MaTOS™
Masters in Thoracic Oncology Summit
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Future Challenges for Immunotherapy in the Fight Against NSCLC

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FOX CHASE CANCER CENTER
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- “Immunotherapy” is a general term referring to the use of drugs that can modulate the immune system in a way that would control cancer
- Checkpoint inhibitors are the most successful drugs so far in this category
- Vaccines, monoclonal antibodies, BiTes etc. fall into this category
- Every drug now is considered to have immunogenic potential!
- Radiation is thought to have immunomodulatory effects

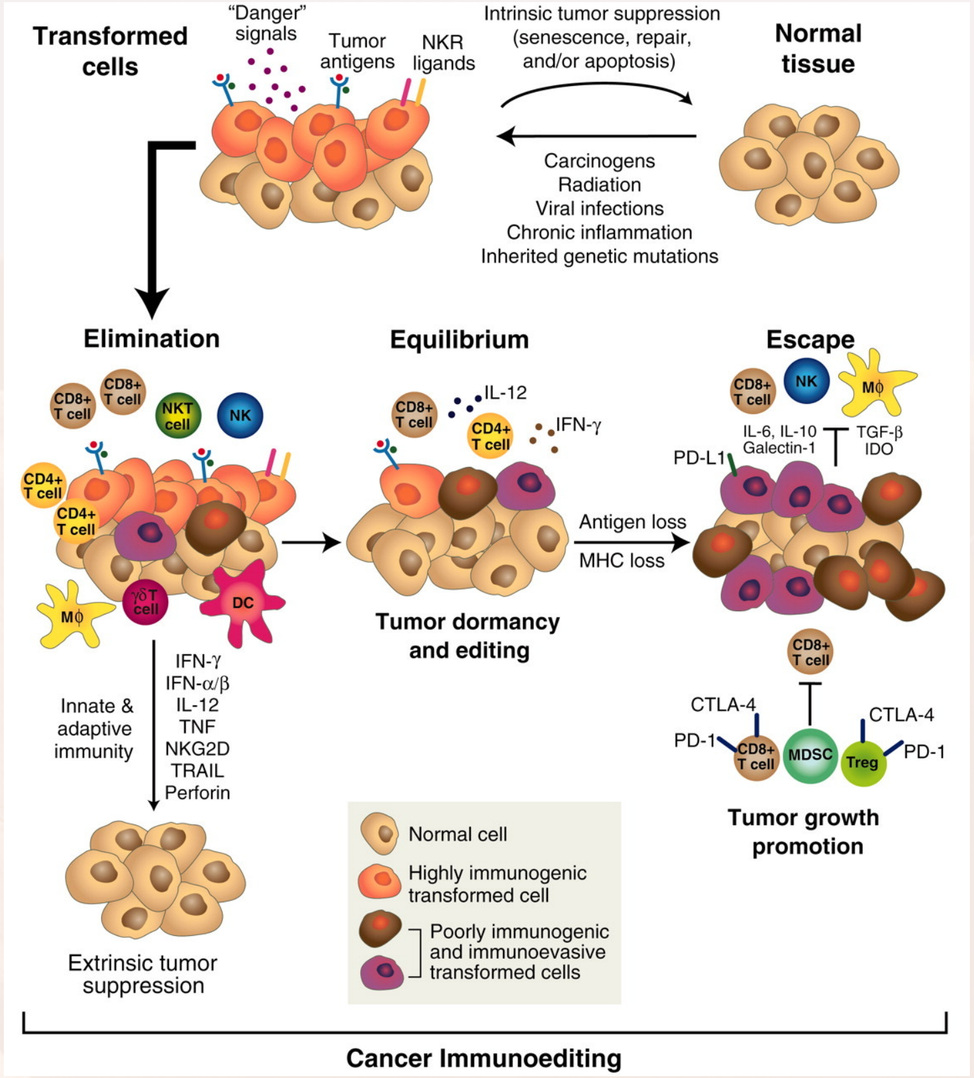
Father of Cancer Immunotherapy

- William B. Coley (1862-1936)
  - Preceded by Drs. W. Busch and F. Fehleisen observations of spontaneous malignant regression s/p erysipelas infection (Streptococcus pyogenes)
- Coley's toxin
  - CR rate ~ 22% (270/1200 patients)
- 1976: BCG vaccine for bladder cancer

Immune System in Cancer

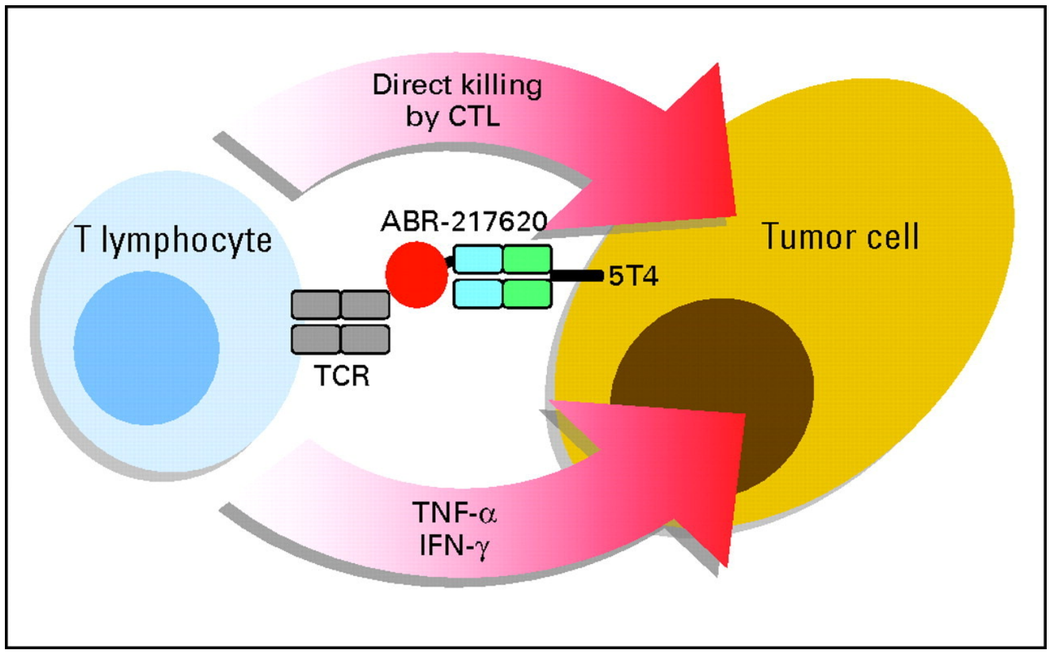
- **Disease control**
  - **Suppress tumor growth**
  - **Durable control**
- **Promote tumor progression**
  - **Select for cells which can grow in immunocompetent host**
  - **Control microenvironment, enhancing growth**
- **Escape recognition**
  - **Loss of MHC antigens**
  - **Inhibitor cytokine production (e.g. IL-10, TGF-β)**
  - **Lack of co-stimulatory effectors (e.g. CD80, CD86, CD40)**
  - **Expression of inhibitory molecules (PD-1, PD-L1)**
  - **Generation of regulatory/suppressor T-cells**
  - **Modulation of stromal environment (IDO production)**

Dunn G, Nature Immu, 2002; Igney FH, J Leuk Bio, 2002



Schreiber, Science;331,2011

Phase I Dose Escalation, Pharmacokinetic and Pharmacodynamic Study of Naptumomab Estafenatox Alone in Patients With Advanced Cancer and With Docetaxel in Patients With Advanced Non–Small-Cell Lung Cancer



- The immunotoxin naptumomab estafenatox was developed in an effort to activate and target the patient's own T cells to their tumor
- By fusing a superantigen (SAg) variant that activates T lymphocytes to the Fab moiety of a tumor-reactive monoclonal antibody.
- Naptumomab estafenatox targets the 5T4 tumor antigen, a 72-kDa oncofetal trophoblast protein expressed on many carcinomas, including renal cell carcinoma.
- The therapeutic effect is associated with activation of SAg-binding T cells.
- The SAg-binding T lymphocytes expand, differentiate to effector cells, and infiltrate the tumor.

Fig 1. ABR-217620 proposed mechanism of action. The ABR-217620 fusion protein binds to the 5T4 tumor-associated antigen and activates a T lymphocyte through its T-cell receptor (TCR). The T cell produces cytokines (tumor necrosis factor [TNF] –α and interferon [IFN]-γ) and executes direct tumor killing if it is a cytotoxic T lymphocyte.

Published in: Hossein Borghaei; Katherine Alpaugh; Gunnar Hedlund; Göran Forsberg; Corey Langer; Andre Rogatko; Robert Hawkins; Svein Dueland; Ulrik Lassen; Roger B. Cohen; *Journal of Clinical Oncology* 2009 274116-4123.
DOI: 10.1200/JCO.2008.20.2515
Eisen, et al, Curr Oncol Rep. 2014 Feb;16(2):370

Phase I Dose Escalation, Pharmacokinetic and Pharmacodynamic Study of Naptumomab Estafenatox Alone in Patients With Advanced Cancer and With Docetaxel in Patients With Advanced Non–Small-Cell Lung Cancer

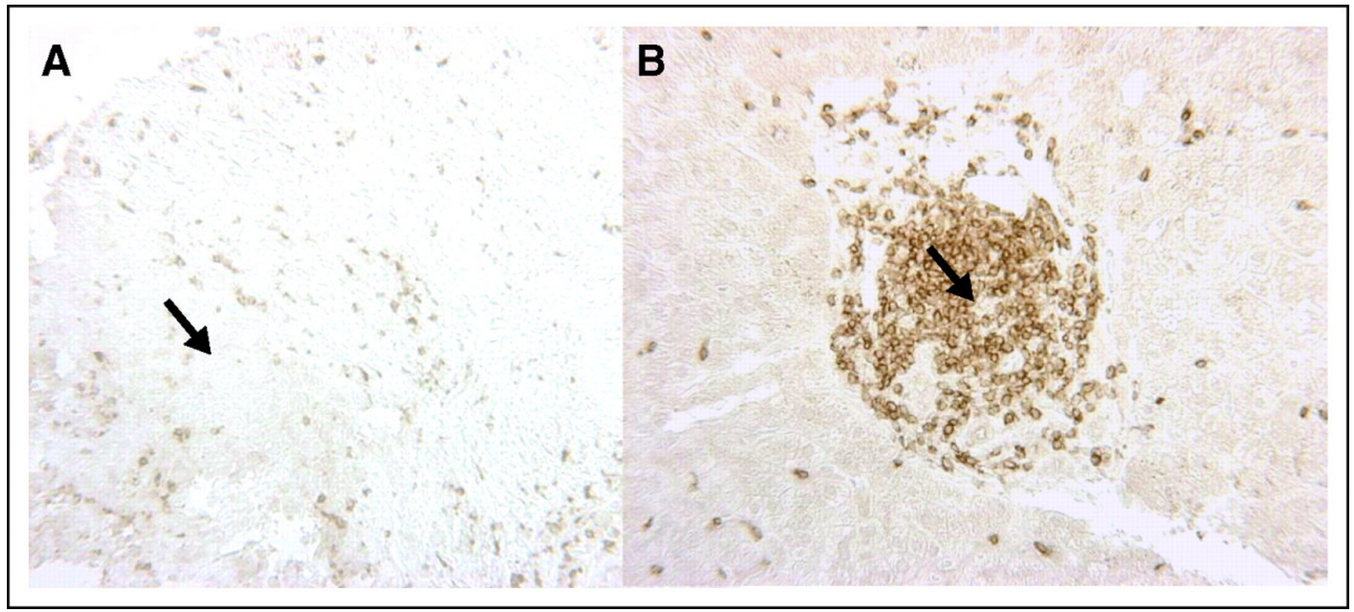


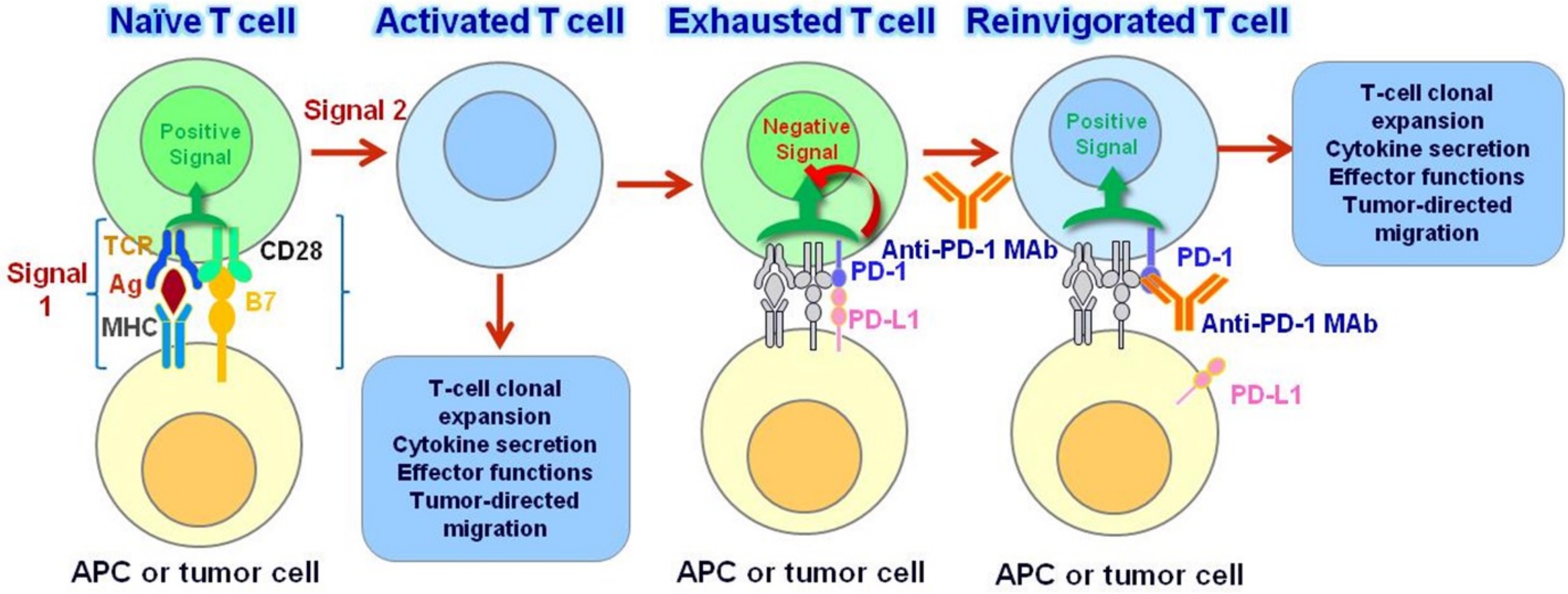
Fig 3. Immunohistochemistry for T-lymphocyte (anti-CD3) infiltration in biopsies taken before treatment (archival tissue) and at the third day of the second cycle treatment with ABR-217620 for patient number 2. The T lymphocytes stain brown and the arrows indicate unstained tumor cells. This patient had a partial response that continues at 30+ months.

Published in: Hossein Borghaei; Katherine Alpaugh; Gunnar Hedlund; Göran Forsberg; Corey Langer; Andre Rogatko; Robert Hawkins; Svein Dueland; Ulrik Lassen; Roger B. Cohen; *Journal of Clinical Oncology* 2009 274116-4123.
DOI: 10.1200/JCO.2008.20.2515

PD(L)-1 and CTLA-4 inhibitors

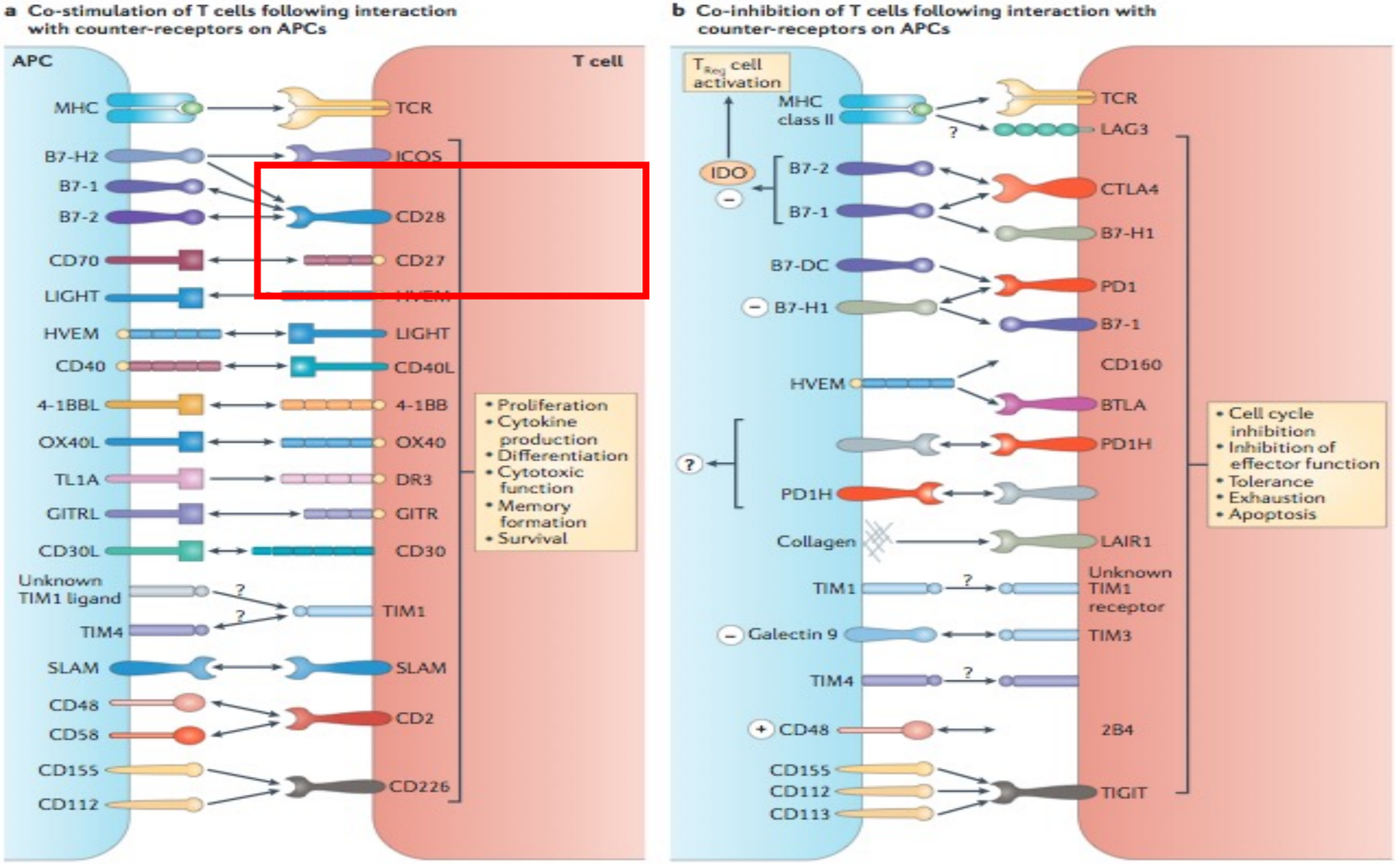
A New Era

Activating and Inhibiting Signals



Topalian SL, et al. *N Engl J Med*. 2012;366(26):2443-2454.

Immunologic Synapsis



Chen L, et al. *Nat Rev Immunol*. 2013;13(4):227-242.

CheckMate 057 (NCT01673867)

- Stage IIIB/IV non-SQ NSCLC
- ECOG PS 0–1
- Failed one prior platinum-based chemotherapy
- Prior maintenance therapy allowed[a]
- Prior TKI therapy allowed for known *ALK* translocation or *EGFR* mutation

(N = 582)

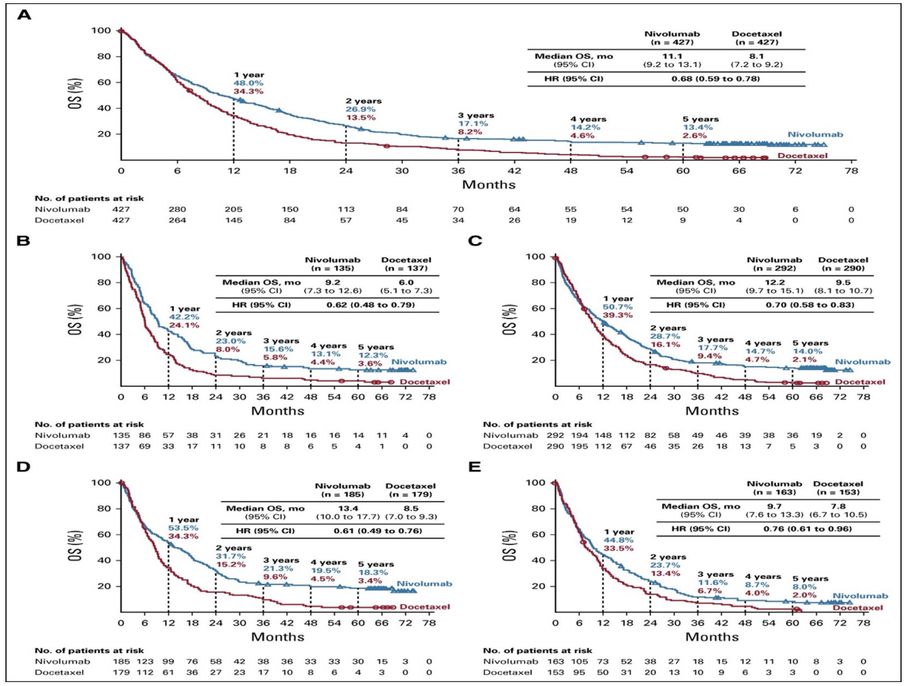
Randomize 1:1

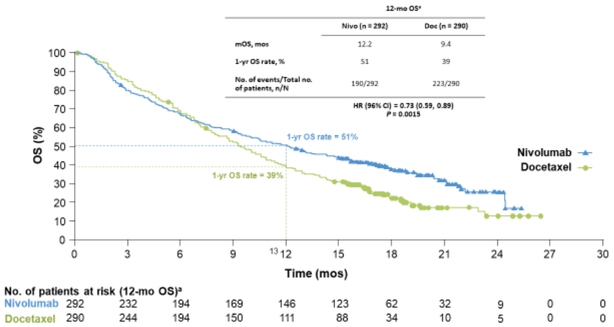
Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
(n = 292)

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
(n = 290)

- Primary end point[b]
  - OS
- Additional end points[c]
  - ORR
  - PFS
  - Safety
  - Efficacy by tumor PD-L1 expression
  - PROs (LCSS)

Patients stratified by prior maintenance therapy and line of therapy (second-line vs third-line)





- Minimum follow-up for 12-mo OS rate, 13.2 mos

[a]Based on a March 18, 2015, DBL.
Symbols represent censored observations.

	Nivolumab (n = 287)		Docetaxel (n = 268)	
	Any grade	Grade 3–4[a]	Any grade	Grade 3–4[a]
	Percentage (%) of patients with an event			
Any event	69	**10**	88	**54**
Fatigue	16	1	29	5
Nausea	12	1	26	1
Decreased appetite	10	0	16	1
Asthenia	10	<1	18	2
Diarrhea	8	1	23	1
Peripheral edema	3	0	10	<1
Myalgia	2	<1	11	0
Anemia	2	<1	20	3
Alopecia	<1	0	25	0
Neutropenia	<1	0	31	27
Febrile neutropenia	0	0	10	10
Leukopenia	0	0	10	8

Borghaei et al, NEJM, 2015; Borghaei, JCO, 2021

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KEYNOTE-024 5-Year Survival Update: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced NSCLC

J. Brahmer, ESMO 2020

Key eligibility criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

Pembrolizumab
200 mg IV Q3W
(2 years)

Platinum-Doublet Chemotherapy
(4-6 cycles)

PD[a] - - → **Pembrolizumab**
200 mg Q3W
for 2 years

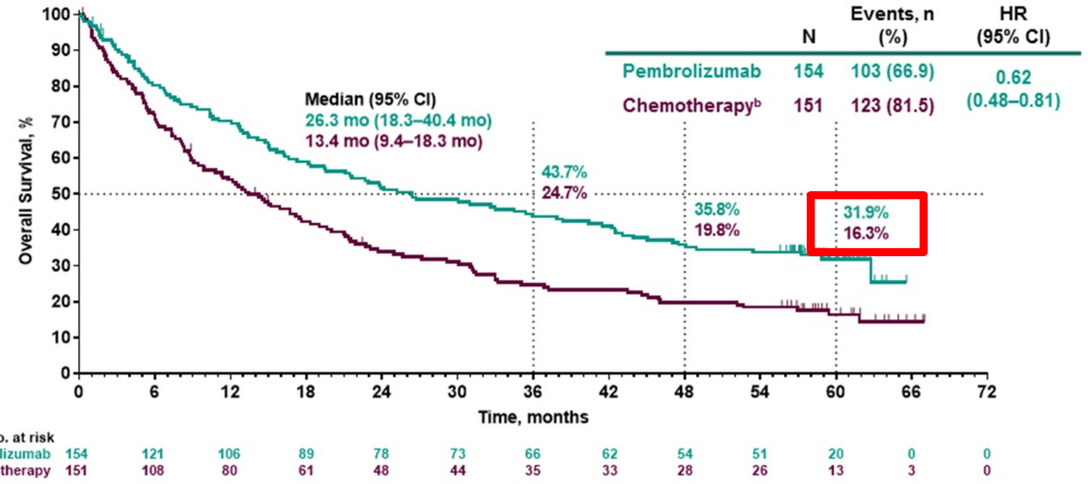
Key endpoints

- Primary: Progression-free survival (PFS) (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: Duration of response (DoR)

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

J Brahmer. ESMO 2020

Overall Survival[a]



[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

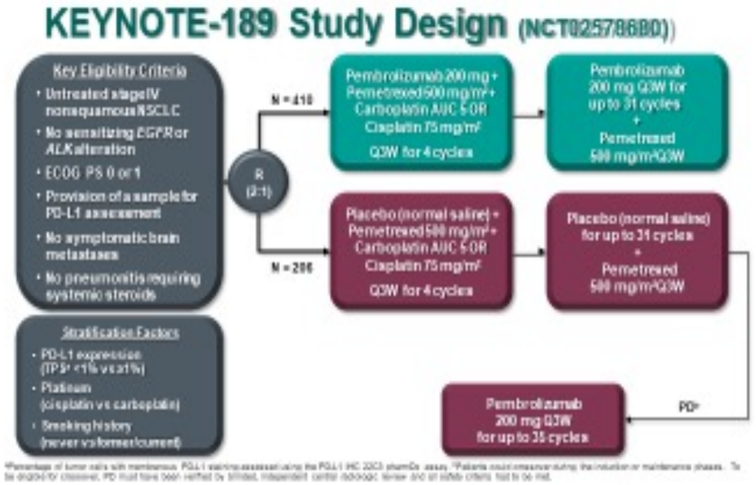
J Brahmer. ESMO 2020

Baseline Characteristics

Characteristic	Pembrolizumab N = 154	Chemotherapy N = 151	35 Cycles (2 Years) of Pembrolizumab N = 39[a]	Second Course of Pembrolizumab N = 12[b]
Age, y, median (range)	64.5 (33–90)	66.0 (38–85)	61.0 (43–80)	60.0 (43–77)
Male	92 (59.7)	95 (62.9)	25 (64.1)	8 (66.7)
ECOG PS 1	99 (64.3)	98 (64.9)	23 (59.0)	9 (75.0)
East Asian enrollment site	21 (13.6)	19 (12.6)	8 (20.5)	3 (25.0)
Squamous histology	29 (18.8)	27 (17.9)[c]	2 (5.1)	1 (8.3)
Current/former smoker	149 (96.8)	132 (87.4)	37 (94.9)	12 (100.0)
Treated brain metastases	18 (11.7)	10 (6.6)	9 (23.1)	1 (8.3)
Prior neoadjuvant therapy	3 (1.9)	1 (0.7)	0	0
Prior adjuvant therapy	6 (3.9)	3 (2.0)	0	0

[a]Includes only those patients initially allocated to pembrolizumab who received 35 cycles (2 years) of pembrolizumab according to actual exposure assessment. [b]Includes only those patients initially allocated to pembrolizumab who received a second course of pembrolizumab therapy according to actual exposure assessment. [c]Includes patients with squamous cell carcinoma and poorly differentiated squamous cell carcinoma. Data in table are n (%), unless otherwise noted. Data cutoff: June 1, 2020.

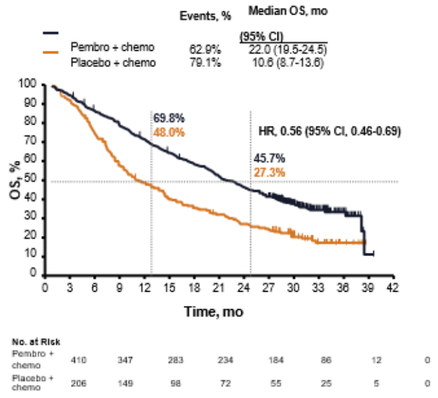
Chemo-IO combination



Gandhi L, et al. AACR Annual Meeting; Chicago, Illinois, April 14-18, 2018; Abstract CT075

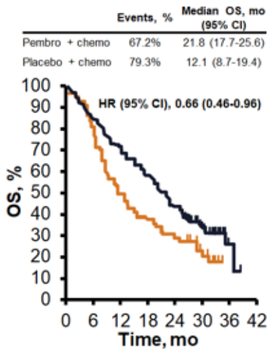
KEYNOTE-189 Final Analysis: OS by PD-L1 status[1]

OS PD-L1 ≥50%



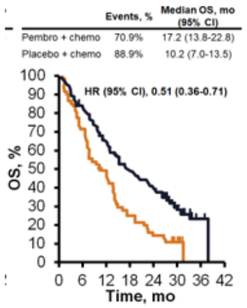
OS: HR = 0.58
(95% CI, 0.46-0.89
Median OS: 22 vs. 10.6 mo

OS PD-L1 1-49%



OS: HR = 0.66
(95% CI, 0.46-0.96)
Median OS: 21.8 vs 12.1 mo

OS PD-L1 <1%

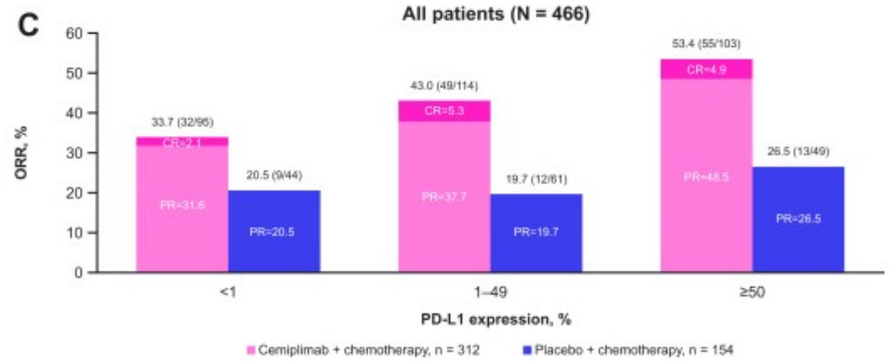


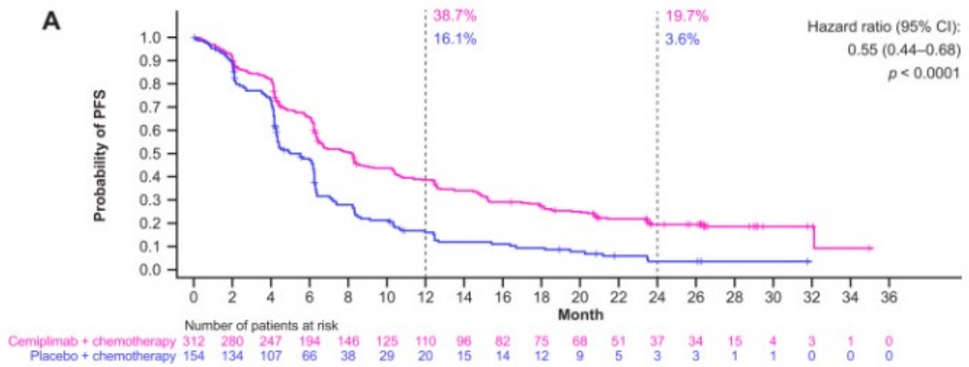
OS: HR = 0.51
(95% CI, 0.36-0.71)
Median OS: 17.2 vs 10.2 mo

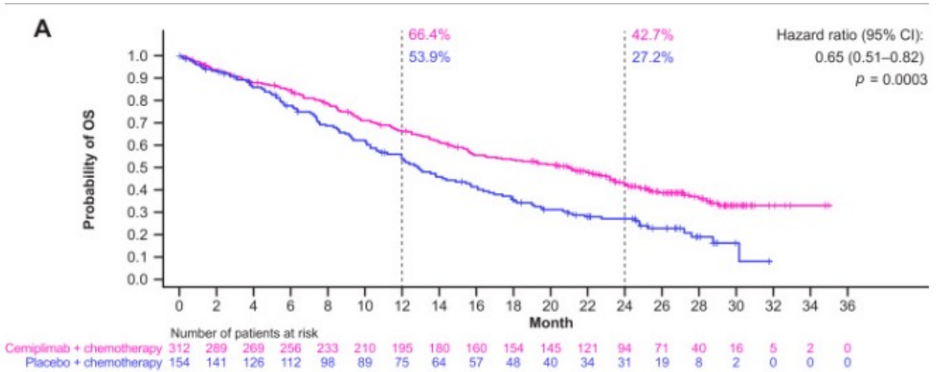
Forde, WCLC 2021

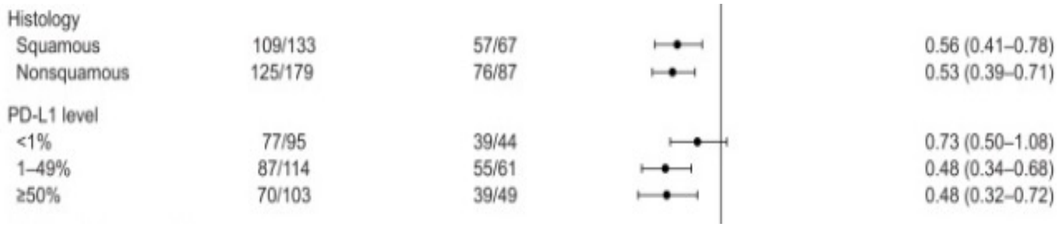
1. Rodriguez-Abreu D et al. ASCO 2020. Abstract 9582.

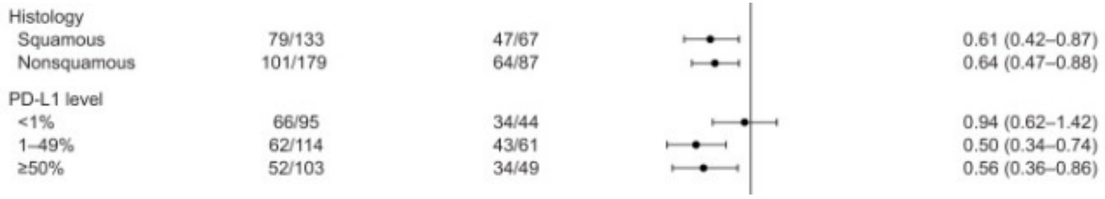
Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial





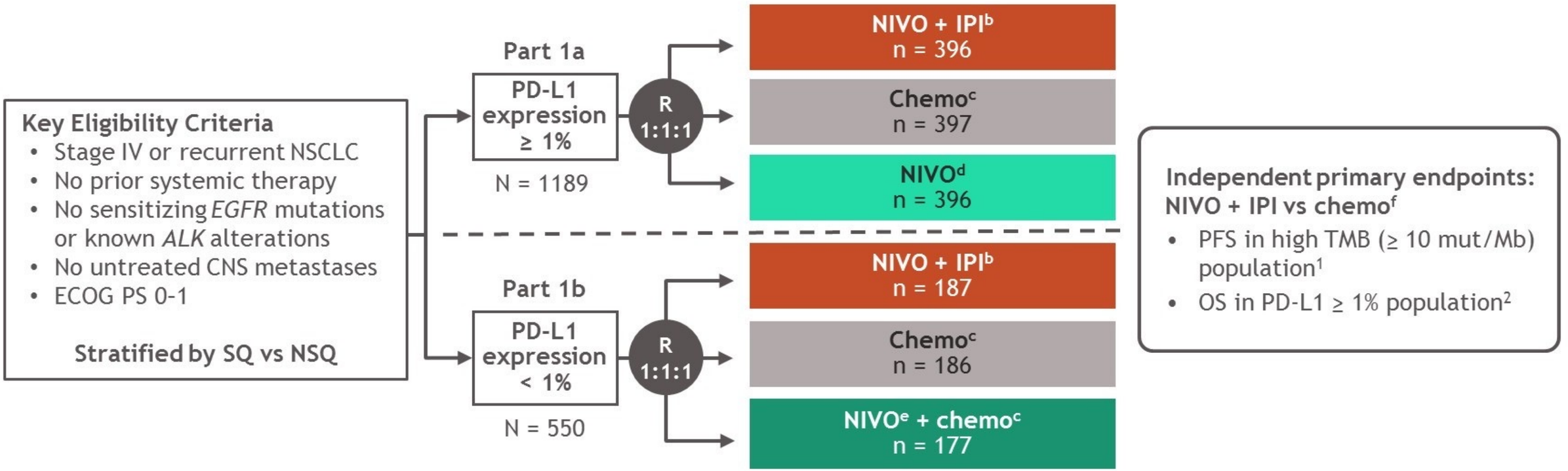






Makharadze, JTO, June 2023

CheckMate 227[a] Part 1 study design



Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [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]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

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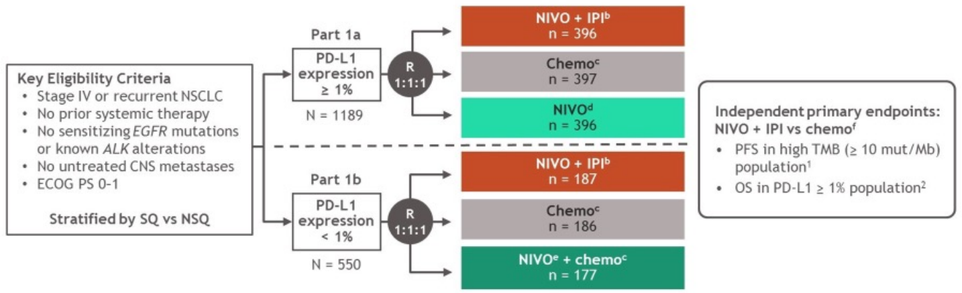

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1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

CheckMate-227, Five Year OS

Figure 4. OS in patients with tumor PD-L1 ≥ 1% by histology

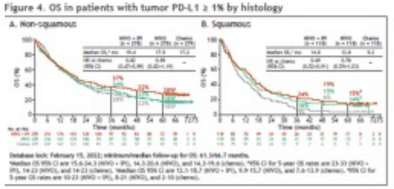


Figure 5. OS in patients with tumor PD-L1 < 1% by histology

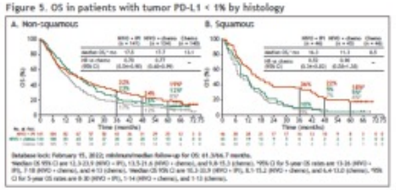
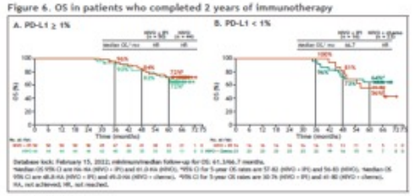


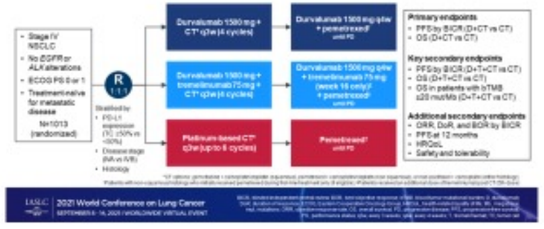
Figure 6. OS in patients who completed 2 years of immunotherapy



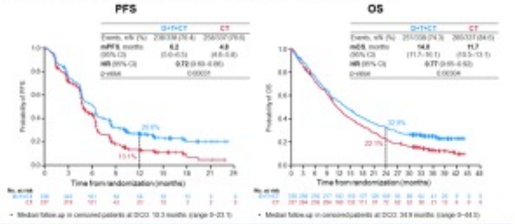
Borghaei, NACLC, Chicago, 2022, Brahmer, JCO, 2022

POSEIDON Study Design

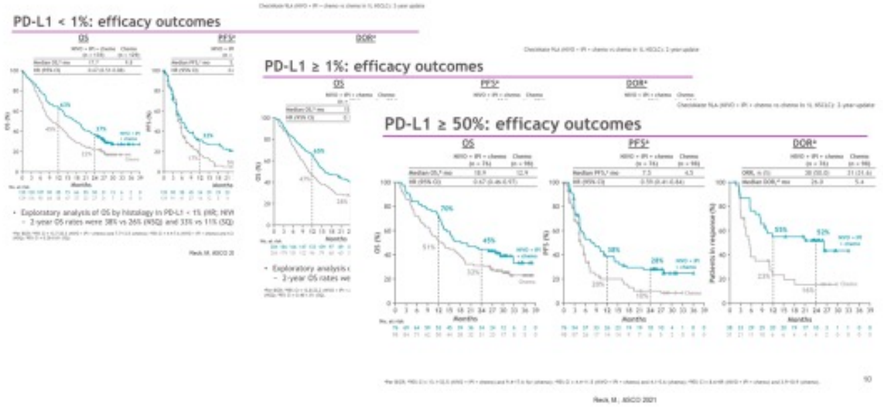
Phase 3, global, randomized, open-label, multicenter study



Durvalumab + Tremelimumab + CT vs CT: PFS and OS



CheckMate-9LA



TROPION-Lung02: Datopotamab Deruxtecan + Pembrolizumab+ChemoT

Key eligibility

- Advanced/metastatic NSCLC
- Dose confirmation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[c]
  - No prior therapy (cohorts 3-6)[c]

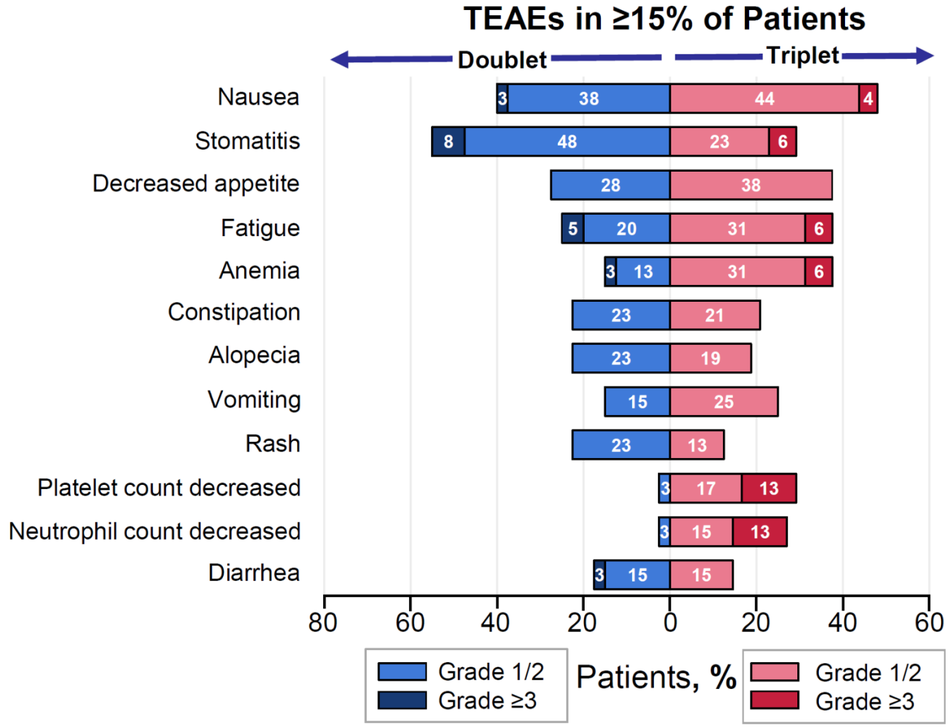
	Dato-DXd IV Q3W	+	pembro IV Q3W	+	platinum CT IV Q3W	
Cohort 1 (n=20)[d]:	4 mg/kg	+	200 mg			"Doublet"
Cohort 2 (n=20)[d]:	6 mg/kg	+	200 mg			
Cohort 3 (n=17)[d]:	4 mg/kg	+	200 mg	+	carboplatin AUC 5	"Triplet"
Cohort 4 (n=20)[d]:	6 mg/kg	+	200 mg	+	carboplatin AUC 5	
Cohort 5 (n=7)[d]:	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m²	
Cohort 6 (n=4)[d]:	6 mg/kg	+	200 mg	+	cisplatin 75 mg/m²	

- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and anti-drug antibodies

Safety

Events, n (%)	Doublet (n=40)	Triplet (n=48)
TEAEs	37 (93%)	47 (98%)
Study treatment-related[a]	33 (83%)	46 (96%)
Grade ≥3 TEAEs	16 (40%)	29 (60%)
Study treatment-related[a]	14 (35%)	26 (54%)
Serious TEAEs	9 (23%)	13 (27%)
Study treatment-related	4 (10%)	7 (15%)
TEAEs associated with		
Death[b]	2 (5%)	1 (2%)
Discontinuation due to any drug	9 (22%)	9 (19%)
Discontinuation due to Dato-DXd	6 (15%)	5 (10%)
ILD adjudicated as drug related[c]		
Grade 1/2	2 (5%)	0
Grade 3	1 (3%)	1 (2%)

Data cutoff: May 2, 2022.
ILD, interstitial lung disease; TEAE, treatment emergent adverse event



Levy B, et al. WCLC 2022

Antitumor Activity

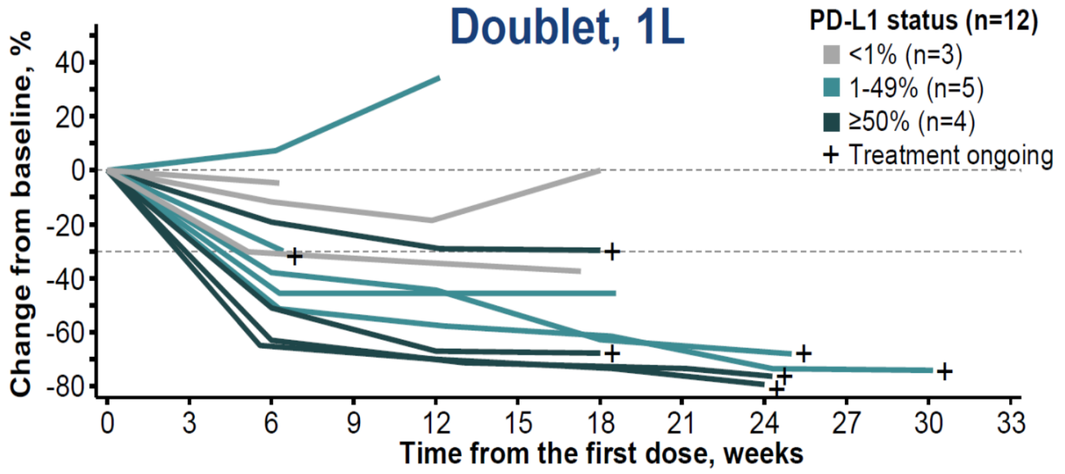
In the overall population:

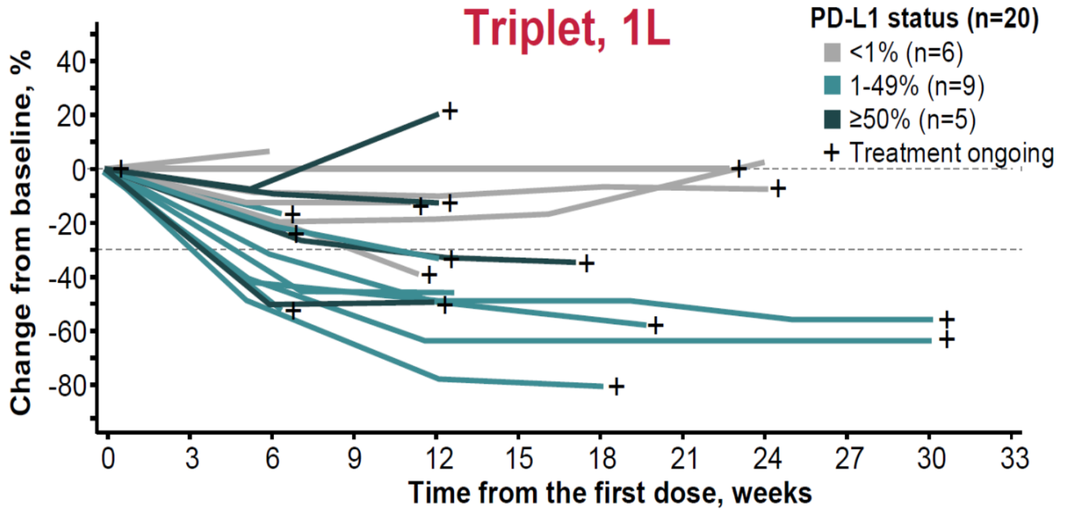
ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%



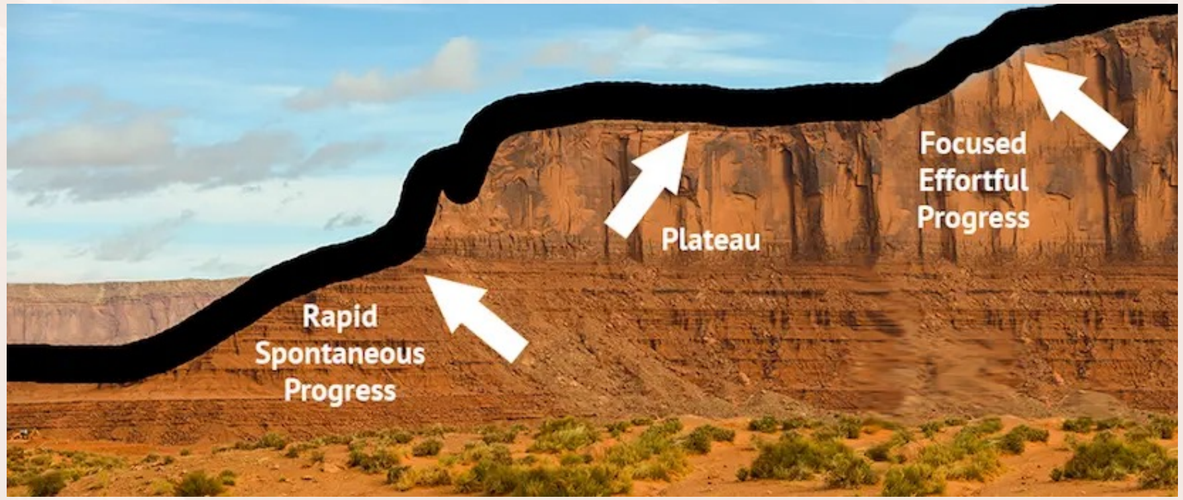


Data cutoff: May 2, 2022.
BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease.
[a] By investigator. [b] BOR is based on response evaluable patients who have ≥1 postbaseline tumor assessment or discontinued.

Levy B, et al. Presented at: WCLC;2022.

First Line Treatment Paradigm

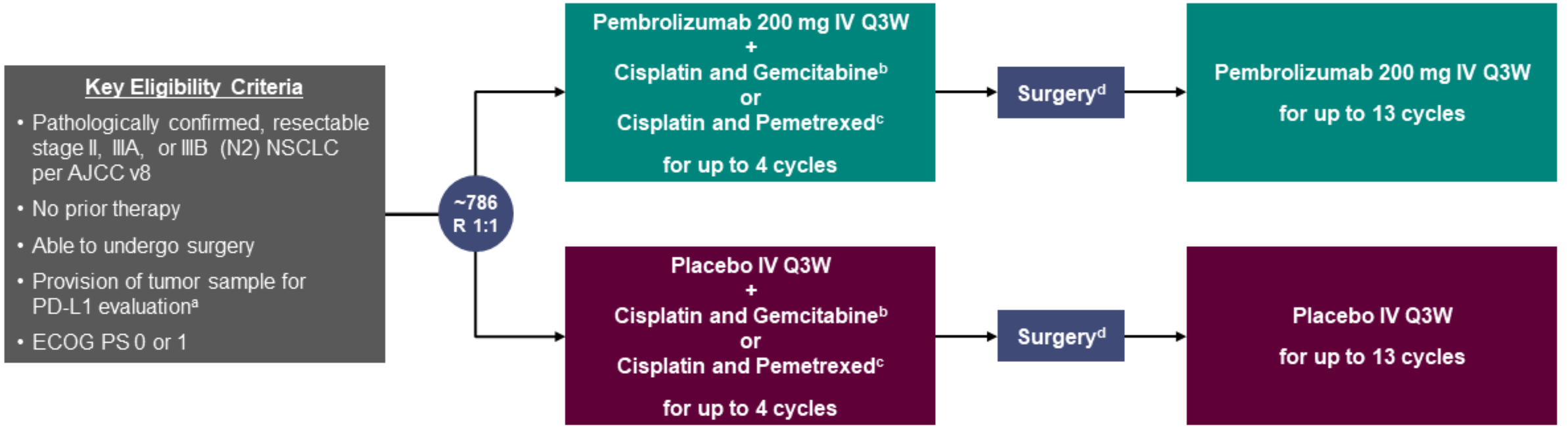
- In the metastatic setting we appeared to have reached a plateau
- Studies with TIGIT, LAG-3 and other checkpoint inhibitors combined with a PD(L)-1 inhibitor could potentially point to a new direction at least for specific subgroups
- Search for a better biomarker for identifying patients who would benefit from various treatment options is ongoing
- Assessment of MRD and either escalation or de-escalation treatment could be another useful approach



Early Stage

KEYNOTE-671 Study Design

Randomized, Double-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

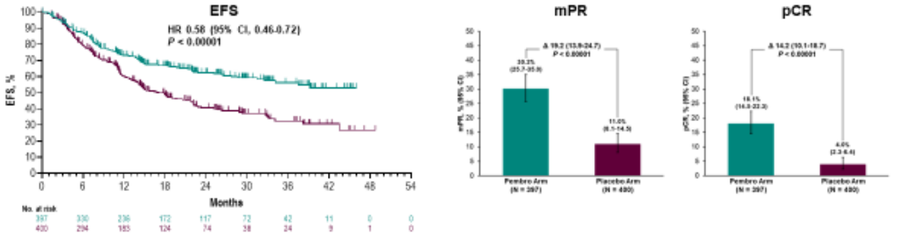
Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

KEYNOTE-671 Results: Interim Analysis 1

Median Follow-Up[a]: 25.2 months (range, 7.5-50.6)

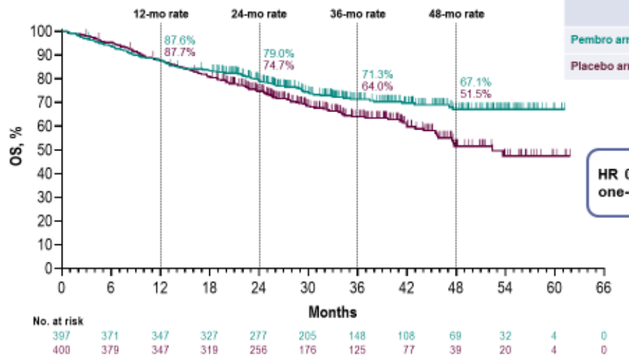
- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components



[a]Defined as time from randomization to data cutoff date of July 29, 2022.
Wakelee H et al. *N Engl J Med* 2023;389:491-503.

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

OS defined as time from randomization to death from any cause. [a]Significance boundary at IA2, one-sided *P* = 0.00543.
Data cutoff date for IA2: July 10, 2023.

Overall Survival in Subgroups, IA2

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Age			
<65 y	54/221	82/214	0.57 (0.40-0.80)
≥65 y	56/176	62/186	0.96 (0.67-1.38)
Sex			
Female	21/118	30/116	0.69 (0.39-1.20)
Male	89/279	114/284	0.73 (0.55-0.96)
Race			
White	73/250	97/239	0.66 (0.49-0.90)
All others	34/134	39/145	0.93 (0.59-1.48)
Geographic region			
East Asia	32/123	30/121	1.05 (0.64-1.73)
Not east Asia	78/274	114/279	0.63 (0.48-0.85)
Smoking status			
Current	31/96	48/103	0.59 (0.38-0.93)
Former	69/247	87/250	0.76 (0.56-1.05)
Never	10/54	9/47	1.00 (0.41-2.46)
Histology			
Nonsquamous	49/226	64/227	0.73 (0.50-1.06)
Squamous	61/171	80/173	0.71 (0.51-0.99)

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Clinical stage			
II	26/118	39/121	0.67 (0.41-1.10)
IIIA	62/217	79/224	0.74 (0.53-1.03)
IIIB	22/62	26/55	0.69 (0.39-1.22)
N status			
cN0	40/148	52/142	0.70 (0.46-1.06)
cN1	21/81	24/71	0.74 (0.41-1.33)
cN2	49/168	68/187	0.74 (0.52-1.07)
PD-L1 TPS			
≥50%	23/132	39/134	0.55 (0.33-0.92)
1-49%	35/127	44/116	0.69 (0.44-1.07)
<1%	52/138	61/151	0.91 (0.63-1.32)
***EGFR* mutation**			
No	20/111	33/124	0.64 (0.37-1.11)
Yes	1/14	5/19	0.24 (0.03-2.03)
Unknown	89/272	106/257	0.75 (0.56-0.99)
***ALK* translocation**			
No	22/104	38/132	0.70 (0.41-1.18)
Unknown	87/281	105/259	0.72 (0.54-0.96)

Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA2: July 10, 2023.

Exposure and AE Summary Across Treatment Phases, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)

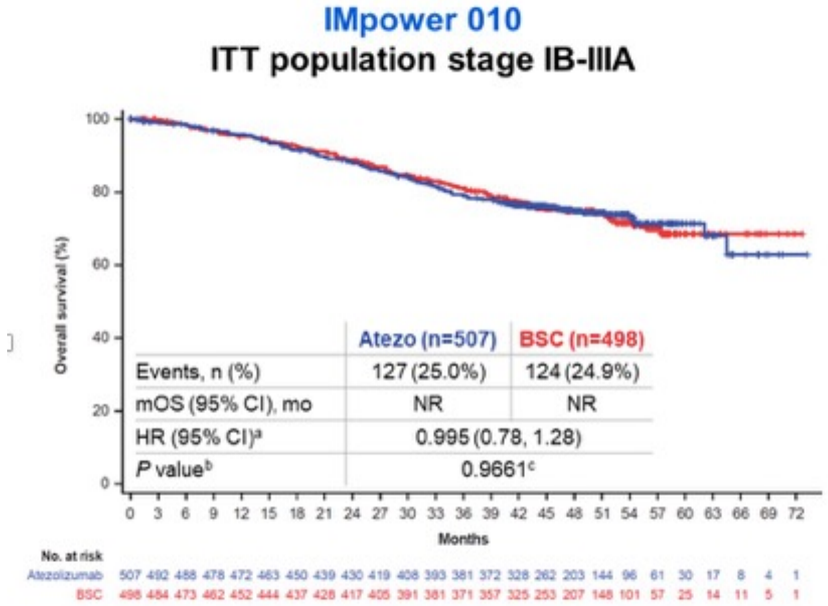
	Pembro Arm (n = 396)	Placebo Arm (n = 399)
Exposure		
Study days on pembro or placebo, median (range)	375.5 days (1-728)	337.0 days (1-644)
No. pembro or placebo administrations, median (range)	15 (1-17)	12 (1-17)
Treatment-related AEs[a]	383 (96.7%)	381 (95.5%)
Grade 3-5	179 (45.2%)	151 (37.8%)
Serious	73 (18.4%)	58 (14.5%)
Led to death	4 (1.0%)[b]	3 (0.8%)[c]
Led to discontinuation of all study treatment	54 (13.6%)	21 (5.3%)
Immune-mediated AEs and infusion reactions	103 (26.0%)	36 (9.0%)
Grade 3-5	26 (6.6%)	6 (1.5%)
Serious	24 (6.1%)	6 (1.5%)
Led to death	1 (0.3%)[d]	0
Led to discontinuation of all study treatment	23 (5.8%)	3 (0.8%)

[a]Considered by the investigator to be related to chemotherapy, pembrolizumab, and placebo. [b]AEs leading to death (n = 1 each): atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death (no new treatment-related deaths vs IA1). [c]AEs leading to death (n = 1 each): acute coronary syndrome, pneumonia, and pulmonary hemorrhage (no new treatment-related deaths vs IA1). [d]AE leading to death: pneumonitis (recorded in the database as immune-mediated lung disease; no new immune-mediated deaths vs IA1). Data cutoff date for IA2: July 10, 2023.

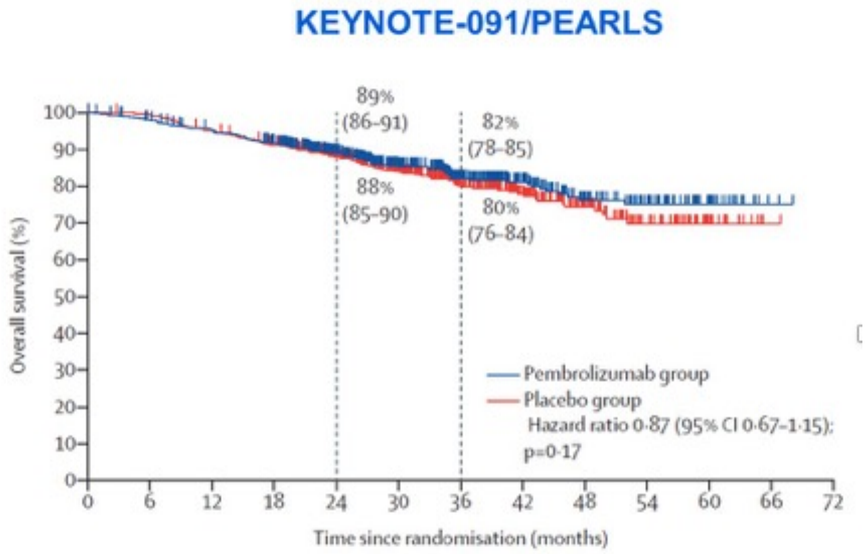
J. Spicer, ESMO 2023

surgery → chemotherapy → immunotherapy

Trial	DFS	OS (immature)
Impower010 (PD-L1+)	NR vs 35 mo	HR 0.66 (0.5-0.88)
PEARLS	54 vs 42 mo	HR 0.87 (0.67-1.15)

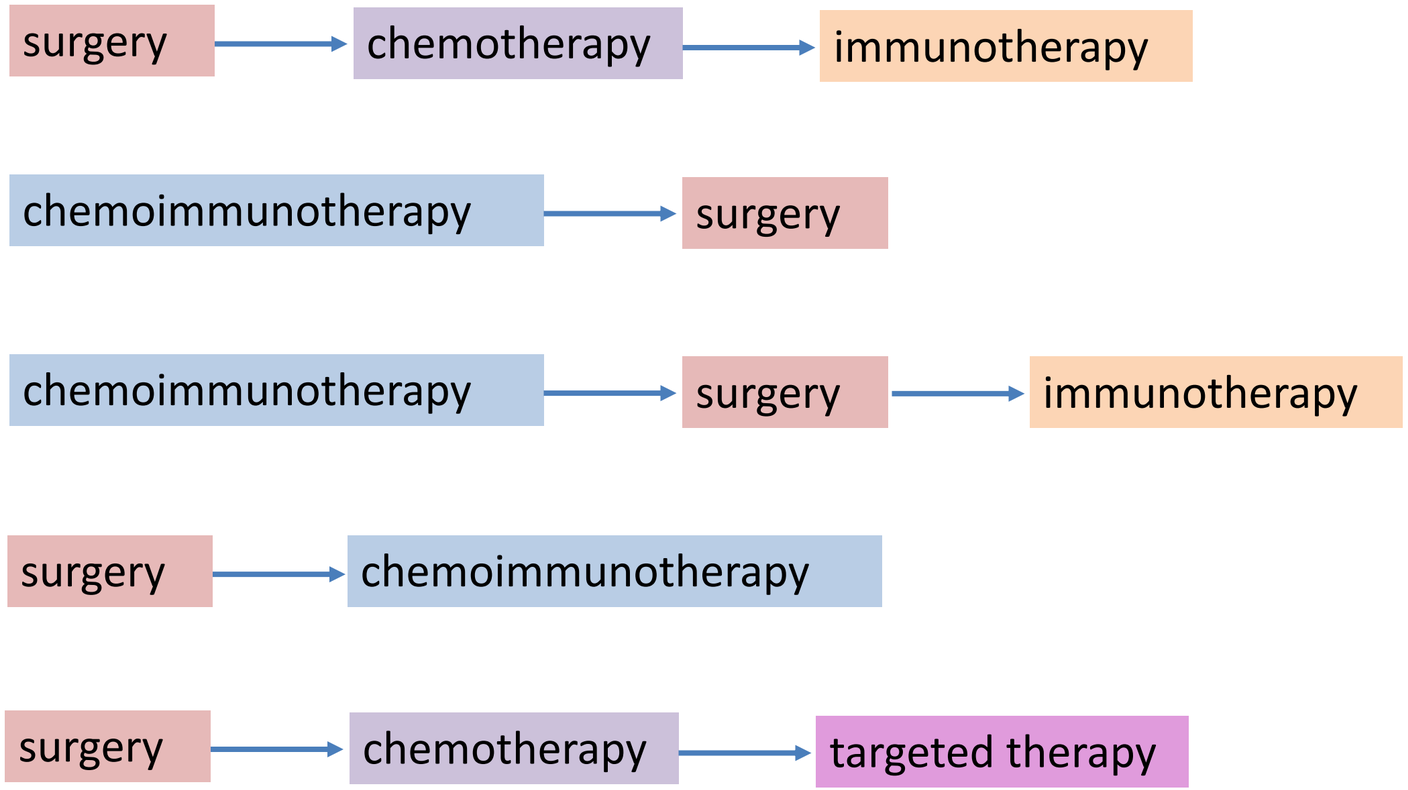


Median Follow Up: 45 months (interim analysis)



Median Follow Up: 35.6 months (interim analysis)

Jessica Bauman, MD; ASCO Direct, Philadelphia 2023



And for which patient population?

Jessica Bauman, MD; ASCO Direct, Philadelphia 2023

Second Line and Beyond
Is there a clear path?

Overcoming Resistance to Immunotherapy

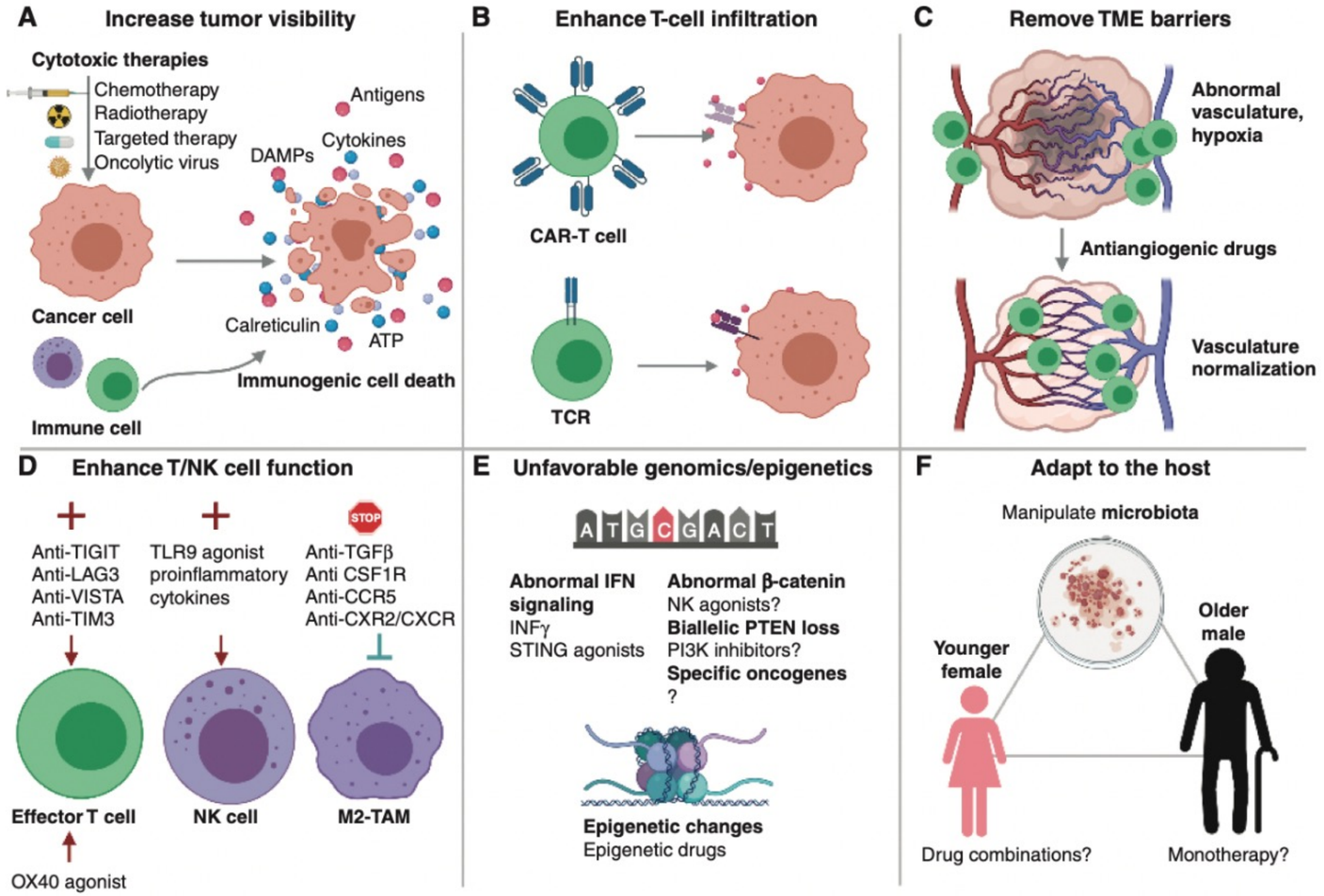
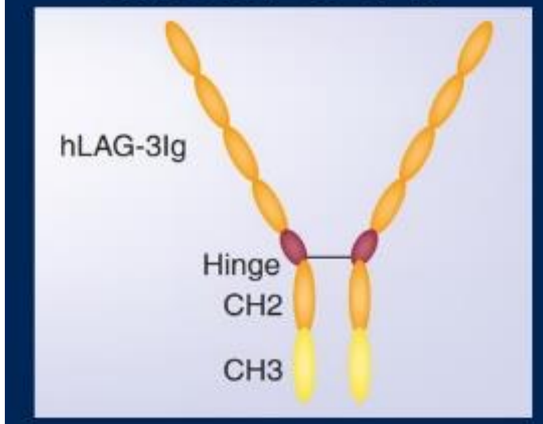


Figure 4. Overcoming resistance to immunotherapy. **A,** Increase tumor visibility. **B,** Enhance T-cell infiltration. **C,** Remove TME barriers. **D,** Enhance T-cell/NK-cell function. **E,** Unfavorable genomics/epigenetics. **F,** Adapt to the host.

Aldea M, et al. *Cancer Discov*. 2021;11(4):874-899.

Eftilagimod alpha (efti) – soluble LAG-3

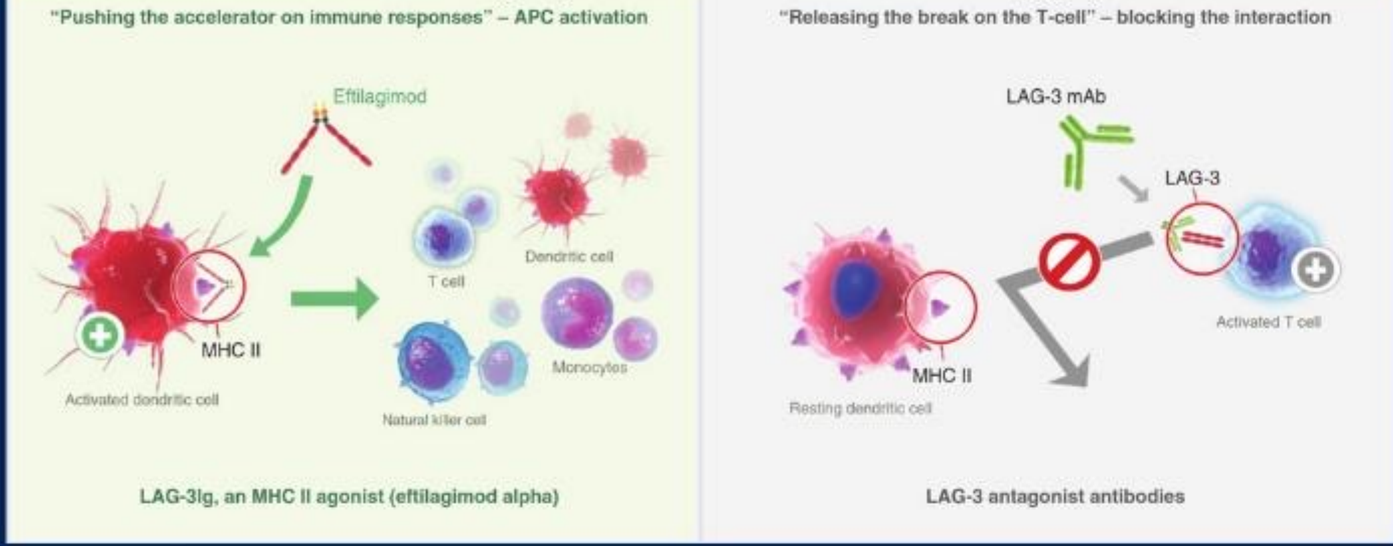
STRUCTURE OF EFTI[4]



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

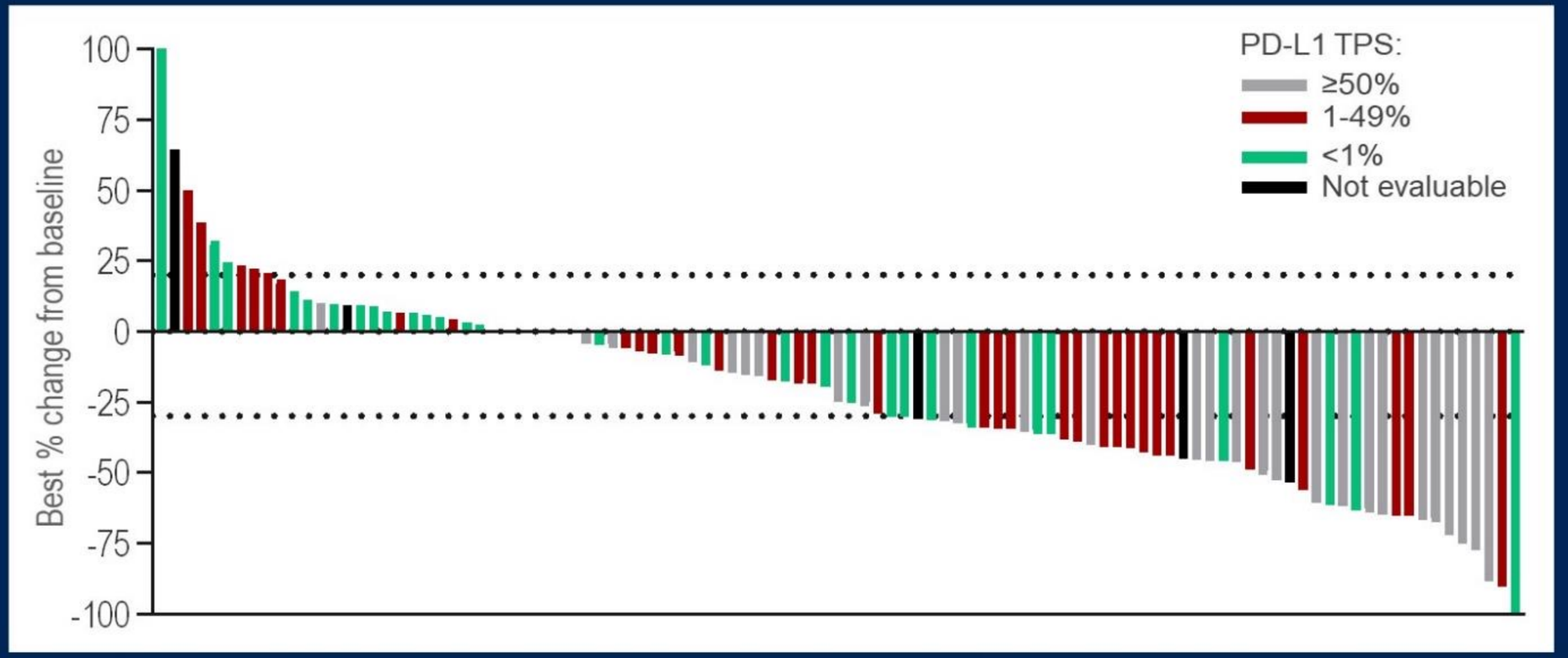


MoA: mechanism of action
PD-1/PD-L1: programmed death-(ligand) 1
s.c.: subcutaneous

[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.

Felip E, et al. Presented at: ASCO;2022.

Efficacy – Waterfall plot[1] – TACTI-002



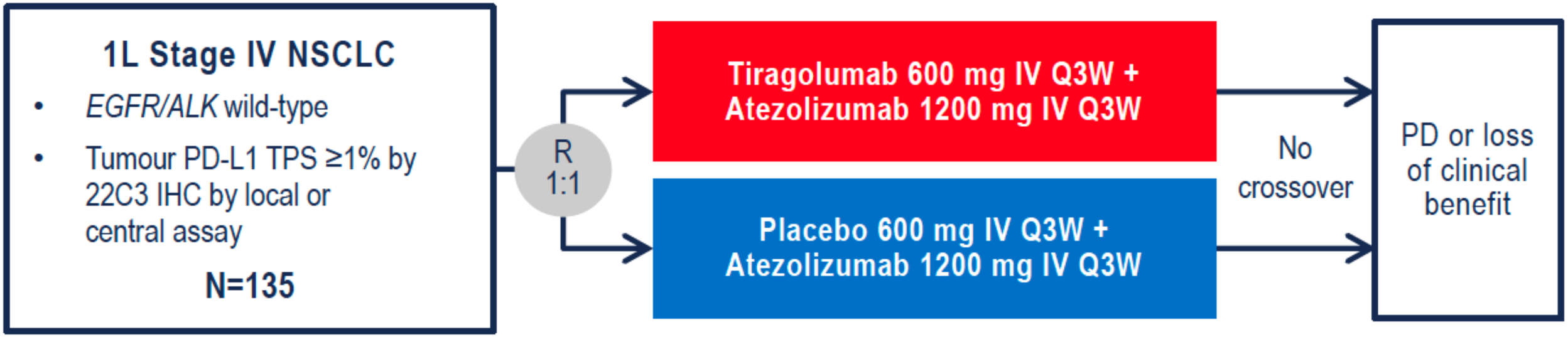
[1] all patients with ≥1 post-baseline CT scan n=103; [2] PD-L1 assessed by central assessment (Dako kit); n=79; [3] local assessment included due to non evaluable central assessment results, n=19; [4] no results available for neither central nor local testing, n=5.

- 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

Felip E, et al. Presented at: ASCO;2022.

CITYSCAPE: Randomized Phase 2 Study of Tiragolumab + Atezolizumab in PD-L1+ Patients with NSCLC



Stratification factors
- PD-L1 TPS (1–49% vs ≥50%)
- Histology (non-squamous vs squamous)
- Tobacco use (yes vs no)

Co-primary endpoints
- ORR and PFS

Key secondary endpoints
- Safety, DOR, OS

Exploratory endpoints
- Efficacy analysis by PD-L1 status, PROs

Primary analysis[1]
- Cut-off date of 30 June 2019
- Median follow-up of 5.9 months

Updated analysis
- Follow-up performed to assess safety and efficacy
- Cut-off date of 16 August 2021
- Median follow-up of 30.4 months

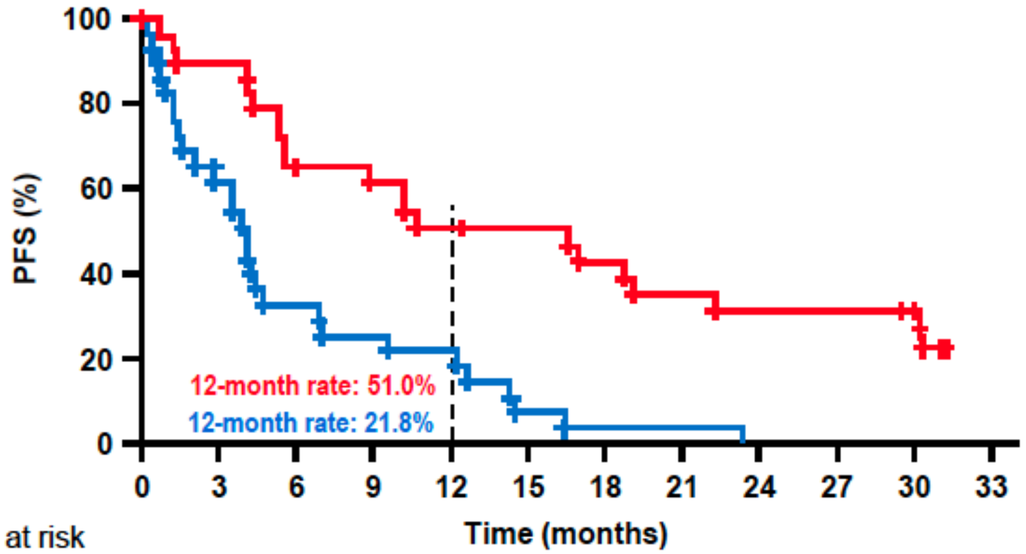
IHC, immunohistochemistry; PROs, patient-reported outcomes; TPS, tumor proportion score.

Rodriguez-Abreu D, et al. Presented at: ASCO;2020.

Investigator-Assessed PFS: PD-L1 Subgroups

PD-L1 TPS ≥50% (n=58)

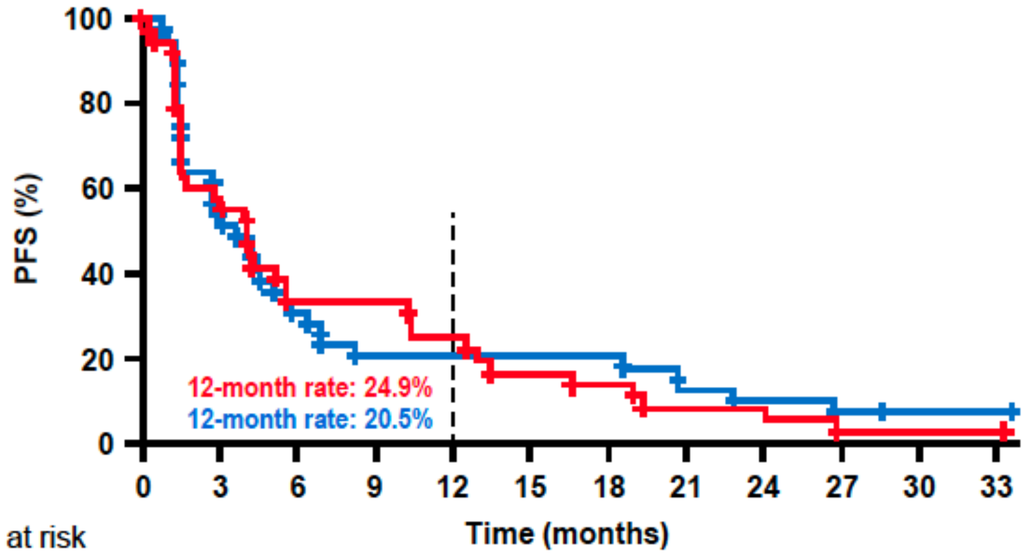
	Events n (%)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, %	Median DOR, months (95% CI)
Tira + atezo	21 (72.4)	16.6 (5.5–22.3)	0.29* (0.15–0.53)	69.0	15.7 (9.1–NE)
Placebo + atezo	28 (96.6)	4.1 (2.1–6.8)		24.1	8.2 (5.6–10.4)



No. at risk												
T + A	29	26	19	17	14	13	11	9	8	8	7	NE
P + A	29	17	9	7	6	2	1	1	NE	NE	NE	NE

PD-L1 TPS 1–49% (n=77)

	Events n (%)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, %	Median DOR, months (95% CI)
Tira + atezo	36 (94.7)	4.0 (1.6–5.6)	1.07* (0.67–1.71)	15.8	17.8 (8.3–24.2)
Placebo + atezo	36 (92.3)	3.6 (1.4–5.5)		17.9	18.8 (15.9–22.8)

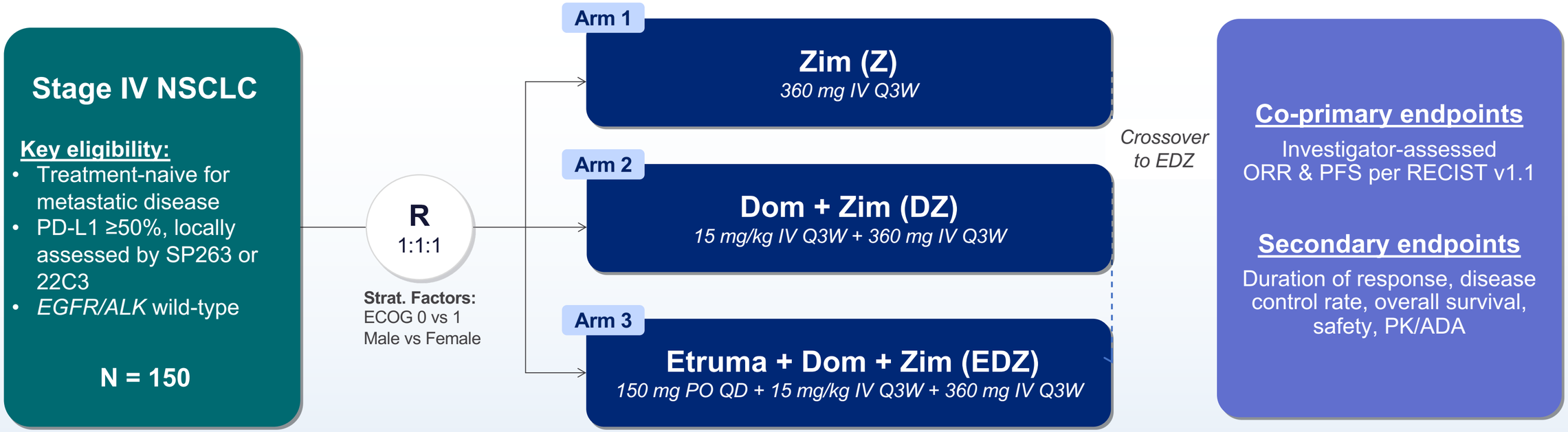


No. at risk												
T + A	38	22	12	12	9	6	5	3	3	1	1	1
P + A	39	21	12	8	8	8	8	5	4	3	2	2

*Unstratified.
Updated analysis data cut-off: 16 August 2021 (median follow-up: 30.4 months)
PD-L1 status determined by 22c3 IHC assay.

Rodriguez-Abreu D, et al. Presented at: ASCO;2020.

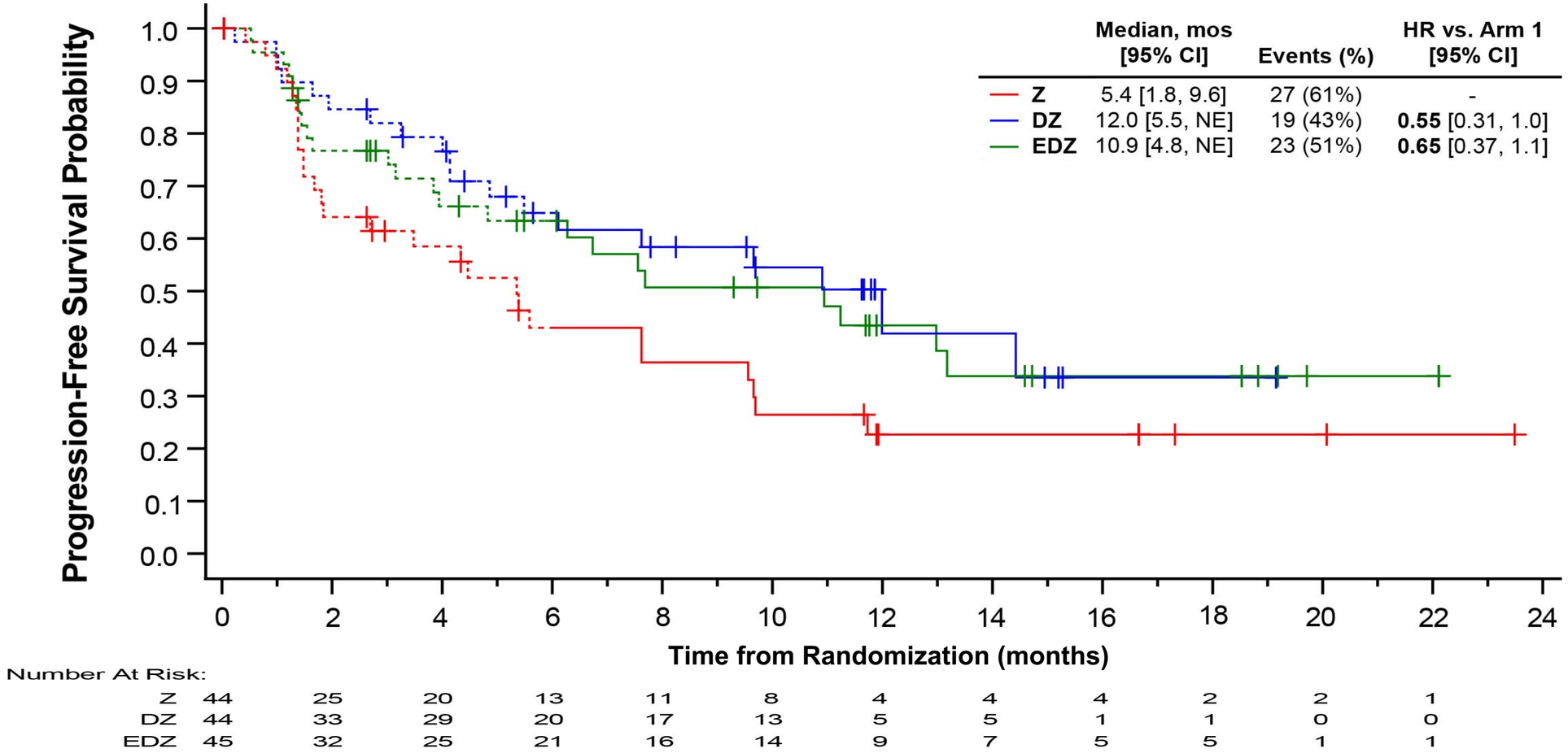
ARC-7: Randomized, Open-label, Phase 2 Study in First-Line, Metastatic, PD-L1-High NSCLC



- As of the clinical cut-off date (31 August 2022), a total of 150 patients were randomized with a median follow-up of 11.8 months (range: 0.03 – 23.5)

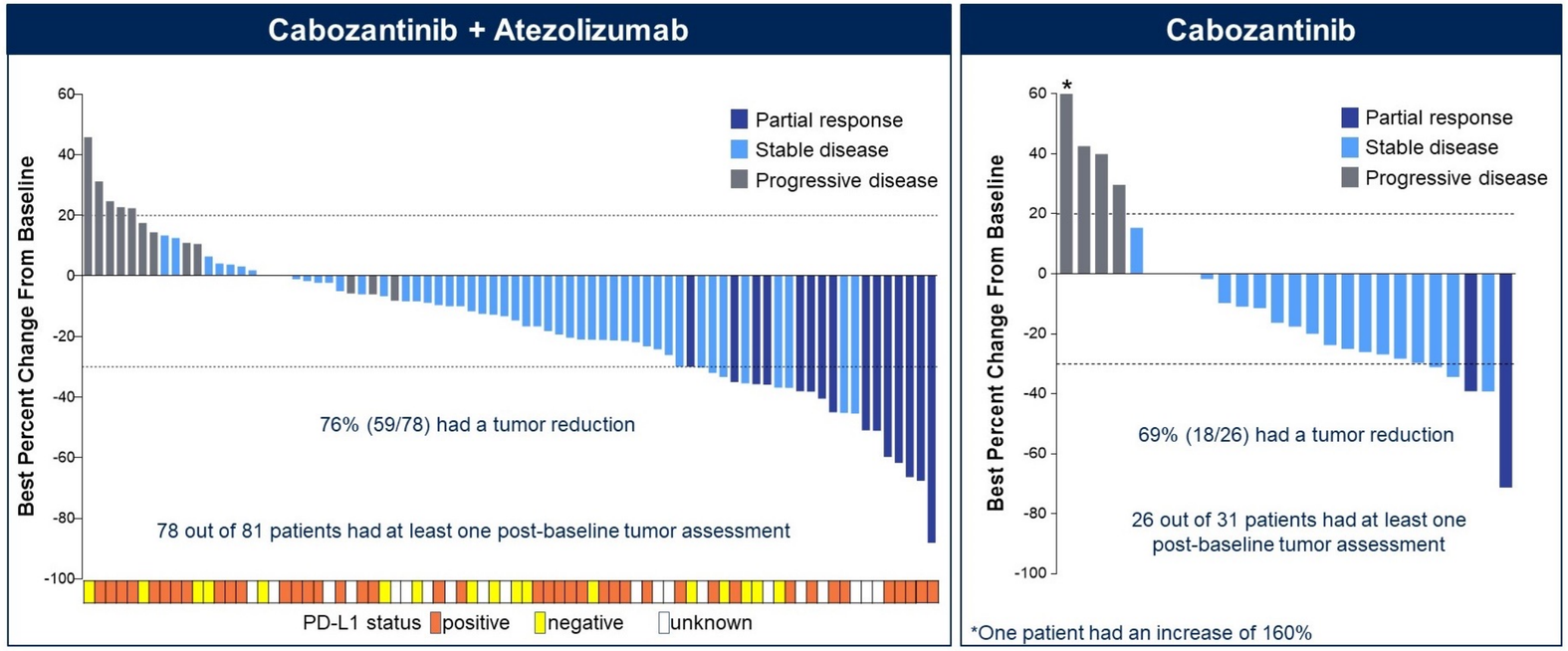
M. Johnson, ASCO Plenary, 2022

Progression-Free Survival – ITT-13



M. Johnson, ASCO Plenary, 2022

Cabozantinib Plus Nivolumab



Per investigator by RECIST v1.1.

December 8, 2022
ALAMEDA, Calif. today it was announced that the CONTACT-01 study did not meet its primary endpoint of overall survival at the final analysis. CONTACT-01 is a phase 3 trial evaluating cabozantinib in combination with atezolizumab versus docetaxel in patients with metastatic non-small cell lung cancer (NSCLC) without actionable mutations who experienced disease progression on or after treatment with an immune checkpoint inhibitor and platinum-containing chemotherapy.

Neal JW, et al. Presented at: ASCO;2022. Abstract 9005.

SAPPHIRE Phase 3 Study in NSCLC: Trial Design

Key Eligibility Criteria

- Unresectable, locally advanced, or metastatic NSQ NSCLC
- No EGFR, ROS1, or ALK alterations
- One or two prior regimens with most recent including CPI (≥4 months) with or after PBC
- Discontinuation of prior CPI <90 days prior to randomization
- ECOG PS 0 or 1
- No active brain metastases[a]

R 1:1

- **Sitravatinib (100 mg QD) + Nivolumab (240 mg Q2W or 480 mg Q4W) n=284[b]**
- **Docetaxel (75 mg/m² Q3W) n=293[b]**

Stratification Factors

- Prior treatment regimens in the advanced setting: 1 vs 2
- Baseline ECOG PS 0 vs 1
- Treated and/or stable brain metastases at baseline: presence vs absence

Study Objectives

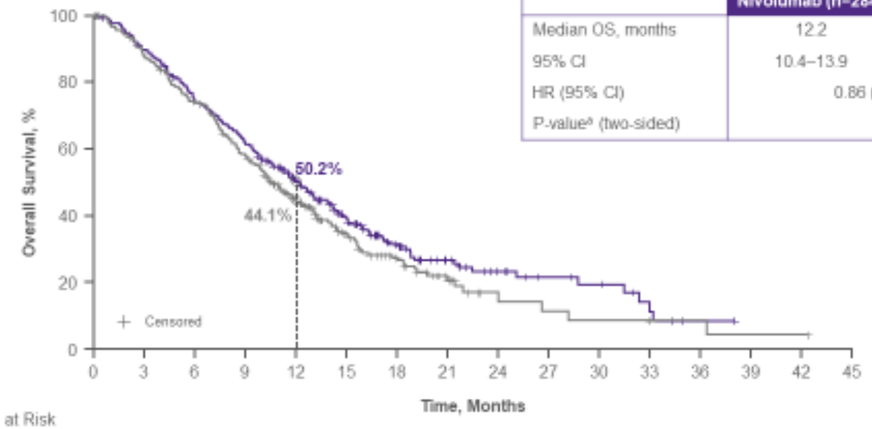
- Primary
- Secondar ORR (RE PFS, and

- In the Phase 2 MRTX-500 study, sitravatinib in combination with nivolumab demonstrated a tolerable safety profil patients with NSQ NSCLC who initially had clinical benefit on prior CPI treatment but subsequently experienced d
- Here we report Phase 3 data evaluating sitravatinib plus nivolumab vs docetaxel in patients with advanced NSQ N (median follow-up: 17.1 months)

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; E intent-to-treat; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every two weeks; Q3W, every three weeks; Q4W, every four weeks; QD, onc RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1
[a]Treated and/or stable brain metastases were allowed. [b]ITT population. [c]Data presented per BICR
ClinicalTrials.gov. NCT03906071

Overall Survival

	Sitravatinib + Nivolumab (n=284)	Docetaxel (n=293)
Median OS, months	12.2	10.6
95% CI	10.4–13.9	9.4–12.3
HR (95% CI)	0.86 (0.70–1.05)	
P-value[a] (two-sided)	0.144	



No. at Risk															
Sitravatinib + Nivolumab	284	246	202	168	116	74	44	25	16	11	9	4	1	0	0
Docetaxel	293	244	199	155	98	56	33	15	5	4	3	3	2	1	1

CI, confidence interval; HR, hazard ratio
[a]P-value is based on the log-rank test.
Censoring rate, n (%): sitravatinib plus nivolumab, 96 (35%); docetaxel, 102 (35%)
Data as of March 28, 2023 (median duration of follow-up: 17.1 months)

Borghaei, ESMO 2023

PRAGMATICA LUNG, Phase 3 trial ongoing……..

NCT03971474

Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities

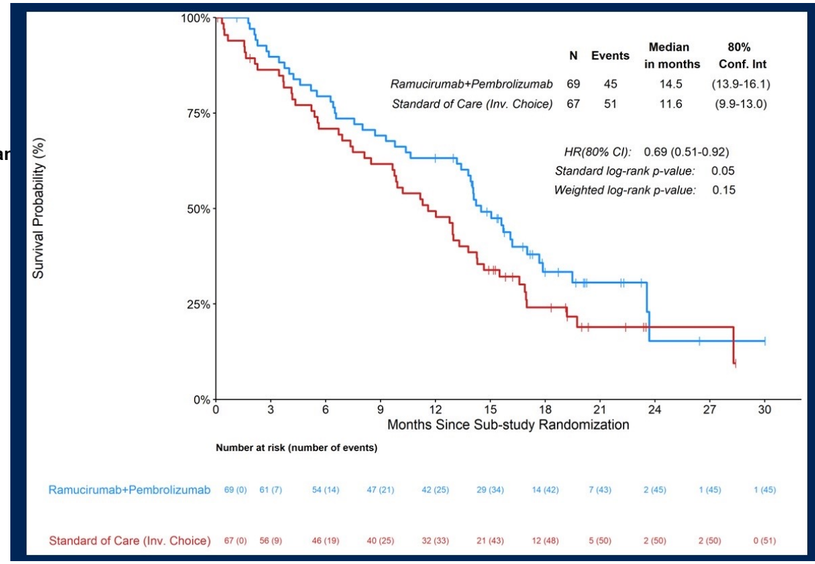
ARM A
Investigator's Choice Standard of Care
docetaxel + ramucirumab; docetaxel; gemcitabine; pemetrexed (nonSCC only)

Randomization

R (1:1)
N= 130

ARM B
Pembrolizumab
200 mg Q3W for up to 35 cycles
+
Ramucirumab
10 mg/kg Q3W

Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab



- 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)

Reckamp KL, et al. Presented at: ASCO;2022. Abstract 9004.

LUNAR Phase 3 Study Design

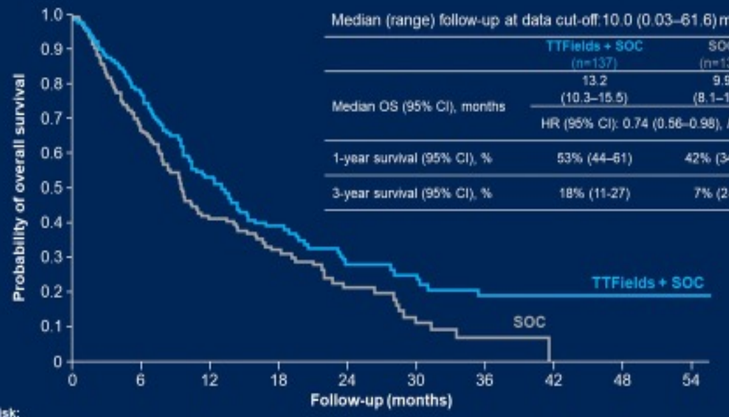
Objective: To evaluate safety and efficacy of TTFields therapy with standard of care (SOC) compared to SOC alone in metastatic NSCLC progressing on or after platinum-based therapy

Data cut-off: November 26, 2022
Study sites: 124 in 17 countries (North America, Europe, Asia)

Following a planned interim analysis (March 2021), DMC recommended reducing patient accrual from 534 to 276 patients and follow-up from 18 to 12 months.

* 150 kHz; †pembrolizumab, nivolumab, or atezolizumab;
ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; ITT, intent to treat; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care; TTFields, Tumor Treating Fields

Overall Survival in the ITT Population



Median (range) follow-up at data cut-off: 10.0 (0.03–61.6) months

	TTFields + SOC (n=137)	SOC (n=139)
Median OS (95% CI), months	13.2 (10.3–15.5)	9.9 (8.1–11.5)
	HR (95% CI): 0.74 (0.56–0.98), *P*=0.035	
1-year survival (95% CI), %	53% (44–61)	42% (34–50)
3-year survival (95% CI), %	18% (11-27)	7% (2-15)

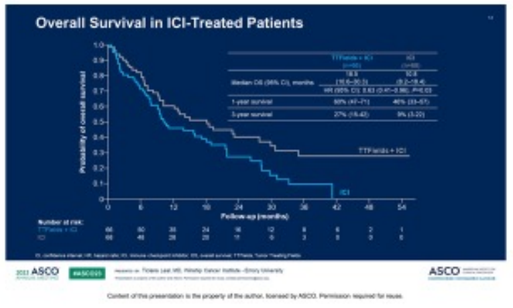
Number at risk:

TTFields + SOC	137	100	62	36	22	16	11	9	5	3
SOC	139	96	54	31	16	7	3	0	0	0

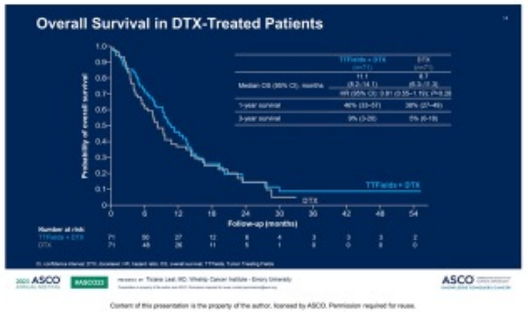
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival; SOC, standard of care; TTFields, Tumor Treating Fields

LUNAR Study

Overall Survival in ICI-Treated Patients



Overall Survival in DTX-Treated Patients



- Pre IO era
- PD-L1 status for most of the patients unknown
- Heterogeneous patient population
- Further trials needed

Summary of Treatment Emergent Adverse Events (TEAEs)

	TTFields + SOC (n=133)		SOC (n=134)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any TEAE	97%	59%	91%	56%
Serious AE	53%		38%	
TEAE leading to discontinuation	36%		20%	
TEAE leading to death	10%		8%	
Most frequent TEAEs				
Dermatitis	43%	2%	2%	0%
Fatigue	28%	4%	37%	8%
Musculoskeletal pain	36%	3%	27%	4%
Anemia	23%	8%	22%	8%
Dyspnea	20%	7%	25%	3%
Diarrhea	19%	2%	19%	0%
Cough	18%	0%	19%	1%
Nausea	19%	0%	16%	1%
Leukopenia	17%	14%	18%	14%
Pneumonia	15%	11%	17%	11%
Respiratory tract infection	15%	3%	16%	0%
Localized edema	15%	1%	16%	2%
Alopecia	10%	0%	17%	1%

- Majority of patients (94%) had ≥1 TEAE
- Incidence of severe AEs was comparable between subgroups

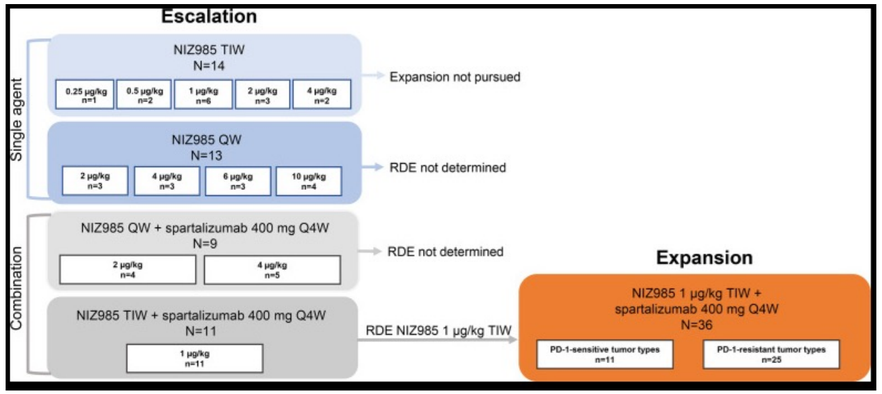
AE, adverse event; SOC, standard of care; TEAE, Treatment Emergent Adverse Event; TTFields, Tumor Treating Fields

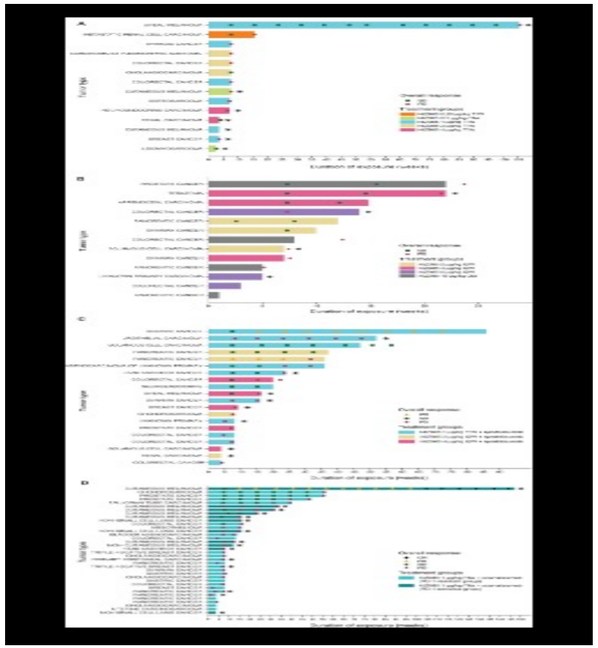
2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Ticiana Leal, MD, Winship Cancer Institute - Emory University

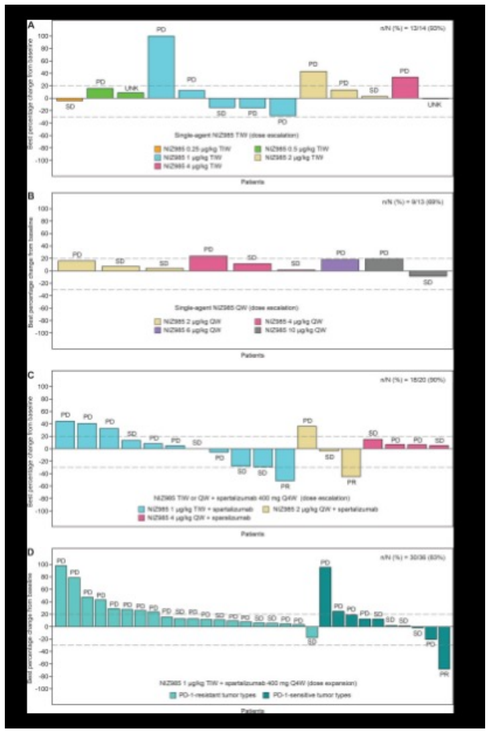
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

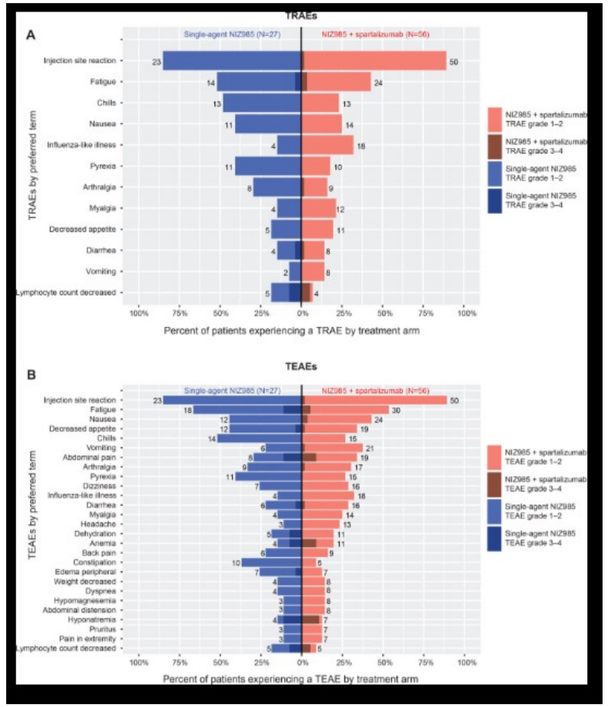
T. Leal, ASCO 2023

First-in-human phase I/Ib study of NIZ985, a recombinant heterodimer of IL-15 and IL-15Rα, as a single agent and in combination with spartalizumab in patients with advanced and metastatic solid tumors



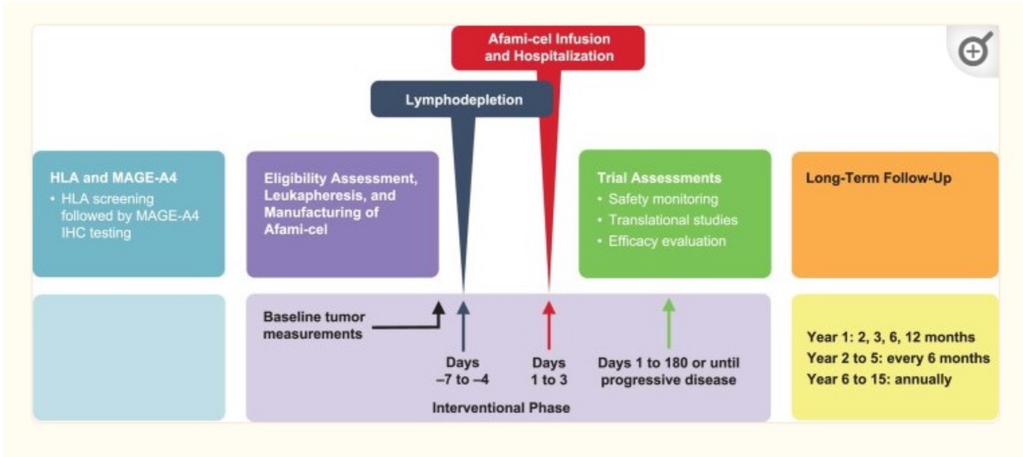




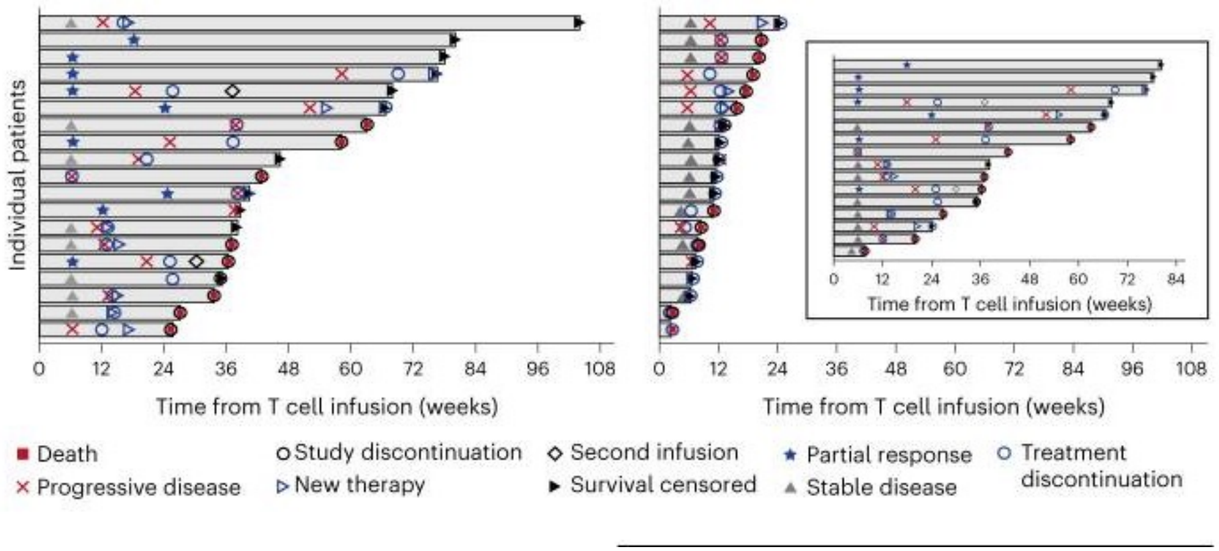


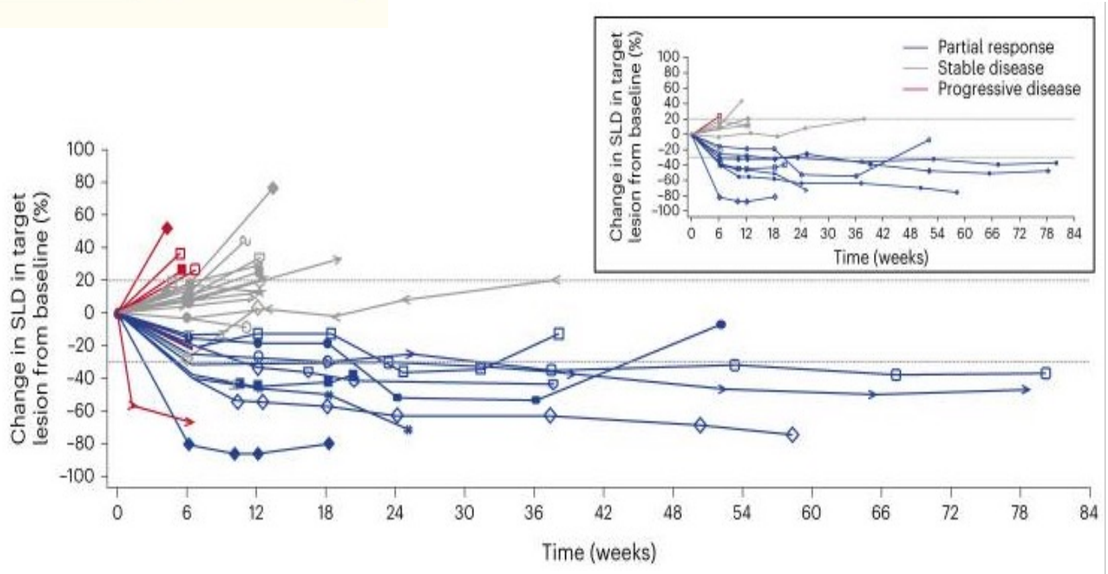
Rom Leidner et al; J Immunother Cancer. 2023 Oct

Autologous T cell therapy for MAGE-A4⁺ solid cancers in HLA-A*02⁺ patients: a phase 1 trial



38 patients treated, 2 with NSCLC





David Hong et al, Nat Med. 2023 Jan

- Treatment of NSCLC at any stage now is significantly more effective
- We now can talk about five year survival in the metastatic setting
- Cure rates are increasing for early stage disease
- Our understanding of the mechanisms of resistance is limited
- Lack of biomarkers hampers tailored and personalized treatment options
- Cancer vaccines, Cellular therapies, oncolytic viruses are all potential options but we need to get away from the all comers approach
- Molecular determinants of response to IO need to be better defined