Overcoming Resistance to Immunotherapy

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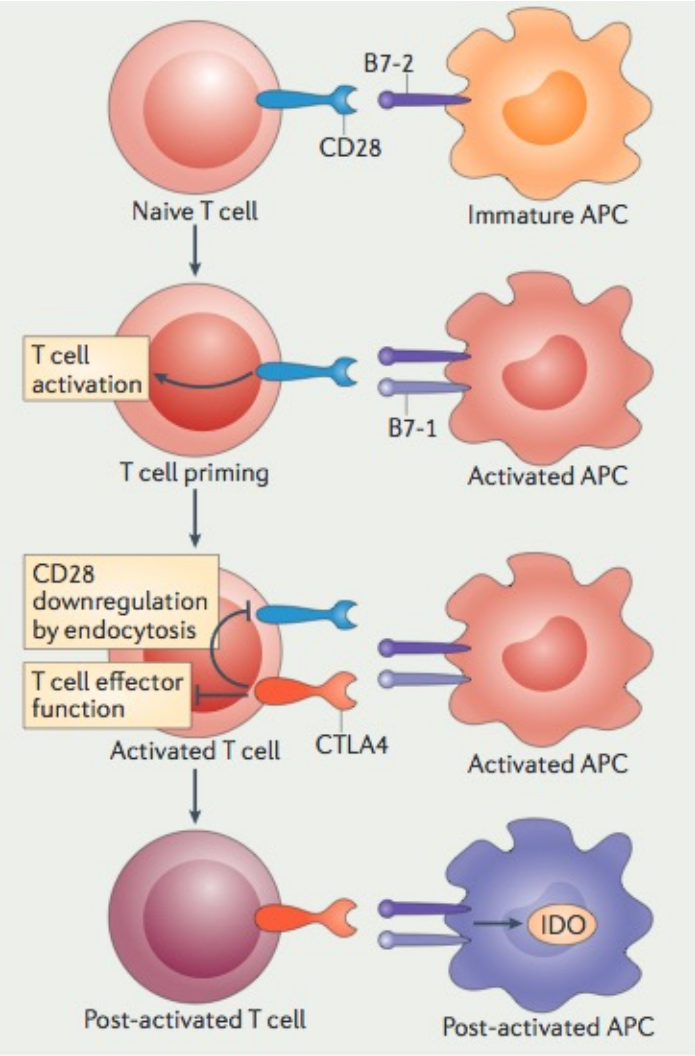
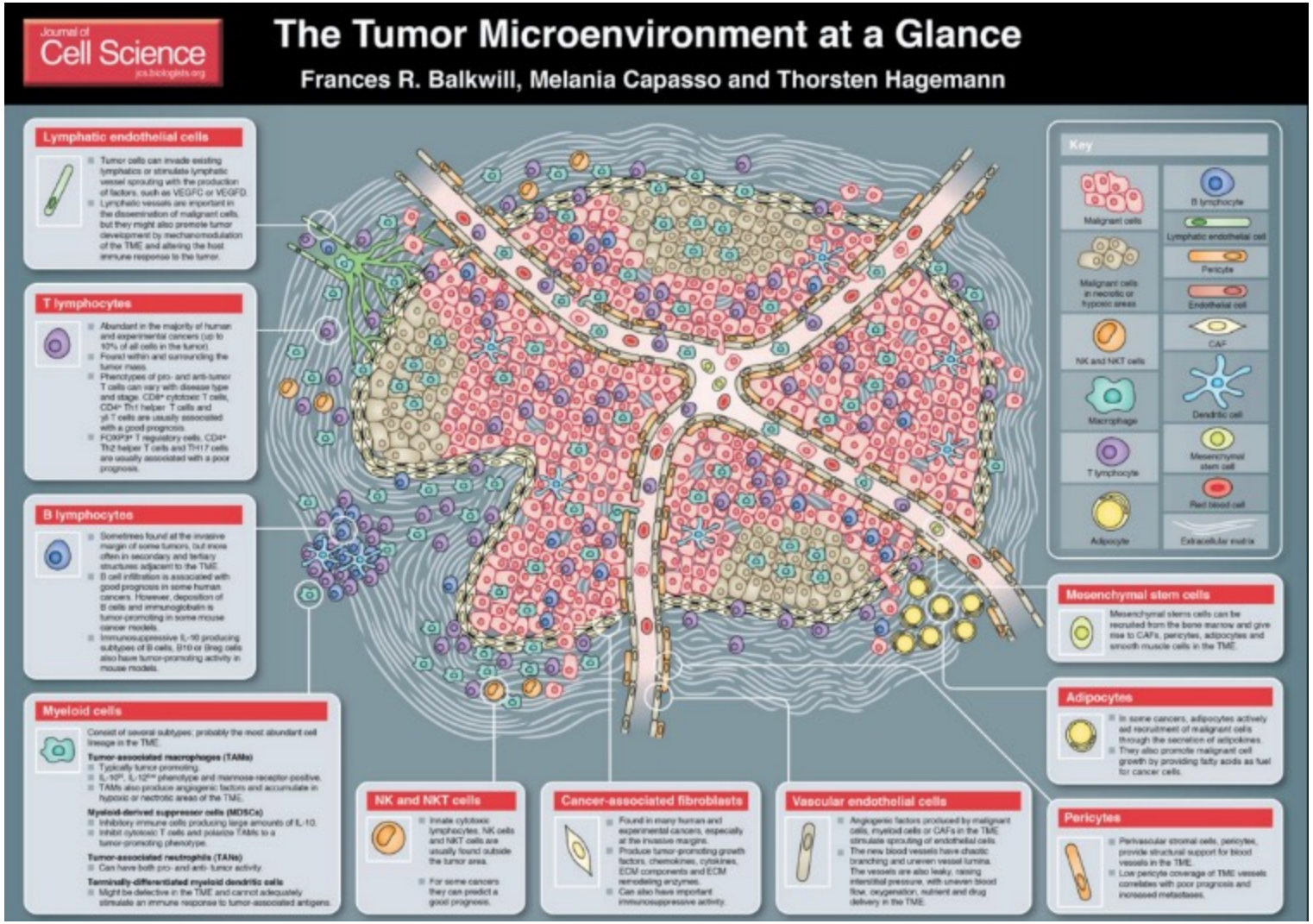
2024

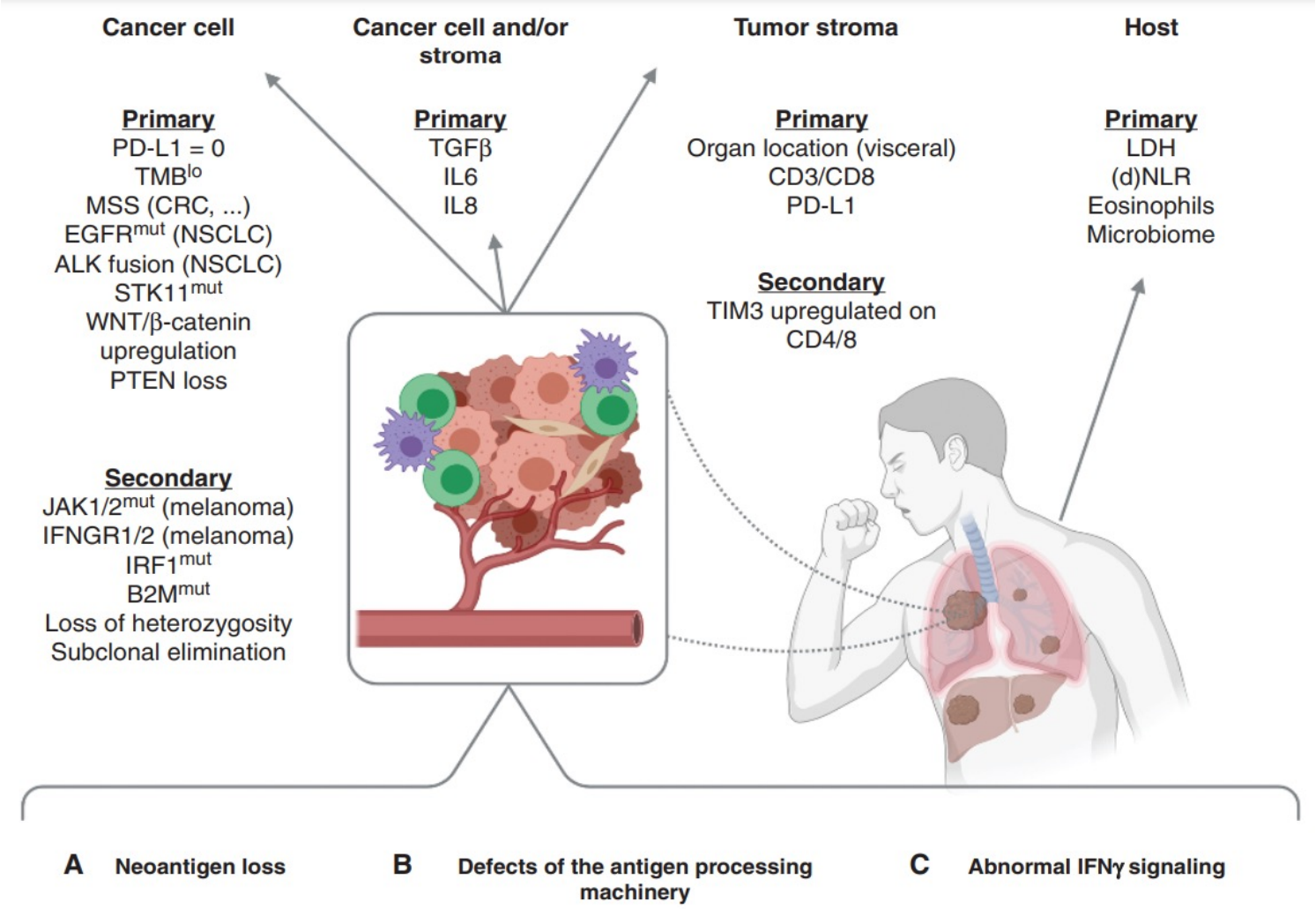
Explanation of the Molecular Mechanisms of Checkpoint Inhibitors and Other Key Emerging Immunologic Strategies





Chen L et al. *Nat Rev Immunol*. 2013;13(4):227-242. Balkwill FR, et al. *J Cell Sci*. 2012;125(pt 23):5591-5596.

Mechanisms Driving Resistance



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

Mechanisms Driving Resistance

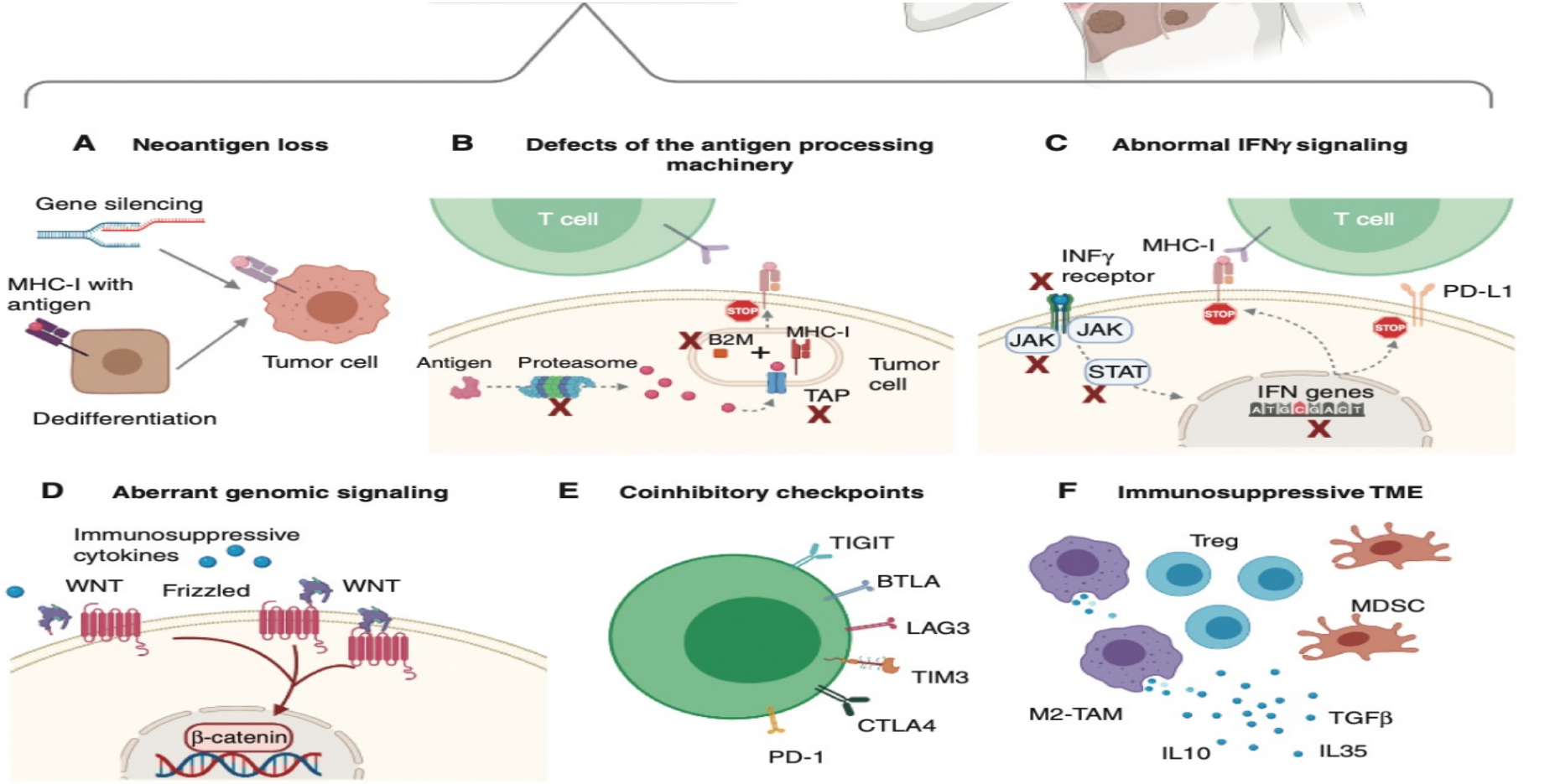


Figure 3. Most commonly described mechanisms driving resistance to immunotherapy. **A,** Neoantigen loss. **B,** Defects of the antigen processing machinery. **C,** Abnormal IFNγ signaling. **D,** Aberrant genomic signaling. **E,** Coinhibitory checkpoints. **F,** Immunosuppressive TME. CRC, colorectal cancer; IL, interleukin; IFNγ, interferon gamma; MDSC, myeloid-derived suppressor cells; MHC I, major histocompatibility complex I; M2-TAM, tumor-associated macrophages type 2; MSS, microsatellite-stable; mut, mutation; Treg, regulatory T cells.

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

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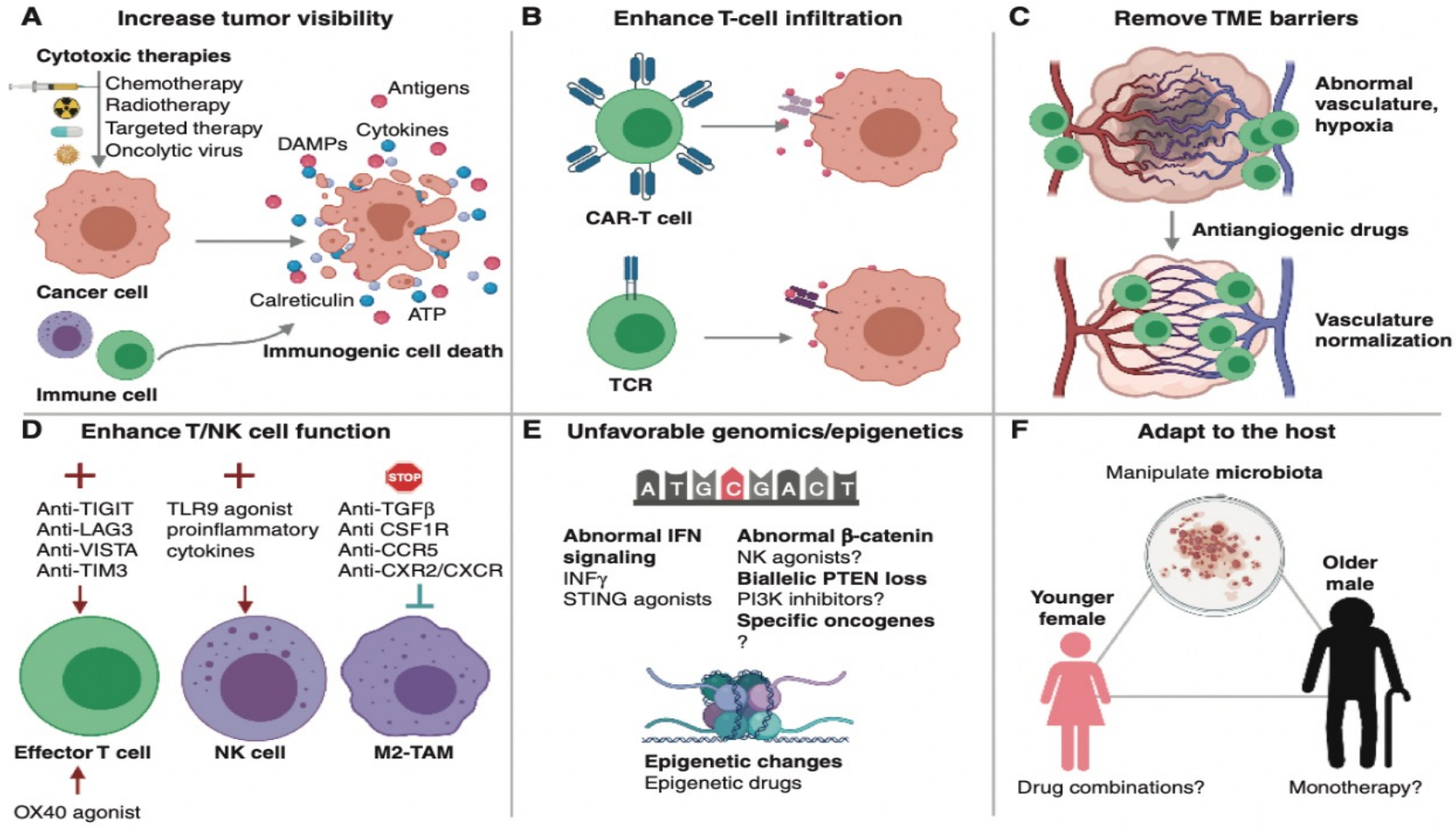
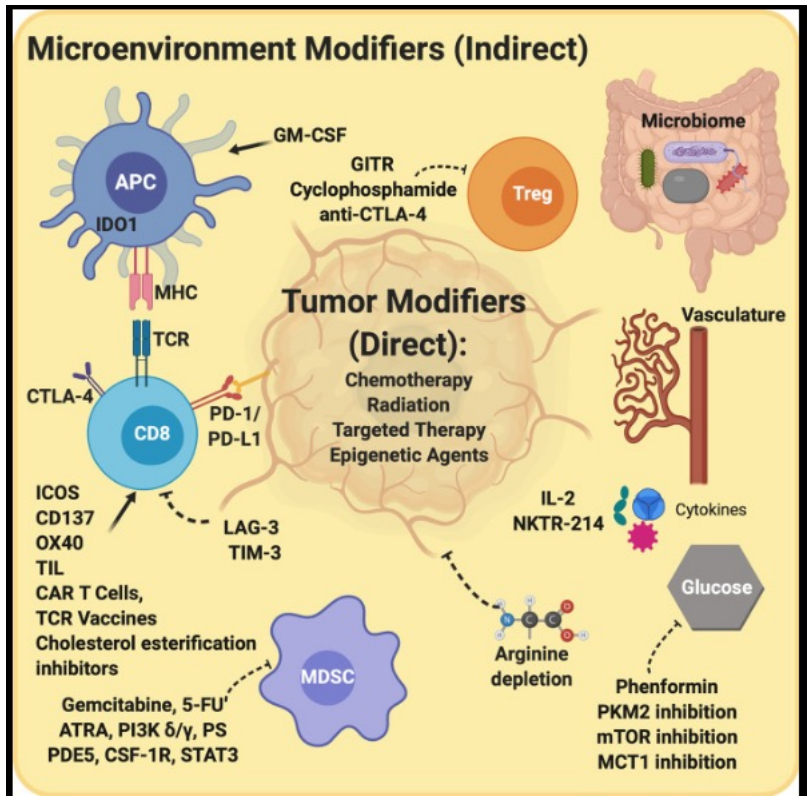


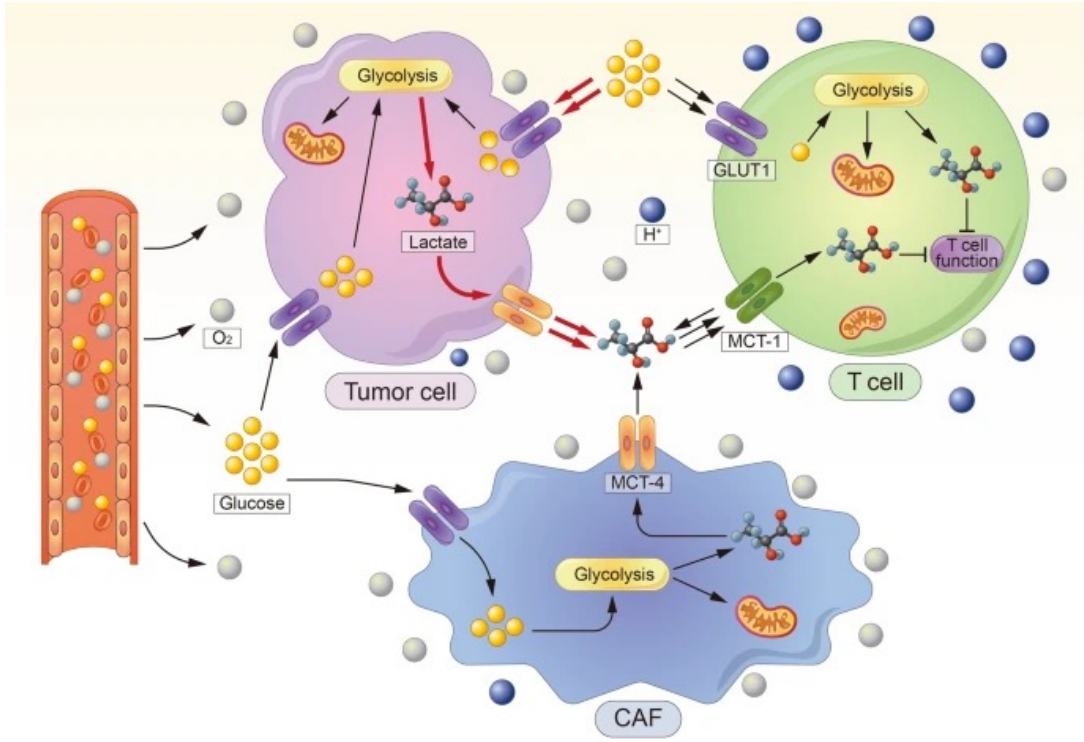
Figure 4. Overcoming resistance to immunotherapy. **A,** Increase tumor visibility. **B,** Enhance T-cell infiltration. **C,** Remove TME barriers. **D,** Enhance T-cell/NK-cell function. **E,** Unfavorable genomics/epigenetics. **F,** Adapt to the host.

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



Y.R. Nurciano-Goroff, Cell Res. 2020 Jun

Glycolysis leading to increased lactate, leading to immunosuppression



Tianyu Tang, Nature Rev, 20 Feb 2021

Overcoming Resistance to Immunotherapy

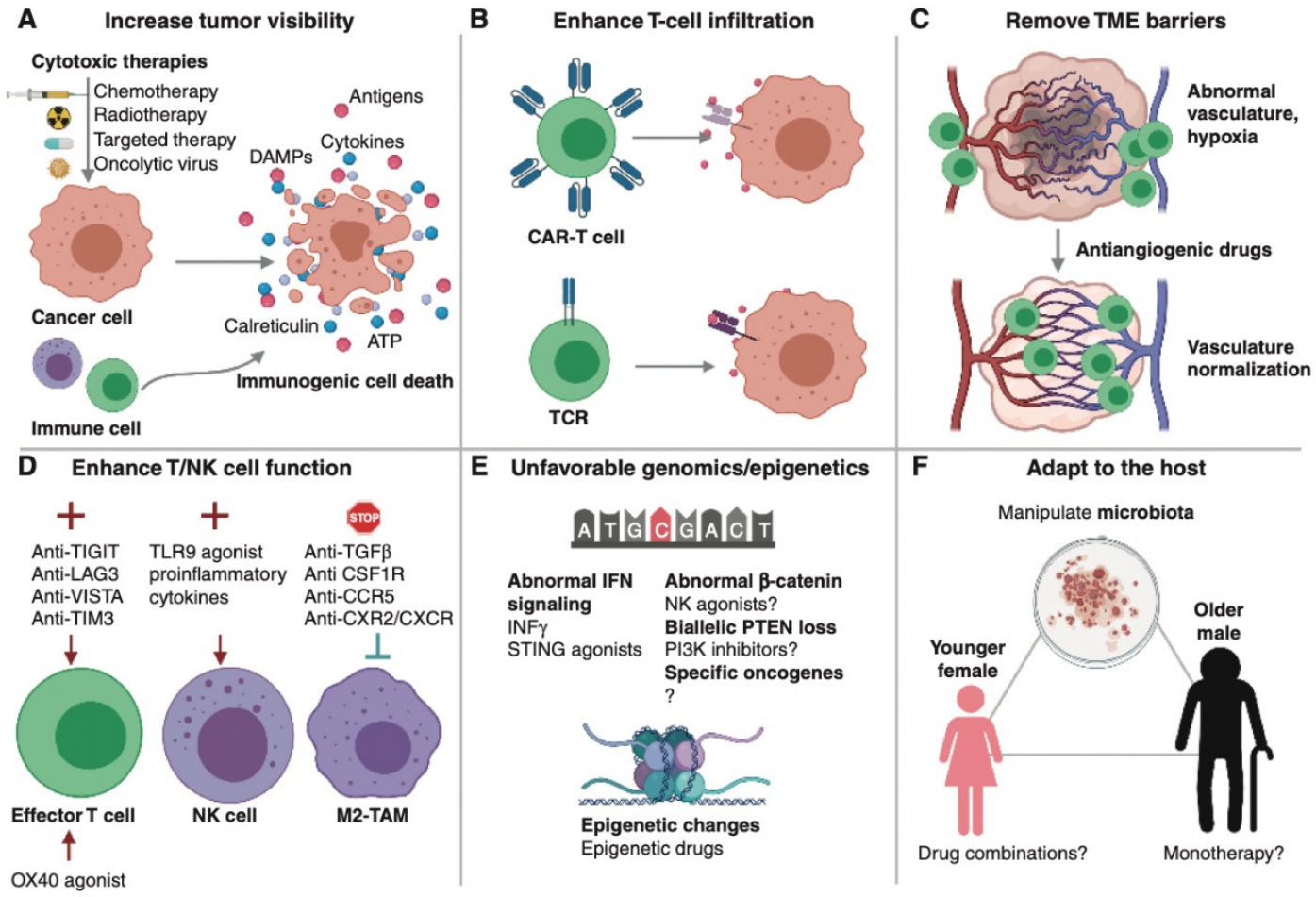


Figure 4. Overcoming resistance to immunotherapy. **A,** Increase tumor visibility. **B,** Enhance T-cell infiltration. **C,** Remove TME barriers. **D,** Enhance T-cell/NK-cell function. **E,** Unfavorable genomics/epigenetics. **F,** Adapt to the host.

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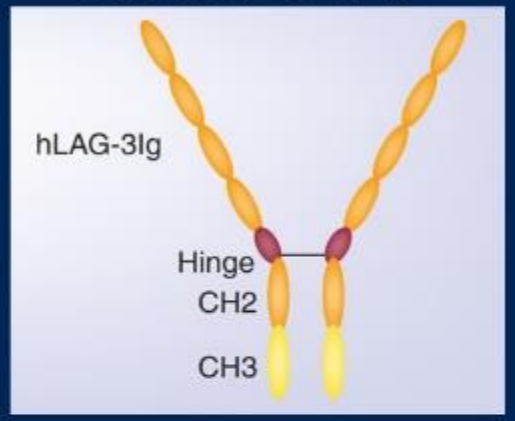
Eftilagimod alpha (efti) – soluble LAG-3

STRUCTURE OF EFTI[4]



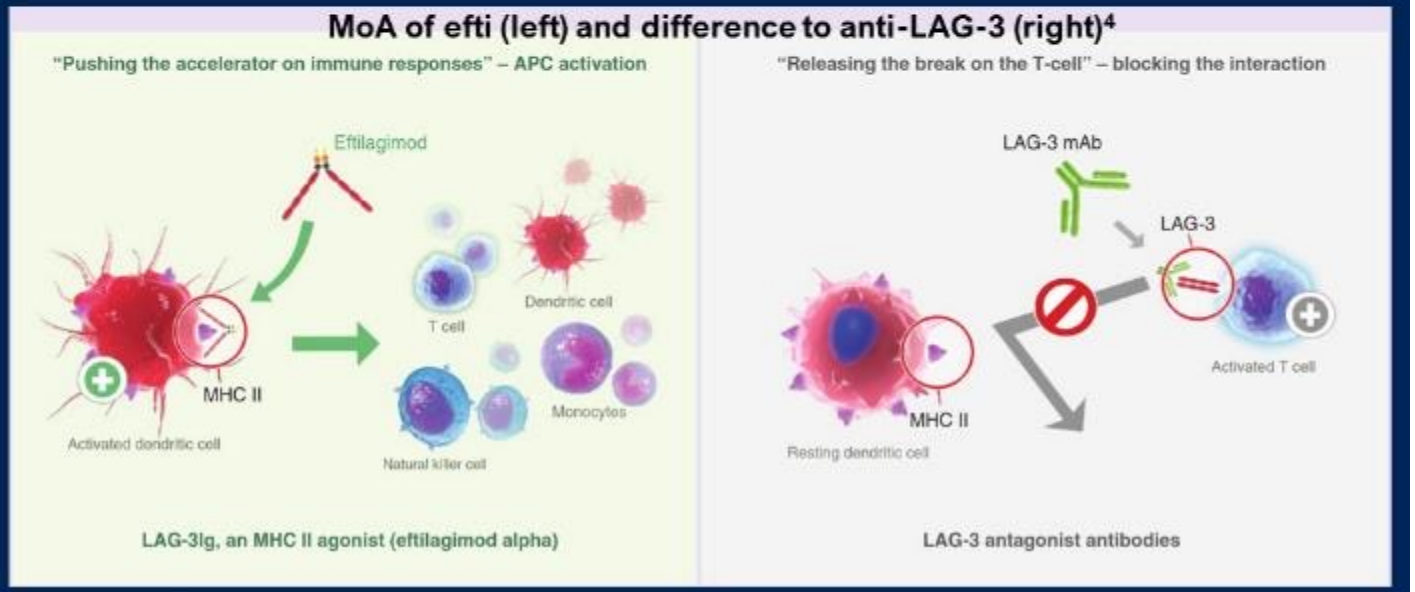
- **MoA: efti** (figure, left) is a **soluble LAG-3 protein** (LAG-3 domains fused to human IgG backbone) **targeting** a subset of **MHC class II molecules** to mediate antigen presenting cells (APCs) and CD8 T-cell activation (figure below left).
- **Difference to Anti-LAG-3:** Efti does not bind to 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

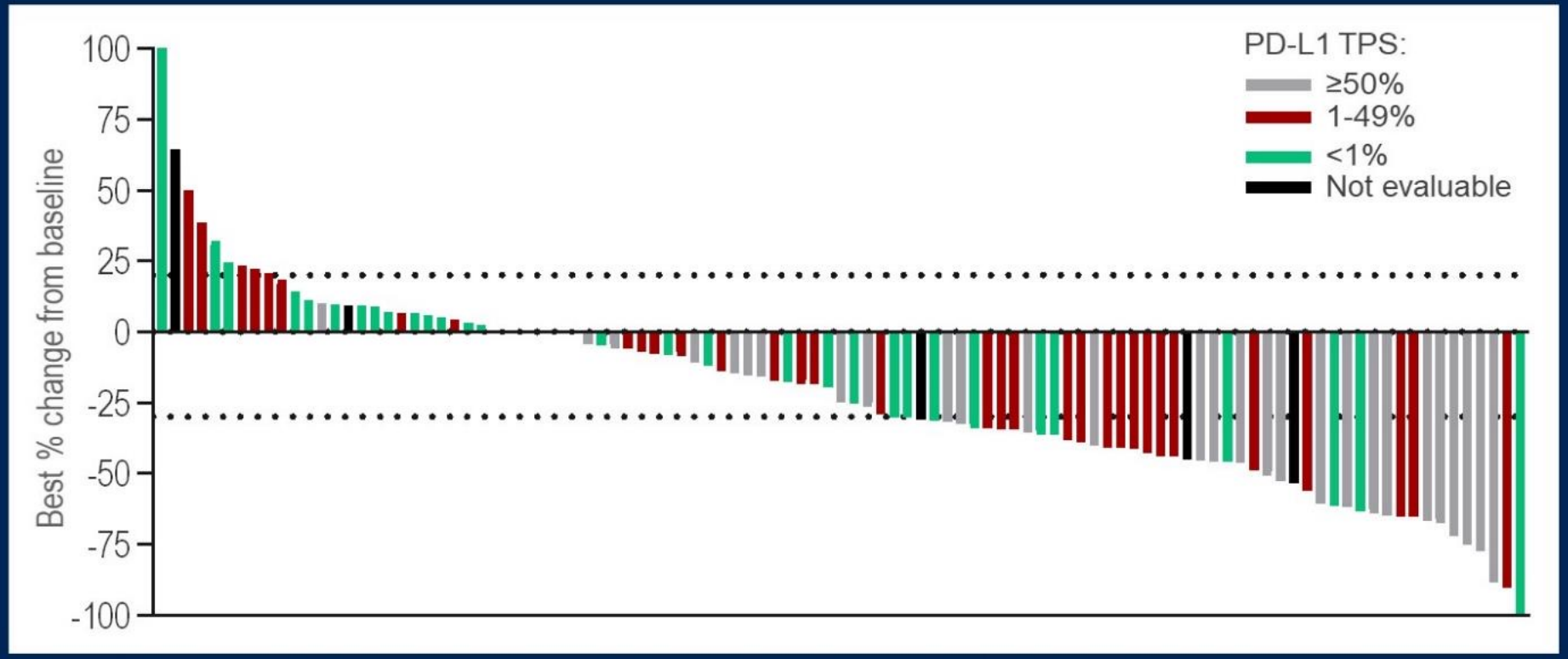
[1] Internal data, Immutep, not yet published.
[2] Brignone C, Clin Cancer Res. 2009;15: 6225- 6231.
[3] Atkinson V, J Immunoth Cancer. 2020; 8(2):e001681.
[4] Dirix L, Triebel F. Future Oncol. 2019;15(17):1963-1973.

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



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

Efficacy – Waterfall plot[1] – TACTI-002



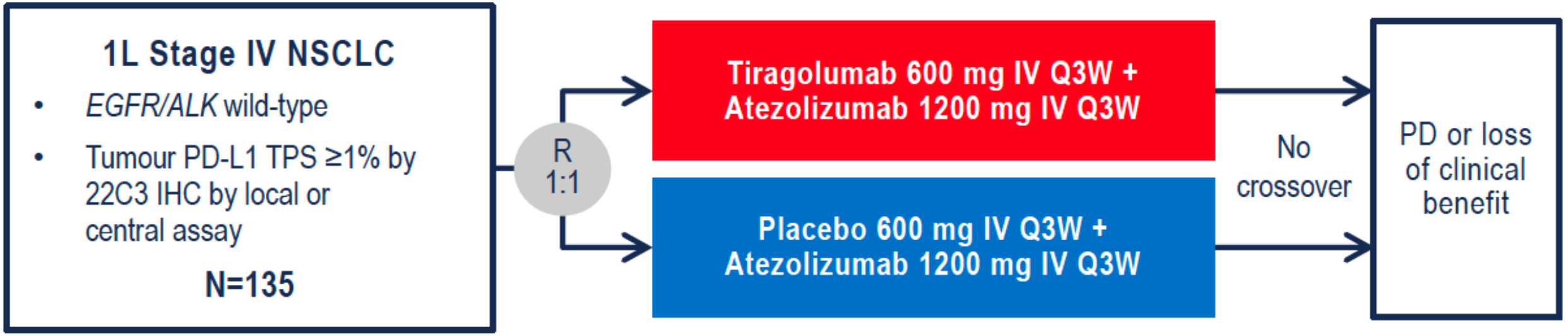
[1] all patients with ≥1 post-baseline CT scan n=103; [2] PD-L1 assessed by central assessment (Dako kit); n=79; [3] local assessment included due to non evaluable central assessment results, n=19; [4] no results available for neither central nor local testing, n=5.

- 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

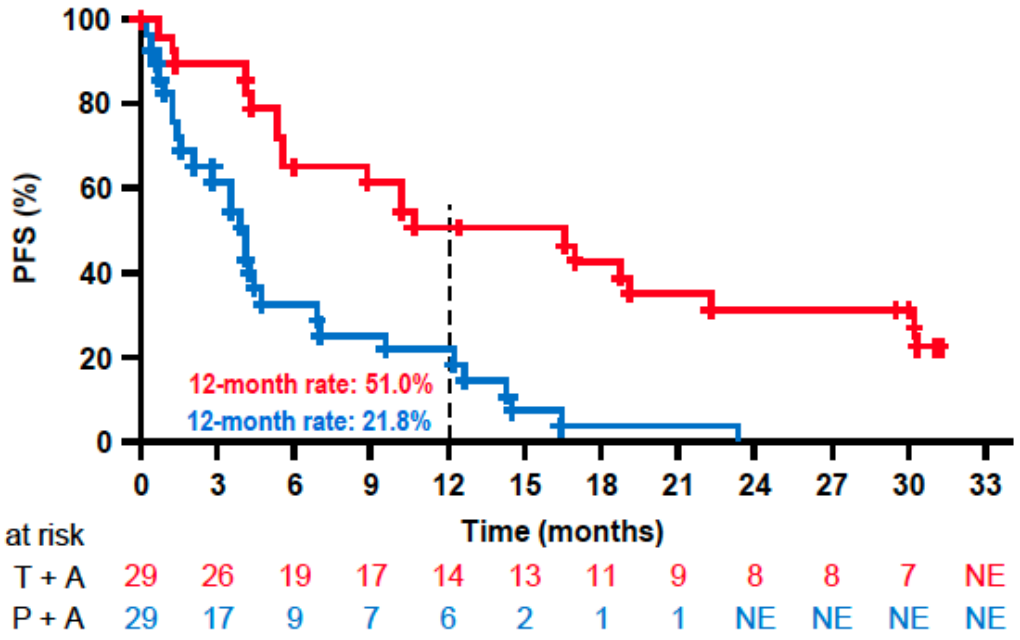
IHC, immunohistochemistry; PROs, patient-reported outcomes; TPS, tumor proportion score.

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

Investigator-Assessed PFS: PD-L1 Subgroups

PD-L1 TPS ≥50% (n=58)

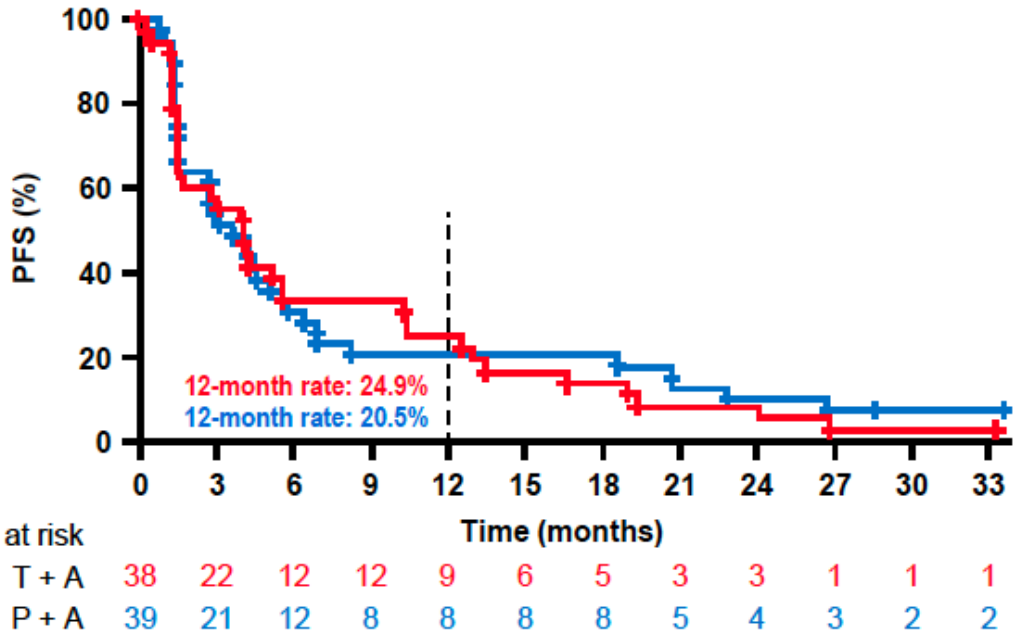
	Events n (%)	Median PFS, months (95% CI)	PFS HR (95% CI)	ORR, %	Median DOR, months (95% CI)
Tira + atezo	21 (72.4)	16.6 (5.5–22.3)	0.29* (0.15–0.53)	69.0	15.7 (9.1–NE)
Placebo + atezo	28 (96.6)	4.1 (2.1–6.8)		24.1	8.2 (5.6–10.4)



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)

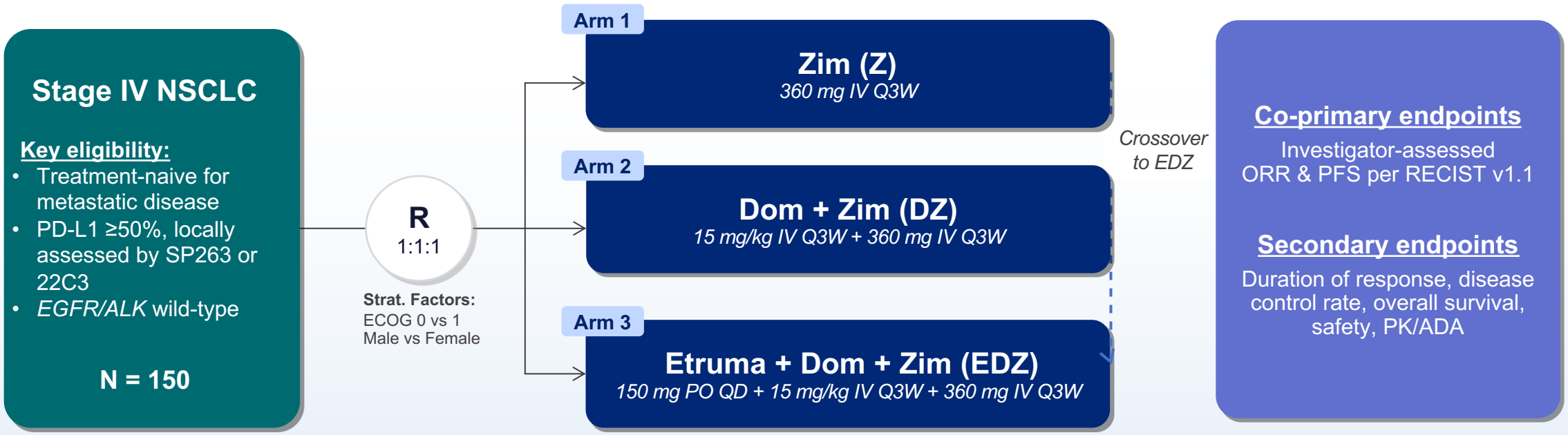


No. at risk												
T + A	38	22	12	12	9	6	5	3	3	1	1	1
P + A	39	21	12	8	8	8	8	5	4	3	2	2

*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.

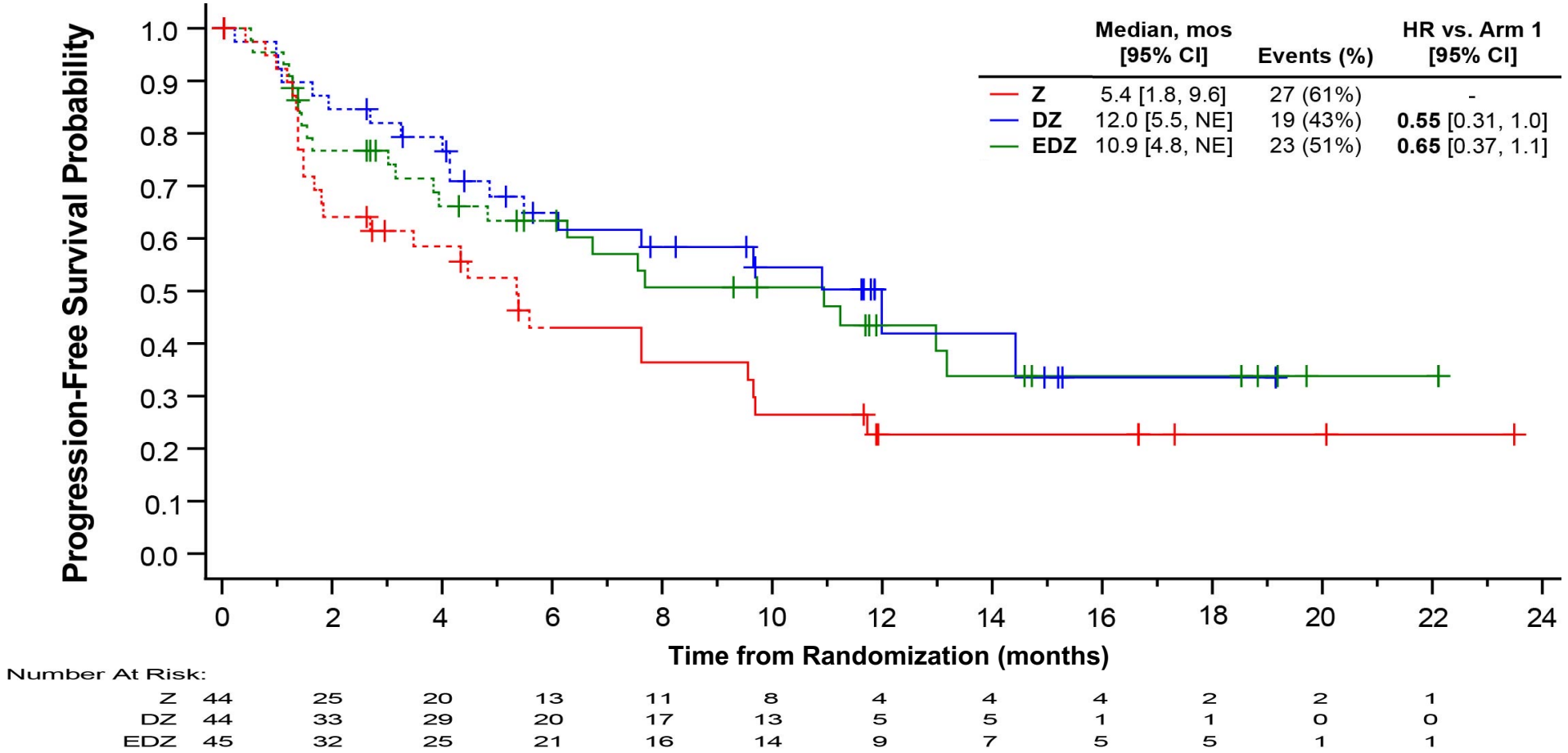
ARC-7: Randomized, Open-label, Phase 2 Study in First-Line, Metastatic, PD-L1-High NSCLC



- 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)

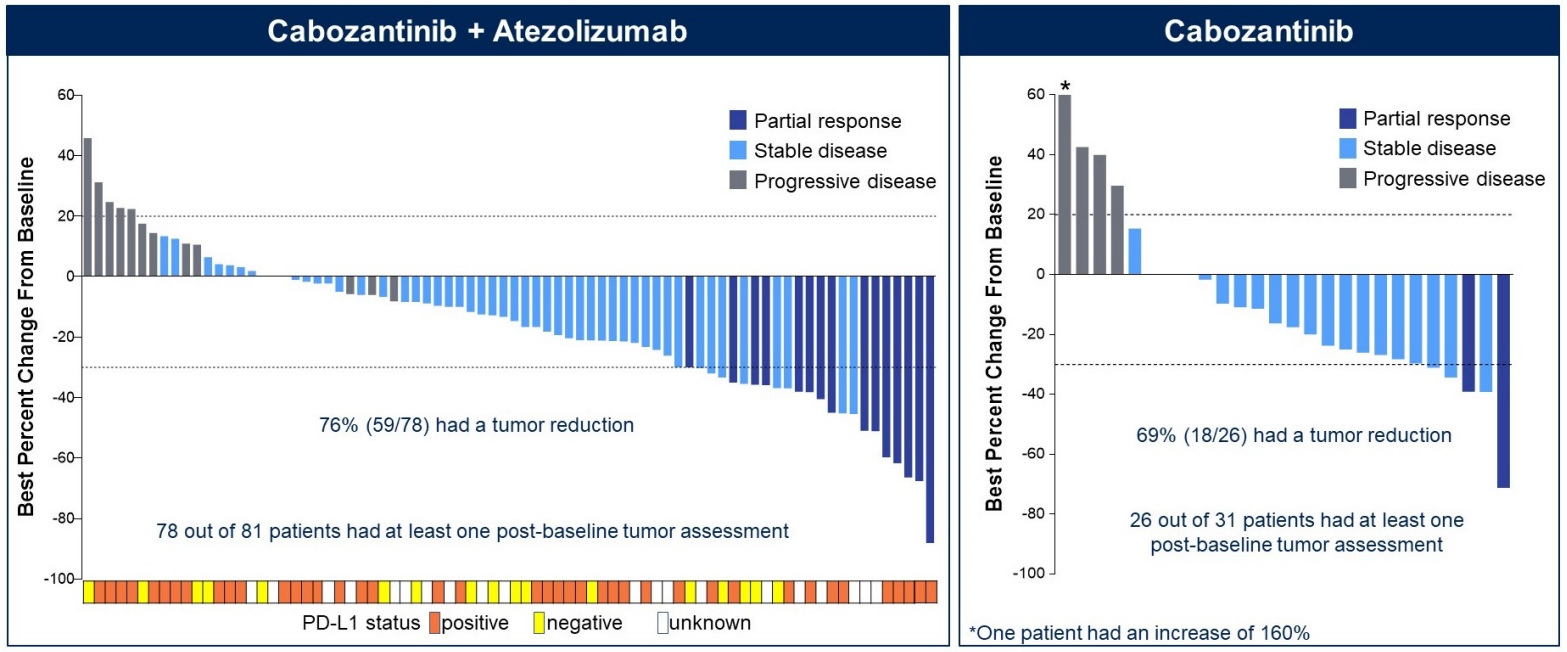
M. Johnson, ASCO Plenary, 2022

Progression-Free Survival – ITT-13



M. Johnson, ASCO Plenary, 2022

Cabozantinib Plus Nivolumab



Per investigator by RECIST v1.1.

December 8, 2022
ALAMEDA, Calif.--(BUSINESS WIRE)--Dec. 8, 2022-- Exelixis, Inc. (Nasdaq: EXEL) today 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

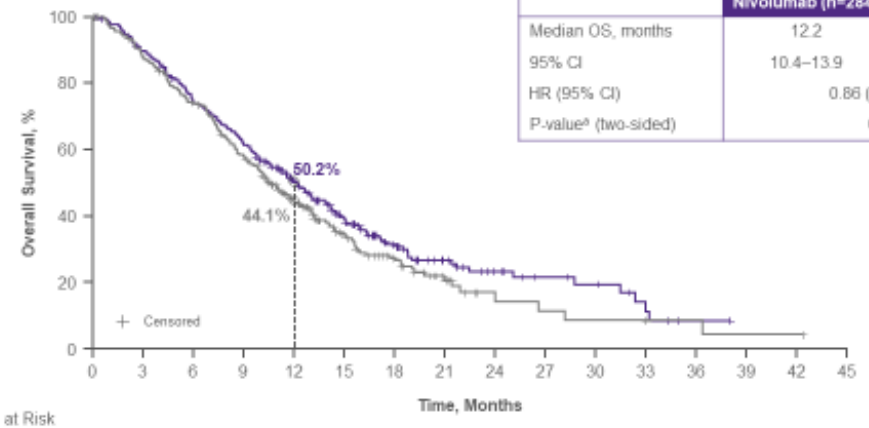
- Primary
- Secondar ORR (RE PFS, and

- 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, 98 (35%); docetaxel, 102 (35%)
Data as of March 28, 2023 (median duration of follow-up: 17.1 months)

Borghaei, ESMO 2023

S1800A Schema—Randomized Phase 2 Trial

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

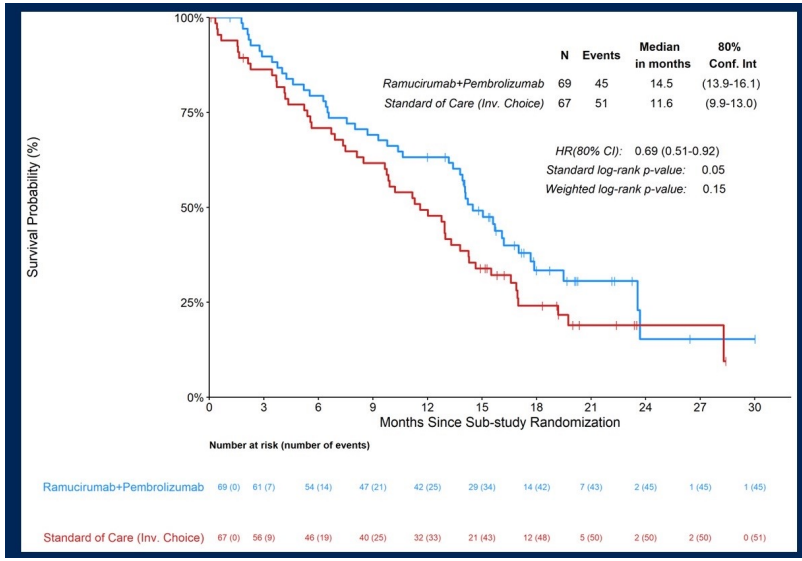
ARM A
Investigator's Choice
Standard of Care
docetaxel + ramucirumab;
docetaxel; gemcitabine;
pemetrexed (nonSCC only)

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

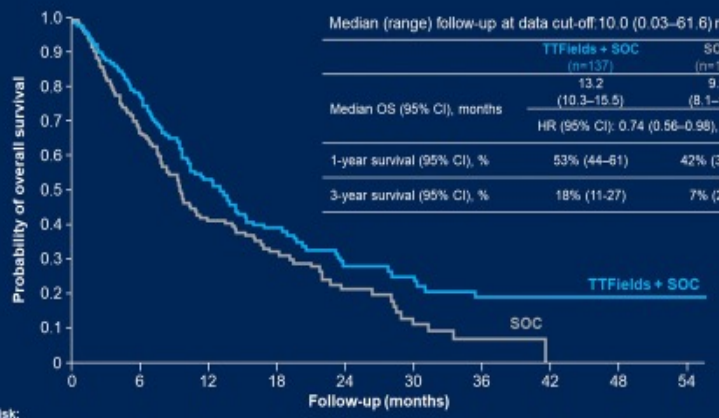
Objective: To evaluate safety and efficacy of TTFields therapy with standard of care (SOC) compared to SOC alone in metastatic NSCLC progressing on or after platinum-based therapy

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; ≥18 h/day; †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

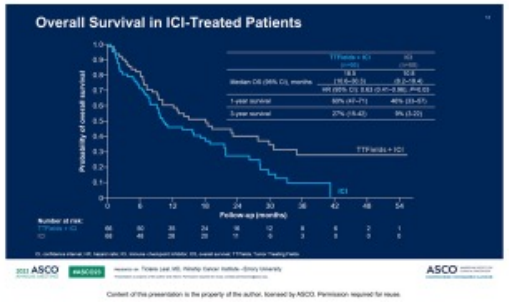
	TTFields + SOC (n=137)	SOC (n=139)
Median OS (95% CI), months	13.2 (10.3–15.5)	9.9 (8.1–11.5)
	HR (95% CI): 0.74 (0.56–0.98), *P*=0.035	
1-year survival (95% CI), %	53% (44–61)	42% (34–50)
3-year survival (95% CI), %	18% (11-27)	7% (2-15)

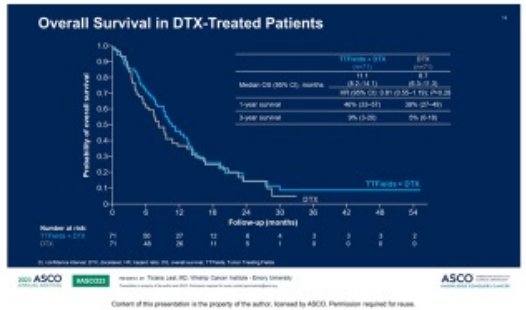
Number at risk:

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





- 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%

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

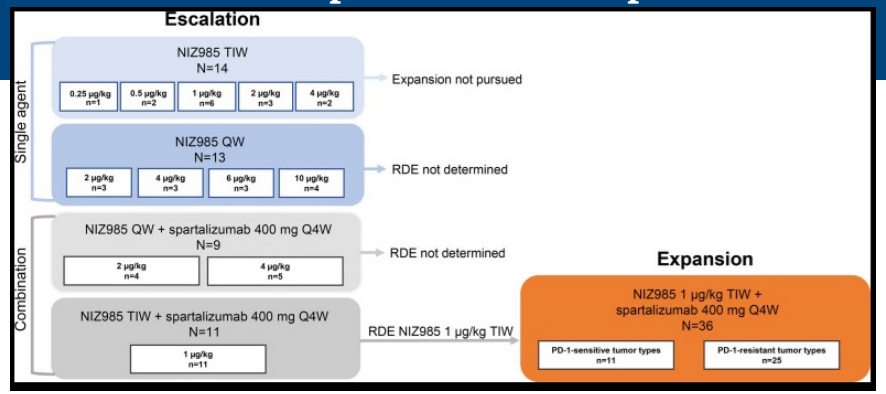
- Majority of patients (94%) had ≥1 TEAE
- Incidence of severe AEs was comparable between subgroups

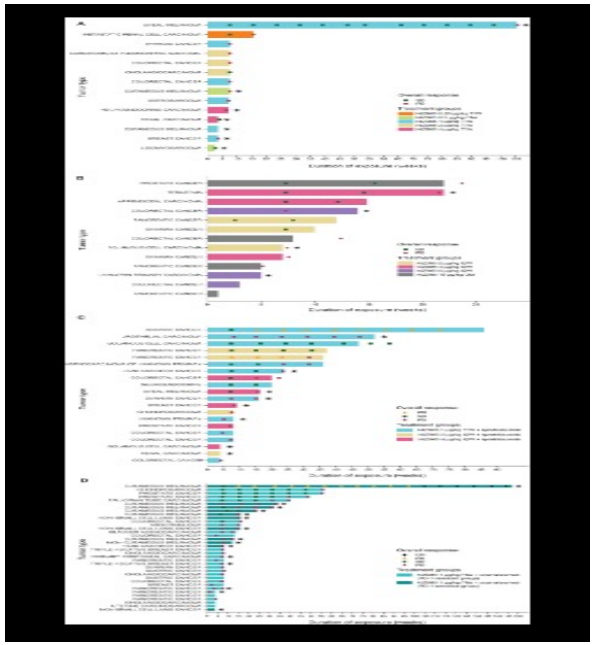
2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Ticiana Leal, MD, Winship Cancer Institute - Emory University

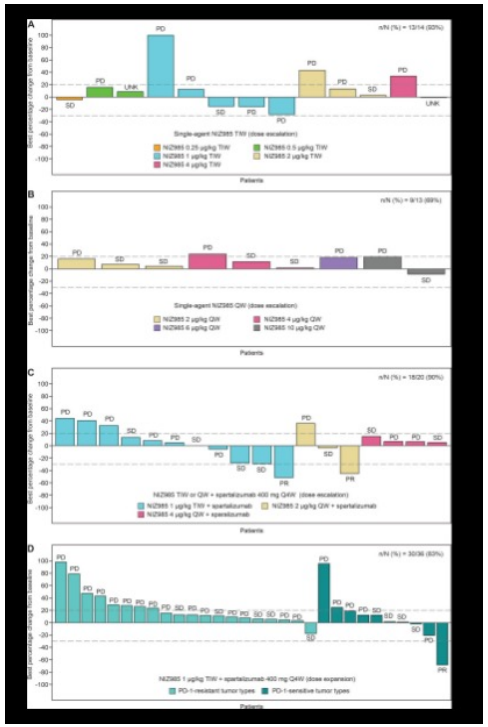
ASCO KNOWLEDGE CONQUERS CANCER

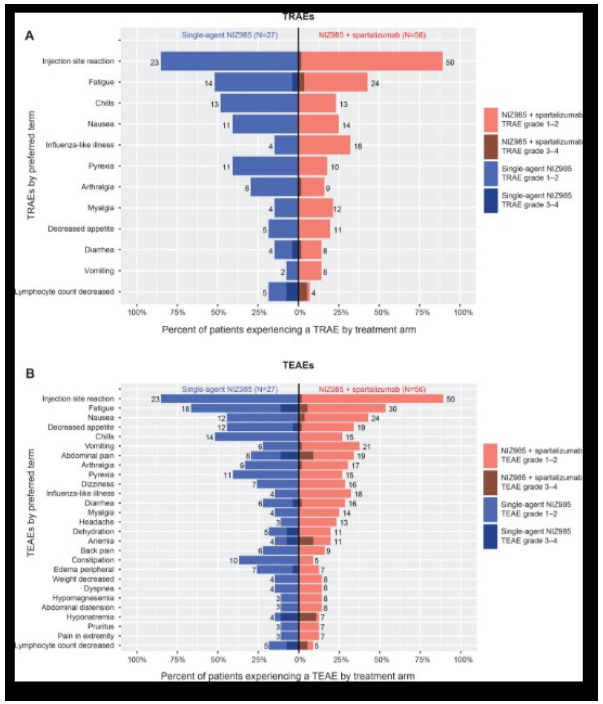
T. Leal, ASCO 2023

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





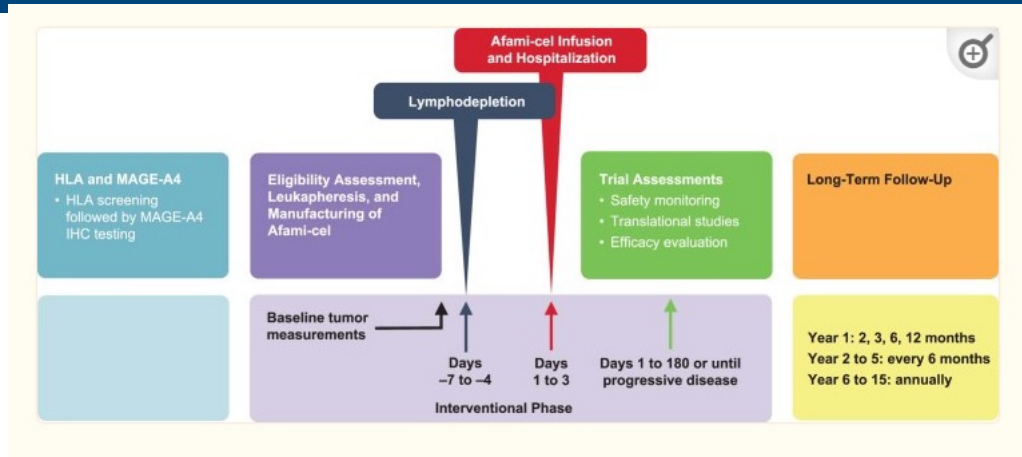


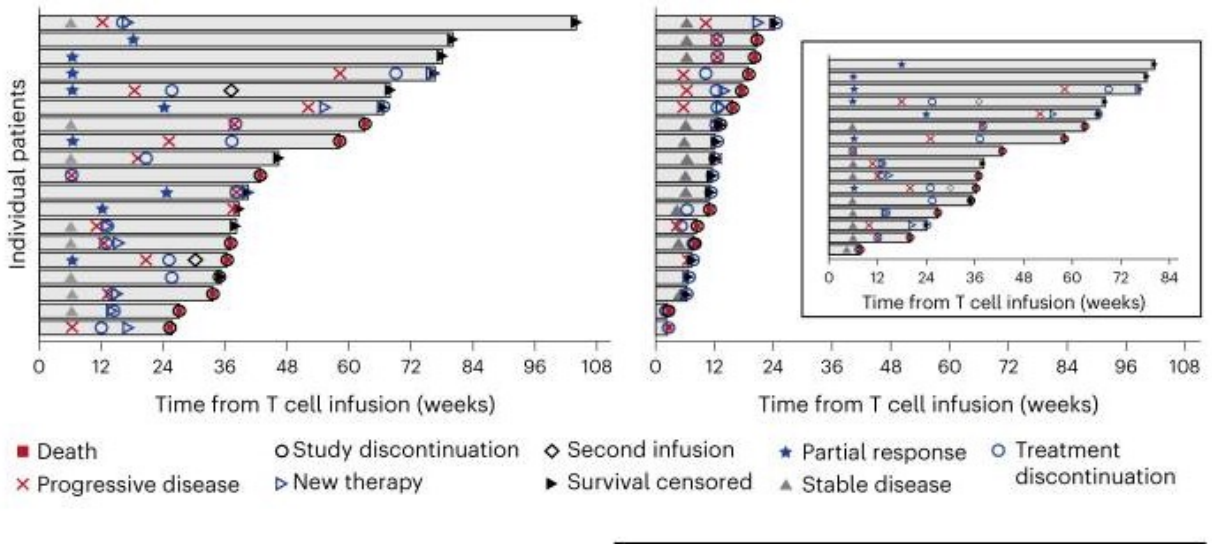


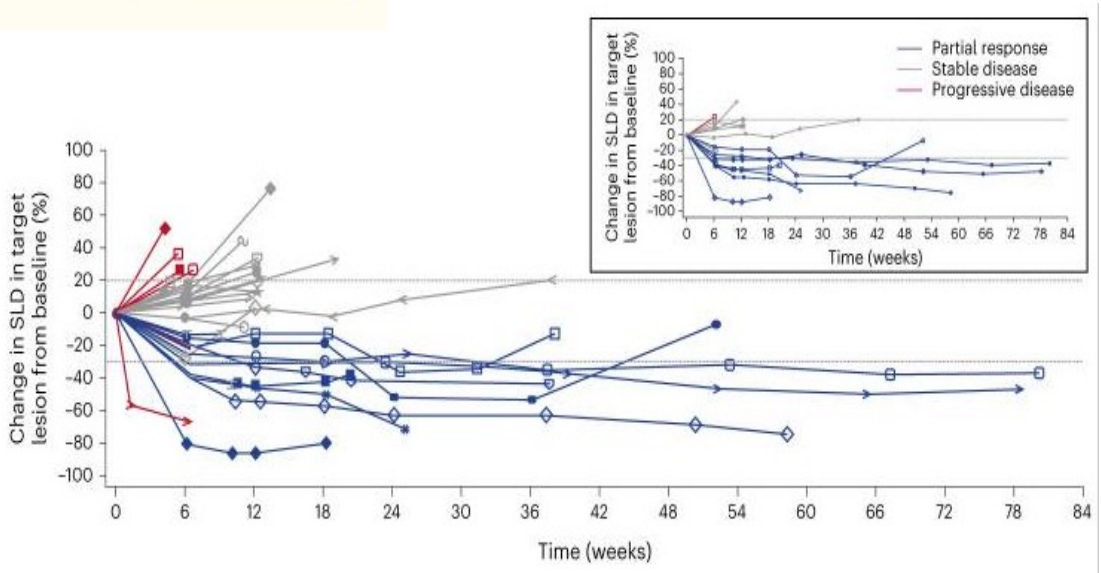
Rom Leidner et al; J Immunother Cancer. 2023 Oct

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

Conclusions

- Resistance to checkpoint inhibitors is a common occurrence
- Several different mechanisms of resistance have been identified
- Tumor biopsies at the time of recurrence is required to identify these mechanisms
- Trials involving various other checkpoint inhibitors are in progress
- Inhibition of the VEGF pathway hold promise as we await the results of the phase 3 PRAGMATICA Lung trial