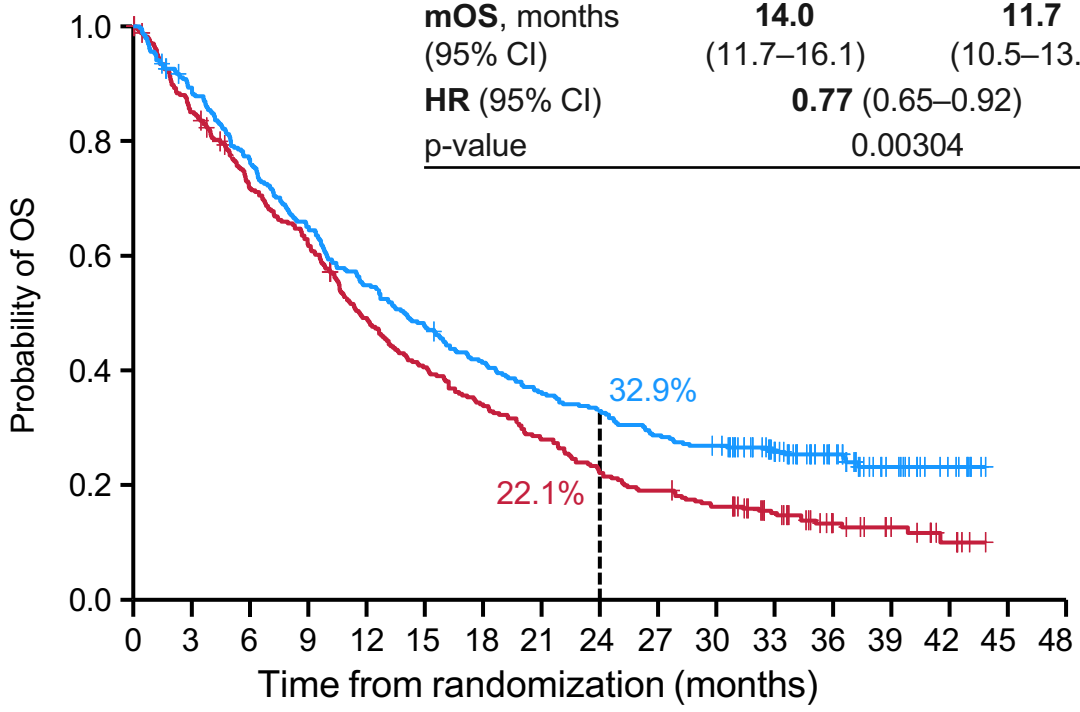


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk																	
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

Conclusions

- In POSEIDON, PFS was significantly improved with first-line durvalumab + CT vs CT in patients with mNSCLC, with a positive trend for OS that did not reach statistical significance
  - PFS HR 0.74 (95% CI 0.62–0.89; p=0.00093)
  - OS HR 0.86 (95% CI 0.72–1.02; p=0.07581)
- First-line durvalumab + tremelimumab + CT demonstrated statistically significant and clinically meaningful improvements in both PFS and OS vs CT in patients with mNSCLC
  - PFS HR 0.72 (95% CI 0.60–0.86; p=0.00031)
  - OS HR 0.77 (95% CI 0.65–0.92; p=0.00304)
  - OS and PFS benefit were more prominent among patients with non-squamous (than squamous) histology
- Overall, the safety profile was similar across all three arms, with no new safety signals identified. Adding tremelimumab to durvalumab + CT did not lead to a meaningful increase in treatment discontinuation
  - TRAE discontinuation rate 15.5% and 14.1% with D+T+CT and D+CT, respectively
- **Durvalumab + tremelimumab + CT represents a potential new first-line treatment option for mNSCLC**

TRAE, treatment-related adverse event

First Line Lung Cancer Therapy with no actionable genes

Chemotherapy/IO Combinations

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]
- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]
- Cemiplimab/Chemotherapy [Empower Lung-3]
- Durvalumab + Tremelimumab/Chemotherapy [Poseidon 3]

IO single Agent (PDL1>50%)

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

ORR slightly in favor of combination chemo+IO

	KN 24 (TPS > 50%)	KN 42 (TPS > 50%)	IMPW 10 TC3/IC3 (>50% and >10%)	KN 407 (TPS > 50%)	KN 189 (TPS > 50%)
ORR	45%	39.5%	30.7%	60.3%	61.4%
DOR	Nr (1.8-20.6 m)	20.2 m	Nr (1.8-29.3m)	7.7 m (all patients)	11.2 m (all patients)

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

Adverse Events more prevalent with Chemo/IO

	KN-42		KN-24		KN-189		KN-407	
	Pembro	CT	Pembro	CT	Pembro + CT	CT	Pembro + CT	CT
All TRAE (%)	62.7%	89.9%	76.6%	90.0%	99.8%	99.0%	98.2%	97.9%
Grade 3-5 TRAE (%)	17.8%	41%	31.2%	53.3%	67.2%	65.0%	69.8%	68.2%
Discontinuation rate (any) (%)	9%	9.4%	13.6%	10.7%	27.7%	14.9%	23.4%	11.8%
Led to death	0.2%	0%	1.3%	2.0%	6.7%	5.9%	8.3%	6.4%

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

2022 ASCO® ANNUAL MEETING

FDA

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Oladimeji Akinboro, MD, MPH

Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

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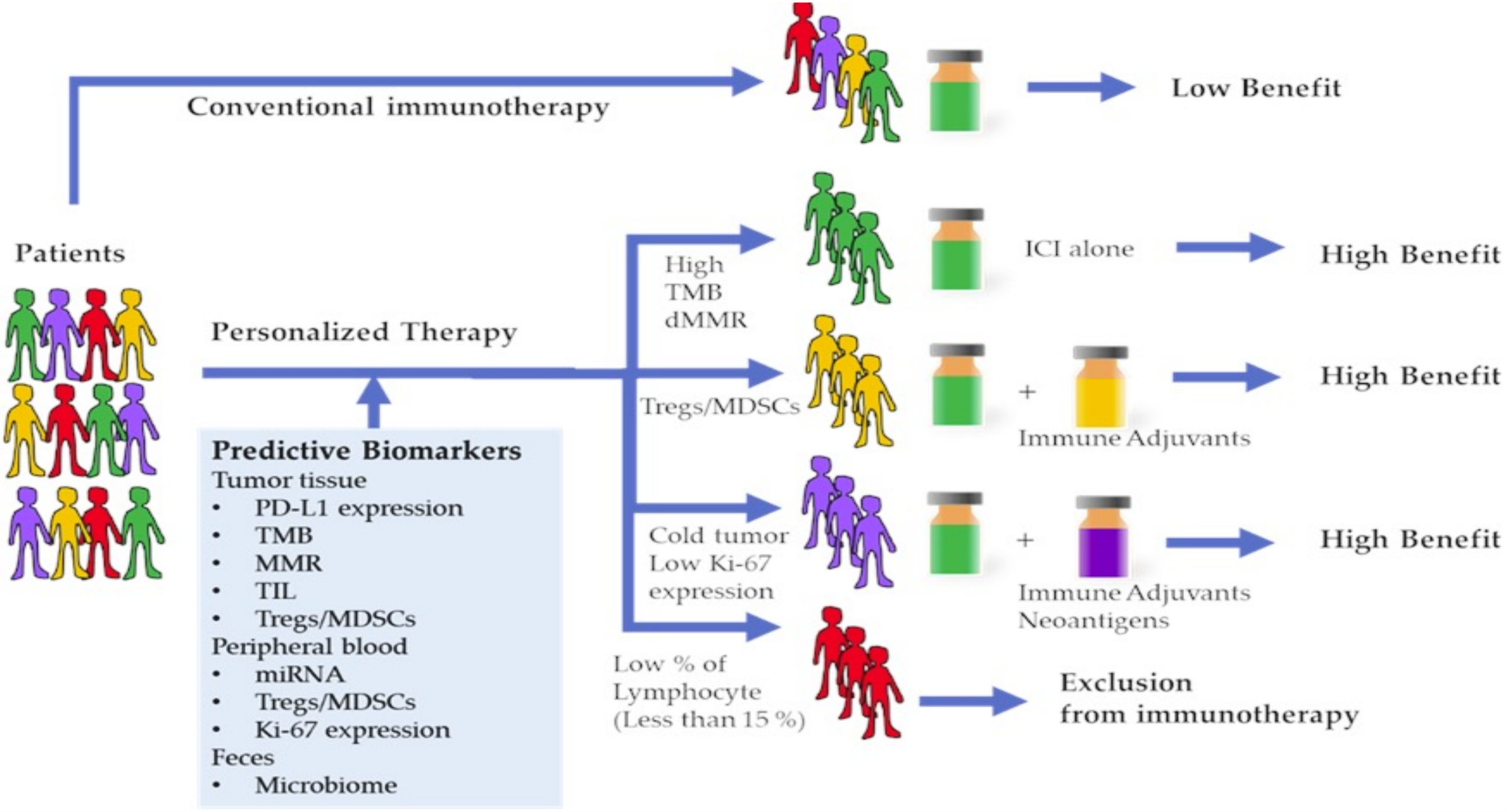
Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

FDA

	Chemo-IO (*N*=455)		IO-alone (*N*=1,298)
OS			
Median, months (95% CI)	25.0 (19.0, NE)		20.9 (18.5, 23.1)
HR (95% CI)		0.82 (0.62, 1.08)	
PFS			
Median, months (95% CI)	9.6 (8.4, 11.1)		7.1 (6.3, 8.3)
HR (95% CI)		0.69 (0.55, 0.87)	
ORR			
% (95% CI)	61 (56, 66)		43 (41, 46)
Odds ratio		1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.


Cancer
Immune-desert tumour
Immune-excluded tumour
Inflamed tumour
Tolerance
Immunologic ignorance
No priming
No co-stimulation
No T-cell help
No danger signals
No APC to LN
No B7.1 B7.2
No other co-stimulatory ligands
Regulatory T cells
Suppressive cytokines
No danger signals
Non-inflammatory conditions
↓ Tapasin
↓ MHC class I
Loss of B2M
No presentation
↓TAP-1 TAP-2
Other
No antigens
No neoantigens
No viral antigens
No cancer-associated antigens
Stromal interactions
Vascular
Fas ligand
VEGF
Extracellular matrix
Collagen
Fibronectin
Chemokines
CXCL12
Chemokine proteases
Dipeptidyl peptidase 4
B cells
Cytokines
PD-L1
Regulatory T cells
Cytokines
PD-1
Exhausted or hyper-exhausted T cells
Chronic TCR stimulation
Apoptosis
Other
PD-1high
Cancer-associated fibroblasts
TGF-β
IDO
Amino-acid catabolism
TDO
PD-L1
Myeloid suppressors
Poliovirus receptor
PD-L1
Cytokines
Amino-acid catabolism
Glutaminase
TDO
Arginase 1
IDO
Tumour cells
PD-L1
Adenosine A2A receptor
Amino-acid catabolism
IDO
TDO
Poliovirus receptor
Cytokines


Conventional immunotherapy
Low Benefit
Patients
Personalized Therapy
High
TMB
dMMR
ICI alone
High Benefit
Tregs/MDSCs
+
Immune Adjuvants
High Benefit
Cold tumor
Low Ki-67
expression
+
Immune Adjuvants
Neoantigens
High Benefit
Low % of
Lymphocyte
(Less than 15 %)
Exclusion
from immunotherapy
Predictive Biomarkers
Tumor tissue
• PD-L1 expression
• TMB
• MMR
• TIL
• Tregs/MDSCs
Peripheral blood
• miRNA
• Tregs/MDSCs
• Ki-67 expression
Feces
• Microbiome

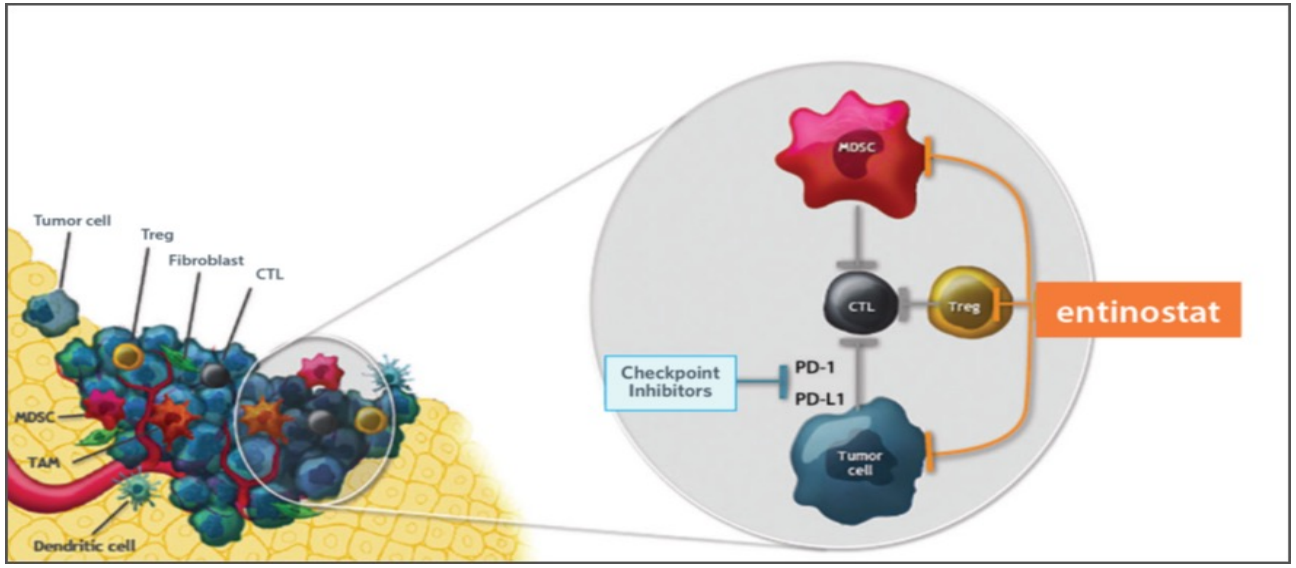
Immunotherapy resistance in NSCLC

- Deacetylase Inhibitors (etinostat, vorinostat)
- Vaccines (Heat Shock Protein gp96)
- STK11/LKB1 and KEAP
- Cytokines (IL-10, IL-15)
- Adenosine pathway
- Combination checkpoints (IDO, TIM, LAG3, TIGIT)
- Adoptive T cell therapies (TILs, TILs + anti PD(L)-1, TCRs)
- B-catenin pathway

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Entinostat plus Pembrolizumab in Patients with Metastatic NSCLC Previously Treated with Anti-PD-(L)1 Therapy

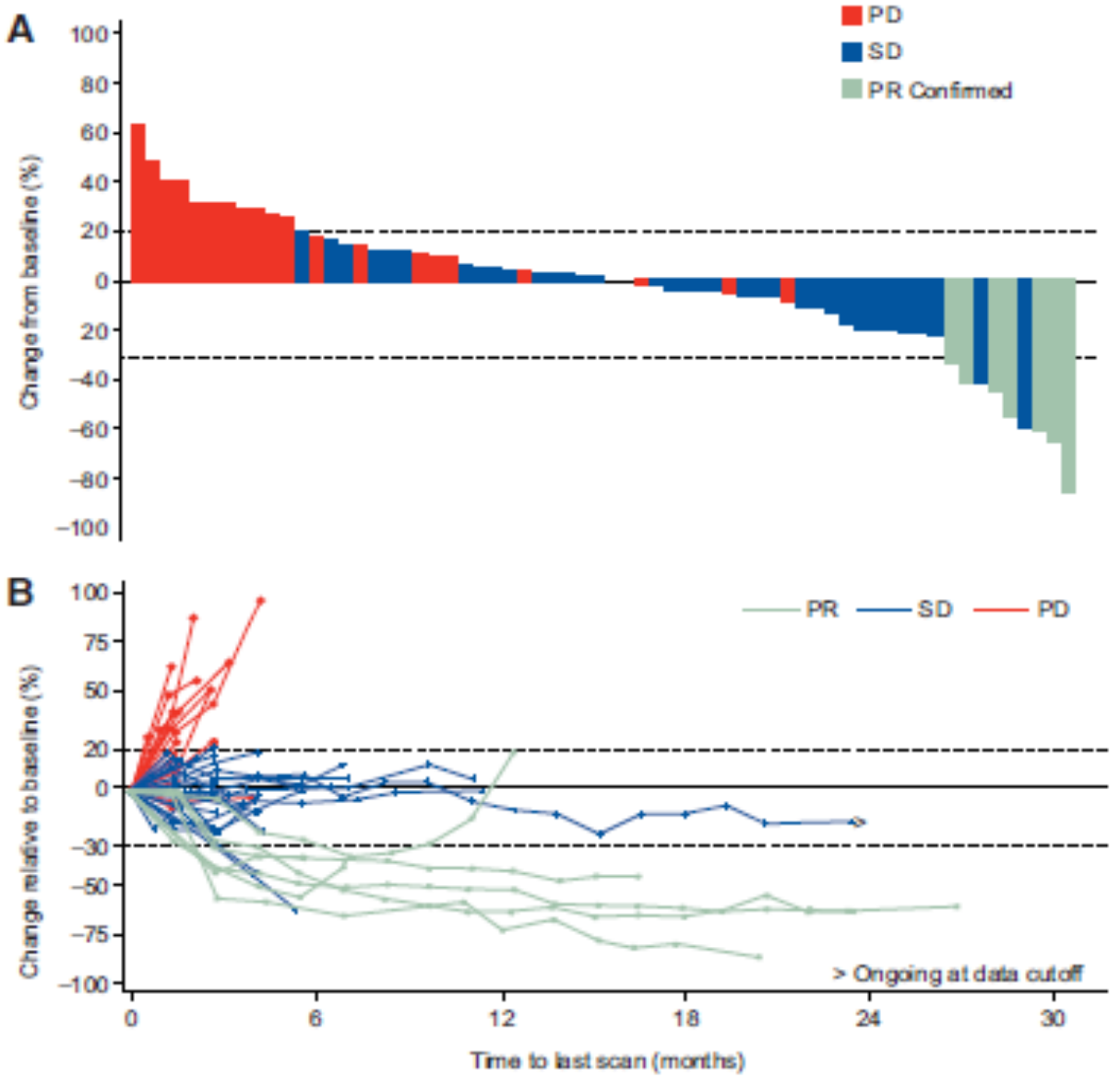
Matthew D. Hellmann[1], Pasi A. Jänne[2], Mateusz Opyrchal[3], Navid Hafez[4], Luis E. Raez[5], Dmitry I. Gabrilovich[6], Fang Wang[6], Jane B. Trepel[7], Min-Jung Lee[7], Akira Yuno[7], Sunmin Lee[7], Susan Brouwer[8], Serap Sankoh[8], Lei Wang[8], David Tamang[8], Emmett V. Schmidt[9], Michael L. Meyers[8], Suresh S. Ramalingam[10], Elaine Shum[11], and Peter Ordentlich[8]



- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to the downregulation of immunosuppressive cell types in the tumor microenvironment
- Synergy with anti-PD1 inhibition in preclinical models
- Promising activity is shown in combination with pembrolizumab in patients with melanoma and lung cancer

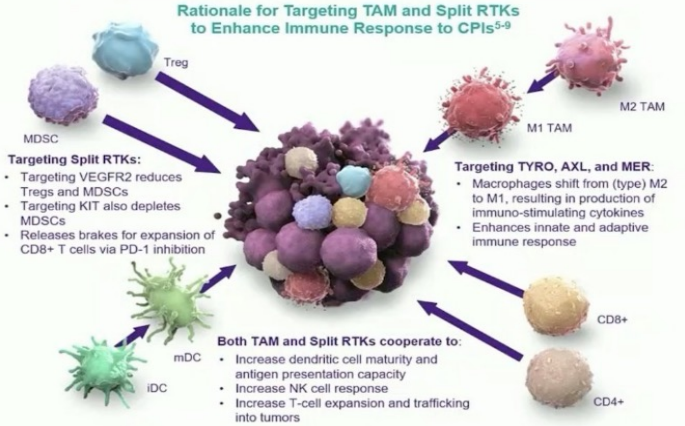
Helllman M (Raez L) Clin Can Research 2021 Feb 15;27(4):1019-1028.

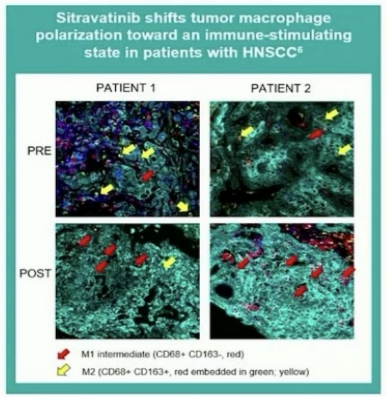
- **Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)**
  - **Median duration of response was 5.3 months**
  - **An additional 50% of patients achieved disease stabilization**
- **Median progression-free survival = 2.8 months (95% CI: 2.1-4.1)**



Helllman M (Raez L) Clin Can Research 2021 Feb 15;27(4):1019-1028.

Sitravatinib Is a TKI That Targets TAM Receptors (TYRO3, AXL, MERTK) and Split-Family Receptors (eg, VEGFR2)





Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

MRTX-500: Phase 2, Open-Label Study of Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From Checkpoint Inhibitor Therapy

Key Eligibility Criteria
(n=68)

- Advanced/metastatic nonsquamous NSCLC[a]
- No actionable driver mutations
- Anti–PD-1/L1 must be the most recent line of therapy
- Prior Clinical Benefit (PCB) to CPI: CR, PR, or SD ≥12 weeks from prior CPI therapy
- No uncontrolled brain metastases
- ECOG PS 0-2

→ **Sitravatinib** 120 mg QD + nivolumab

Primary Endpoint:
- Objective Response Rate[b] (ORR), as defined by RECIST 1.1

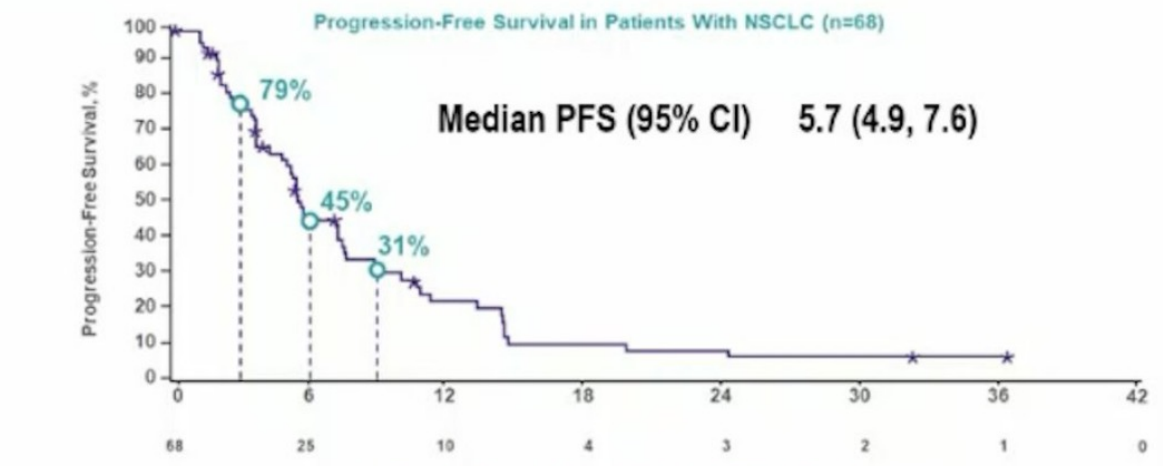
Secondary Endpoints:
- Safety and tolerability
- DOR
- CBR
- PFS
- OS
- 1-year survival rate

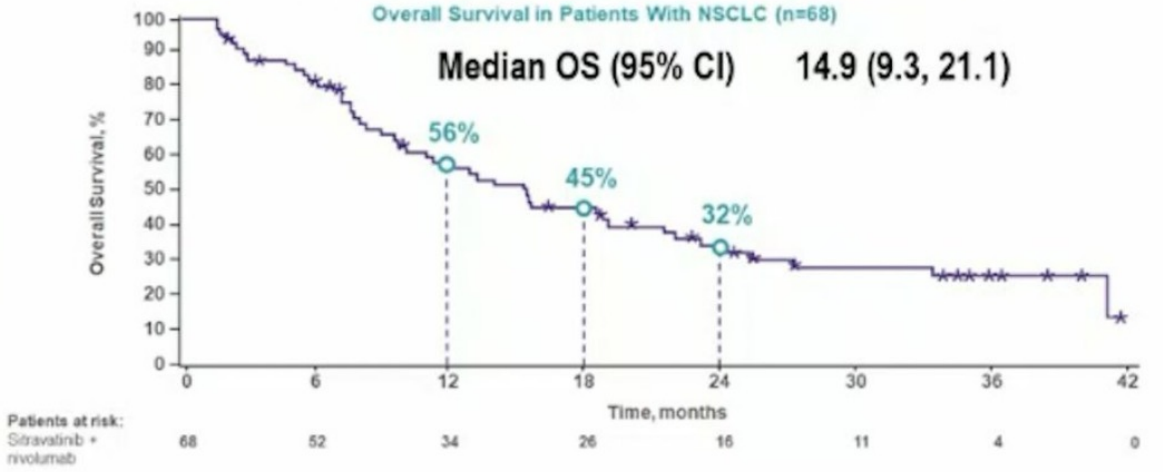
Here we report updated efficacy and safety with sitravatinib + nivolumab in the 2L or 3L setting in patients with nonsquamous NSCLC who have experienced clinical benefit on a prior CPI and subsequent disease progression

Data as of 1 June 2021

[a]Additional cohorts included a CPI-experienced cohort that did not receive prior clinical benefit from CPI therapy (radiographic progression of disease ≤12 weeks after initiation of treatment with CPI) and a CPI-naive cohort in patients that were previously treated with platinum-based chemotherapy. [b]Objective response rate based on investigator assessment. Dosing: sitravatinib free base formulation; nivolumab, 240 mg Q2W or 480 mg Q4W. Treatment discontinuation could be due to (but is not limited to) disease progression, global health deterioration, AEs, protocol violation, lost to follow-up, refusal of further treatment, study termination, or death.

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021



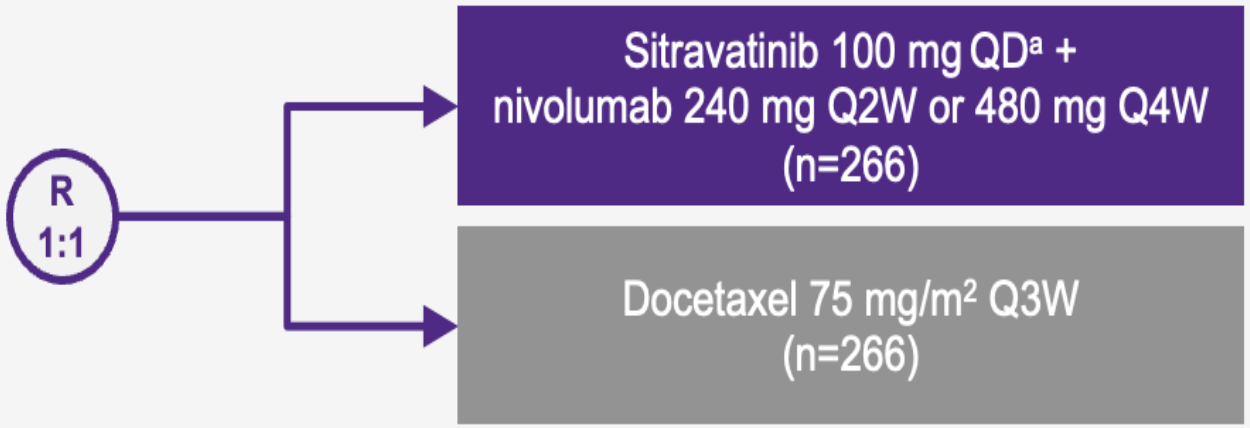


Ticiana Leal. ESMO 2021.

SAPPHIRE: Phase 3, Randomized, Open-Label Trial of 2L/3L Sitravatinib + Nivolumab vs Docetaxel After Progression on or Following CPI in Advanced NSCLC

Key Eligibility Criteria (n=532)

- Advanced, nonsquamous NSCLC
- Prior PD-1/L1 therapy for ≥4 months (prior anti–CTLA-4 therapy allowed)
- Progression on or following PD-1/L1 inhibitor in combination with or following chemotherapy
- Excludes patients with known driver mutations



Primary Endpoint:
- OS

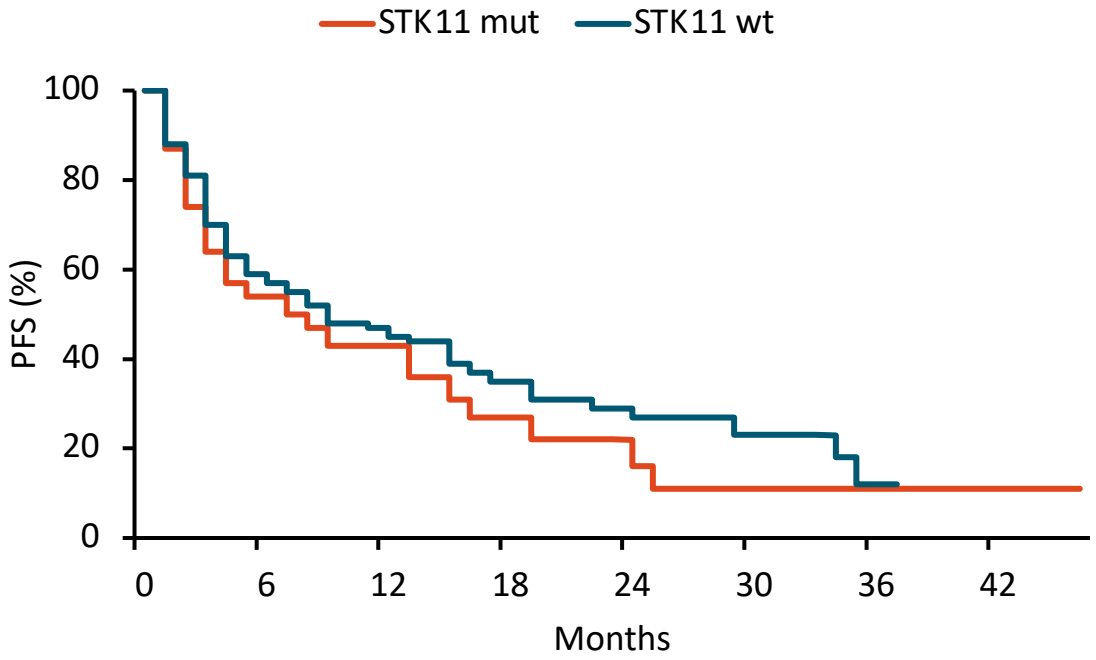
Secondary Endpoints:
- PFS
- ORR
- Safety

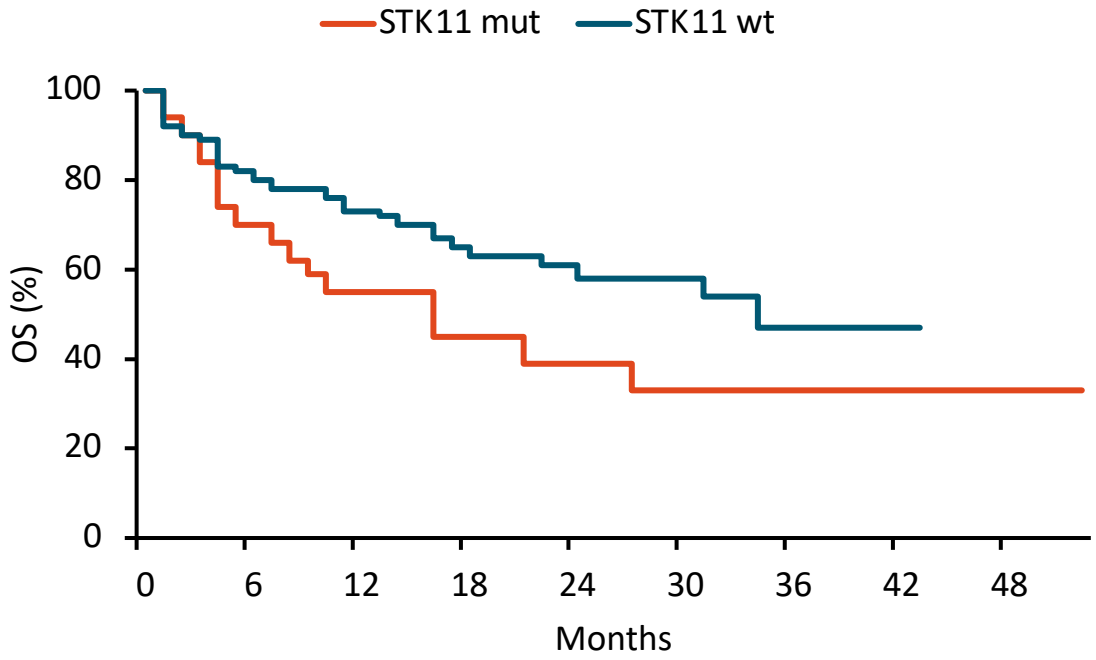
STK11/LKB1, KRAS mutations and immune-related adverse events as predictors of response to immunotherapy in lung cancer

Luis E. Raez, MD[1]; Richie Uba, PharmD[2,3]; Aaron North, PharmD[2,3]; Katerine Dumais, PharmD, MPH[1]; Hermán W. Powery II, PharmD, BCOP[1]; Gelenis Domingo, MD[1]; Brian Hunis, MD[1]; Paola Izquierdo, ARNP[1]; Frank Gentile, PharmD, BCOP[1]

[1]Memorial Cancer Institute, Pembroke Pines, FL; [2]Florida A&M University, Davie, FL; [3]Memorial Regional Hospital, Hollywood, FL

Results: PFS and OS by STK11 Status





	STK11 wt n = 96	STK11 mut n = 31	HR (95% CI)	p
mPFS	6.3m	5.6m	1.35 (0.76-2.1)	0.35
12-m PFS	45%	43%	-	0.85

	STK11 wt n = 96	STK11 mut n = 31	HR (95% CI)	p
mOS	12.1m	8.6m	1.7 (1.0-3.6)	0.03
12-m OS	73%	55%	-	0.03

2022 ASCO® ANNUAL MEETING

SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

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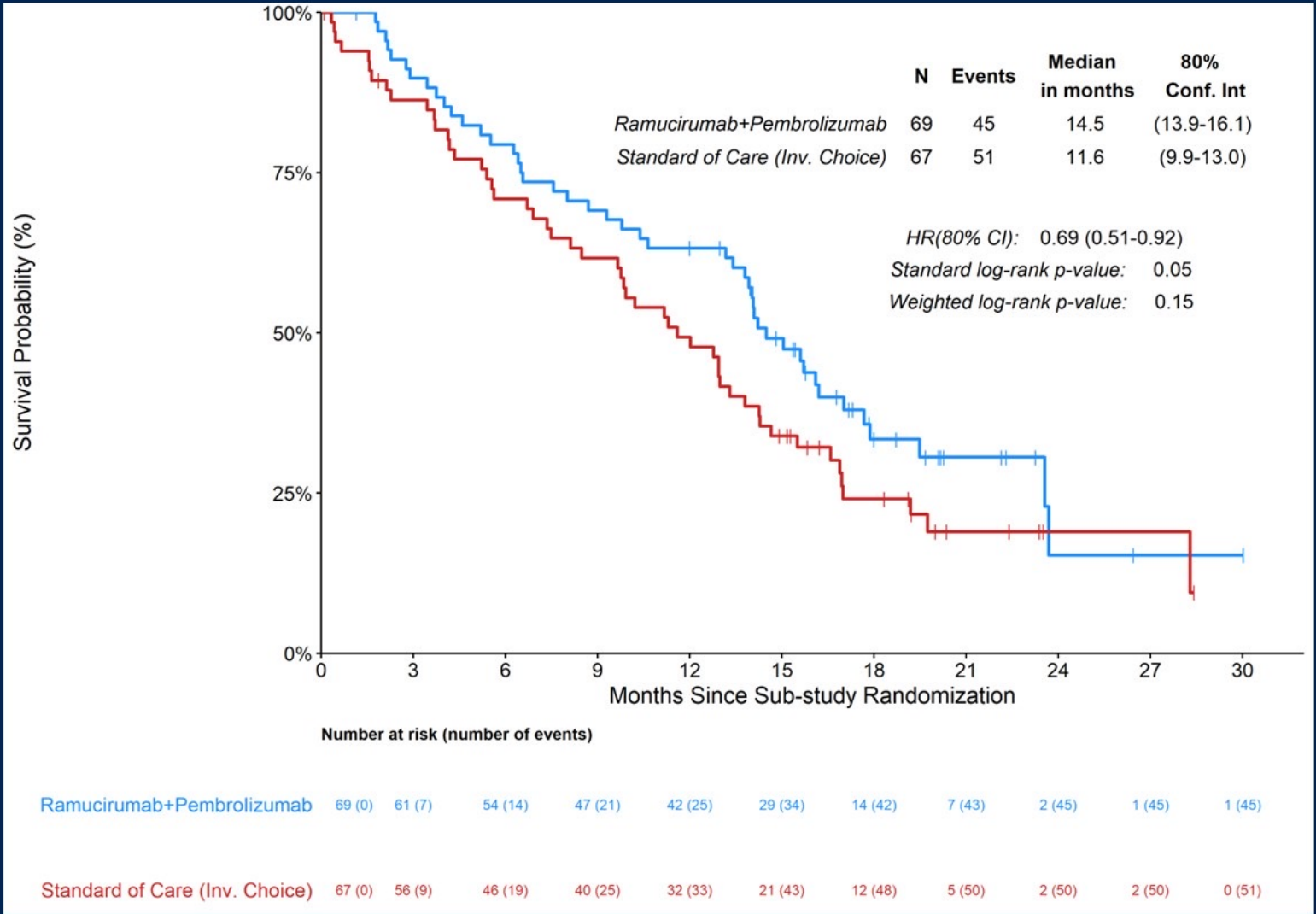
Overall survival



- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

COSMIC-021 Study Design for NSCLC Cohorts

Key Eligibility Criteria

- Stage IV non-squamous NSCLC with radiographic progression on or after one prior ICI for metastatic disease
- ≤2 prior lines of systemic anticancer therapy*
- Patients with known *EGFR*, *ALK*, *ROS1*, or *BRAF* V600E tumor mutations excluded

Cohort 7†
Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV
(N=80)

Cohort 20‡
Cabozantinib 60 mg QD PO
(N=30)

Tumor assessment per RECIST v1.1 by investigator every 6 weeks for the first year and every 12 weeks thereafter

Primary endpoint:	ORR per RECIST v1.1 by investigator
Secondary endpoint:	Safety (AEs, SAEs, AESIs)
Exploratory endpoints:	DOR, PFS per RECIST v1.1 by investigator, OS

*Prior treatment with platinum-based chemotherapy was not required. †Patients were initially enrolled to cohort 7 (n=35). Following an initial assessment of clinical activity, subsequent patients were randomized between cohorts 7 and 20. ‡Patients in cohort 20 may receive combination therapy after radiographic disease progression per RECIST v1.1 by the investigator.
SAEs, serious adverse events; AESIs, adverse events of special interest

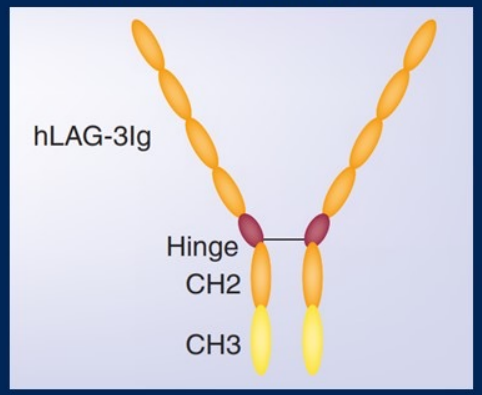
Efficacy Summary

	Cabozantinib + Atezolizumab (N=81)				Cabozantinib (N=31)*
	All patients (N=81)	PD-L1 <1% (n=19)	PD-L1 ≥1% (n=41)	PD-L1 unknown (n=21)	
ORR, n (%)	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Best overall response, n (%)					
Complete response	**0**	0	0	0	**0**
Partial response	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Stable disease	**50 (62)**	12 (63)	25 (61)	13 (62)	**18 (58)**
Progressive disease	**13 (16)**	3 (16)	8 (20)	2 (10)	**6 (19)**
Missing / not evaluable	**3 (4)**	2 (11)	0	1 (5)	**5 (16)**
Disease control rate, n (%)	**65 (80)**	14 (74)	33 (80)	18 (86)	**20 (65)**
PFS, mo (95% CI)	**4.5 (3.5–5.6)**	4.0 (2.6–5.6)	4.7 (2.7–5.6)	5.4 (2.9–10.9)	**3.4 (1.4–5.6)**
Median DOR, mo (95% CI)	**5.8 (4.2–6.9)**	3.4 (2.6–NE)	6.5 (3.5–NE)	6.2 (4.2–NE)	**10.6 (6.3–NE)†**
OS, mo (95% CI)	**13.8 (7.2–15.7)**	6.8 (5.1–15.4)	10.4 (5.9–17.1)	17.4 (9.4–NE)	**9.4 (4.5–11.7)**

*Eight patients in the cabozantinib alone cohort were crossed over to receive cabozantinib plus atezolizumab after experiencing disease progression; the efficacy data of these patients are not reported in this presentation except for OS. †The DOR of the 2 responders was 6.3 and 14.8 months.

Eftilagimod alpha (efti) – soluble LAG-3

STRUCTURE OF EFTI[4]



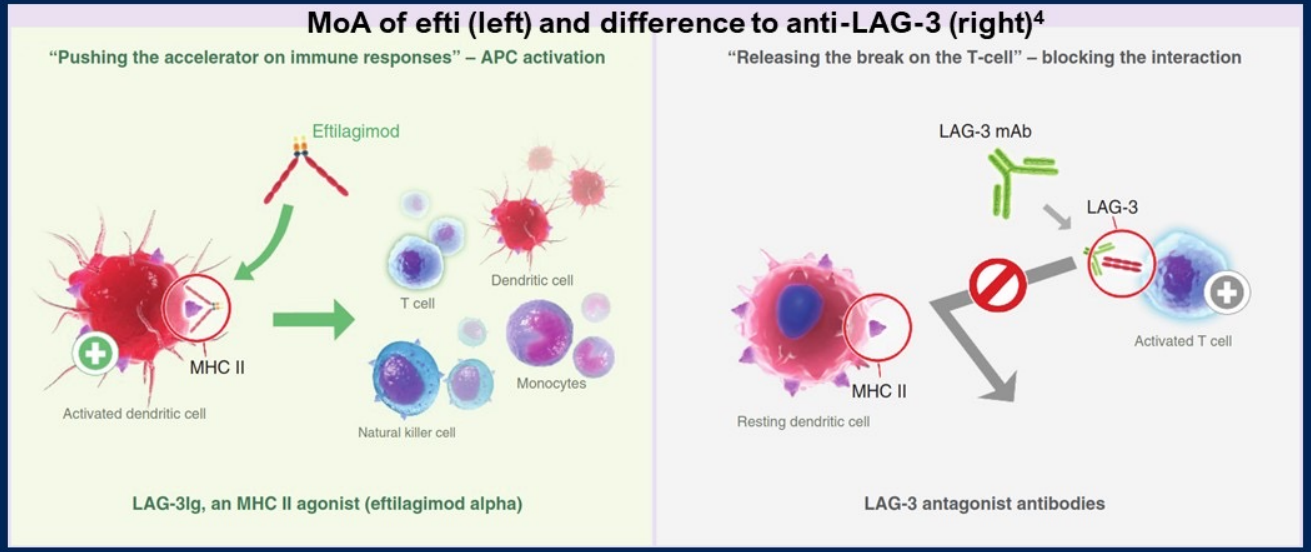
- **MoA: efti** (figure, left) is a **soluble LAG-3 protein** (LAG-3 domains fused to human IgG backbone) **targeting** a subset of **MHC class II molecules** to mediate antigen presenting cells (APCs) and CD8 T-cell activation (figure below left).
- **Difference to Anti-LAG-3:** Efti does not bind to the LAG-3 on the T cell (figure, below right).
- **Rationale:** efti activates APCs, leading to an increase in activated T cells, potentially reducing the number of non-responders to PD-1/PD-L1 antagonists.

- In preclinical models, the antitumor activity of PD-1 antagonists was synergistically enhanced when combined with efti[1].
- Recommended phase II dose of 30 mg efti s.c. every two weeks was determined in phase I studies[2,3].

MoA: mechanism of action
PD-1/PD-L1: programmed death-(ligand) 1
s.c.: subcutaneous

[1] Internal data, Immutep, not yet published.
[2] Brignone C, Clin Cancer Res. 2009;15: 6225- 6231.
[3] Atkinson V, J Immunoth Cancer. 2020; 8(2):e001681.
[4] Dirix L, Triebel F. Future Oncol. 2019;15(17):1963-1973.

MoA of efti (left) and difference to anti-LAG-3 (right)[4]



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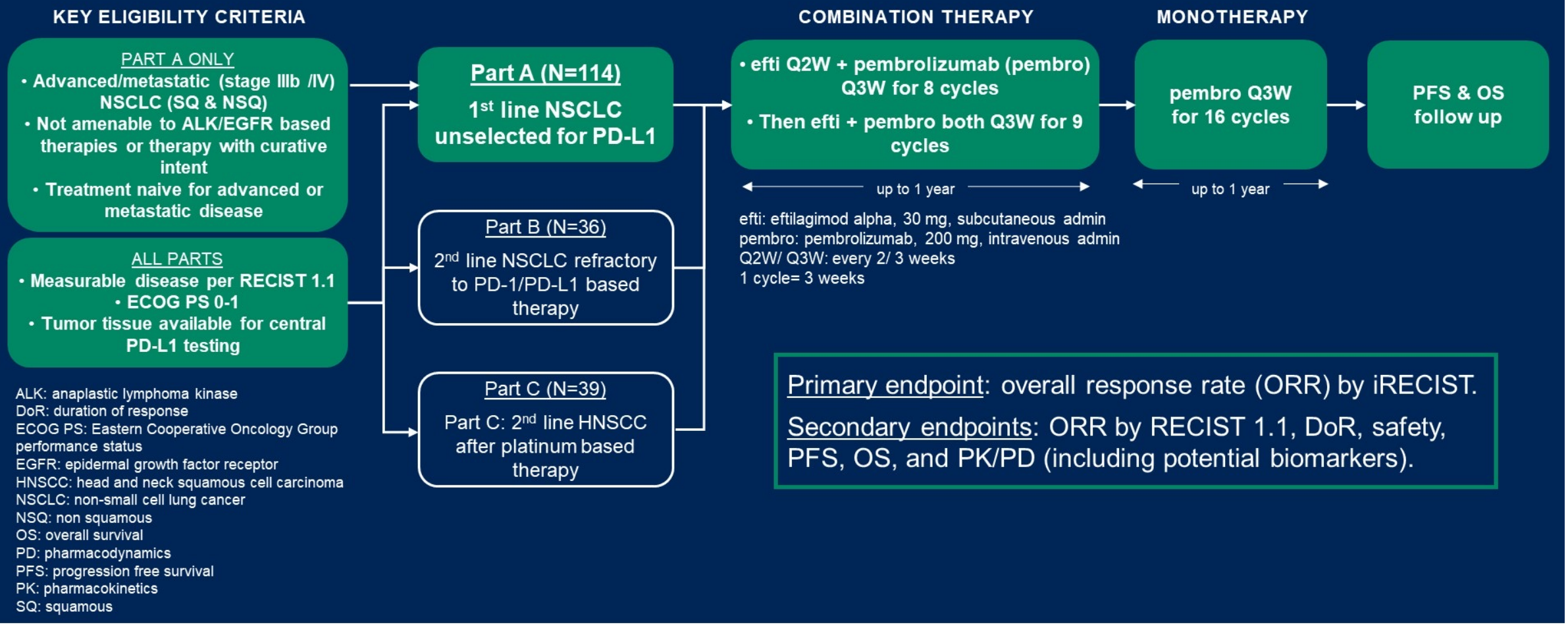
Trial Design – TACTI-002

TACTI-002 is a Phase II, multinational, open label trial with patients from 3 indications unselected for PD-L1.



ALK: anaplastic lymphoma kinase
DoR: duration of response
ECOG PS: Eastern Cooperative Oncology Group performance status
EGFR: epidermal growth factor receptor
HNSCC: head and neck squamous cell carcinoma
NSCLC: non-small cell lung cancer
NSQ: non squamous
OS: overall survival
PD: pharmacodynamics
PFS: progression free survival
PK: pharmacokinetics
SQ: squamous

Primary endpoint: overall response rate (ORR) by iRECIST.

Secondary endpoints: ORR by RECIST 1.1, DoR, safety, PFS, OS, and PK/PD (including potential biomarkers).

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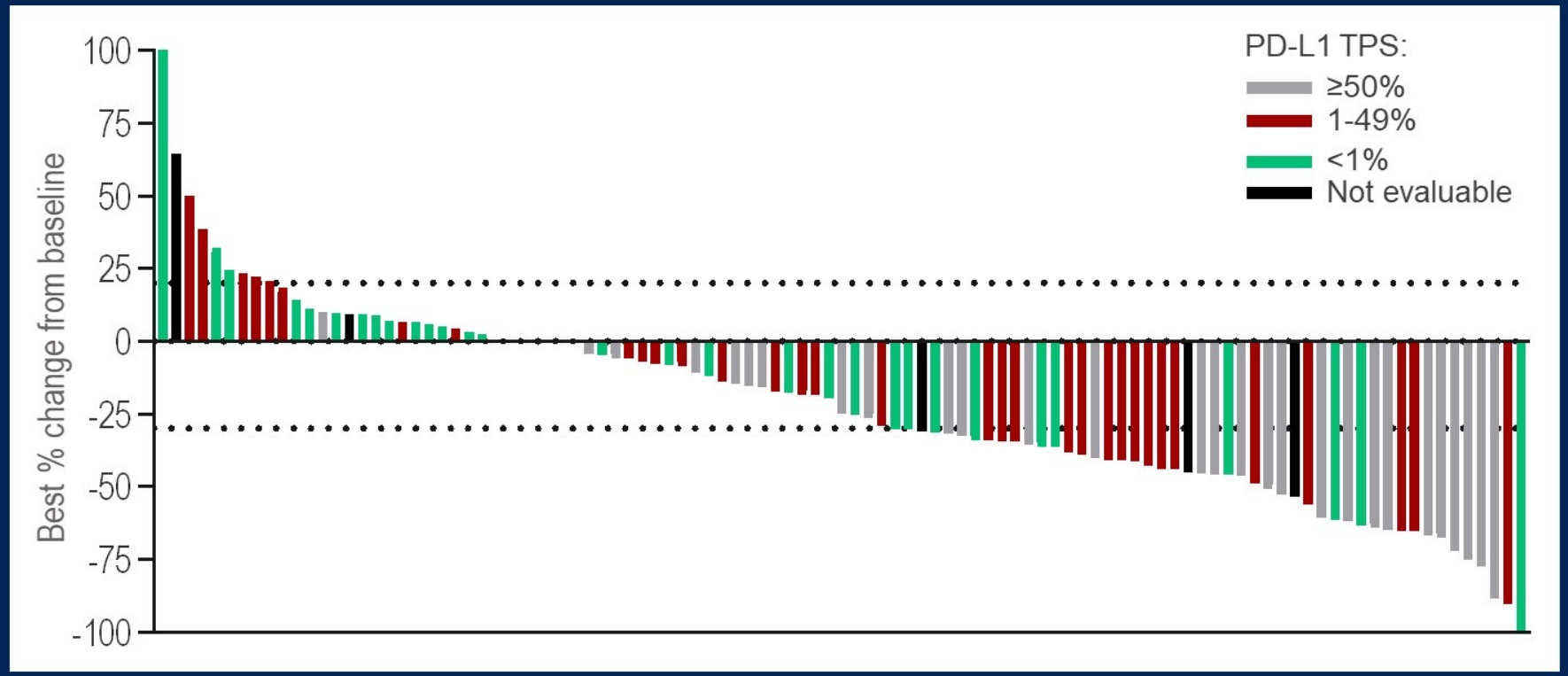
Efficacy – Waterfall plot[1] – TACTI-002



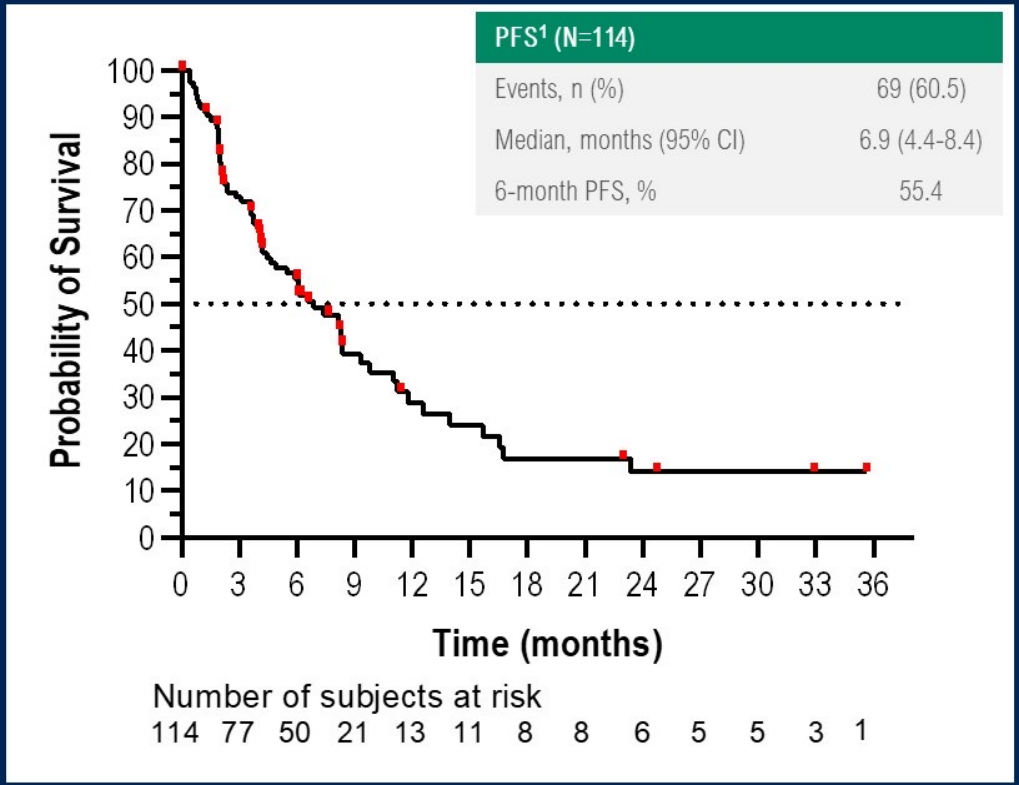
[1] all patients with ≥1 post-baseline CT scan n=103; [2] PD-L1 assessed by central assessment (Dako kit); n=79; [3] local assessment included due to non evaluable central assessment results, n=19; [4] no results available for neither central nor local testing, n=5.

- 2 complete responses and 19.4% of patients with a target lesion decrease ≥50%.
- 68/103 (66.0%) of patients with a post-baseline assessment had a decrease in target lesions.

Data cut-off date: April 15, 2022

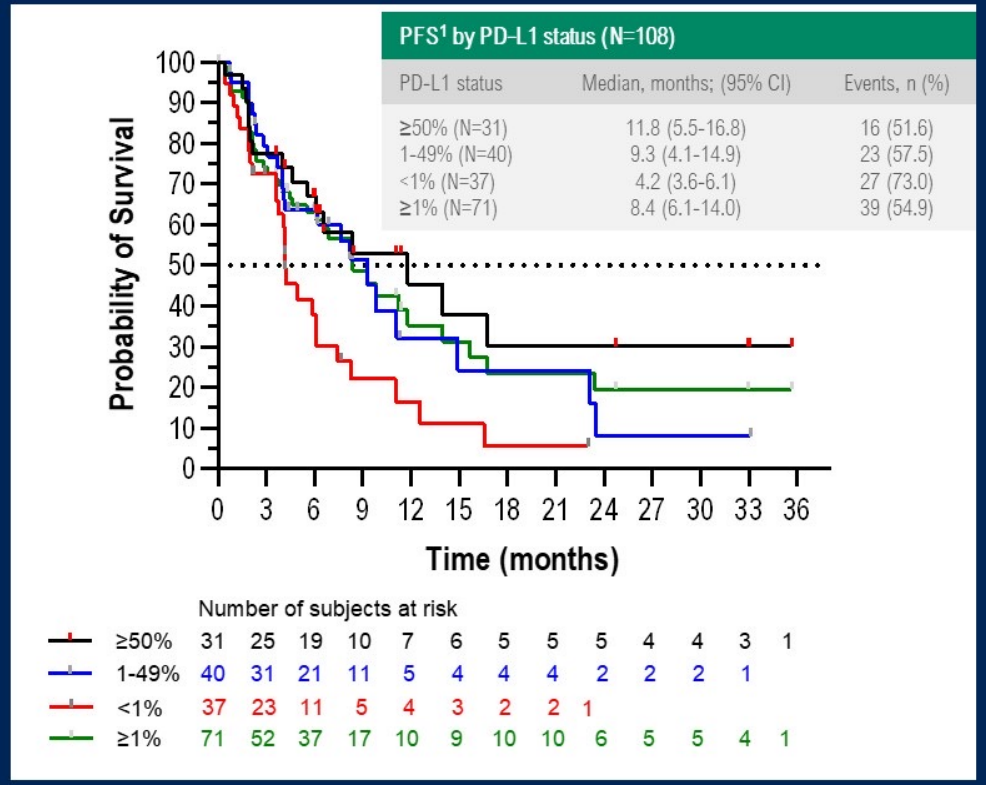
Efficacy – Interim Progression Free Survival[1] (PFS) – TACTI-002

PFS[1] ITT (N=114)



- Interim median PFS[1] in the ITT (unselected for PD-L1) was 6.9 (95% CI: 4.4.-8.4) months.

PFS[1] by PD-L1 status[2] (N=108)



- Interim median PFS[1] in PD-L1 ≥1% was 8.4 (95% CI: 6.1-14.0) months and 11.8 (5.5-16.8) months in PD-L1 ≥50%.

[1] by iRECIST.
[2] central (N=87) & local (N=21) as previously described on slide 9.

Data cut-off date: April 15, 2022

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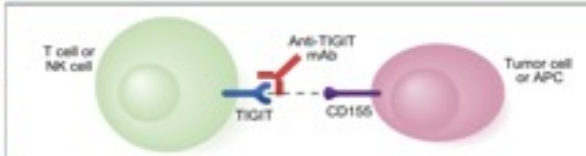
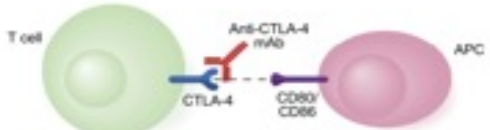
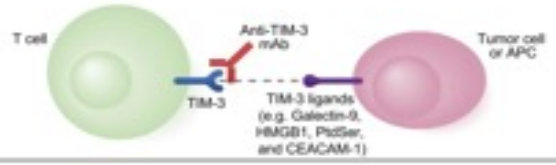
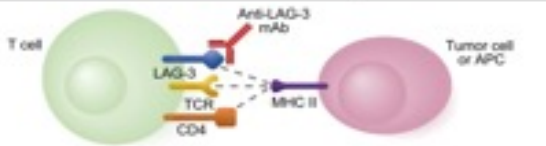
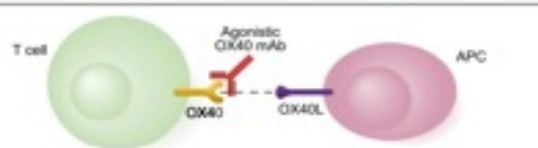
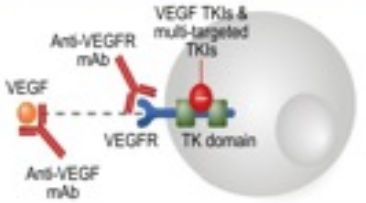
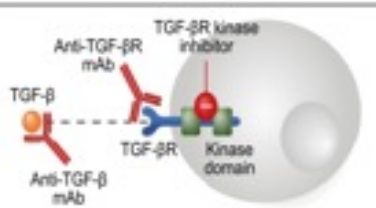
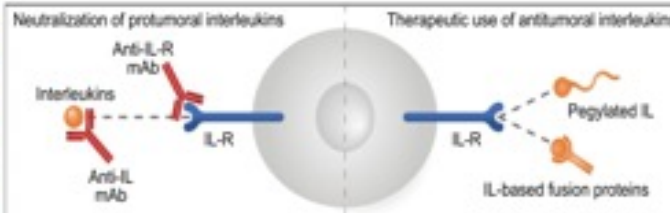
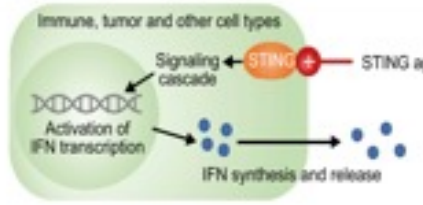
Potential pathways contributing to sensitivity and resistance to PD-(L)1 inhibitors in NSCLC

Pathways & targets		Potential role of pathway in sensitivity or resistance to PD-(L)1 inhibition	Mechanism of action of investigational agents
Upregulation of co-inhibitory checkpoints	TIGIT[21-24]	Downregulation of T-cell responses Inhibition of T-cell activation T-cell exhaustion Immunosuppression	
	CTLA-4[4,25]	Suppression of T-cell priming Inhibition of T-cell activation Increased regulatory T-cell activity Immunosuppression	
	TIM-3[17,26]	Inhibition of T-cell activation Suppression of T-cell proliferation T-cell exhaustion Immunosuppression	
	LAG-3[18,25,27]	Inhibition of T-cell activation Suppression of T-cell proliferation T-cell exhaustion Immunosuppression	
Co-stimulatory checkpoint activity	OX40[28,29]	Enhanced T-cell survival & proliferation Generation of memory T cells Inhibition of regulatory T cell function Enhanced immune response	

Pathways & targets		Potential role of pathway in sensitivity or resistance to PD-(L)1 inhibition	Mechanism of action of investigational agents
Immunosuppressive tumor immune microenvironment	VEGF[30,31]	Promotion of tumor angiogenesis Suppression of DC maturation Inhibition of T-cell proliferation & infiltration Immunosuppression	
	TGF-β[32-37]	Promotion of tumor progression Suppression of T-cell activity Promotion of regulatory T cell-mediated immunosuppression Immunosuppression	
	Interleukins[33,38]	Promotion of inflammation Control of T-cell mediated immune responses Pleiotropic effects – may promote carcinogenesis or antitumoral immune responses	
Oncogenic signaling pathways	Disruption of IFN signaling[17,34,35,39,40]	Suppression of T-cell infiltration Impaired T-cell response Loss of IFNγ-mediated cell-growth inhibition Immune resistance and escape	

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