

Future Challenges for Immunotherapy in the Fight Against NSCLC

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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, BiTees 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

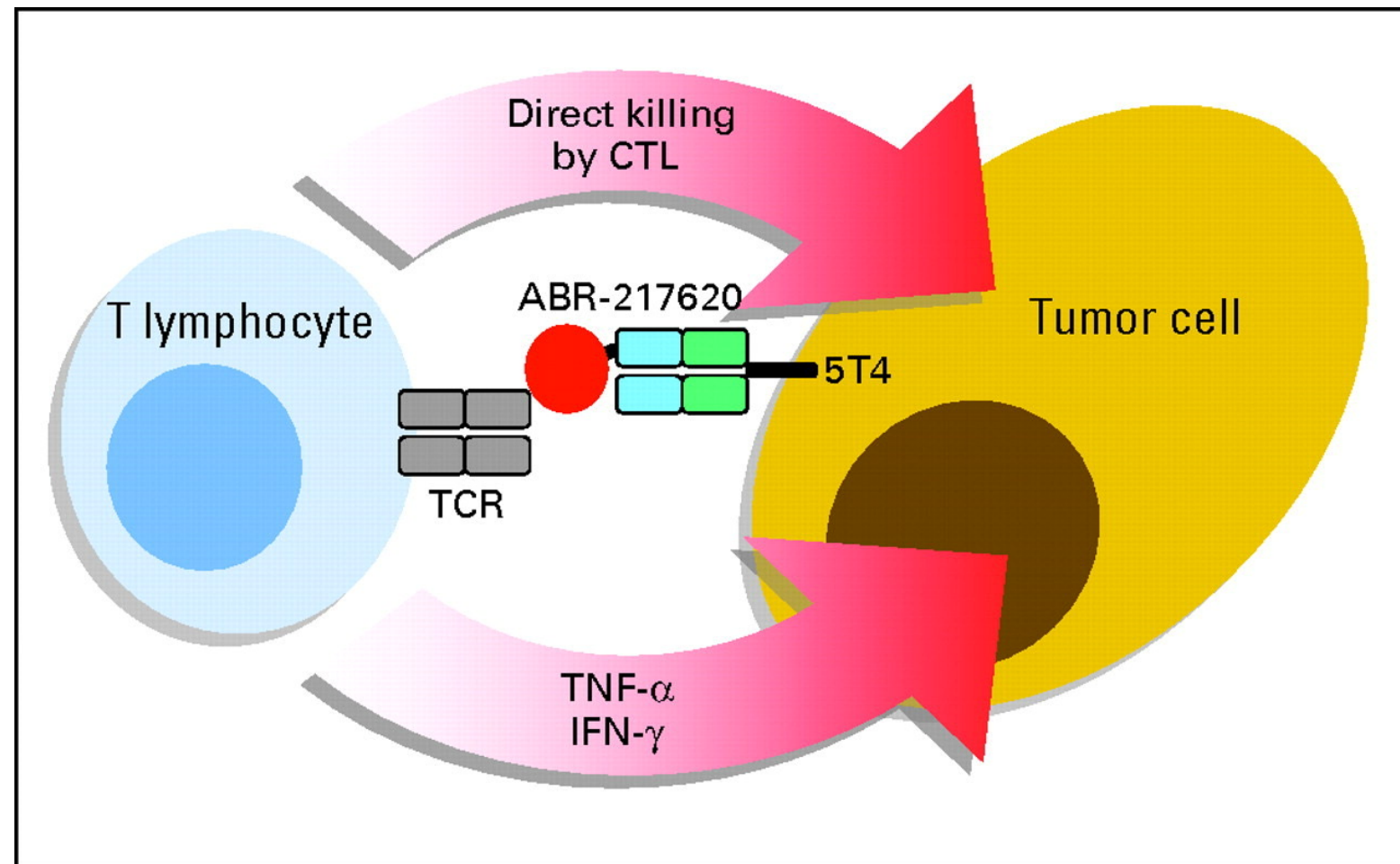
- William B. Coley (1862-1936)
 - Preceded by Drs. W. Busch and F. Fehleisen observations of spontaneous malignant regression s/p erysipelas infection (*Streptococcus pyogenes*)
- Coley's toxin
 - CR rate ~ 22% (270/1200 patients)
- 1976: BCG vaccine for bladder cancer



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)

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.

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

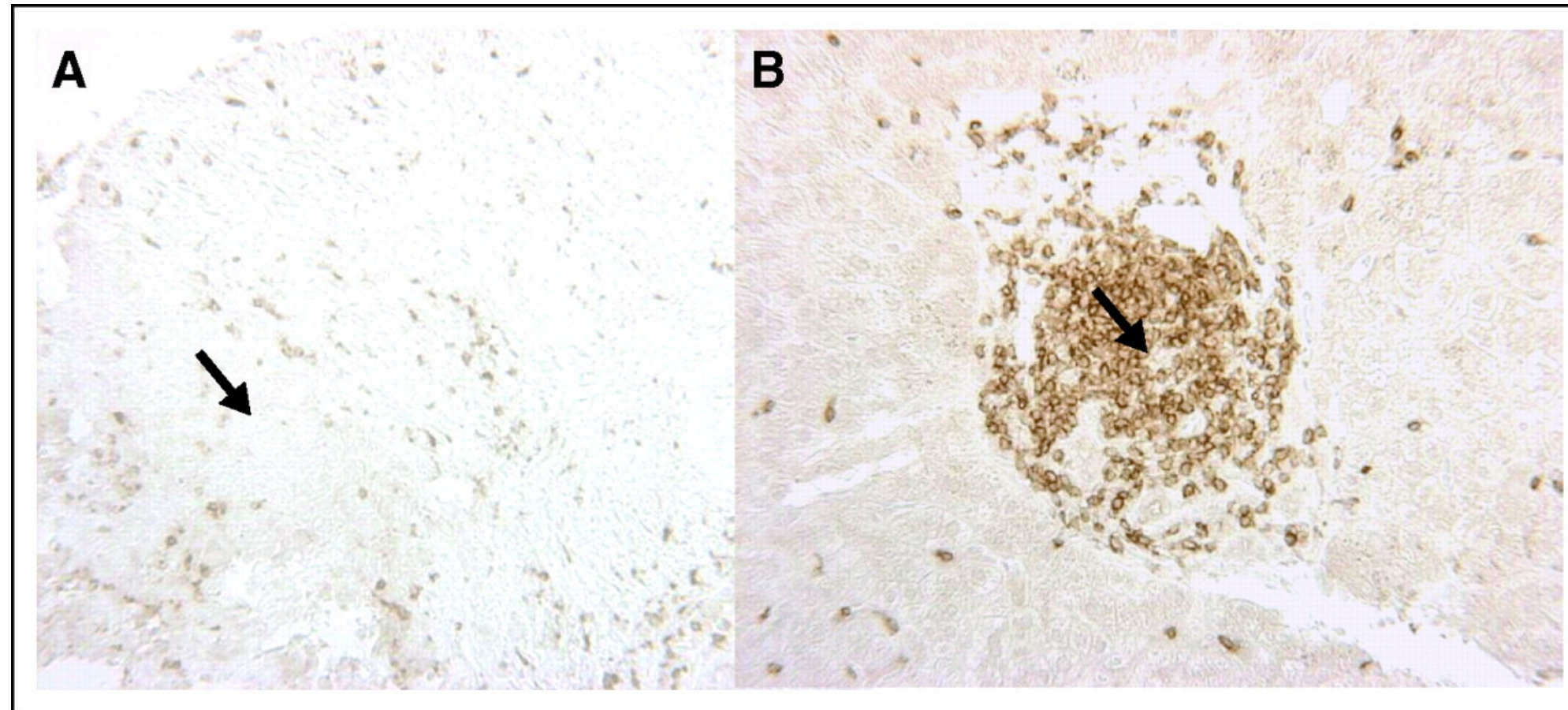
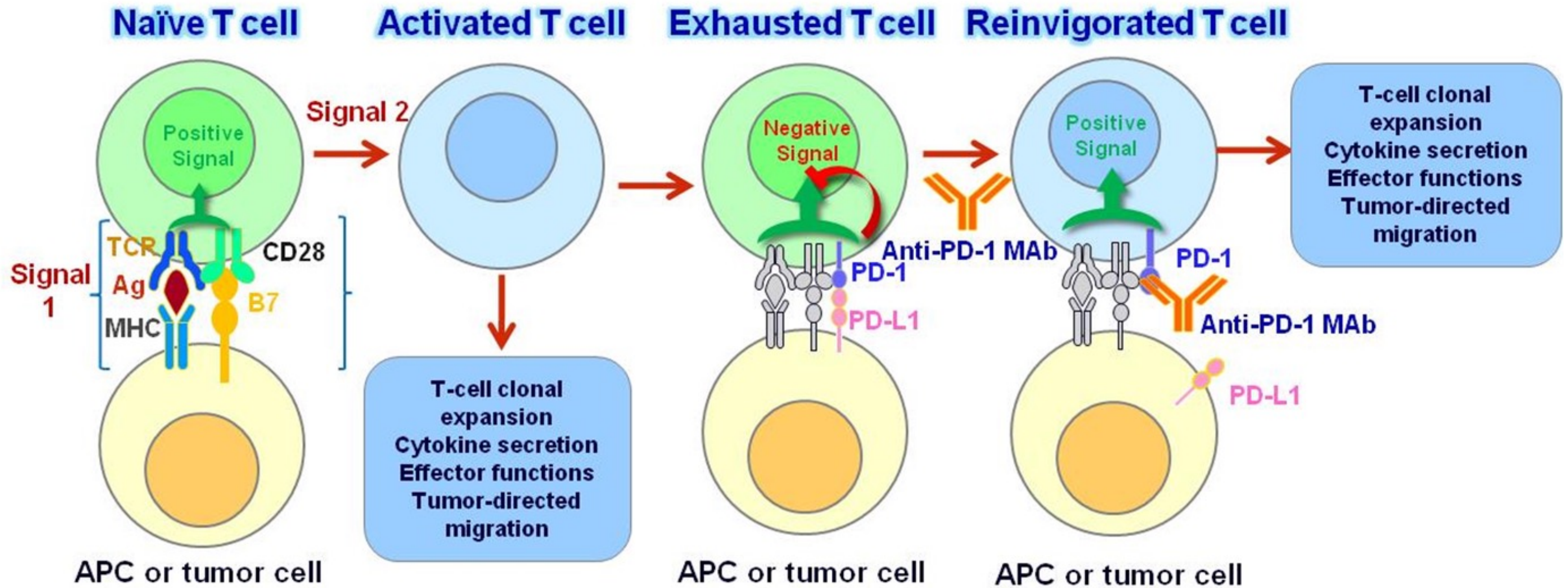


Fig 3. Immunohistochemistry for T-lymphocyte (anti-CD3) infiltration in biopsies taken before treatment (archival tissue) and at the third day of the second cycle treatment with ABR-217620 for patient number 2. The T lymphocytes stain brown and the arrows indicate unstained tumor cells. This patient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

PD(L)-1 and CTLA-4 inhibitors

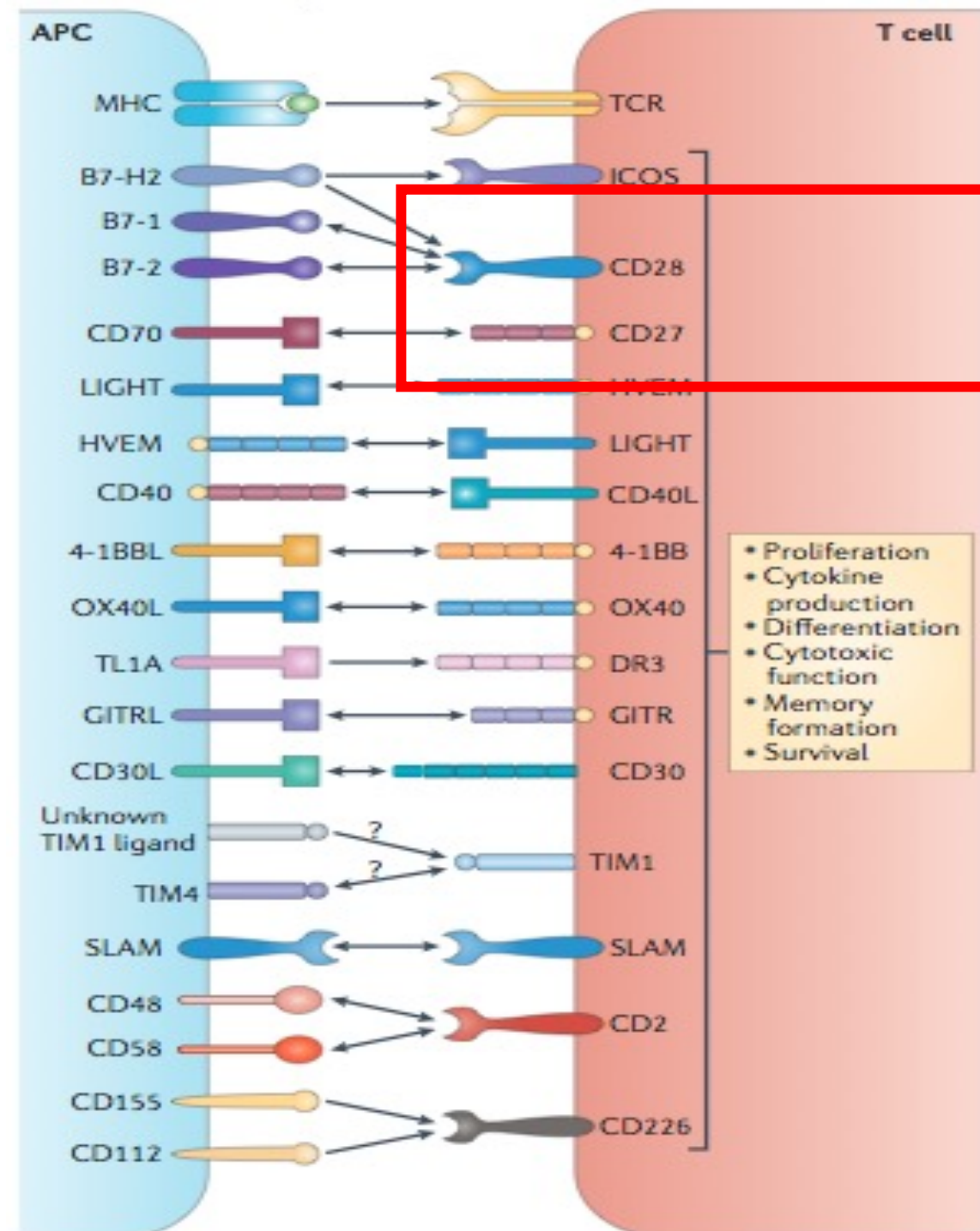
A New Era

Activating and Inhibiting Signals

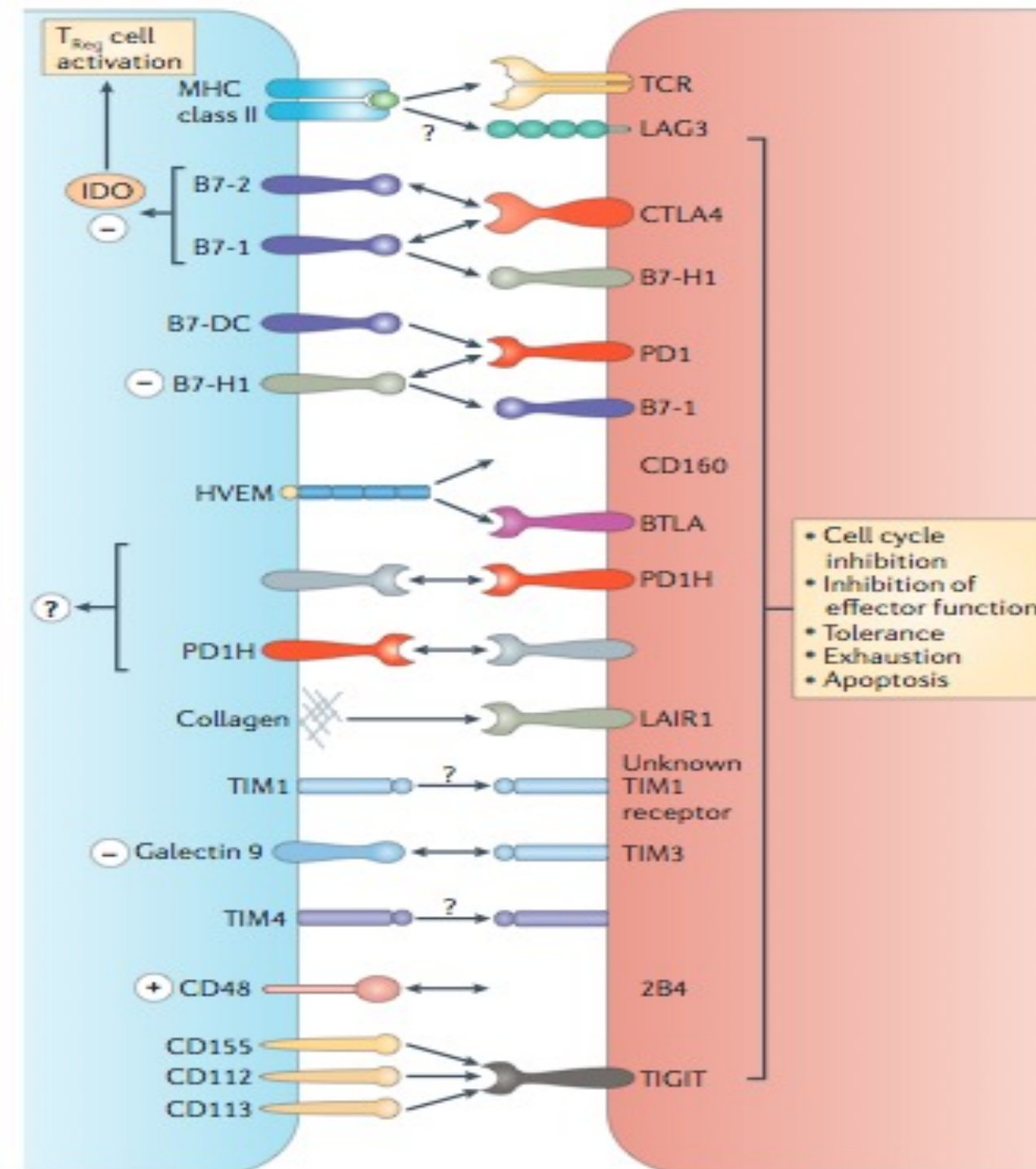


Immunologic Synapsis

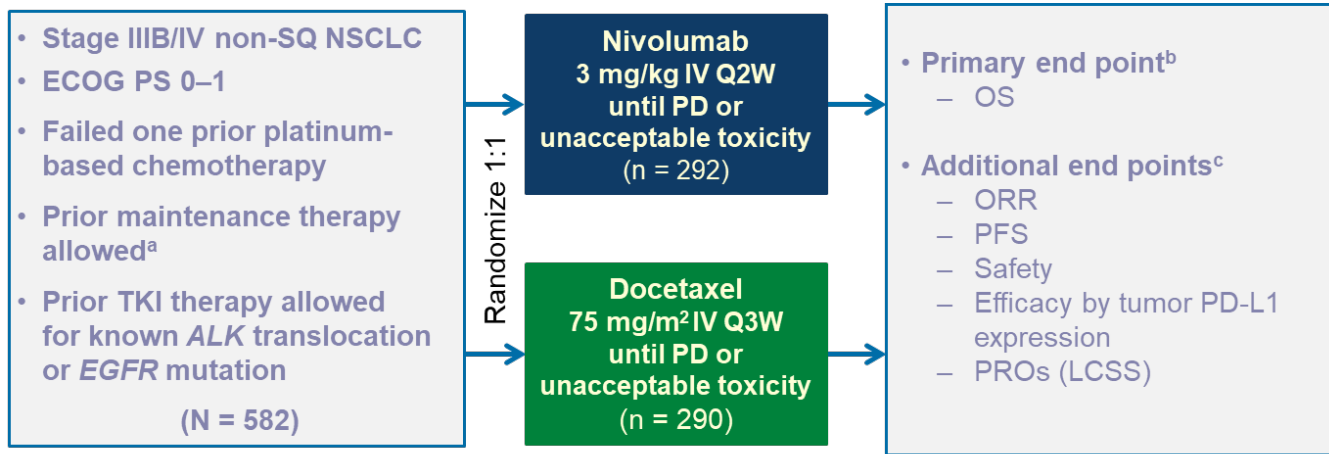
a Co-stimulation of T cells following interaction with counter-receptors on APCs



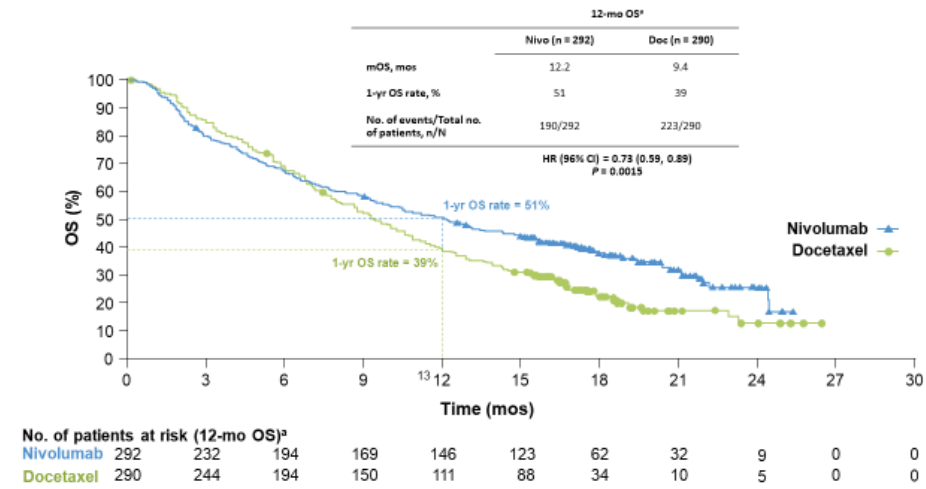
b Co-inhibition of T cells following interaction with counter-receptors on APCs



CheckMate 057 (NCT01673867)

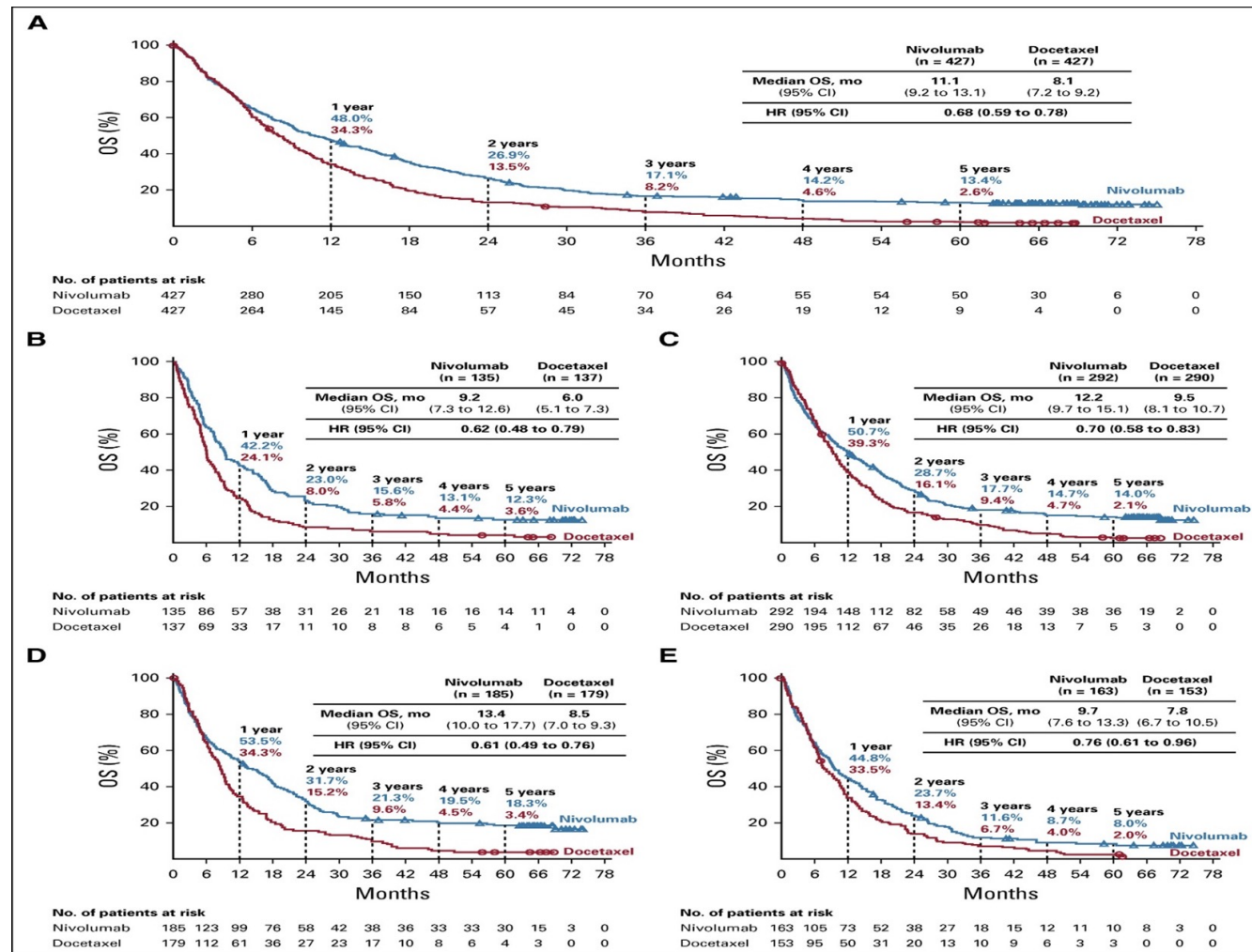


Patients stratified by prior maintenance therapy and line of therapy (second-line vs third-line)



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

^aBased on a March 18, 2015, DBL. Symbols represent censored observations.

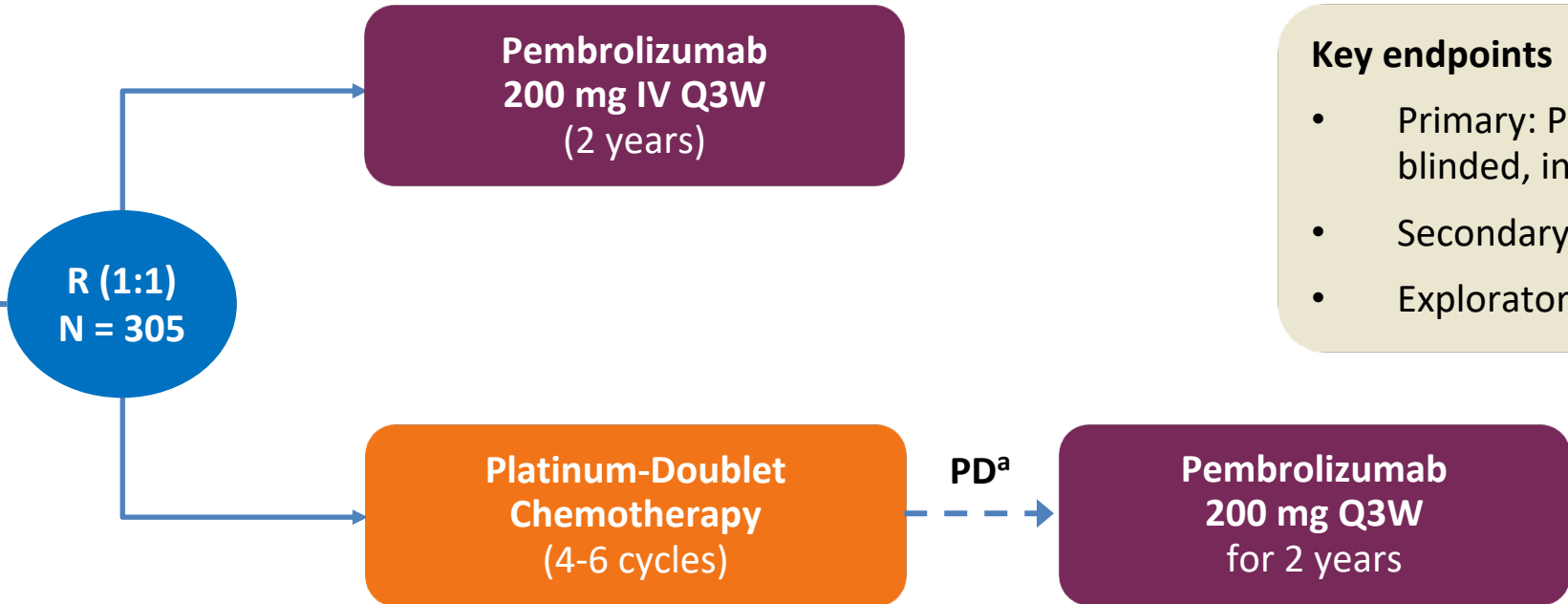


| | Nivolumab (n = 287) | | Docetaxel (n = 268) | |
|---------------------|---------------------|------------------------|---------------------|------------------------|
| | Any grade | Grade 3-4 ^a | Any grade | Grade 3-4 ^a |
| Any event | 69 | 10 | 88 | 54 |
| Fatigue | 16 | 1 | 29 | 5 |
| Nausea | 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 |

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



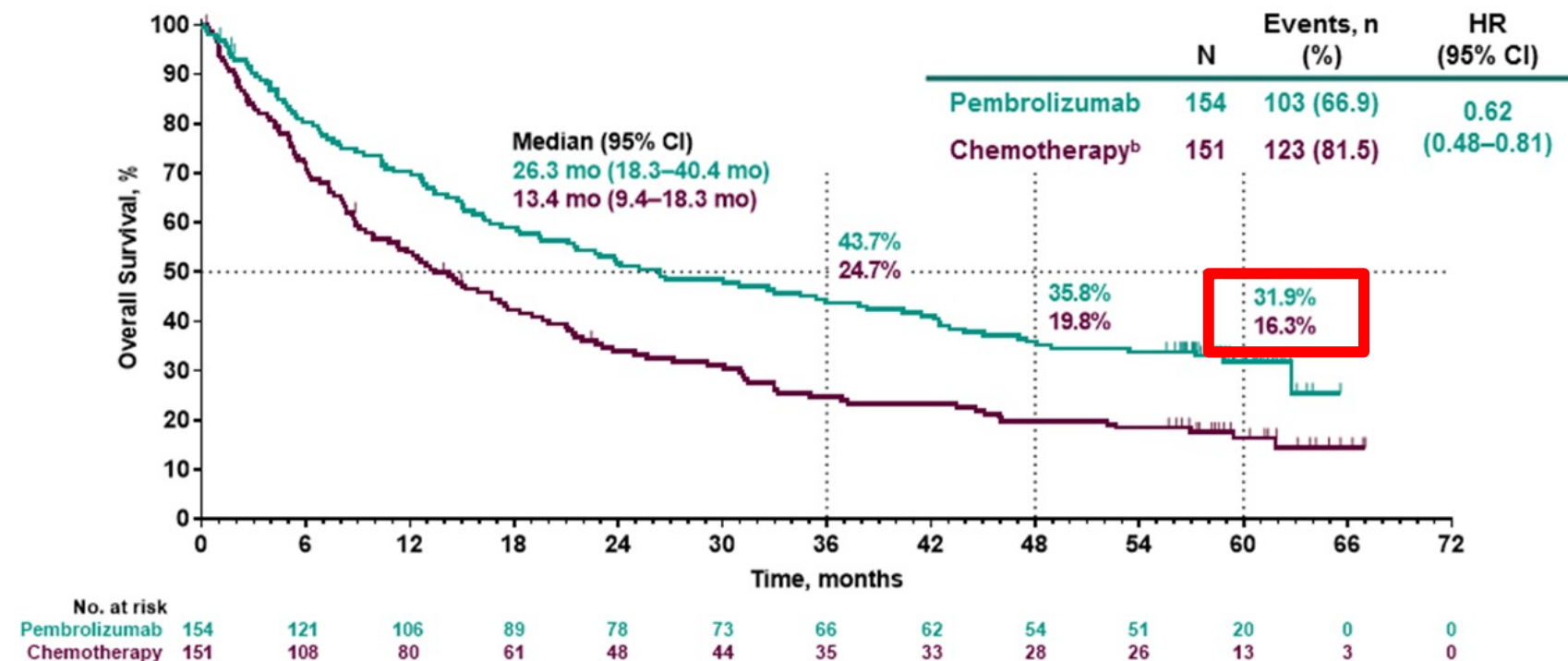
- Key endpoints**
- Primary: Progression-free survival (PFS) (RECIST v1.1 per blinded, independent central review)
 - Secondary: OS, ORR, safety
 - Exploratory: Duration of response (DoR)

^aTo 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

J Brahmer. ESMO 2020



^aITT population.
^bEffective 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.

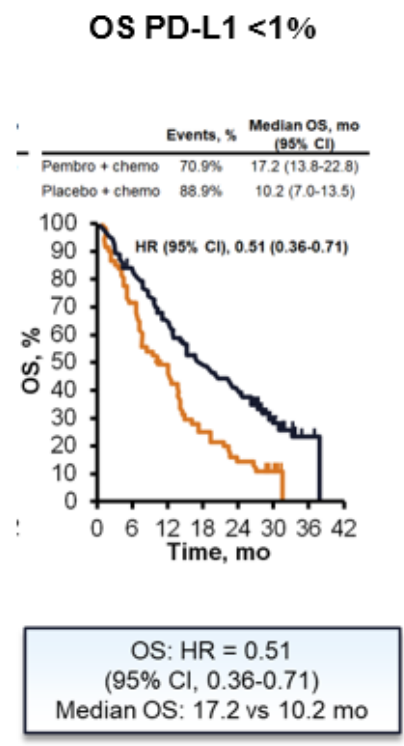
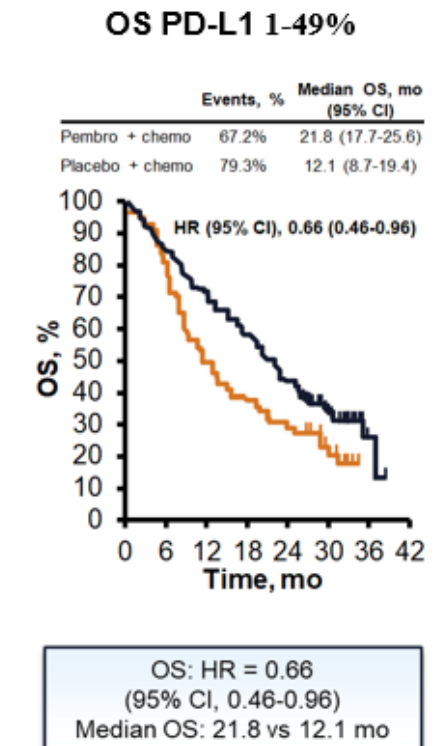
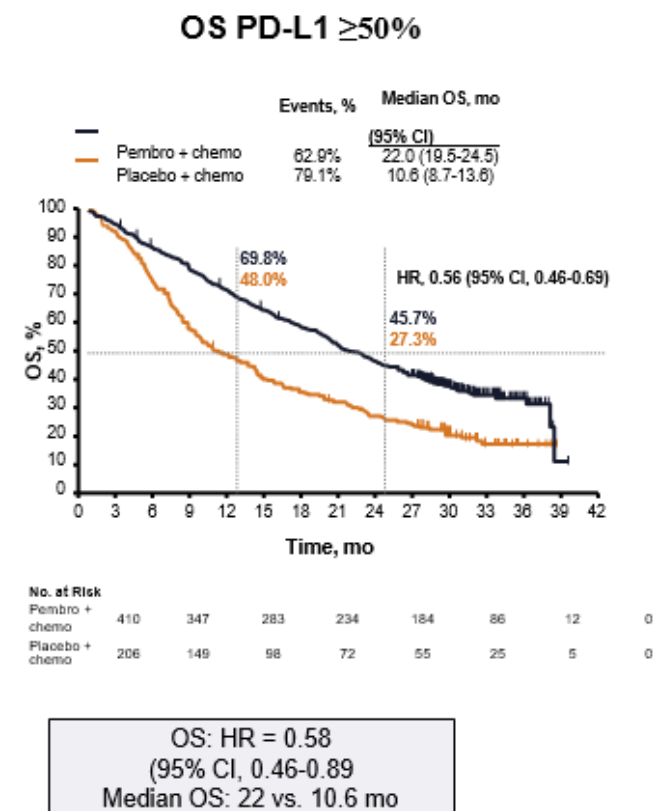
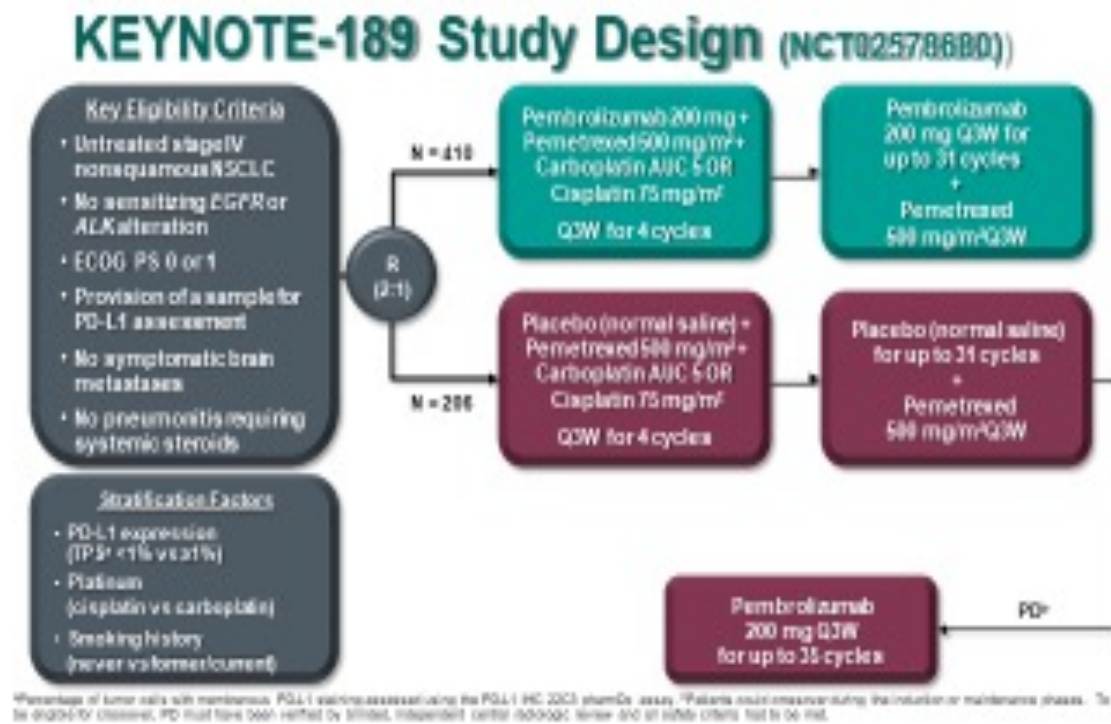
Baseline Characteristics

| 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 |

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

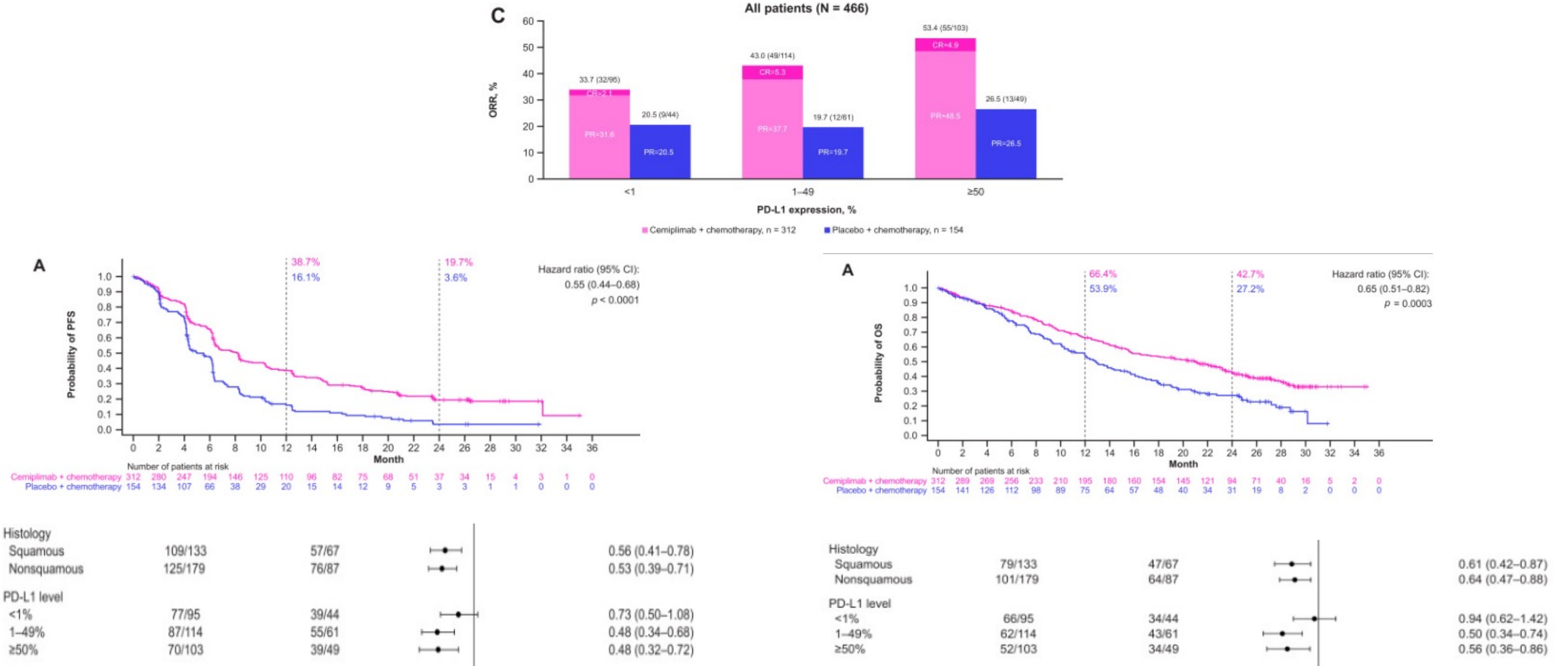
Chemo-IO combination

KEYNOTE-189 Final Analysis: OS by PD-L1 status¹

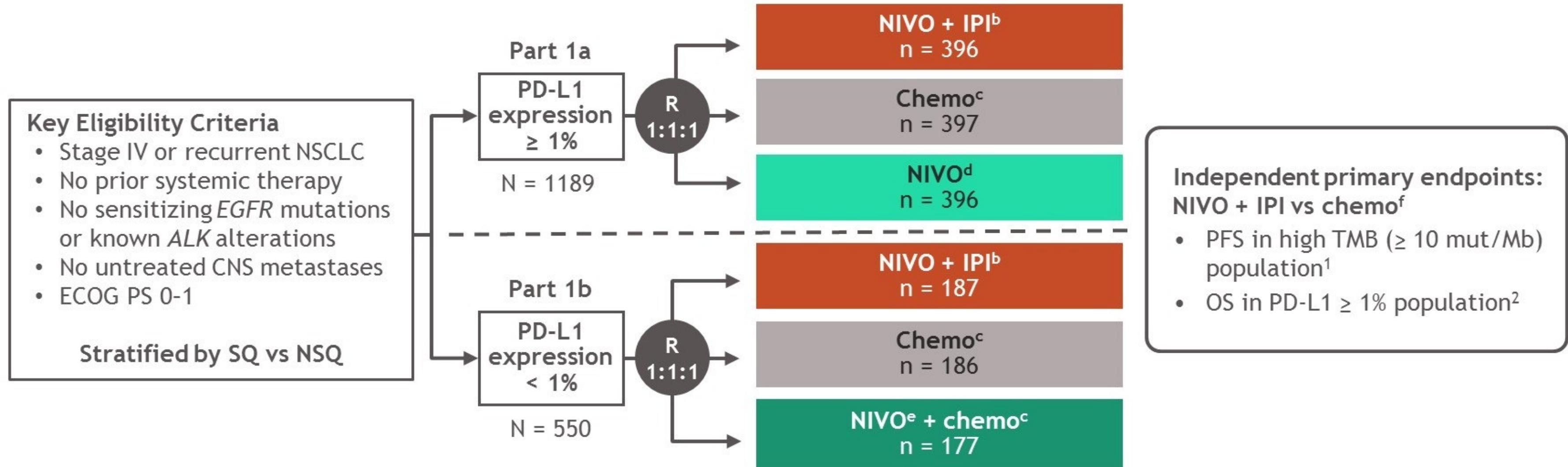


Forde, WCLC 2021

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



CheckMate 227^a Part 1 study design

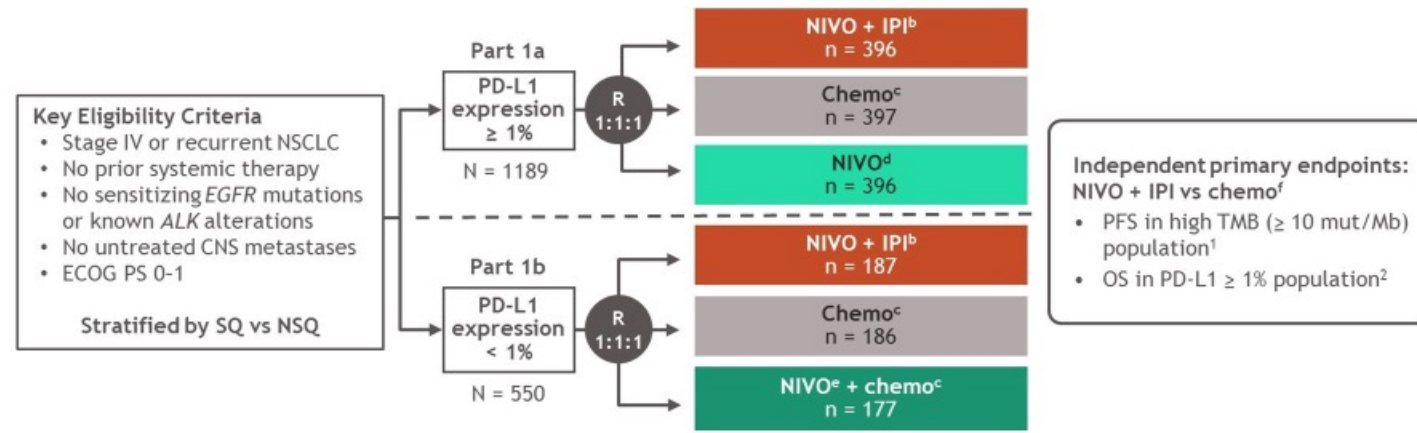


Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; ^aNCT02477826; ^bNIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); ^cNSQ: 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; ^dNIVO (240 mg Q2W); ^eNIVO (360 mg Q3W); ^fBoth endpoints were met; results were previously reported.

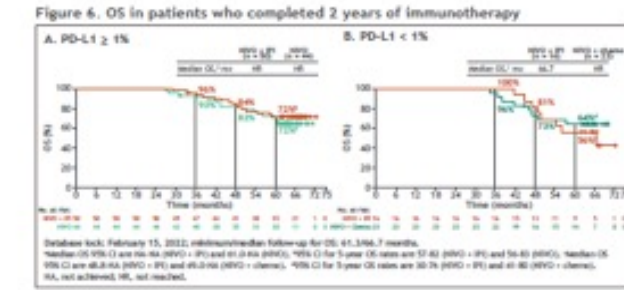
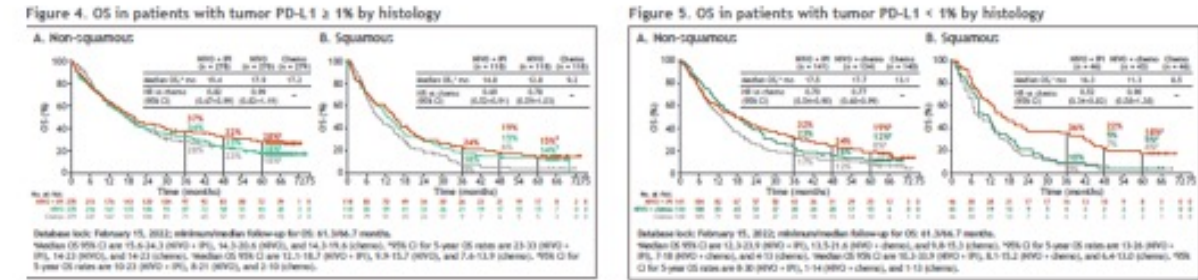
1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

CheckMate 227^a Part 1 study design



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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



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

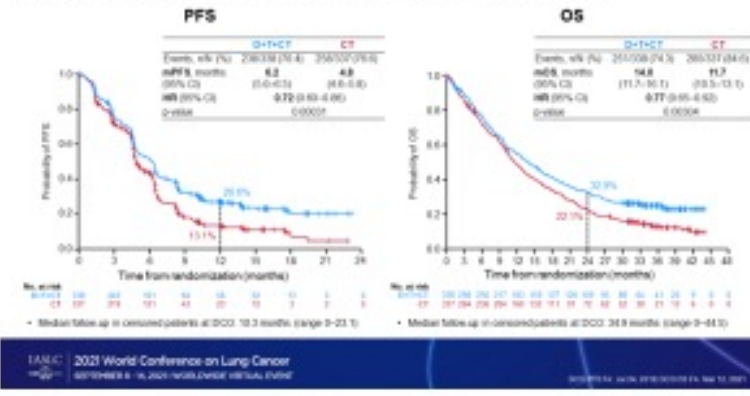
CheckMate-9LA

POSEIDON Study Design

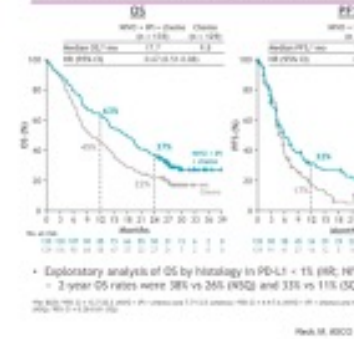
Phase 3, global, randomized, open-label, multicenter study



Durvalumab + Tremelimumab + CT vs CT: PFS and OS

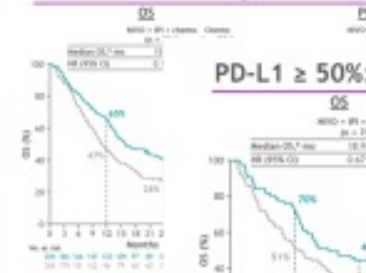


PD-L1 < 1%: efficacy outcomes



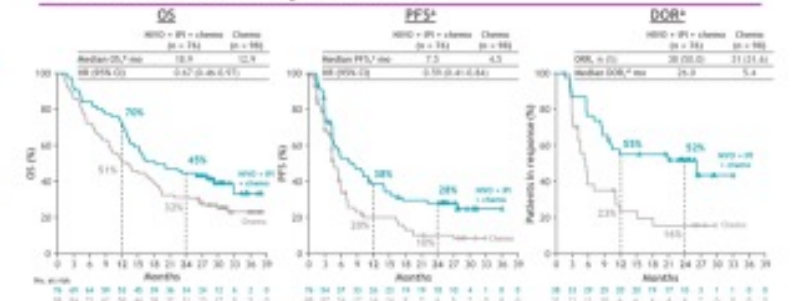
CheckMate 9LA 2022 - PD + chemo vs chemo in NSCLC: 3-year update

PD-L1 ≥ 1%: efficacy outcomes



CheckMate 9LA 2022 - PD + chemo vs chemo in NSCLC: 3-year update

PD-L1 ≥ 50%: efficacy outcomes



Check M, ASCO 2021

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

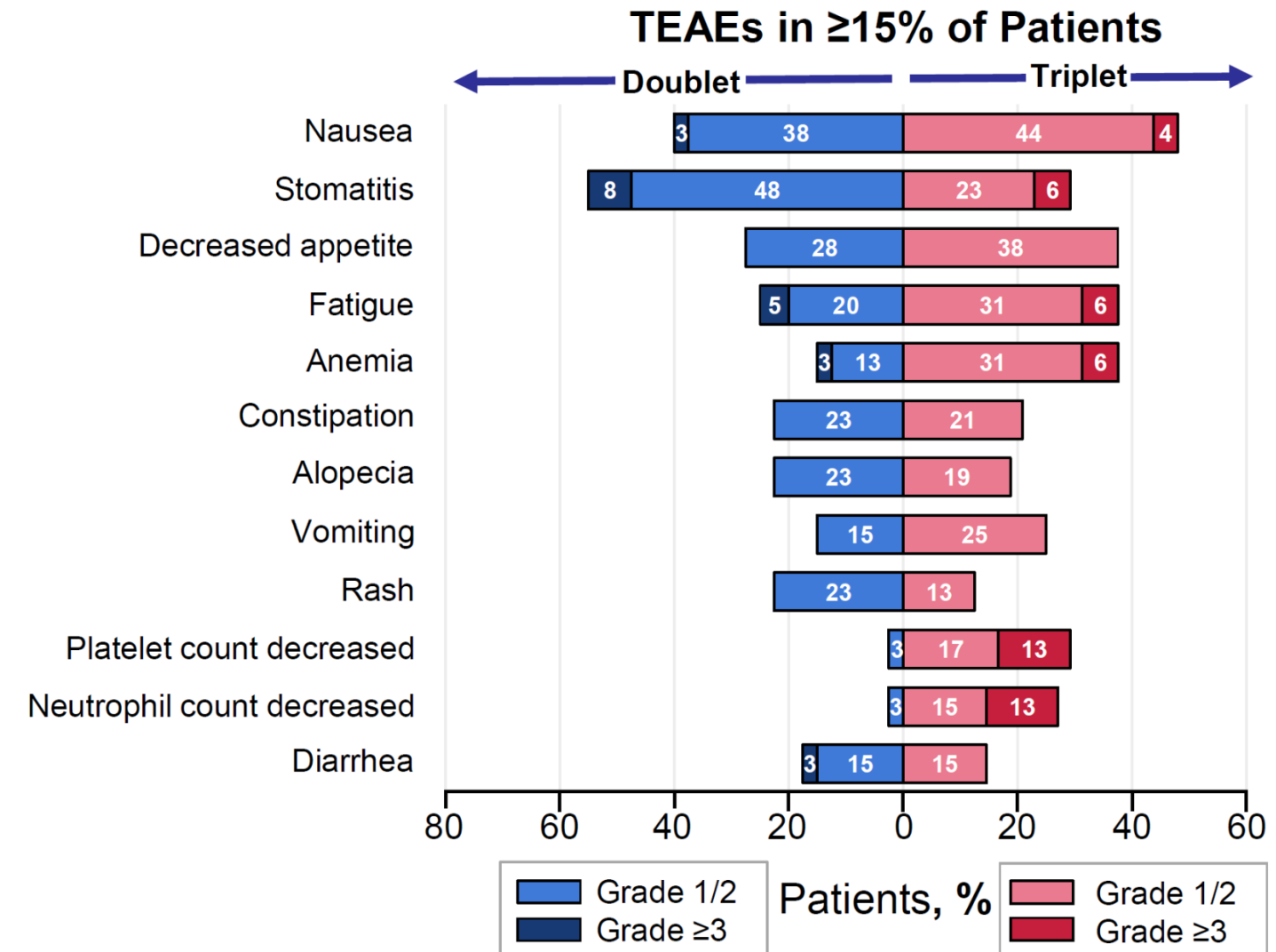
| | Dato-DXd IV Q3W | + | pembro IV Q3W | + | platinum CT IV Q3W |
|--------------------------------|--------------------|---|------------------|----------------------------------|-----------------------|
| Cohort 1 (n=20) ^d : | 4 mg/kg | + | 200 mg | } “Doublet” | |
| Cohort 2 (n=20) ^d : | 6 mg/kg | + | 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/m ² | |
| Cohort 6 (n=4) ^d : | 6 mg/kg | + | 200 mg | + cisplatin 75 mg/m ² | |

- **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



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}

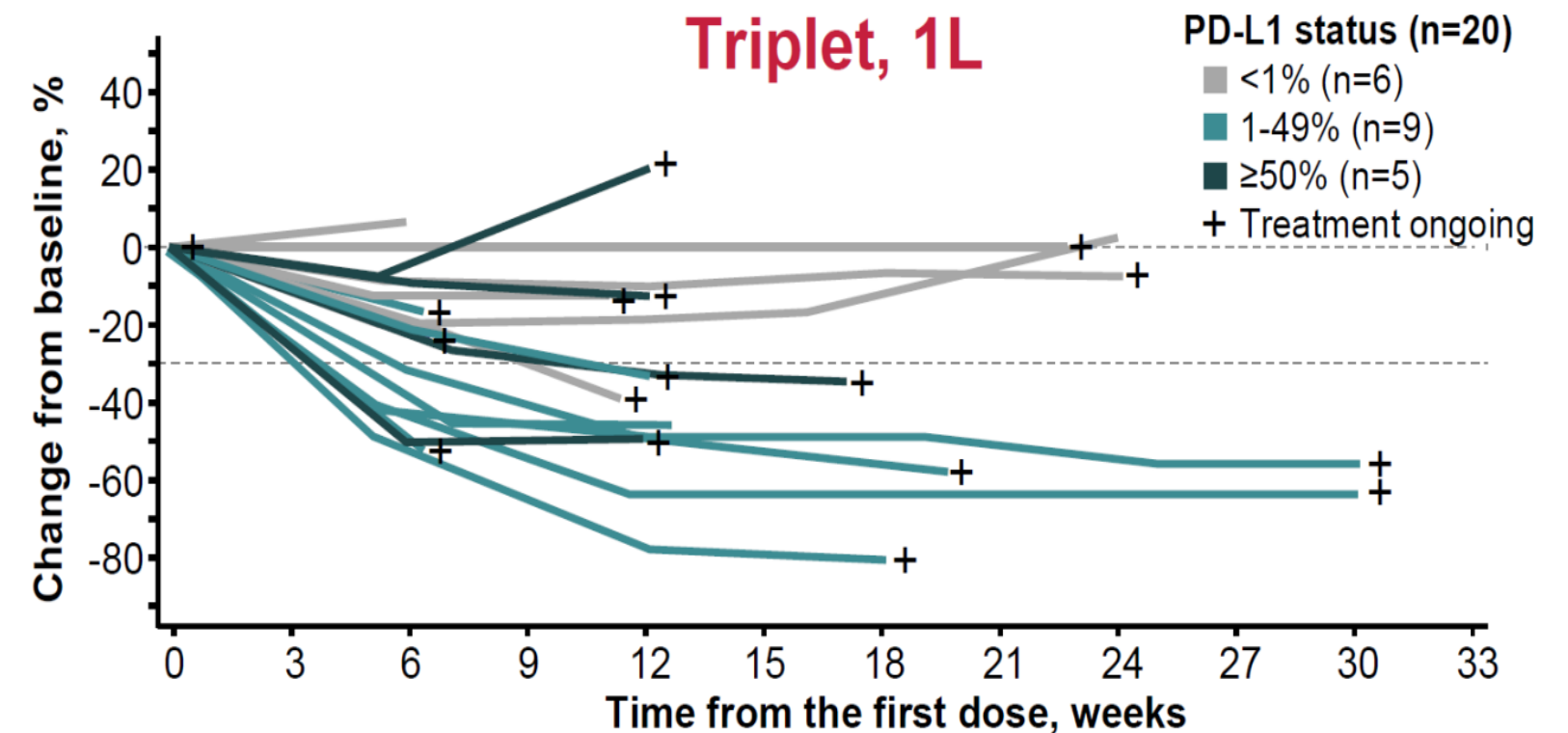
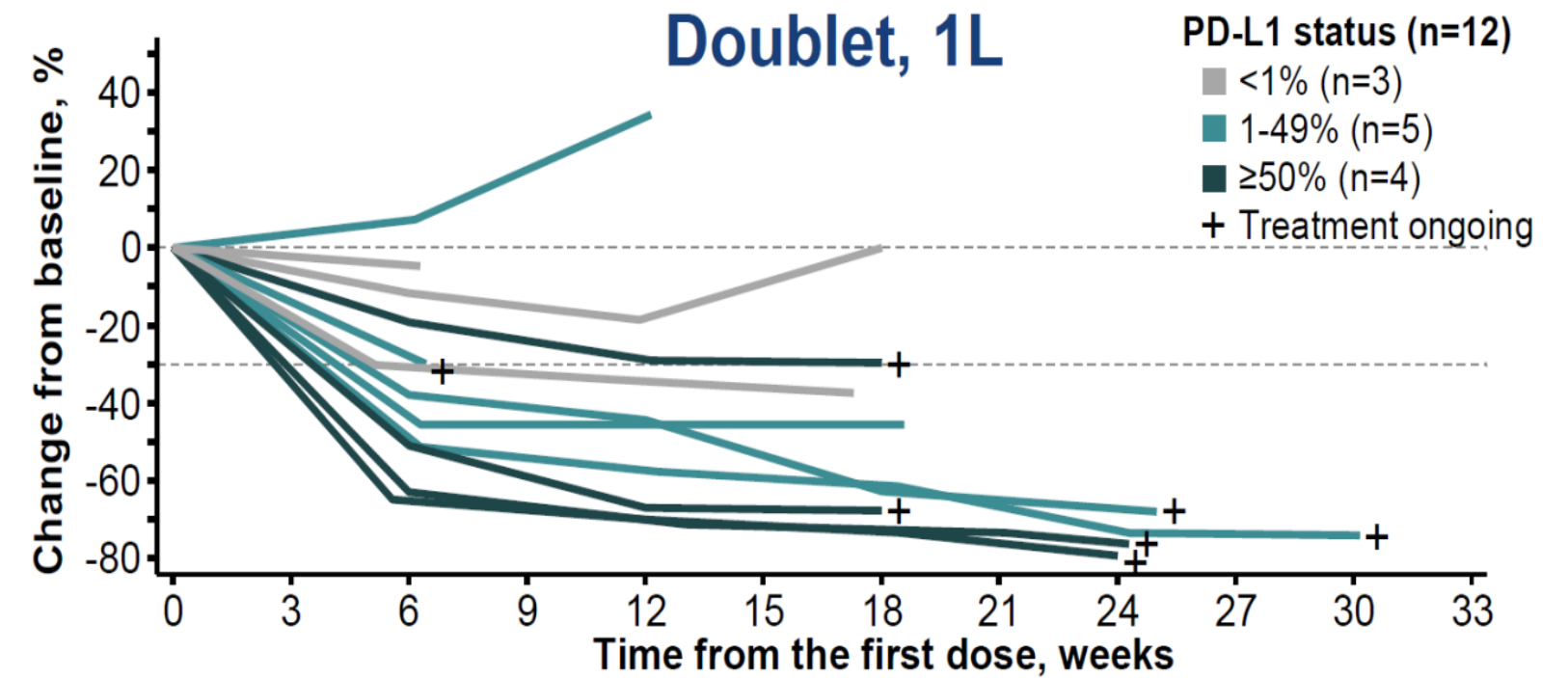
| Response, n (%) | Doublet (n=13) | Triplet (n=20) |
|--------------------------------|----------------|-----------------|
| ORR confirmed + pending | 8 (62%) | 10 (50%) |
| CR | 0 | 0 |
| PR confirmed | 8 (62%) | 7 (35%) |
| PR pending | 0 | 3 (15%) |
| SD | 5 (39%) | 8 (40%) |
| DCR | 13 (100%) |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

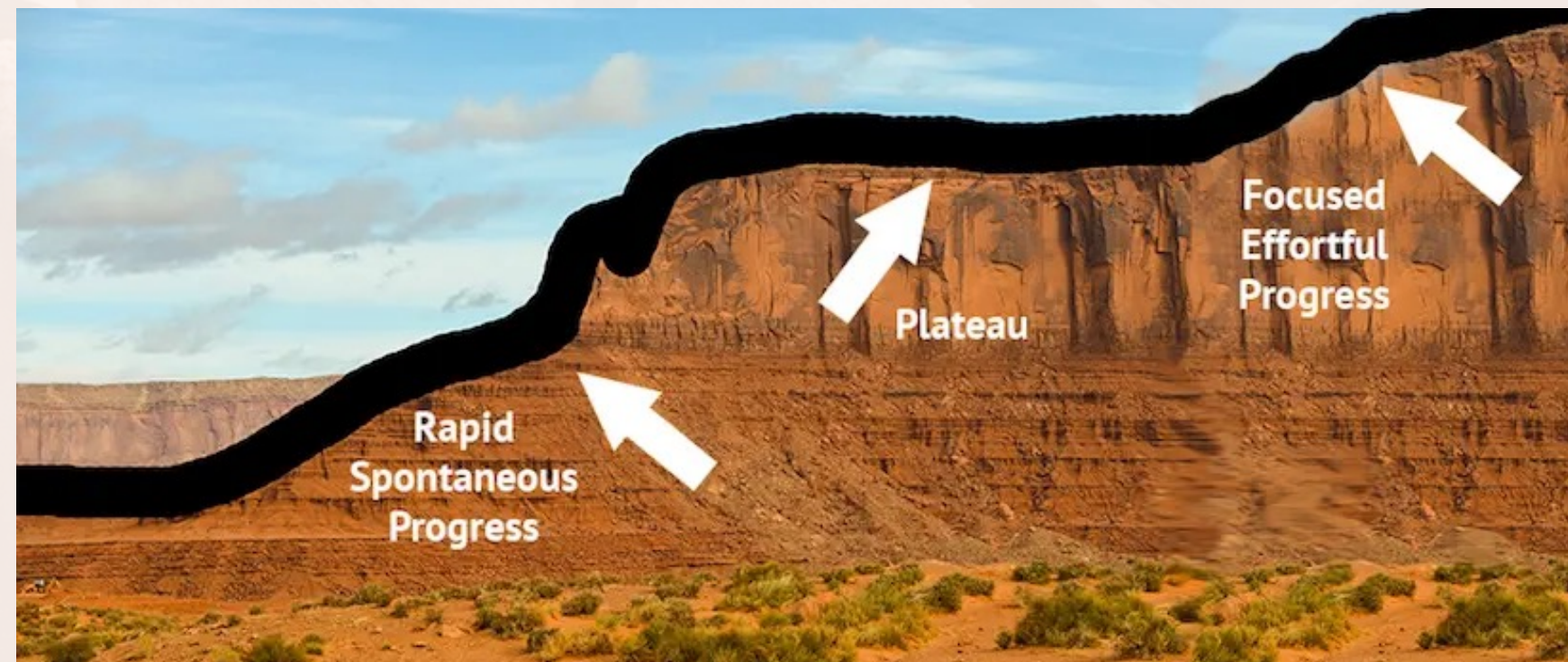
BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease.

^a By investigator. ^b BOR is based on response evaluable patients who have ≥1 postbaseline tumor assessment or discontinued.



First Line Treatment Paradigm

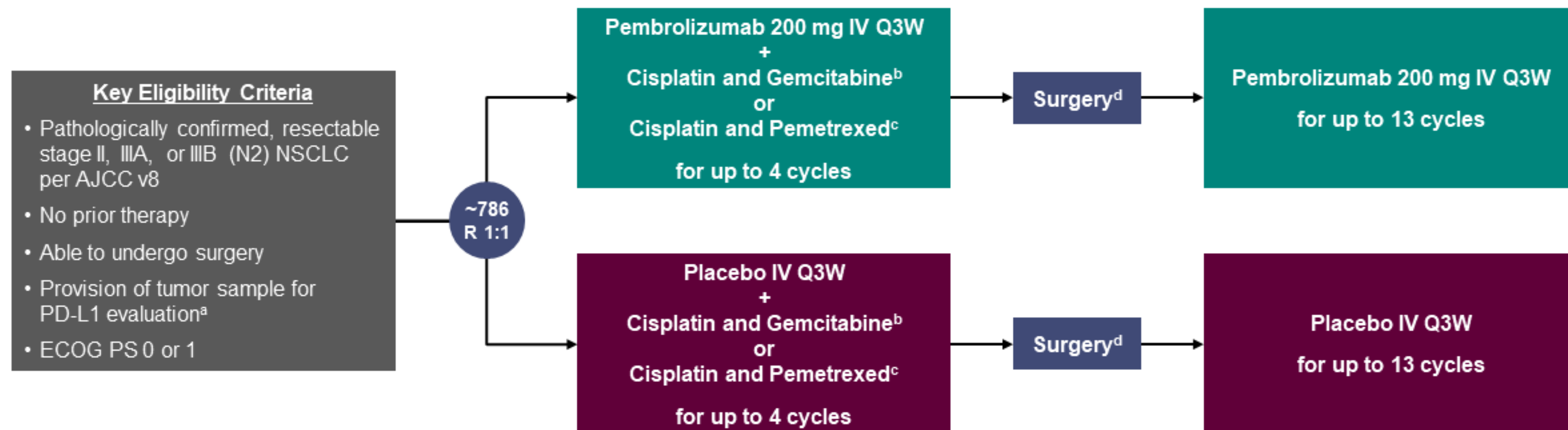
- In the metastatic setting we appeared to have reached a plateau
- Studies with TIGIT, LAG-3 and other checkpoint inhibitors combined with a PD(L)-1 inhibitor could potentially point to a new direction at least for specific subgroups
- Search for a better biomarker for identifying patients who would 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/m² IV Q3W + gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W was permitted for squamous histology only.

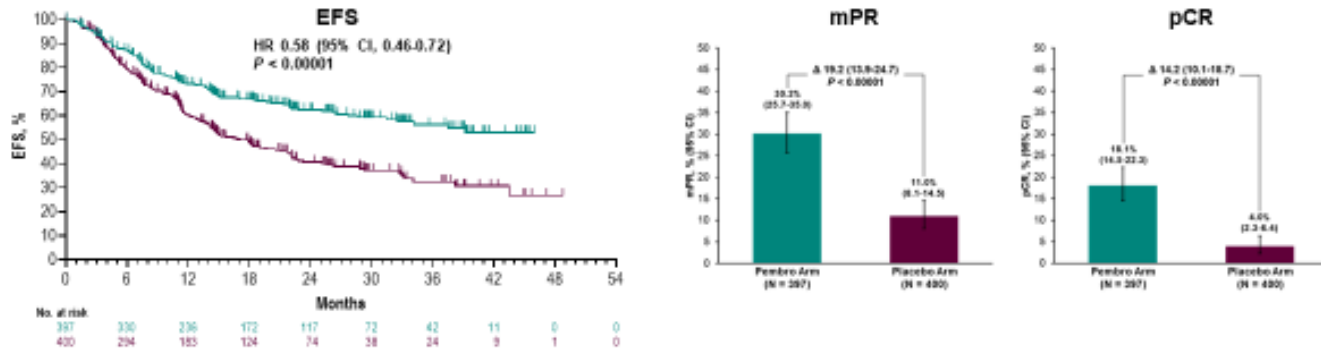
^c Cisplatin 75 mg/m² IV Q3W + pemetrexed 500 mg/m² IV Q3W was permitted for nonsquamous histology only. ^d Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease.

ClinicalTrials.gov identifier: NCT03425643.

KEYNOTE-671 Results: Interim Analysis 1

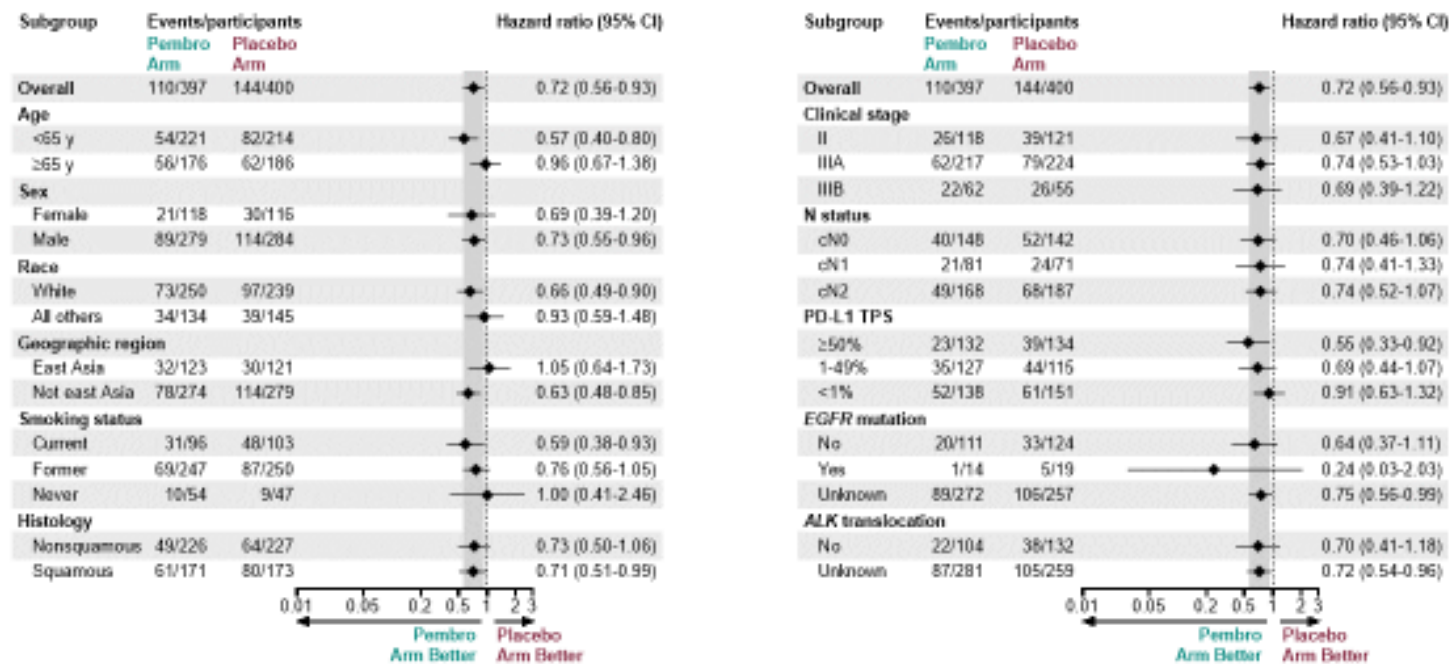
Median Follow-Up^a: 25.2 months (range, 7.5-50.6)

- 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



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

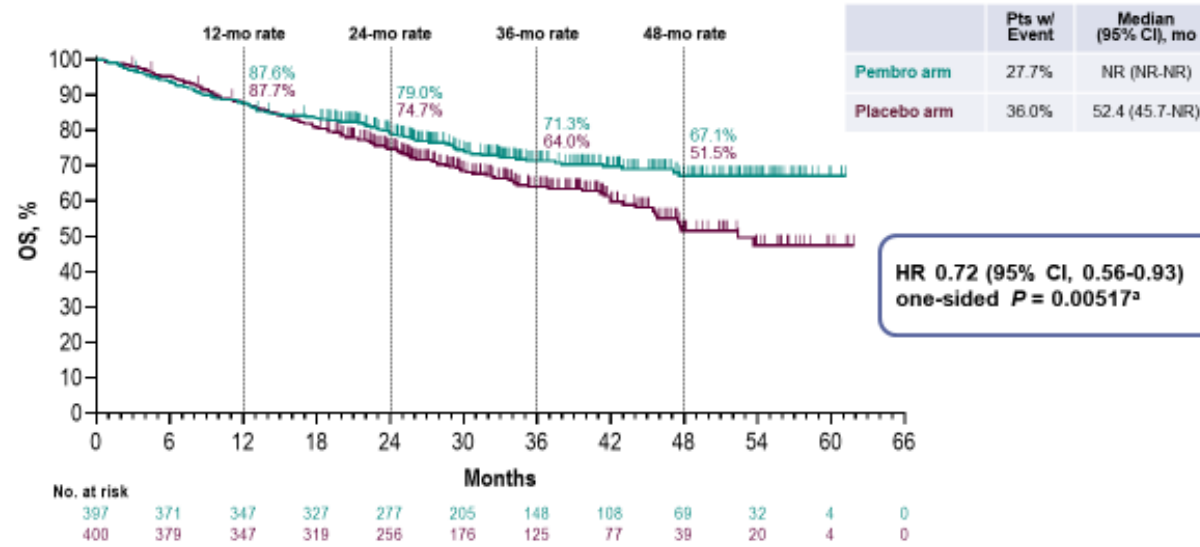
Overall Survival in Subgroups, IA2



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

Overall Survival, IA2

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



OS defined as time from randomization to death from any cause. *Significance boundary at IA2, one-sided $P = 0.00543$. 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%) |

^aConsidered by the investigator to be related to chemotherapy, pembrolizumab, and placebo. ^bAEs leading to death (n = 1 each): atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death (no new treatment-related deaths vs IA1). ^cAEs leading to death (n = 1 each): acute coronary syndrome, pneumonia, and pulmonary hemorrhage (no new treatment-related deaths vs IA1). ^dAE 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.

surgery



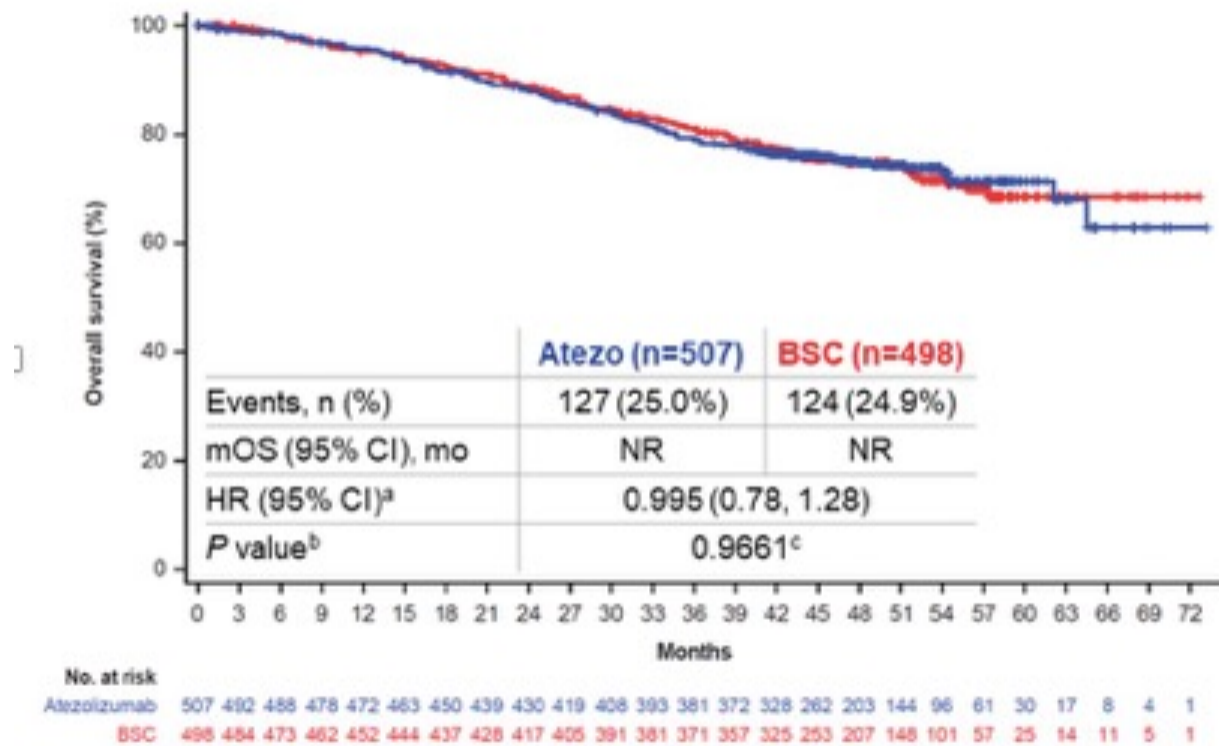
chemotherapy



immunotherapy

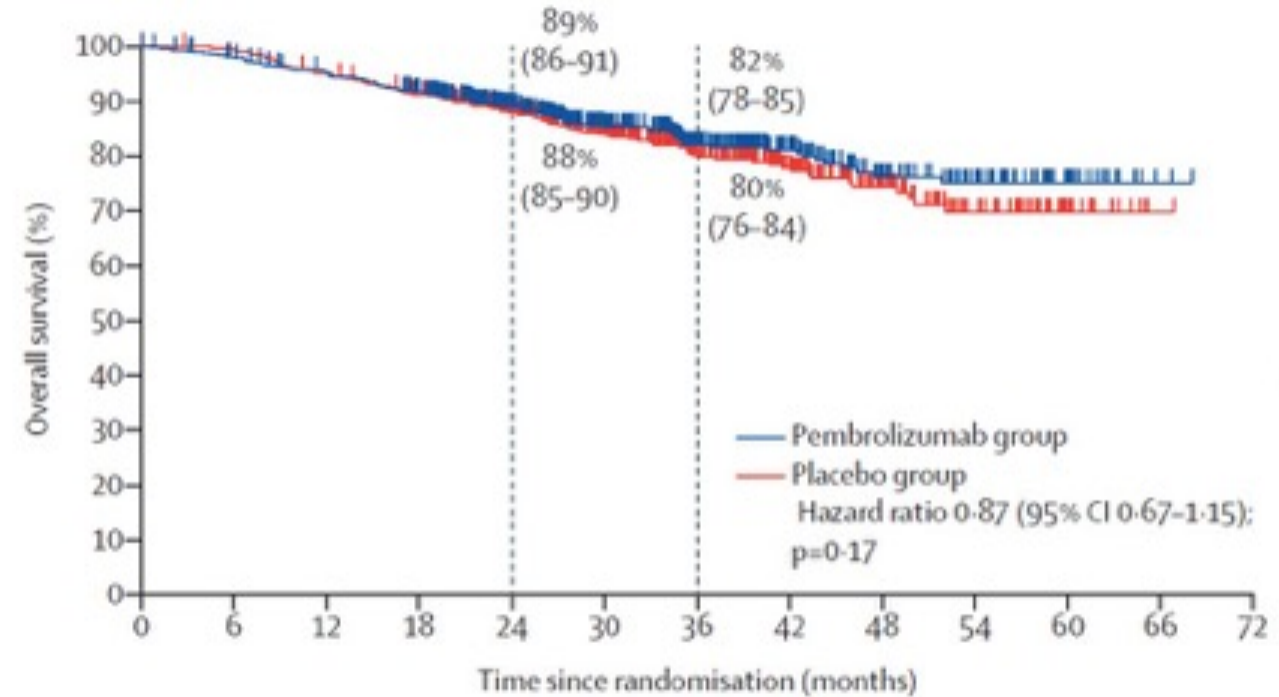
| Trial | DFS | OS (immature) |
|---------------------|-------------|---------------------|
| Impower010 (PD-L1+) | NR vs 35 mo | HR 0.66 (0.5-0.88) |
| PEARLS | 54 vs 42 mo | HR 0.87 (0.67-1.15) |

IMpower 010
ITT population stage IB-III A

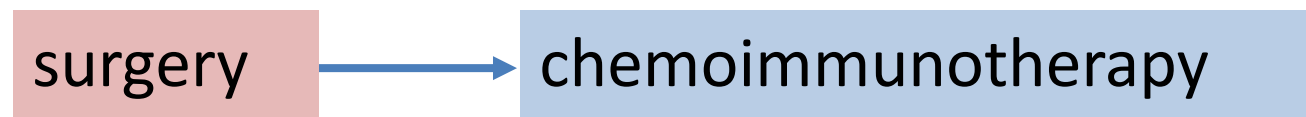
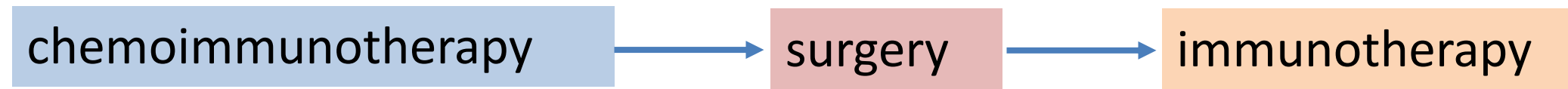


Median Follow Up: 45 months (interim analysis)

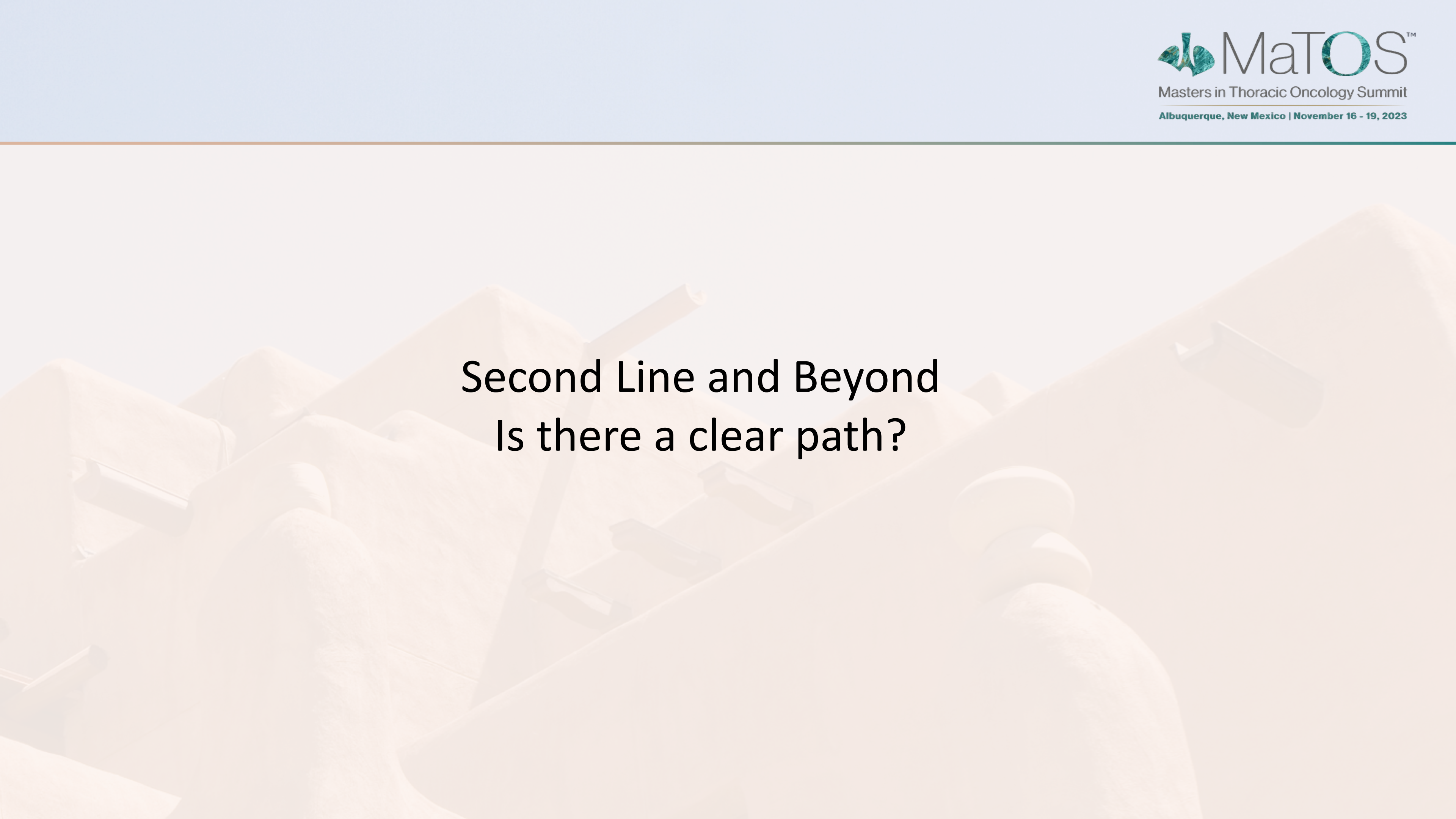
KEYNOTE-091/PEARLS



Median Follow Up: 35.6 months (interim analysis)



And for which patient population?



Second Line and Beyond

Is there a clear path?

Overcoming Resistance to Immunotherapy

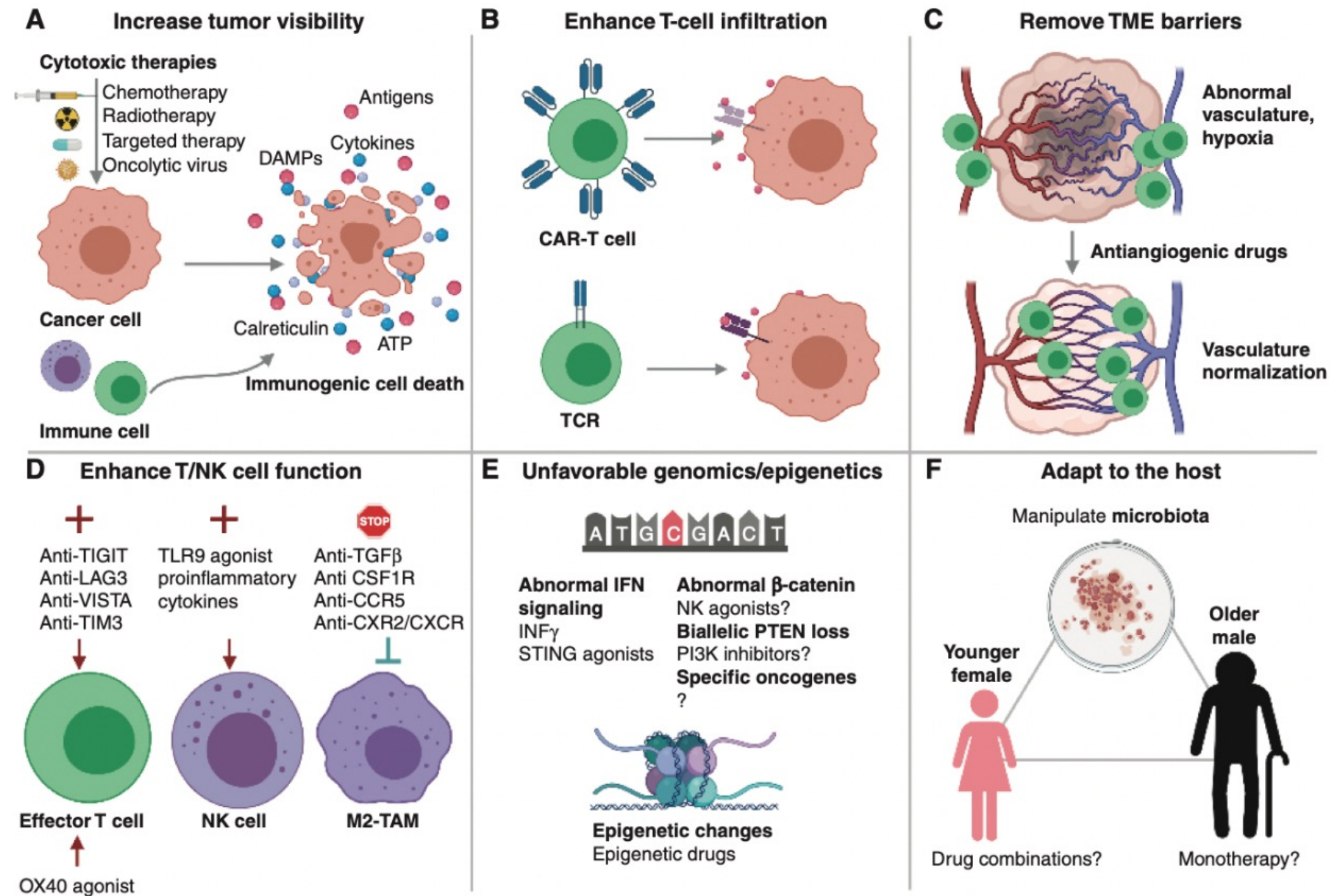
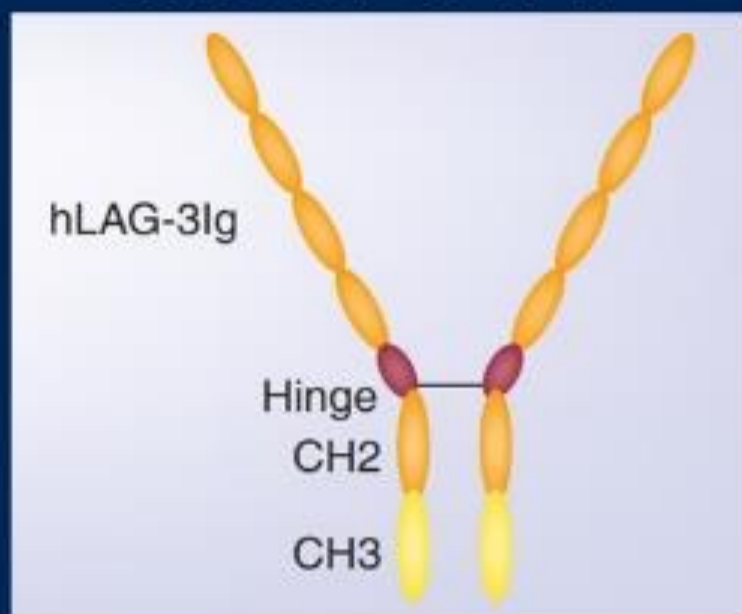


Figure 4. Overcoming resistance to immunotherapy. **A**, Increase tumor visibility. **B**, Enhance T-cell infiltration. **C**, Remove TME barriers. **D**, Enhance T-cell/NK-cell function. **E**, Unfavorable genomics/epigenetics. **F**, Adapt to the host.

Eftilagimod alpha (efti) – soluble LAG-3

STRUCTURE OF EFTI⁴



- **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 efti¹.
- 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

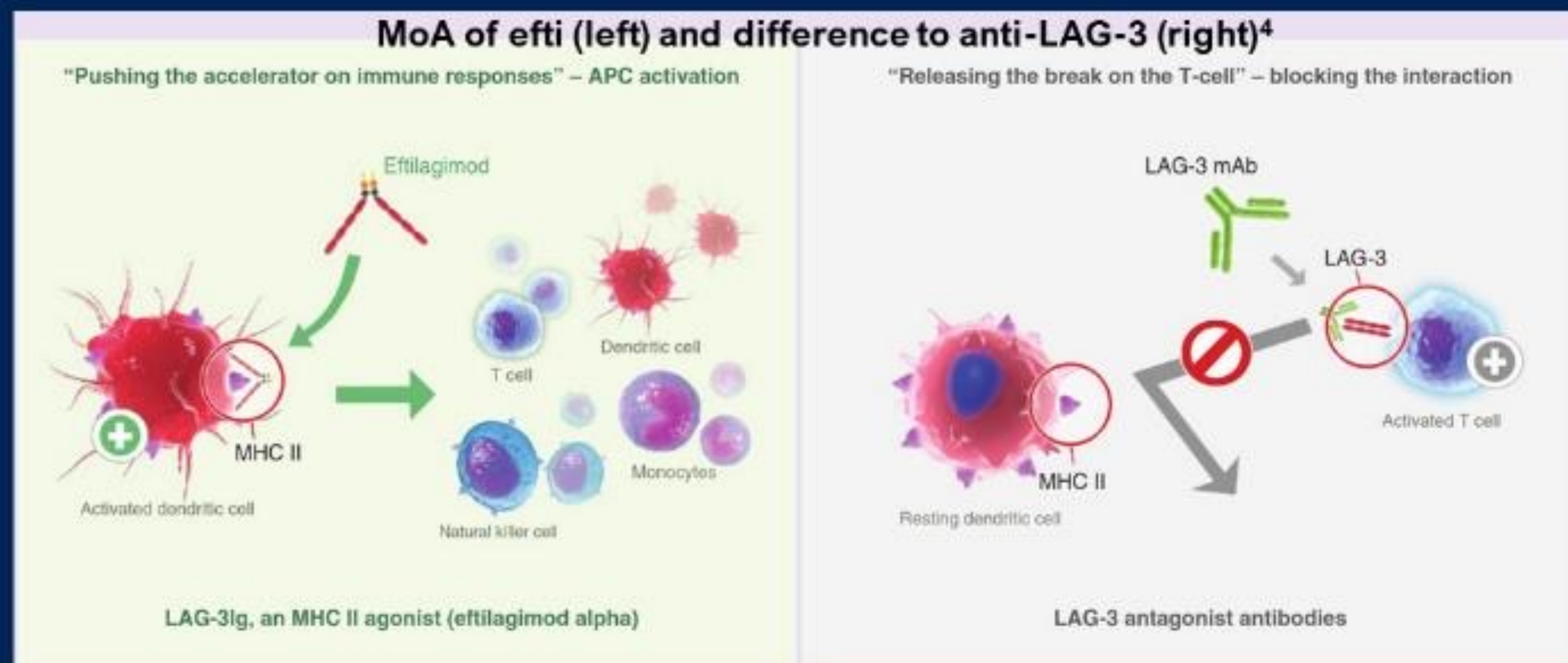
s.c.: subcutaneous

¹ Internal data, Immutep, not yet published.

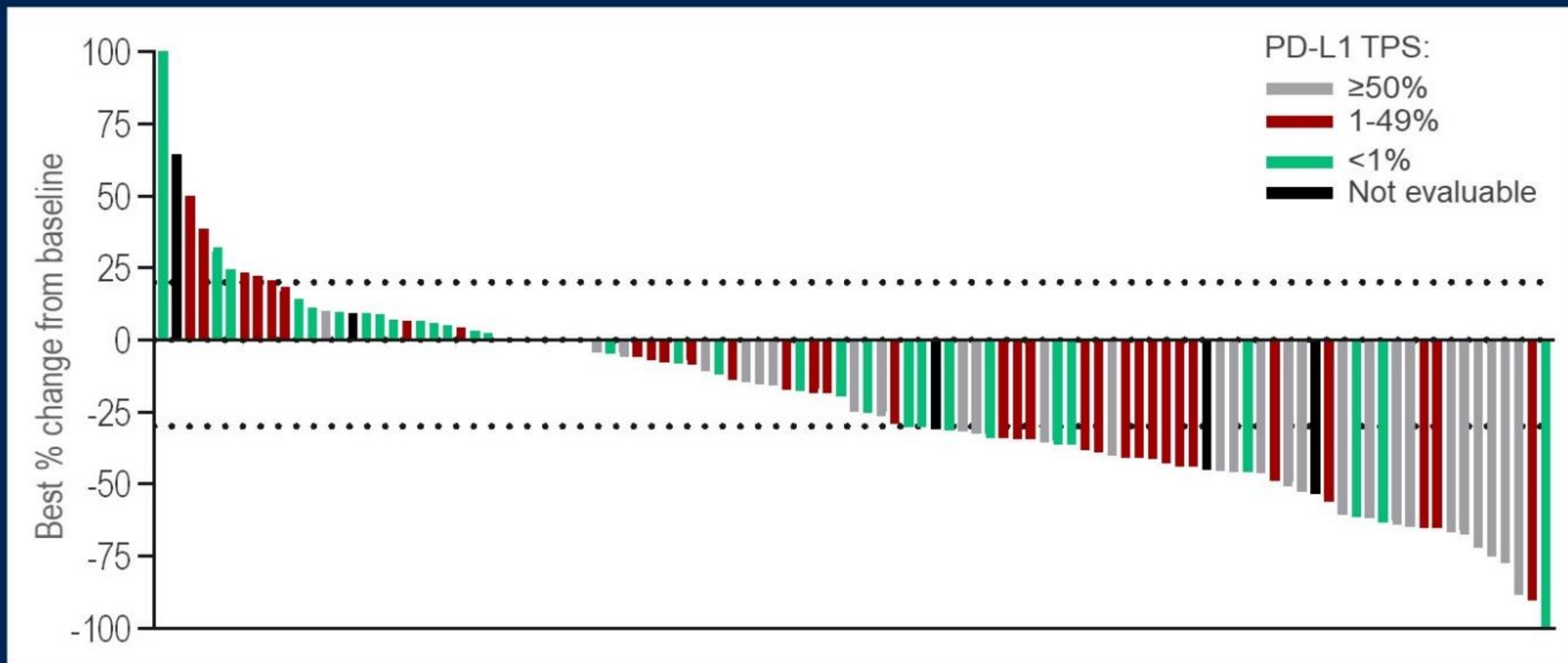
² Brignone C, Clin Cancer Res. 2009;15: 6225- 6231.

³ Atkinson V, J Immunoth Cancer. 2020; 8(2):e001681.

⁴ Dirix L, Triebel F. Future Oncol. 2019;15(17):1963-1973.



Efficacy – Waterfall plot¹ – TACTI-002

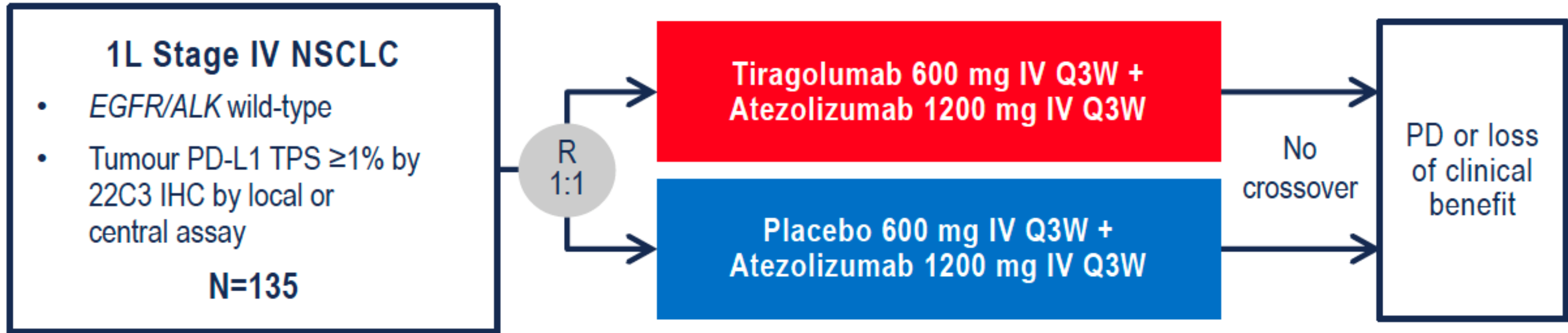


¹ all patients with ≥ 1 post-baseline CT scan n=103; ² PD-L1 assessed by central assessment (Dako kit); n=79; ³ local assessment included due to non evaluable central assessment results, n=19; ⁴ no results available for neither central nor local testing, n=5.

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

Data cut-off date: April 15, 2022

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 analysis¹

- 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

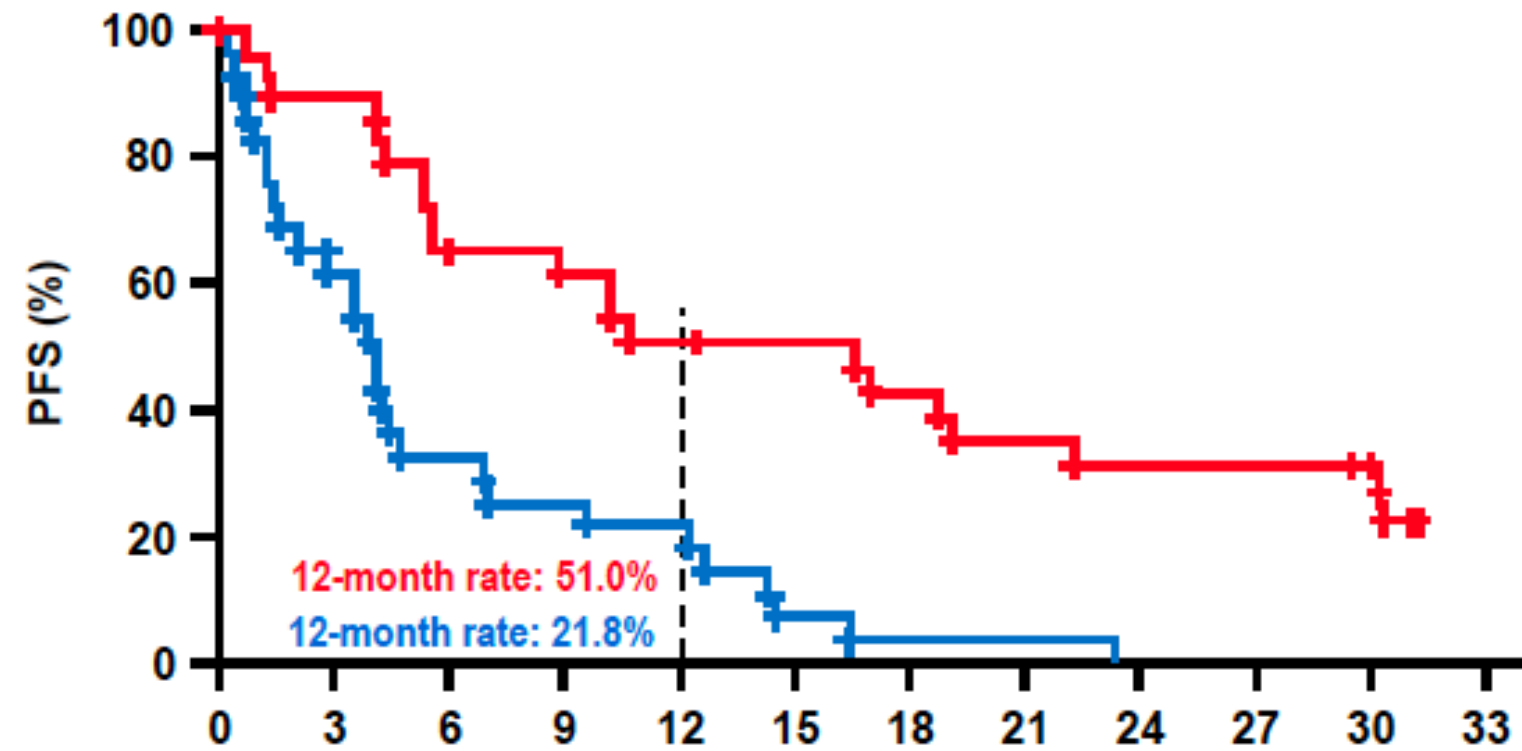
IHC, immunohistochemistry; PROs, patient-reported outcomes; TPS, tumor proportion score.

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

Investigator-Assessed PFS: PD-L1 Subgroups

PD-L1 TPS $\geq 50\%$ (n=58)

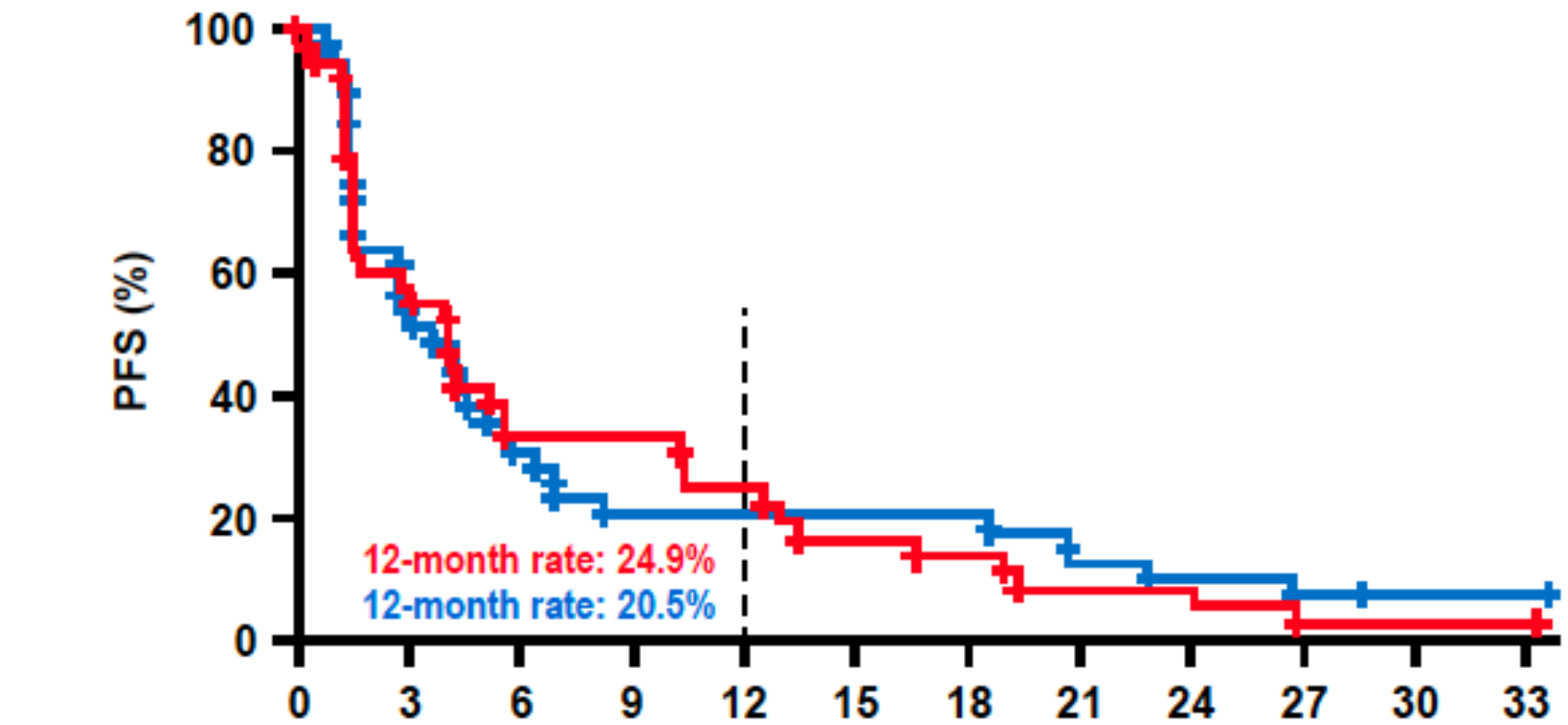
| | Events n (%) | Median PFS, months (95% CI) | PFS HR (95% CI) | ORR, % | Median DOR, months (95% CI) |
|------------------------|-----------------|--------------------------------|----------------------|--------|-----------------------------------|
| Tira + atezo | 21 (72.4) | 16.6 (5.5–22.3) | 0.29* (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 | Time (months) | | | | | | | | | | | |
|-------------|---------------|----|----|----|----|----|----|----|----|----|----|----|
| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 |
| 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) |



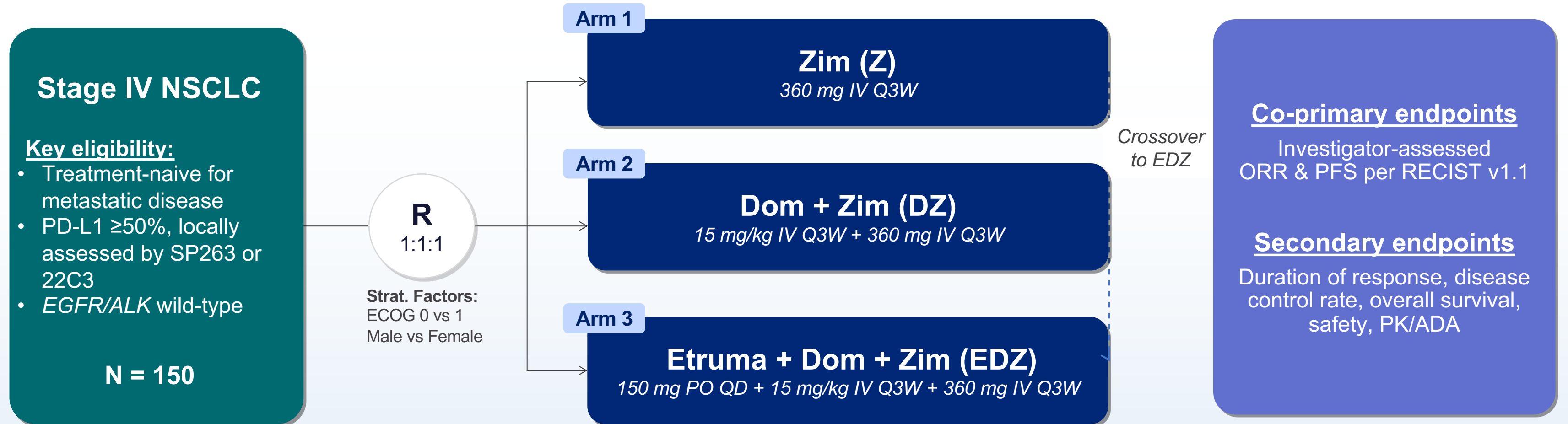
| No. at risk | Time (months) | | | | | | | | | | | |
|-------------|---------------|----|----|----|----|----|----|----|----|----|----|----|
| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 |
| T + A | 38 | 22 | 12 | 12 | 9 | 6 | 5 | 3 | 3 | 1 | 1 | 1 |
| P + A | 39 | 21 | 12 | 8 | 8 | 8 | 8 | 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.

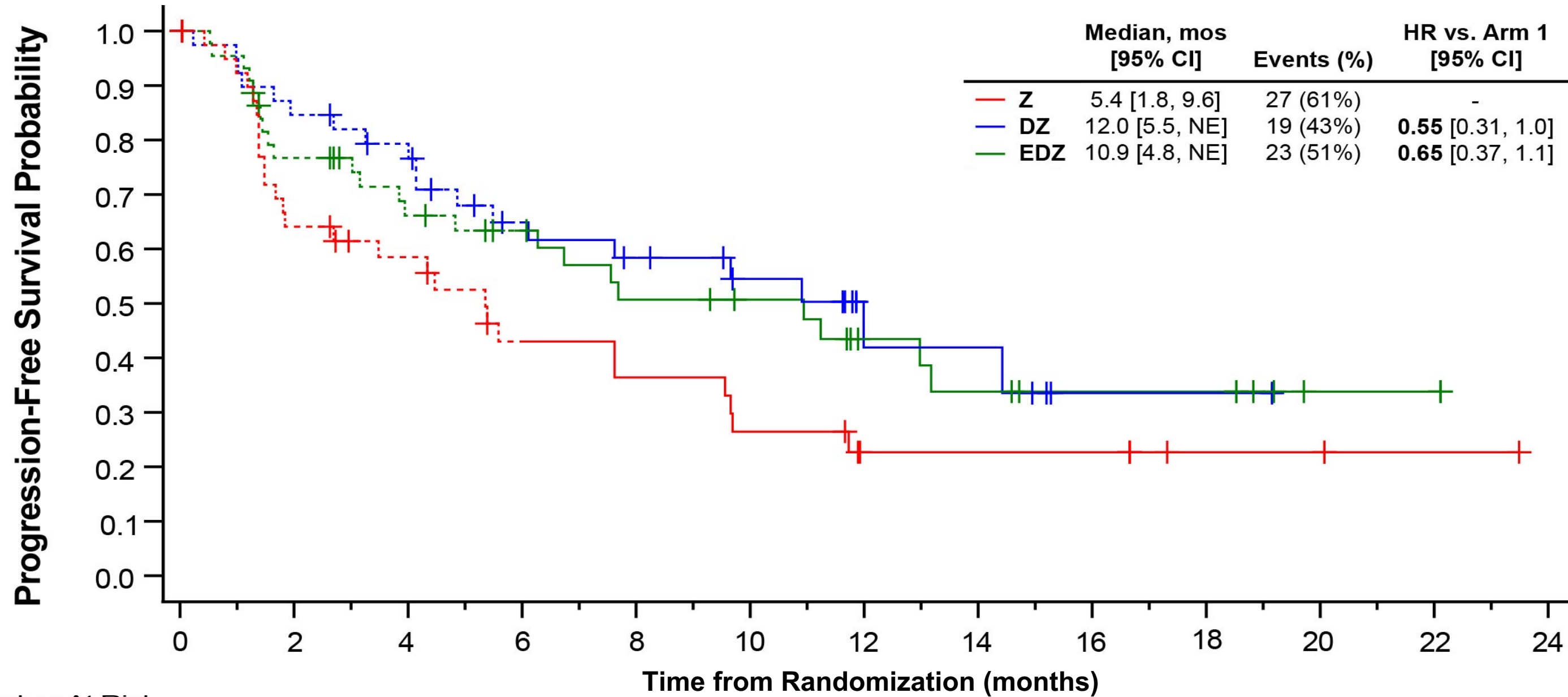
ARC-7: Randomized, Open-label, Phase 2 Study in First-Line, Metastatic, PD-L1-High NSCLC



Participants randomized to Arm 1 have the option to crossover to EDZ upon radiographically confirmed disease progression (PD)

- 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)

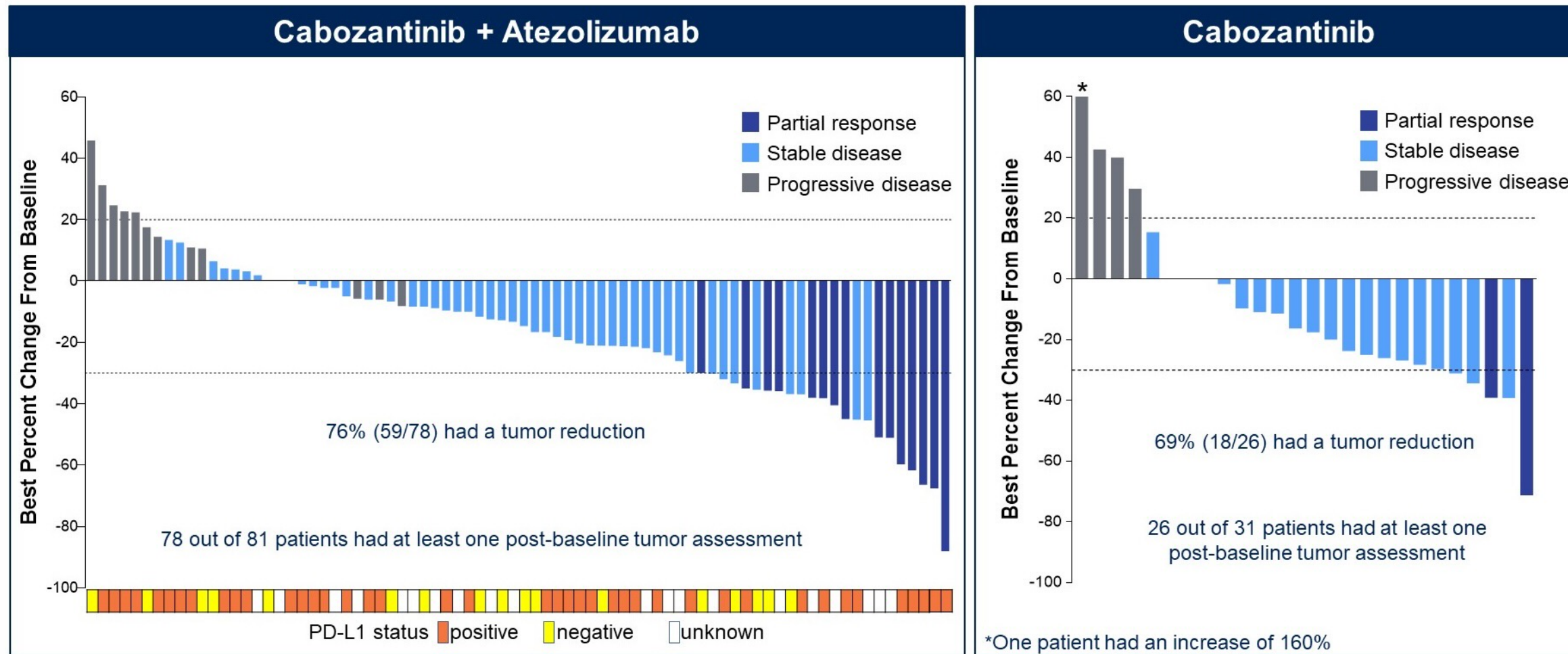
Progression-Free Survival – ITT-13



Number At Risk:

| | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 |
|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Z | 44 | 25 | 20 | 13 | 11 | 8 | 4 | 4 | 4 | 2 | 2 | 1 | |
| DZ | 44 | 33 | 29 | 20 | 17 | 13 | 5 | 5 | 1 | 1 | 0 | 0 | |
| EDZ | 45 | 32 | 25 | 21 | 16 | 14 | 9 | 7 | 5 | 5 | 1 | 1 | |

Cabozantinib Plus Nivolumab

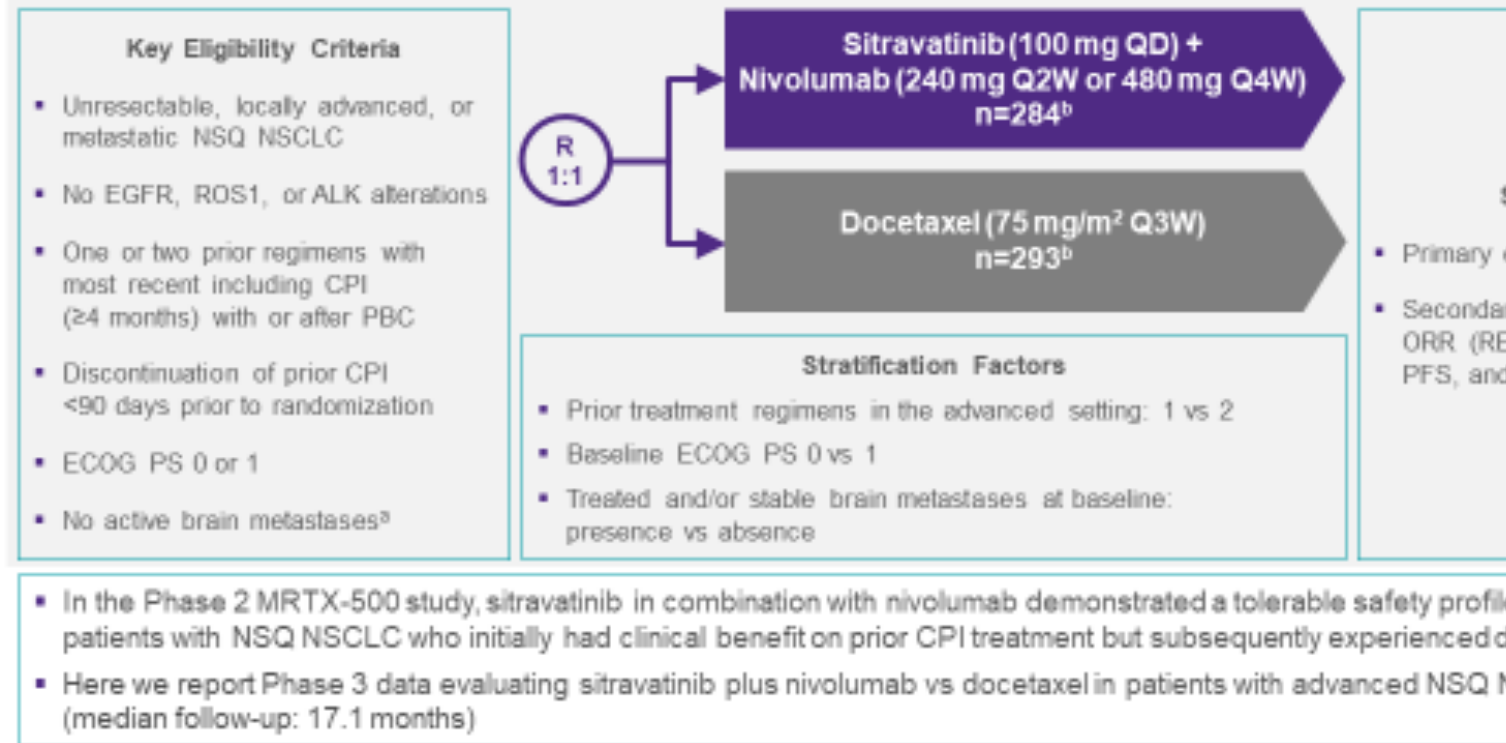


Per investigator by RECIST v1.1.

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.

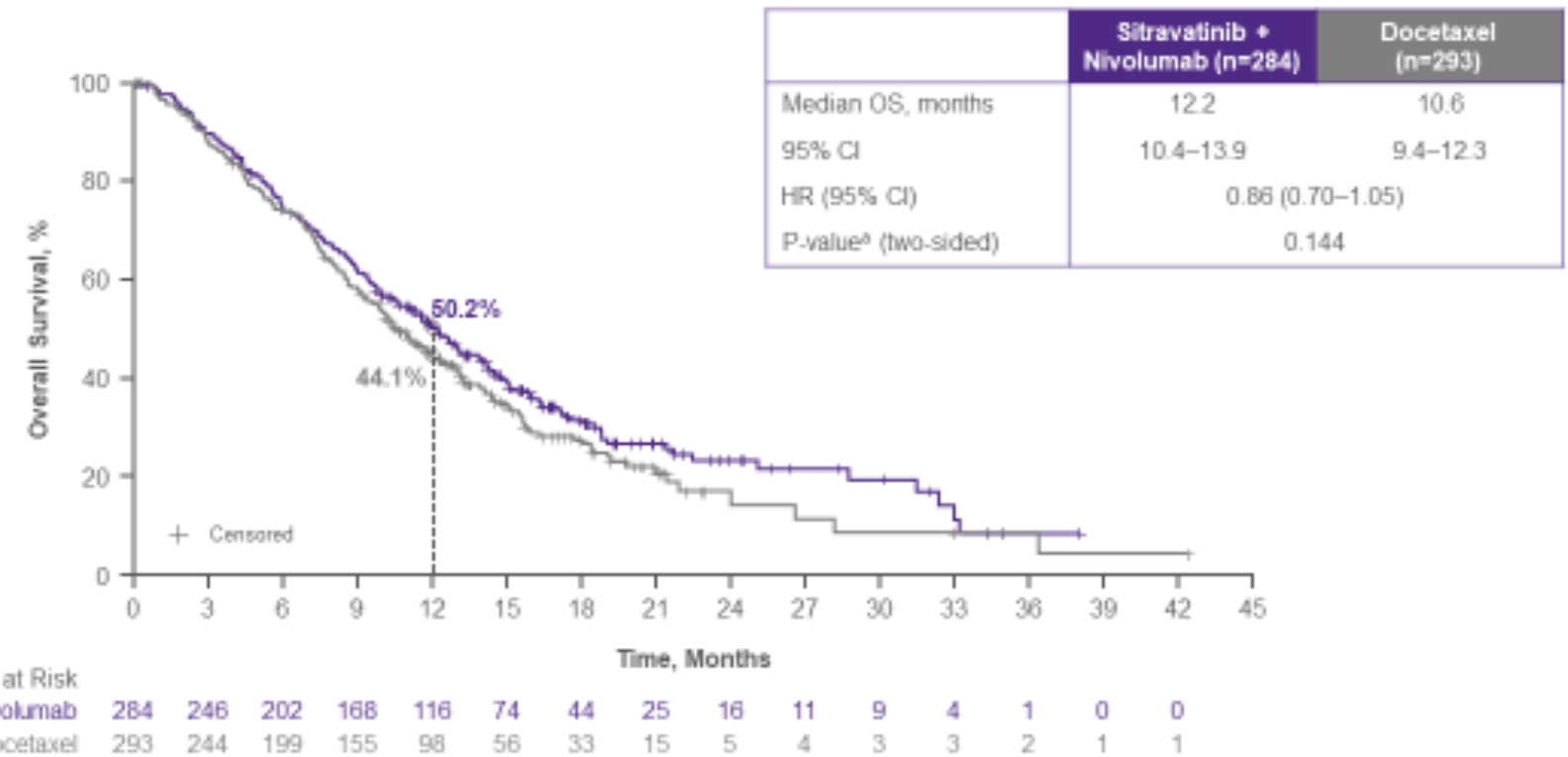
SAPPHIRE Phase 3 Study in NSCLC: Trial Design



Study Objectives

- Primary objective: Overall Survival (OS)
- Secondary objectives: Response Rate (RR), Progression-Free Survival (PFS), and Quality of Life (QoL)

Overall Survival



CI, confidence interval; HR, hazard ratio
^aP-value is based on the log-rank test
 Censoring rate, n (%): sitravatinib plus nivolumab, 98 (35%); docetaxel, 102 (35%)
 Data as of March 28, 2023 (median duration of follow-up: 17.1 months)

ALK, anaplastic lymphoma kinase; BCR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; E inter-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, once daily; R, randomization; ROS1, c-ros oncogene 1; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1
^aTreated and/or stable brain metastases were allowed. ^bITT population. ^cData presented per BCR
 ClinicalTrials.gov: NCT03900071

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)

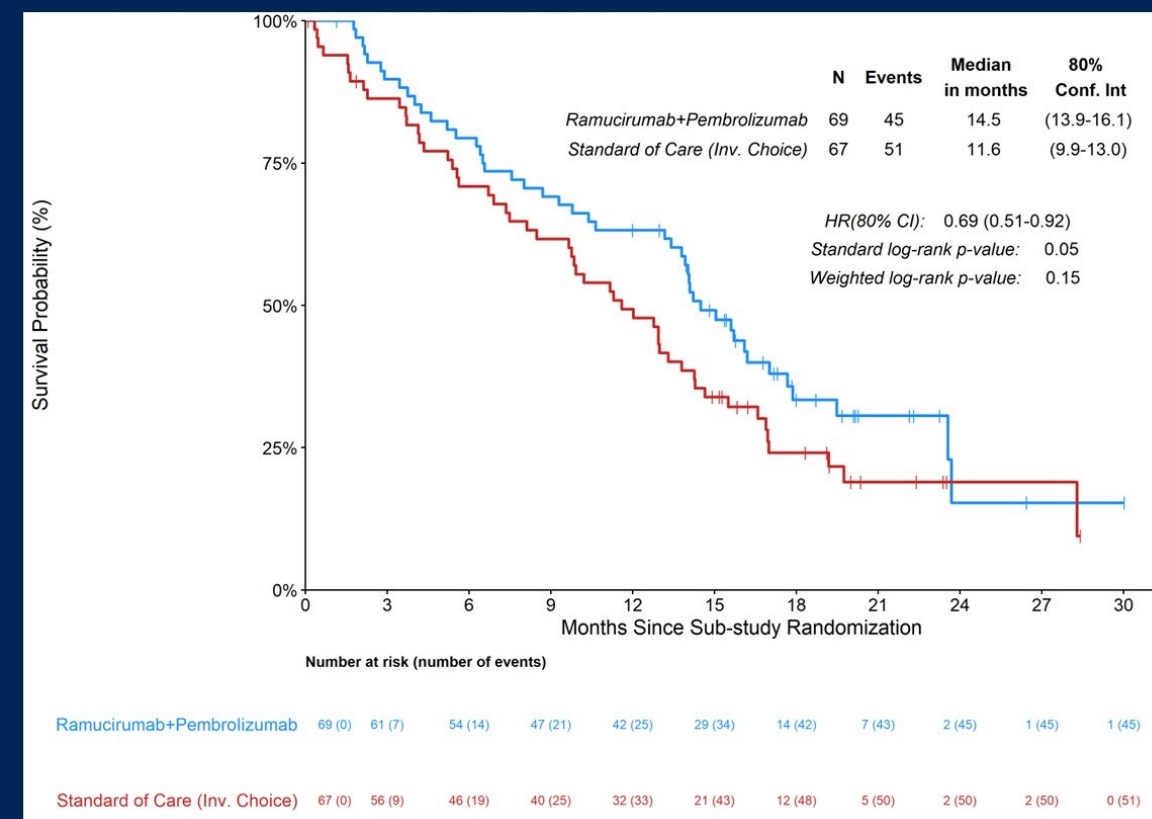
Randomization

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



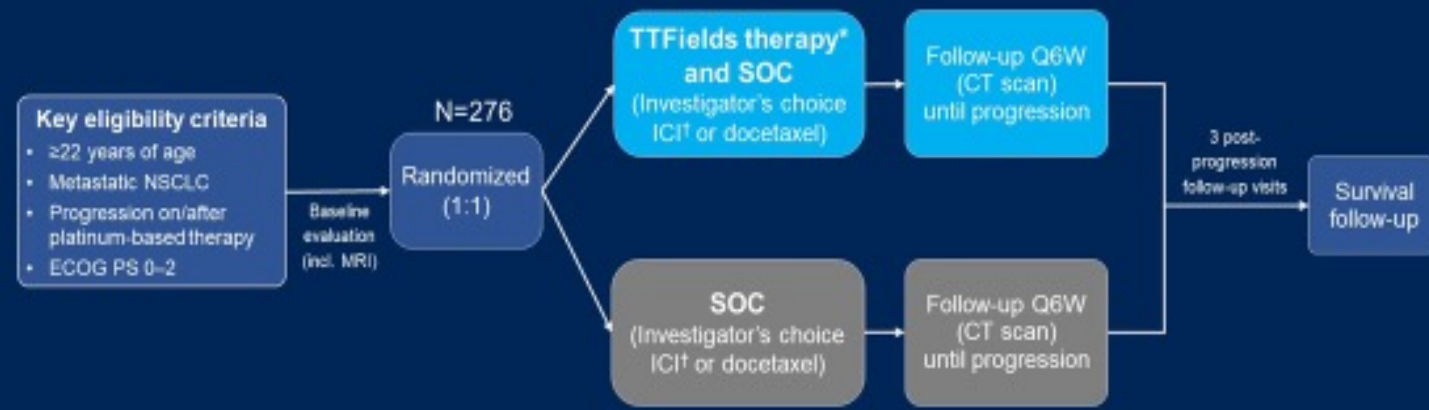
- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

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

LUNAR Phase 3 Study Design

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



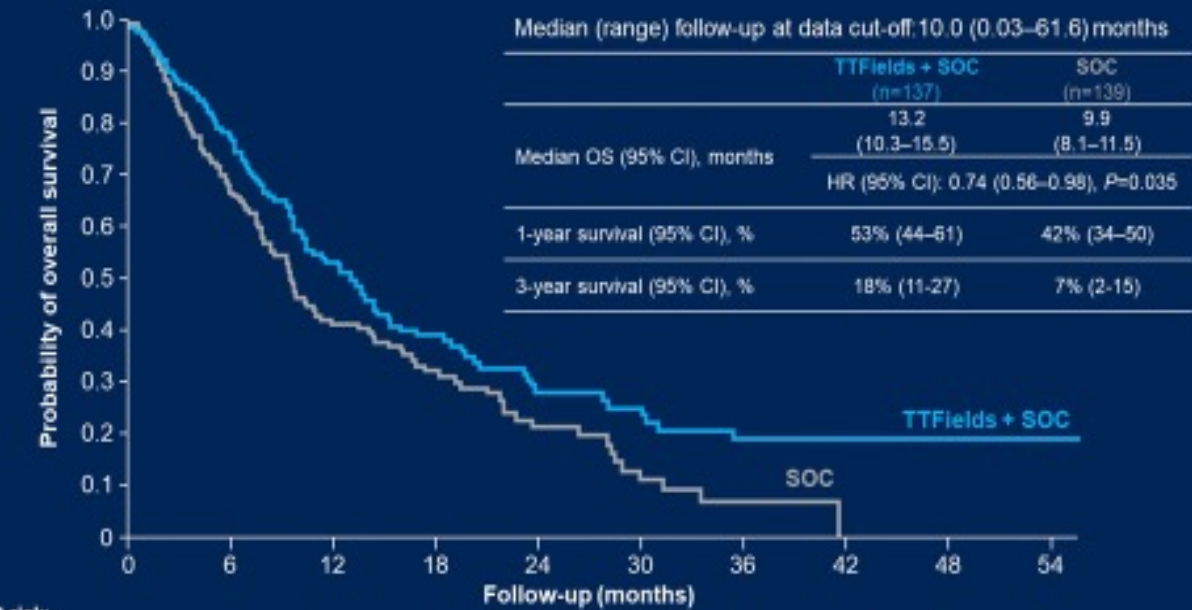
Data cut-off: November 26, 2022

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 mg; 210 mg; 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; TTFelds, Tumor Treating Fields

Overall Survival in the ITT Population



Number at risk:

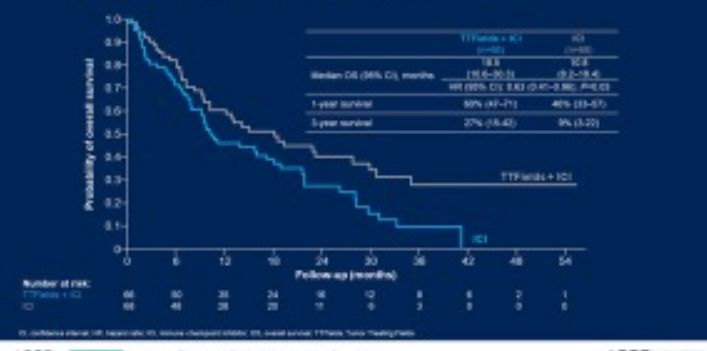
TTFelds + SOC

SOC

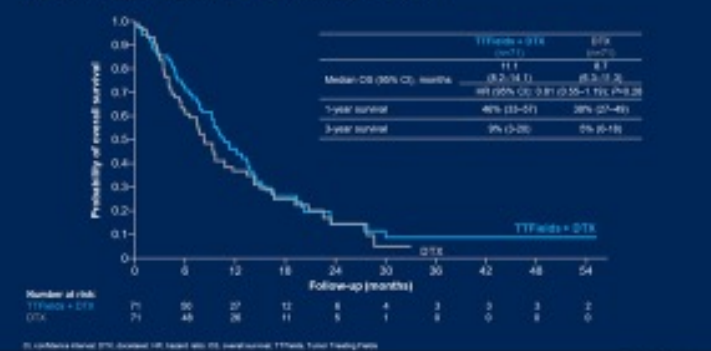
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival; SOC, standard of care; TTFelds, Tumor Treating Fields

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)

| | TTFelds + SOC (n=133) | | SOC (n=134) | |
|---------------------------------|--------------------------|----------|----------------|----------|
| | All grades | Grade ≥3 | All grades | Grade ≥3 |
| Any TEAE | 97% | 58% | 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; TTFelds, Tumor Treating Fields

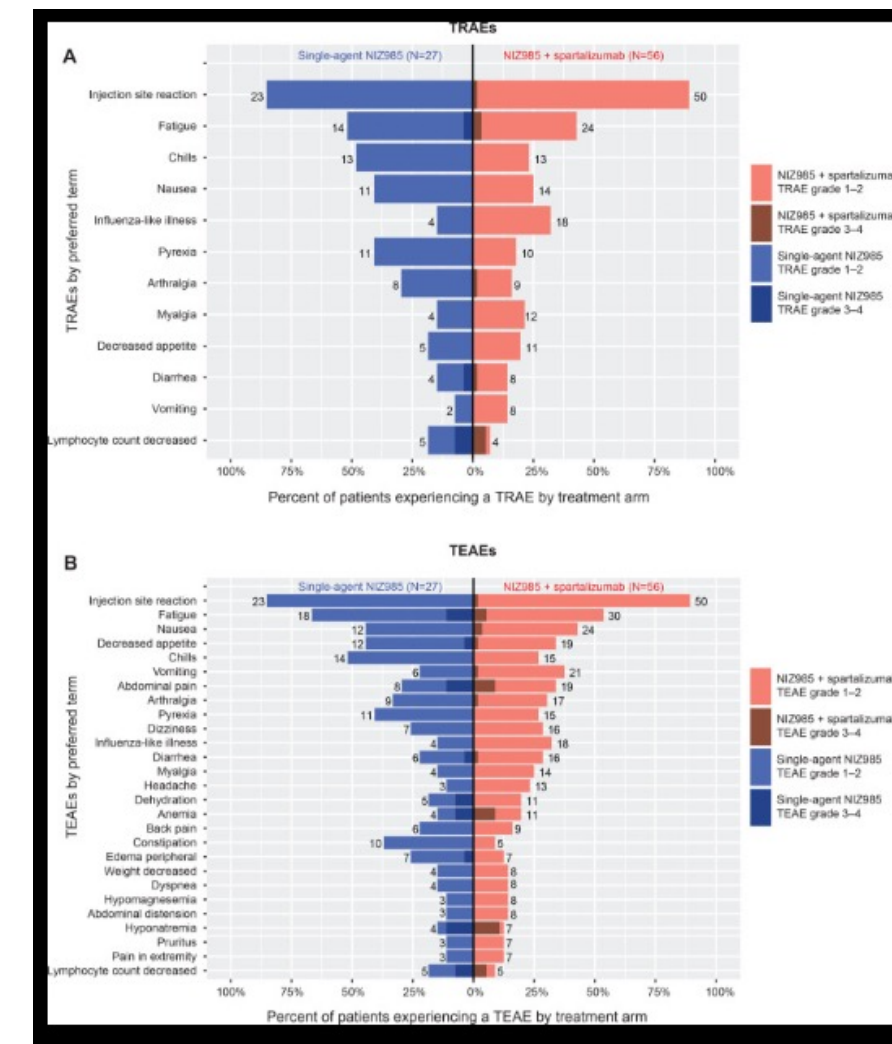
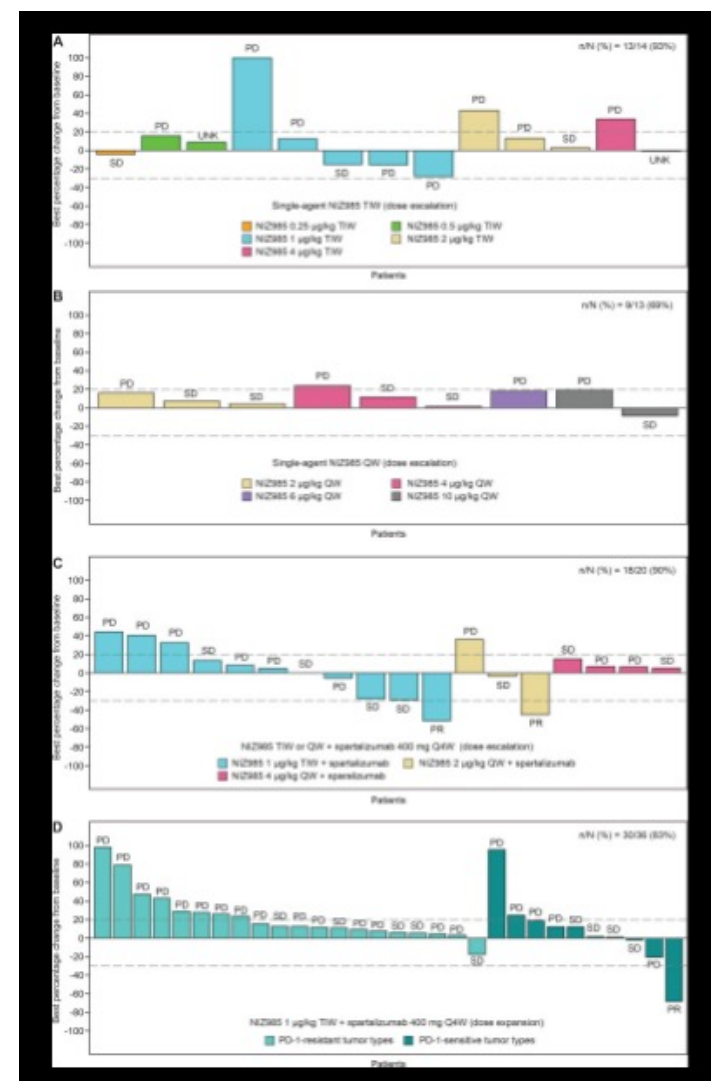
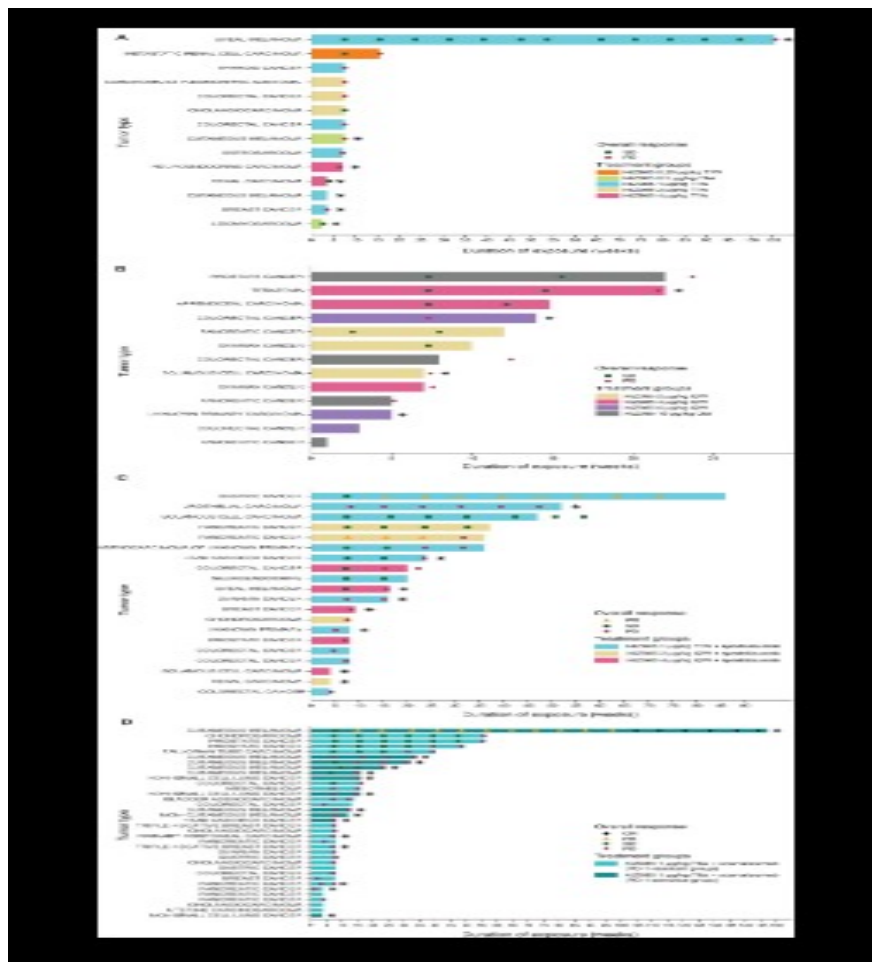
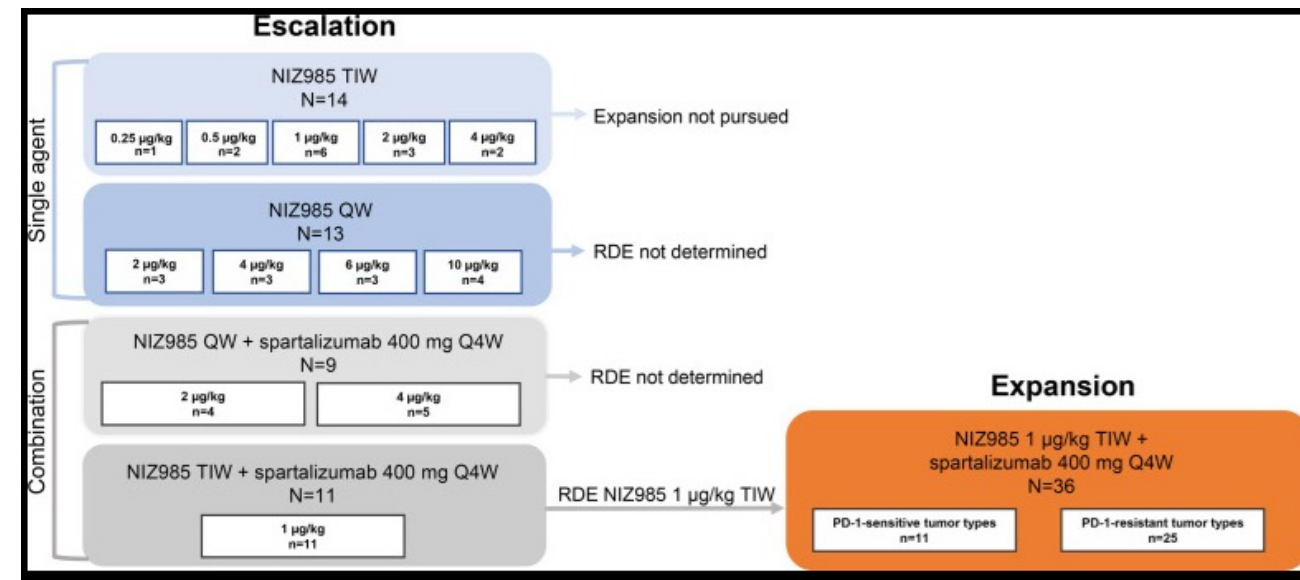
2023 ASCO ANNUAL MEETING

#ASCO23

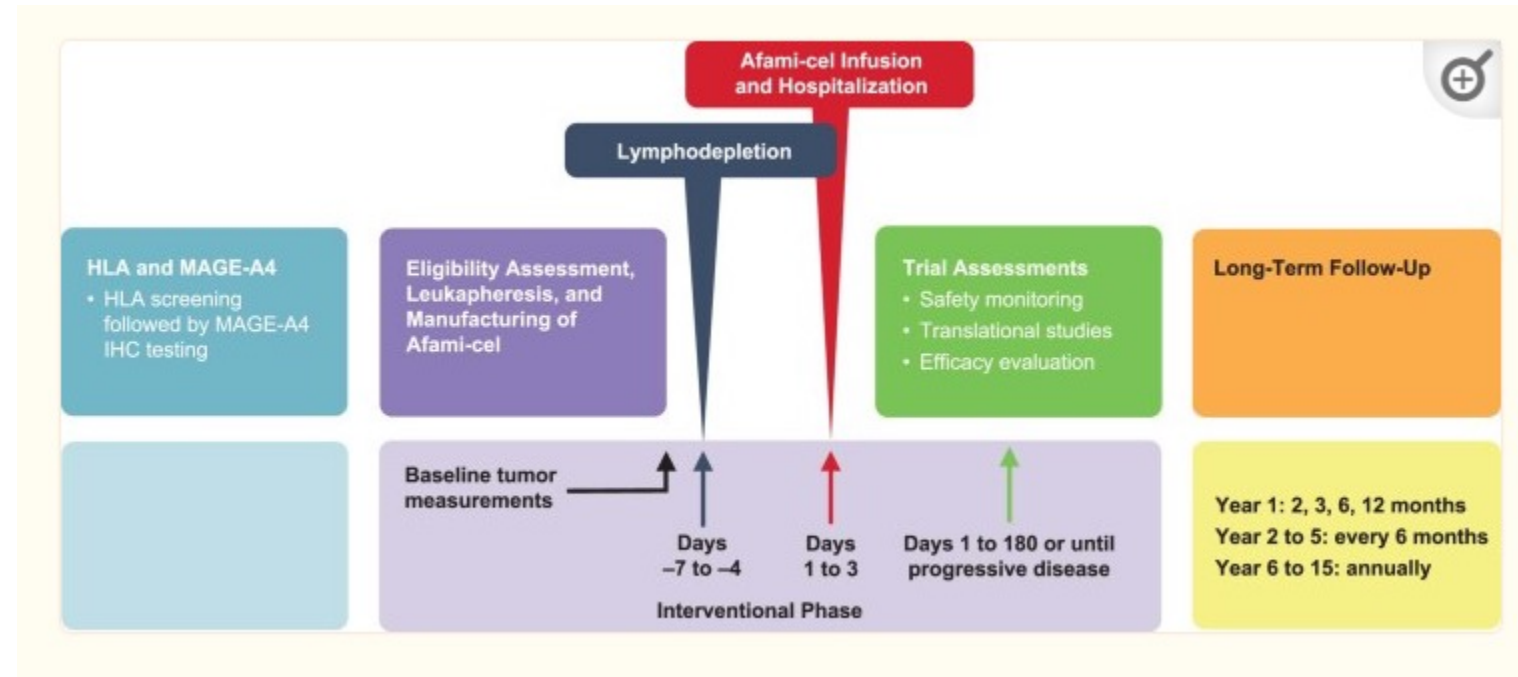
Presented by: Tiziana Leal, MD, Winship Cancer Institute - Emory University
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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

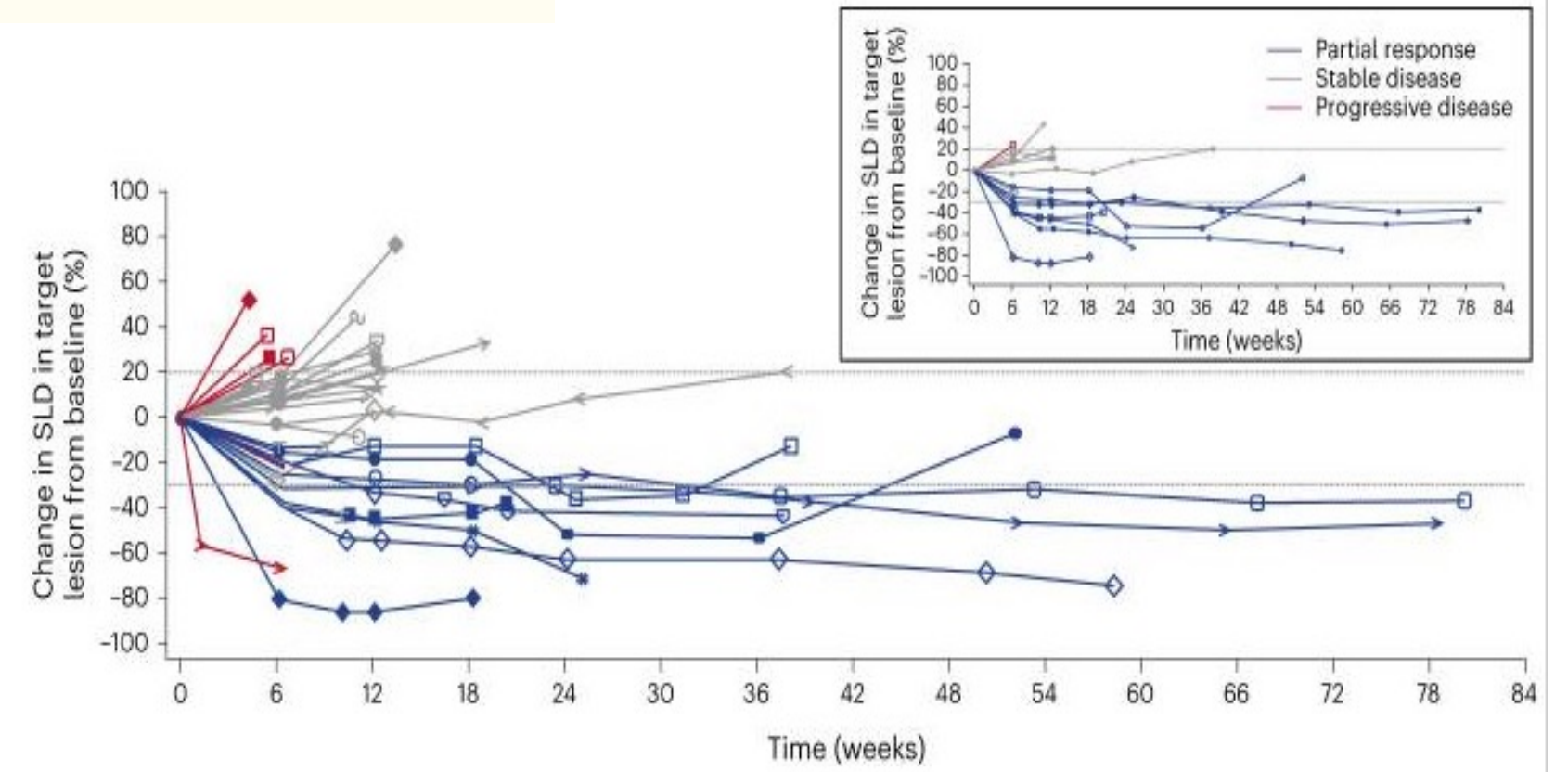
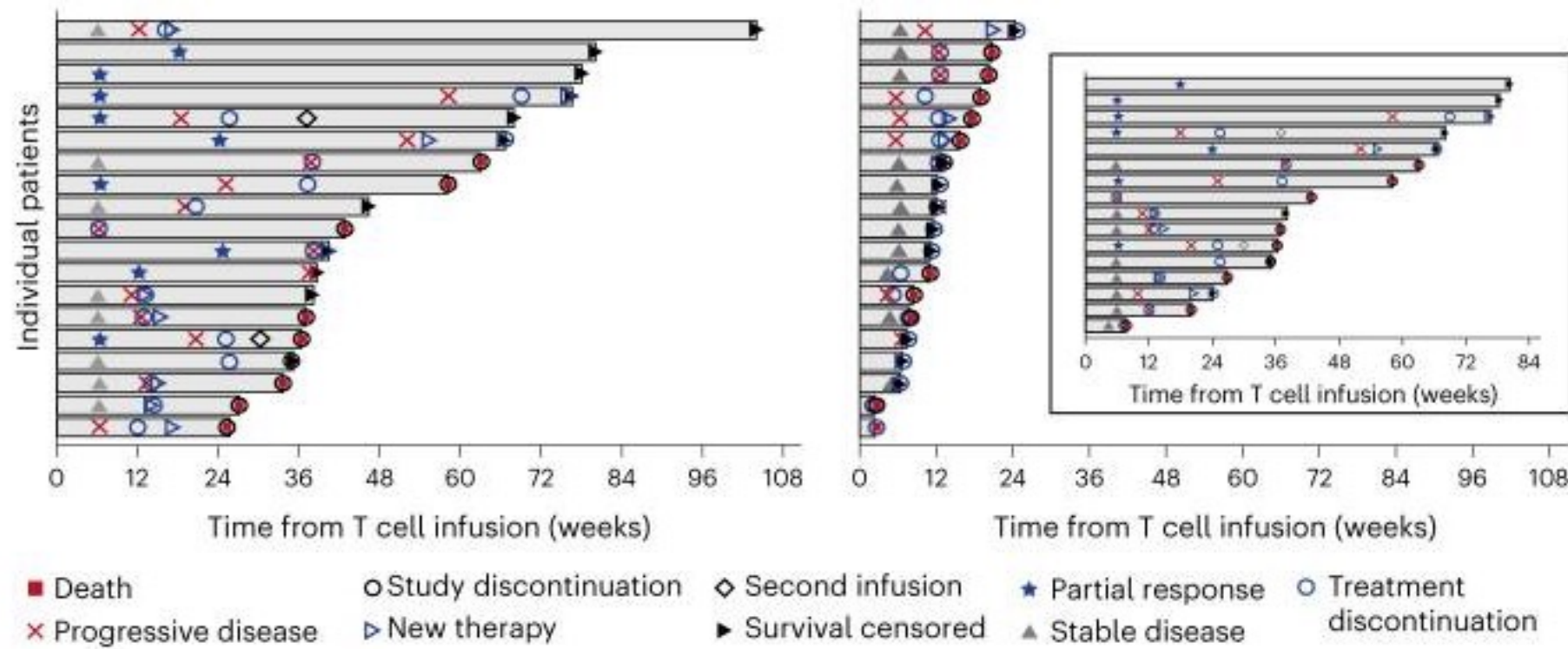
First-in-human phase I/Ib study of NIZ985, a recombinant heterodimer of **IL-15** and **IL-15R α** , as a single agent and in combination with spartalizumab in patients with advanced and metastatic solid tumors



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



38 patients treated, 2 with NSCLC



- 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

