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Frontline: What are We Adding to CheckPoint Inhibitors and Chemotherapy?

Immunotherapy in Advanced NSCLC

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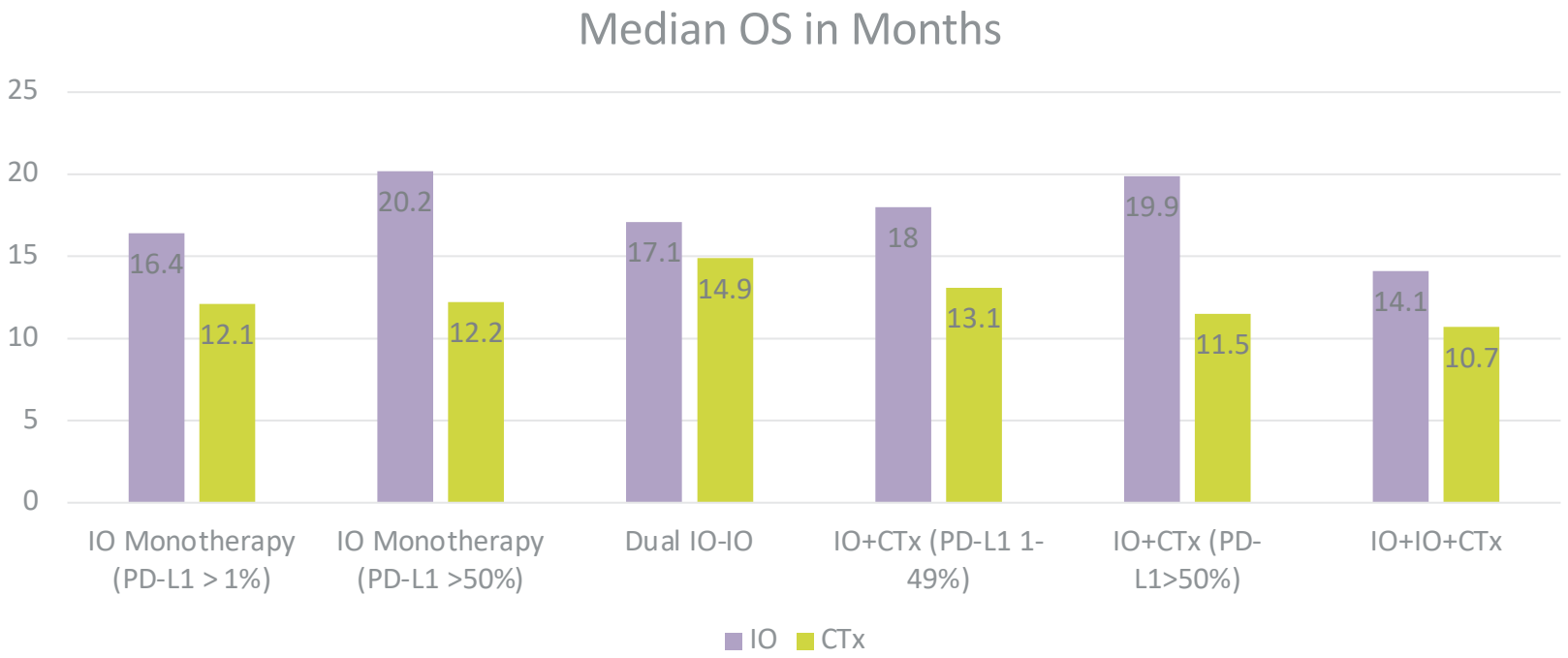
MaTOS 2023

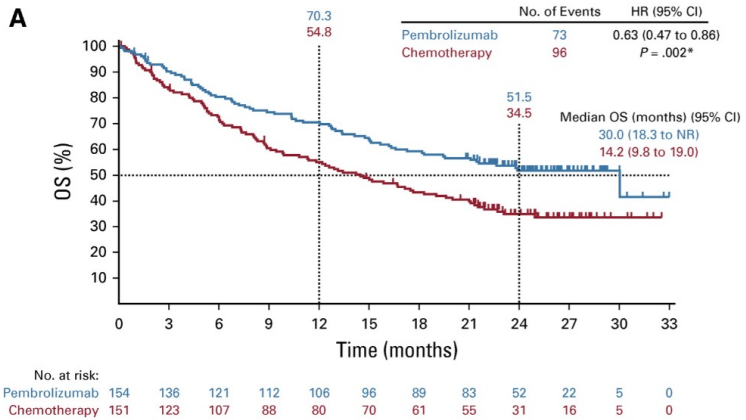
Median OS in 1L Advanced NSCLC



De Castro et al J Clin Oncol 2023; 41:1986-91; Hellmann et al, N Engl J Med 2019; 381; Novello S et al J Clin Oncol 2023: 41:1999-2006, Paz Ares L et al, Lancet Oncol 2021: 22: 198-211

How Can We Improve Outcomes

- In PD-L1 ≥ 50% (KEYNOTE-24)



KEYNOTE-42 Subset

Outcome	PD-L1 TPS ≥ 50% Pembrolizumab (n = 299)	PD-L1 TPS ≥ 50% Chemotherapy (n = 300)
OS		
Months, median (95% CI)	20.0 (15.9 to 24.2)	12.2 (10.4 to 14.6)
HR (95% CI)	0.68 (0.57 to 0.81)	
5-year rate,[b] % (95% CI)	21.9 (17.3 to 26.9)	9.8 (6.6 to 13.7)

Reck, JCO 2019; De Castro, JCO 2023

Next Generation of Immune Checkpoint Inhibitors and Beyond

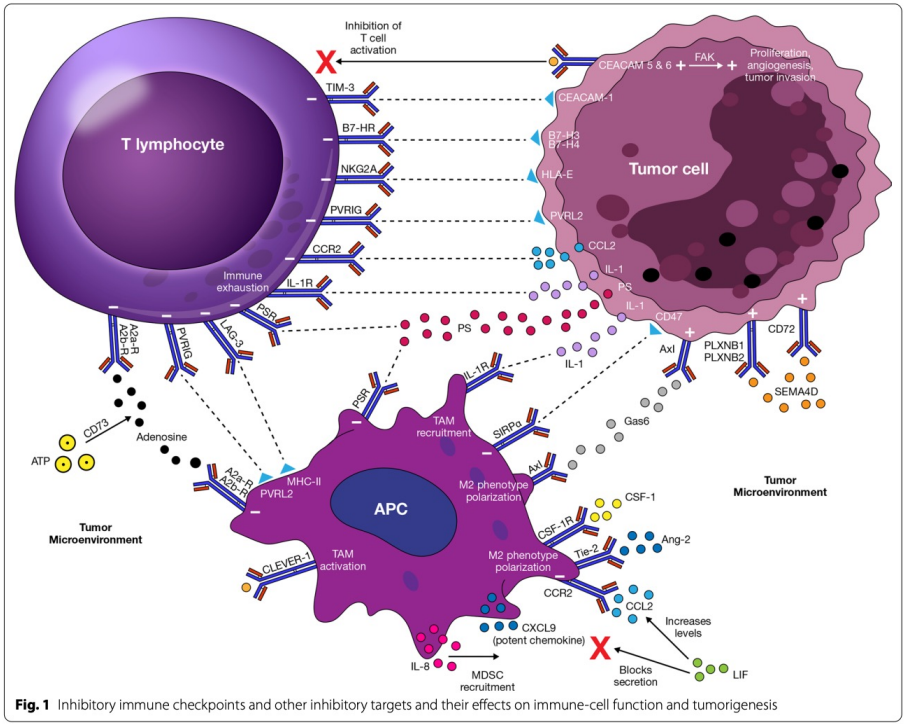


Fig. 1 Inhibitory immune checkpoints and other inhibitory targets and their effects on immune-cell function and tumorigenesis

Let's Go Beyond—ADCs

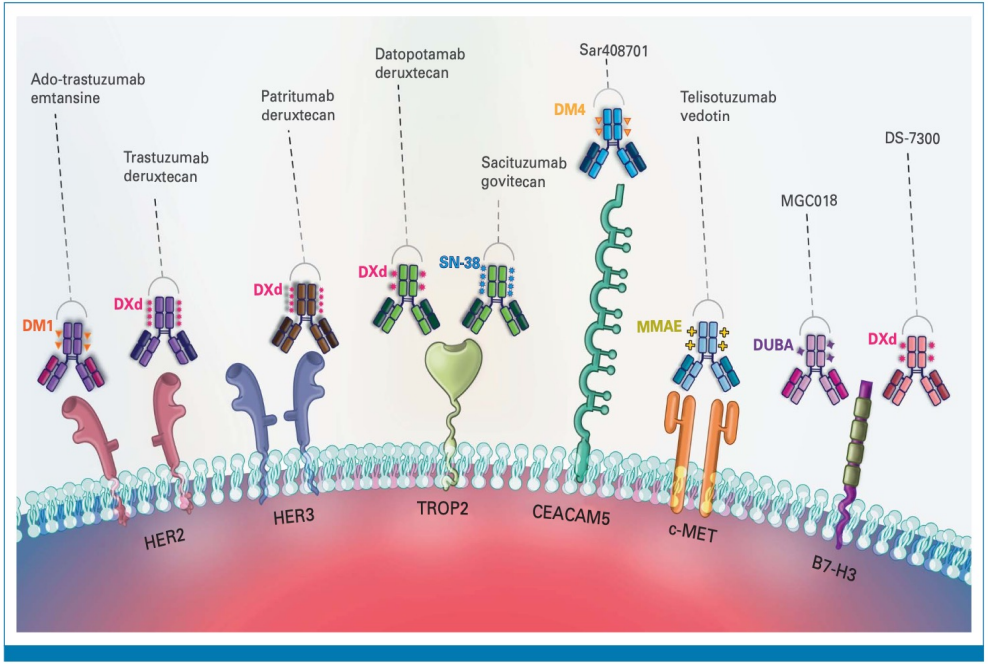


FIG 1. Overview of ADCs for lung cancer. In the illustration are reported the main ADCs for lung cancer treatment. For each ADC molecule, the corresponding payload and cell surface antigen are represented. ADC, antibody-drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; HER, human epidermal growth factor receptor; TROP2, trophoblast cell surface antigen 2.

Synergy with ICIs?

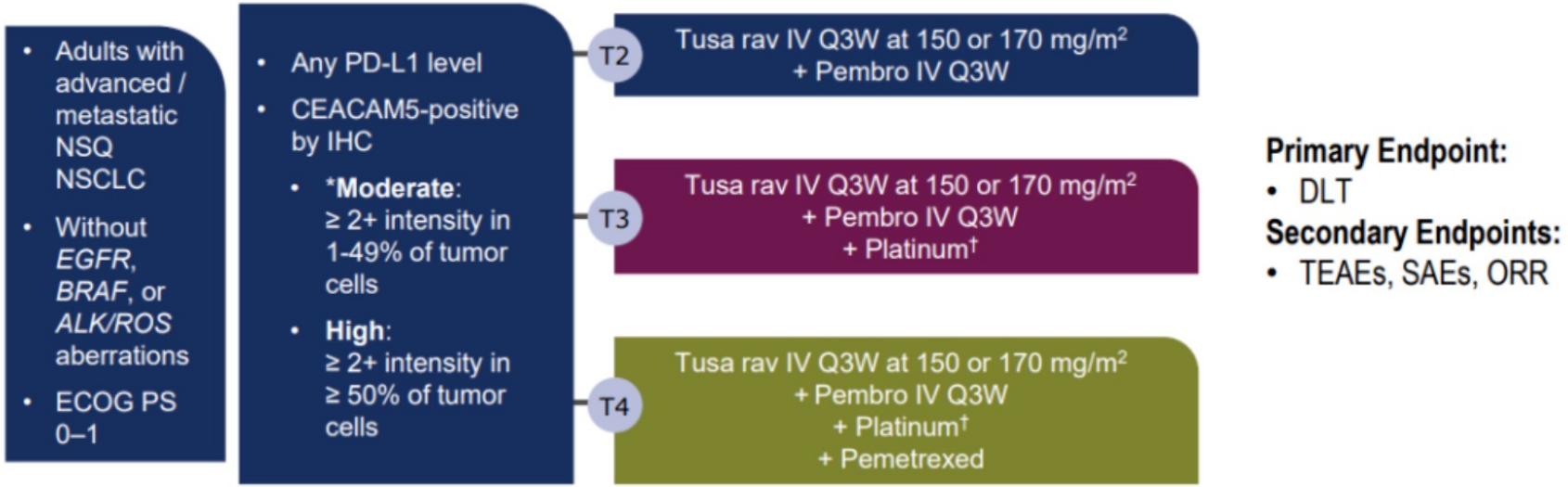
ADCs work by triggering various processes in cancer and immune cells:

- Immunogenic cell death
- Ab-dependent cell-mediated cytotoxicity
- Dendritic cell activation

Tusamitamab ravtansine + IO +/-CTx

CARMEN-LC05, Ps 2 study, safety and efficacy

CARMEN-LC05 (NCT04524689): Phase 2, open-label study assessing efficacy and safety of tusa rav in combination with pembro ± platinum† with or without pemetrexed



Paz-Ares, ELCC 2023

Tusamitamab ravtansine + IO +/-CTx

CARMEN-LC05, Ps 2 study, safety and efficacy

CARMEN-LC05: Safety summary

Regimen	T2		T3		T4		
Tusa rav dose (mg/m^2)	150 (n=3)	170 (n=2)	150 (n=4)	170 (n=1)	150 (n=12)	170 (n=3)	All (n=25)
Any TEAE, n (%)	3 (100)	2 (100)	4 (100)	1 (100)	12 (100)	3 (100)	25 (100)
Grade ≥3 TEAE, n (%)	2 (66.7)	2 (100)	2 (50.0)	1 (100)	8 (66.7)	2 (66.7)	17 (68.0)
Any treatment-emergent SAE	1 (33.3)	0	1 (25.0)	1 (100)	6 (50.0)	2 (66.7)	11 (44.0)
Grade 5 TEAE including due to PD, n (%)	0	0	0	0	4 (33.3)	0	4 (16.0)
TEAE leading to permanent discontinuation (all treatments), n (%)	0	0	0	1 (100)	3 (25.0)	1 (33.3)	5 (20.0)
Corneal TEAE, n (%)	2 (66.7)	1 (50.0)	0	1 (100)	1 (8.3)	1 (33.3)	6 (24.0)

Overall safety:

- DLT: increase aspartate aminotransferase (n=1, 170 mg/m^2 dose)
- Grade ≥3 events occurred in 68% and Grade 5 events in 16% of patients in the treatment period (all unrelated to tusa rav or any treatments)
- Corneal TEAEs of any grade occurred in 24% of patients and were manageable with dose modification
  - Only 1 was Grade 3 (keratitis) and occurred in the T2 tusa rav 170 mg/m^2 group; and no Grade 4 corneal events occurred
- Pneumonitis/ILD and peripheral neuropathy occurred in 16% (4% Grade 3) and 28% (all Grade 1–2) of all patients, respectively

CARMEN-LC05: Summary of best overall response

As 1L therapy, at the time of data cut-off, confirmed ORR was 52% (95% CI: 31.3–72.2), and DCR was 88% (95% CI: 68.8–97.5) across all treatment regimens and dose levels

Regimen	T2		T3		T4		
Tusa rav dose (mg/m^2)	150 (n=3)	170 (n=2)	150 (n=4)	170 (n=1)	150 (n=12)	170 (n=3)	All (n=25)
Best Overall Response,* n (%)							
PR (confirmed)	3 (100)	0	2 (50)	0	6 (50)	2 (66.7)	13 (52)
SD†	0	2 (100)	2 (50)	1 (100)	3 (25)	1 (33.3)	9 (36)
PD	0	0	0	0	3 (25)	0	3 (12)
ORR,‡ n (%)	3 (100)	0	2 (50)	0	6 (50)	2 (66.7)	13 (52)
DCR,§ n (%)	3 (100)	2 (100)	4 (100)	1 (100)	9 (75)	3 (100)	22 (88)
Median treatment duration, weeks	92.4	13.2	48.2	6	21	33.3	24.3

Paz-Ares, ELCC 2023

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab ± Carboplatin in Advanced/Metastatic NSCLC: Initial Results from the Phase 1b TROPION-Lung04 Study

Kyriakos P. Papadopoulos,[1] Debora S. Bruno,[2] Satoru Kitazono,[3] Shuji Murakami,[4] Martin Gutierrez,[5] Kazushige Wakuda,[6] Alexander Spira,[7] Kristof Cuppens,[8,9] Susan Lovick,[10] Adriana Hepner,[11] Gabriel Mak,[11] Saiama N. Waqar[12]

Key eligibility
- Adults (≥18 years) with previously treated or treatment-naïve advanced or metastatic NSCLC[a]
- No actionable genomic alterations
- ECOG PS 0–1

	1 Part 1: Sequential dose escalation[b]	2 Part 2: Dose expansion
Cohort 1 (Doublet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg, Q3W (n=5)	
Cohort 2 (Doublet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=3)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=16)
Cohort 3[c] (Triplet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W	
Cohort 4 (Triplet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=6)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=8)

- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** ORR and disease control rate by investigator assessment per RECIST v1.1

TROPION-Lung04

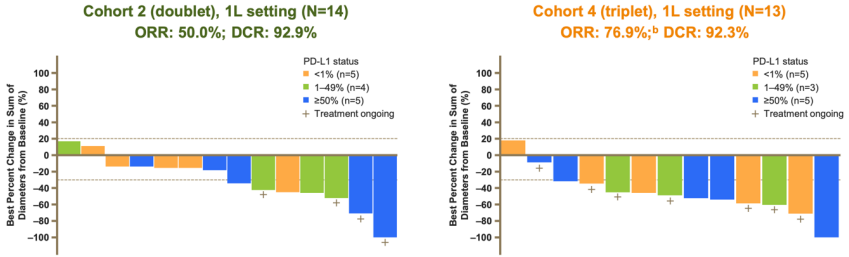
Safety Summary

Events, n (%)		Cohort 2 (doublet) N=19	Cohort 4 (triplet) N=14
TEAEs		**19 (100)**	**14 (100)**
Study treatment-related[a]		19 (100)	14 (100)
Grade ≥3 TEAEs		**8 (42.1)**	**10 (71.4)**
Study treatment-related[a]		6 (31.6)	8 (57.1)
SAEs		**7 (36.8)**	**5 (35.7)**
Study treatment-related[a]		6 (31.6)	5 (35.7)
TEAEs associated with	Death	0	0
	Discontinuation of any drug	4 (21.1)	3 (21.4)
	Discontinuation of Dato-DXd	4 (21.1)	2 (14.3)
ILD adjudicated as drug-related		**3 (15.8)**	**1 (7.1)**
Grade 1		1 (5.3)	0
Grade 2		1 (5.3)	1 (7.1)
Grade ≥3		1 (5.3)[b]	0

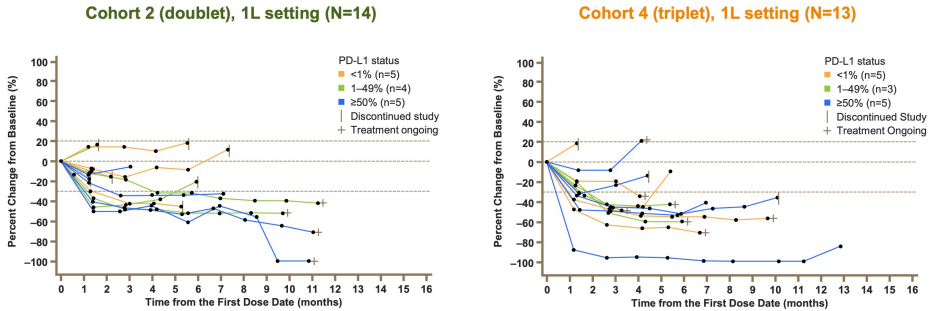
- There were **no DLTs** in **Cohort 1** or **Cohort 2** during Part 1 (dose escalation)
- **Two patients** reported DLTs in **Cohort 4** (1 patient had Grade 3 febrile neutropenia and 1 patient had both Grade 3 stomatitis and Grade 3 maculo-papular rash)[c]
- Dose expansion subsequently occurred in Cohort 2 (doublet) and Cohort 4 (triplet)
- There were **no Grade 5 adjudicated ILD events**. There was one Grade 4 adjudicated ILD event in a patient in Cohort 2[b]

TROPION-Lung04

Best Change in Sum of Diameters of Target Lesions[a]



Depth and Durability of Response[a]

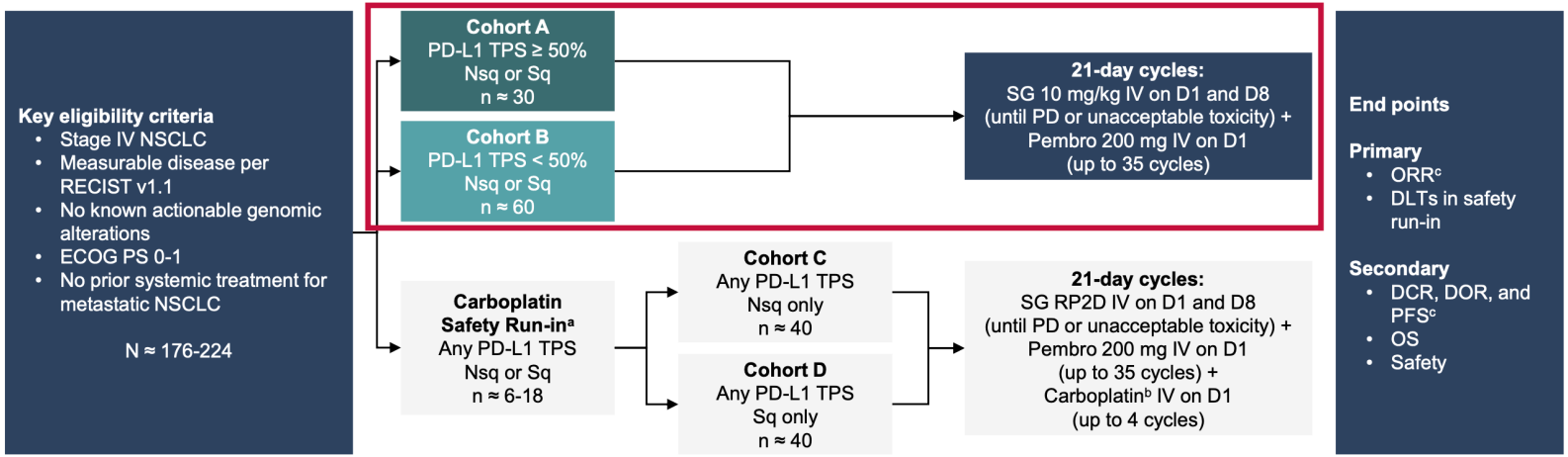


Waqar, WCLC 2023

Sacituzumab Govitecan + Pembrolizumab in 1L Metastatic Non-Small Cell Lung Cancer: Preliminary Results of the EVOKE-02 Study

Byoung Chul Cho,[1] Manuel Cobo Dols,[2] Roxana Reyes Cabanillas,[3] David Vicente,[4] Jose Fuentes Pradera,[5] Salvatore Grisanti,[6] Afshin Eli Gabayan,[7] Ki Hyeong Lee,[8] Eun Kyung Cho,[9] Sabeen Mekan,[10] Farnoush Safavi,[10] Nelumka Fernando,[10] Michael J. Chisamore,[11] Martin Reck[12]

EVOKE-02: An Open-Label, Multicohort Phase 2 Study



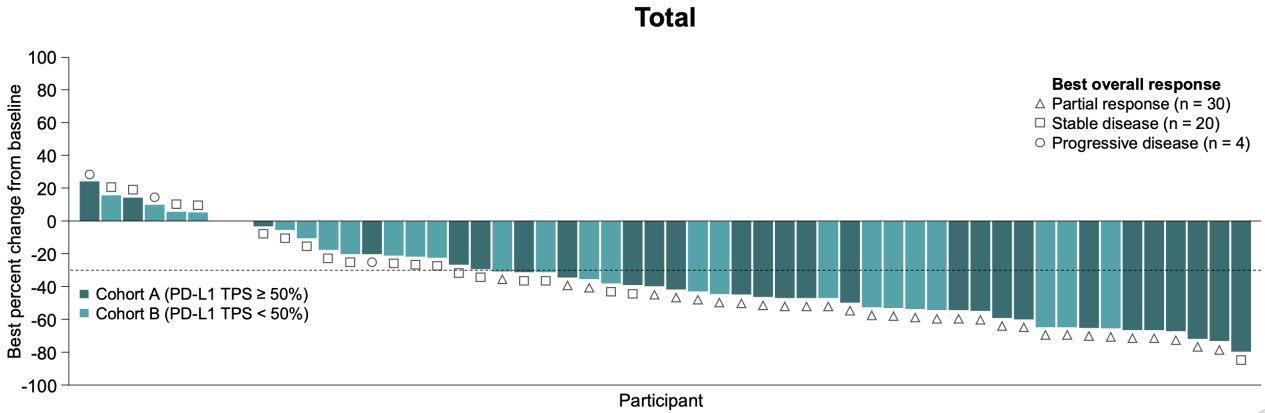
EVOKE-02

Safety Summary

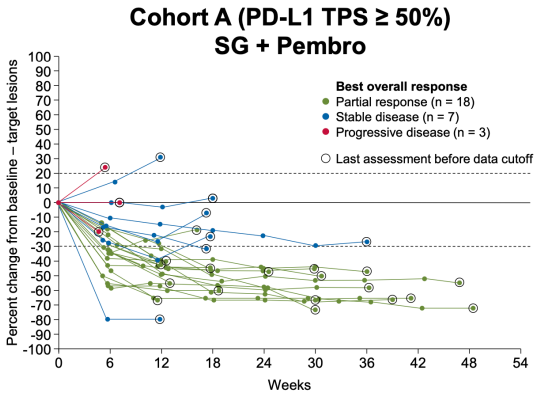
Safety-evaluable patients, n (%)	Total SG + Pembro n = 63
Any-grade TEAEs	63 (100)
Related to study treatment	57 (90)
Grade ≥ 3 TEAEs	44 (70)
Related to study treatment	24 (38)
Serious TEAEs	34 (54)
Related to study treatment	9 (14)
TEAEs leading to treatment discontinuation	11 (18)
TEAEs leading to discontinuation of SG	9 (14)
TEAEs leading to discontinuation of Pembro	8 (13)
TEAEs leading to SG dose reductions	11 (18)
TEAEs leading to death[a]	4 (6)
Related to study treatment	1 (2)

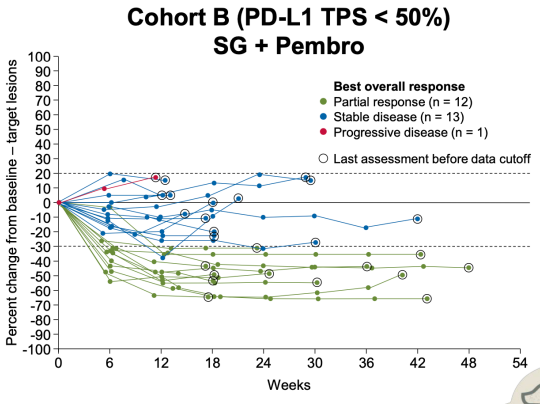
[a]TEAEs leading to death included: malignant lung neoplasm (n = 1), respiratory tract infection (n = 1), sepsis (n = 1), and sudden death (n = 1). The 1 case of sepsis leading to death was deemed related to study treatment.

EVOKE-02

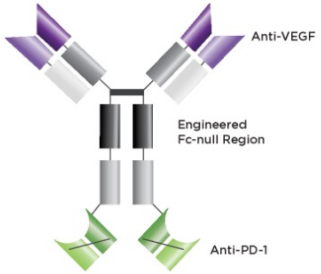


Depth and Duration of Response

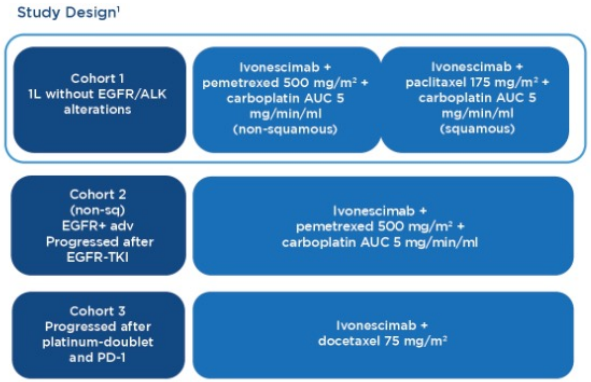


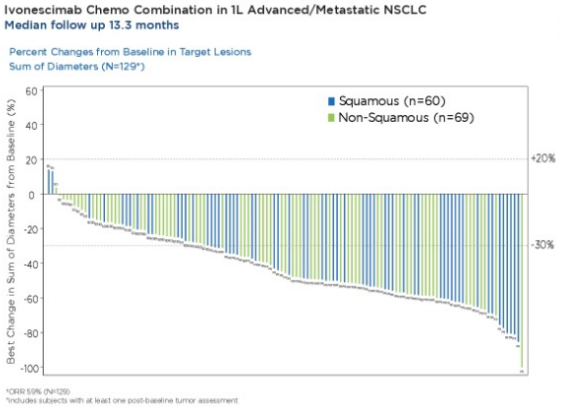


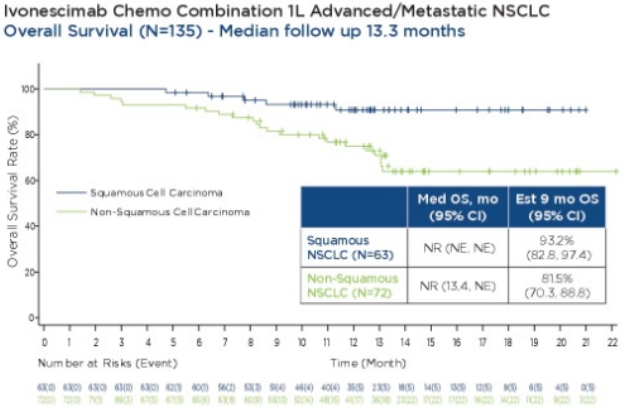
What else? Anti-VEGF?



Ivonescimab (AK112/SMT112) a novel PD-1/VEGF



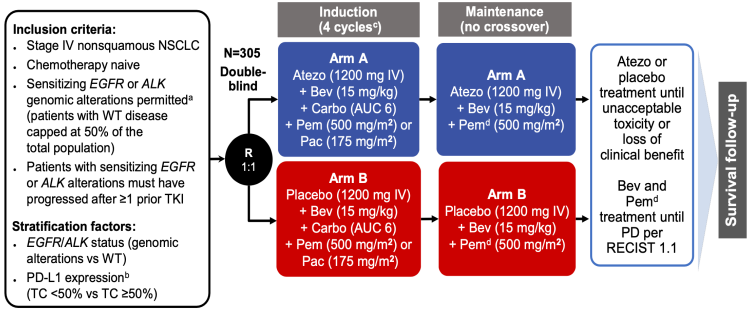


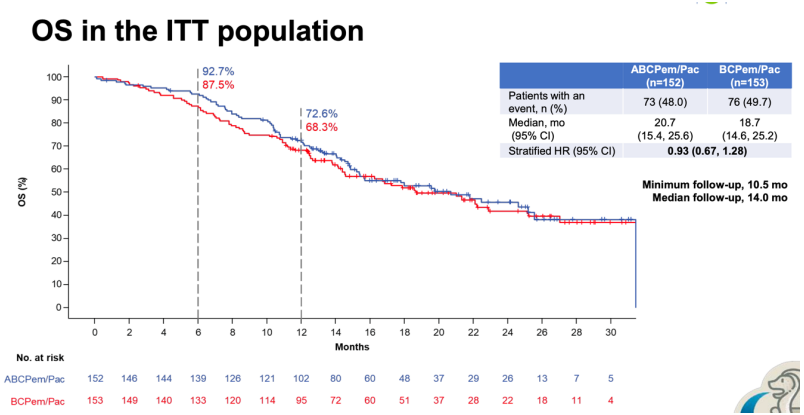


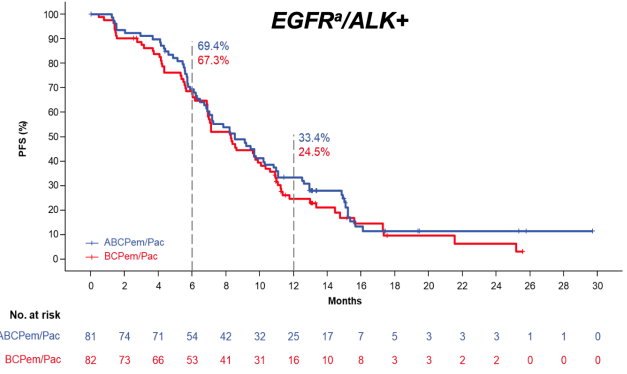
Zhang, ASCO, 2022, P9087

Efficacy of Chemo with Atezo/Bev

IMPower 151







Zhou, WCLC 2023

Frontline: Beyond ICI

- Antibody Drug Conjugates are promising
  - Unclear if they can overcome the “KN198 bar” in terms of efficacy and tolerability
  - Likely in select populations
- Anti-VEGF continues to be of interest
  - Modest and inconsistent benefit in front line
- Optimization of first line therapy remains a challenge