

The Potential Role of PD-1 x VEGF Bispecific Antibodies in the Management of Non-Small Cell Lung Cancer: Translating Emerging Evidence into Community Oncology Practice

Liza C Villaruz, MD

Chief, Thoracic Medical Oncology Program

Co-Leader, Immunotherapy and Drug Development Center

UPMC Hillman Cancer Center

Professor of Medicine

University of Pittsburgh School of Medicine

Pittsburgh, Pennsylvania



Contributing Clinical Investigators



Christina Baik, MD, MPH
Thoracic, Head and Neck Medical Oncology
University of Washington School of Medicine
Fred Hutchinson Cancer Research Center
Seattle, Washington



Antonio Passaro, MD, PhD
Director
Division of Thoracic Oncology
European Institute of Oncology
Milan, Italy



Jonathan Goldman, MD
Professor of Medicine, UCLA Hematology
and Oncology
Director of Clinical Trials in Thoracic Oncology
Associate Director of Drug Development
UCLA Health
Santa Monica, California



Zofia Piotrowska, MD, MHS
Associate Professor of Medicine
Harvard Medical School
Clinical Co-Director, MGB Thoracic Medical
Oncology Program
Massachusetts General Brigham Cancer Institute
Boston, Massachusetts



Paul K Paik, MD
Attending Physician
Clinical Director, Thoracic Oncology Service
Memorial Sloan Kettering Cancer Center
New York, New York



Julia Rotow, MD
Assistant Professor of Medicine
Harvard Medical School
Clinical Director, Director of Clinical Research
Lowe Center for Thoracic Oncology
Boston, Massachusetts

Learning Objectives

- Appraise the scientific rationale for the development of bispecific antibodies directed at PD-1 and VEGF, and understand the mechanism of action and the similarities and differences among the various investigational agents in this class.
- Evaluate the documented efficacy of PD-1 x VEGF bispecific antibodies in combination with chemotherapy for patients with progressive EGFR-mutated metastatic non-small cell lung cancer (NSCLC), and consider the potential role of these agents.
- Review published research findings with PD-1 x VEGF bispecific antibodies alone and in combination with chemotherapy as first-line therapy for patients with metastatic NSCLC without actionable genomic alterations, and reflect on ongoing trials attempting to further validate the effectiveness of these strategies.
- Recognize the spectrum, frequency and severity of toxicities associated with PD-1 x VEGF bispecific antibodies, and appreciate management strategies to facilitate the safe and effective administration of these agents.

Accreditation Statement

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation Statement

Research To Practice designates this live activity for a maximum of 0.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Content Validation and Disclosures

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education and adheres to the ACCME's Standards for Integrity and Independence in Accredited Continuing Education. Any individuals in a position to control the content of an accredited continuing education activity, including faculty, planners, reviewers and others, are required to disclose all relevant financial relationships with ineligible entities (commercial interests). All relevant financial relationships have been mitigated prior to the commencement of this activity. In addition, all activity content is reviewed by RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

Dr Villaruz — Disclosures

Faculty

Advisory Committees	AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Caris Life Sciences, EMD Serono Inc, Genentech, a member of the Roche Group, Natera Inc, Pfizer Inc, Regeneron Pharmaceuticals Inc
----------------------------	---

Contributing Clinical Investigators — Disclosures

Prof Passaro has no relevant financial relationships to disclose. The following faculty reported relevant financial relationships with ineligible entities:

Dr Baik — Consulting Agreements: AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Janssen Biotech Inc, Lilly, Natera Inc, Nuvalent, Pfizer Inc, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc, UCB Japan; **Research Funding (to Institution):** AbbVie Inc, AstraZeneca Pharmaceuticals LP, Avenzo Therapeutics, Black Diamond Therapeutics Inc, BlossomHill Therapeutics, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Daiichi Sankyo Inc, Ellipses Pharma, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, Nuvalent, Pfizer Inc, Summit Therapeutics, Syntrix Biosystems, SystImmune Inc; **Nonrelevant Financial Relationships:** Bristol Myers Squibb Foundation. **Dr Goldman — Consulting Agreements:** AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, Pfizer Inc, Summit Therapeutics; **Contracted Research:** AbbVie Inc, Agenus Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, GSK, Janssen Biotech Inc, Lilly, Merck, Pfizer Inc, Puma Biotechnology Inc, RayzeBio, Summit Therapeutics, Tango Therapeutics; **Honoraria:** AbbVie Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Lilly, Summit Therapeutics; **Research Grants:** AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, GSK, Summit Therapeutics, Tango Therapeutics. **Dr Paik — Advisory Committees:** EMD Serono Inc, Janssen Biotech Inc, Summit Therapeutics; **Consulting Agreements:** AbbVie Inc, EMD Serono Inc; **Contracted Research:** Bicara Therapeutics, EMD Serono Inc, Novartis, Nuvectis Pharma Inc, Summit Therapeutics. **Dr Piostrowska — Consulting Agreements:** AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Black Diamond Therapeutics Inc, BlossomHill Therapeutics, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Janssen Biotech Inc, Lilly, Natera Inc, Nuvalent, Regeneron Pharmaceuticals Inc, Revolution Medicines Inc, Summit Therapeutics, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tubulis; **Contracted Research:** AbbVie Inc, AstraZeneca Pharmaceuticals LP, BlossomHill Therapeutics, Blueprint Medicines, Cullinan Therapeutics, Daiichi Sankyo Inc, GSK, Janssen Biotech Inc, Novartis, Nuvalent, Nuvectis Pharma Inc, Spectrum Pharmaceuticals Inc, SystImmune Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company; **Data and Safety Monitoring Boards/Committees:** Genentech, a member of the Roche Group. **Dr Rotow — Consulting Agreements:** AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, BioAtla, BioNTech SE, BlossomHill Therapeutics, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Caris Life Sciences, Catalyst Pharmaceuticals Inc, Daiichi Sankyo Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, Jazz Pharmaceuticals Inc, Johnson & Johnson, Merus, Novocure Inc, Nuvalent, Nuvation Bio Inc, Ottimo Pharma, Pfizer Inc, Regeneron Pharmaceuticals Inc, Sanofi, Summit Therapeutics, Takeda Pharmaceuticals USA Inc; **Contracted Research (All to Institution):** AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bicycle Therapeutics, BioAtla, BioNTech SE, Black Diamond Therapeutics Inc, BlossomHill Therapeutics, Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo Inc, Duality Biologics, Enliven Therapeutics, EpimAb Biotherapeutics Inc, ImmunityBio, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Nuvalent, ORIC Pharmaceuticals, RedCloud Bio, Regeneron Pharmaceuticals Inc, Summit Therapeutics, SyntheKine; **Honoraria:** AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Johnson & Johnson, Pfizer Inc.

Commercial Support

This activity is supported by an educational grant from Summit Therapeutics.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant financial relationships to disclose.

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

Agenda

Module 1: Ivonescimab for Previously Untreated Metastatic Non-Small Cell Lung Cancer (mNSCLC)

Module 2: Ivonescimab for Relapsed/Refractory EGFR-Mutated mNSCLC

Module 3: Other Novel PD-1/PD-L1 x VEGF Bispecific Antibodies Under Investigation

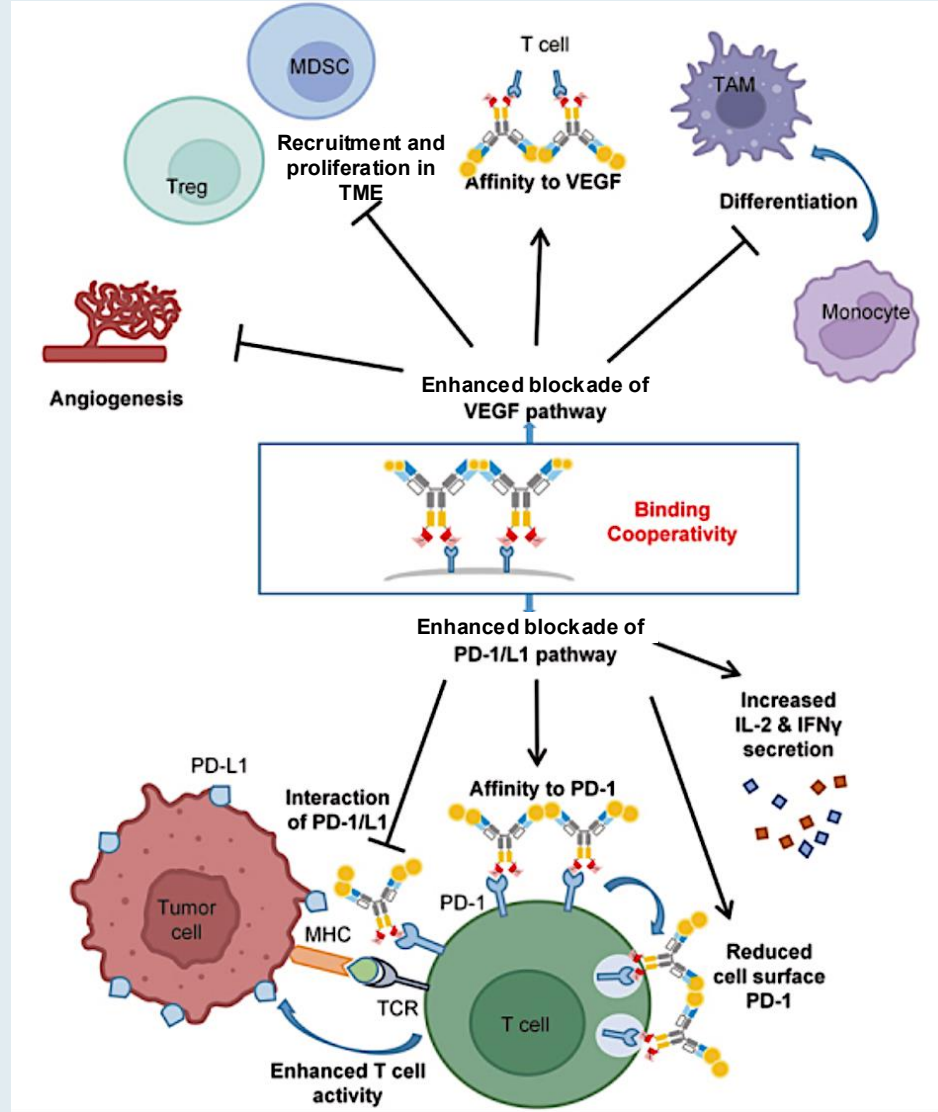
Agenda

Module 1: Ivonescimab for Previously Untreated Metastatic Non-Small Cell Lung Cancer (mNSCLC)

Module 2: Ivonescimab for Relapsed/Refractory EGFR-Mutated mNSCLC

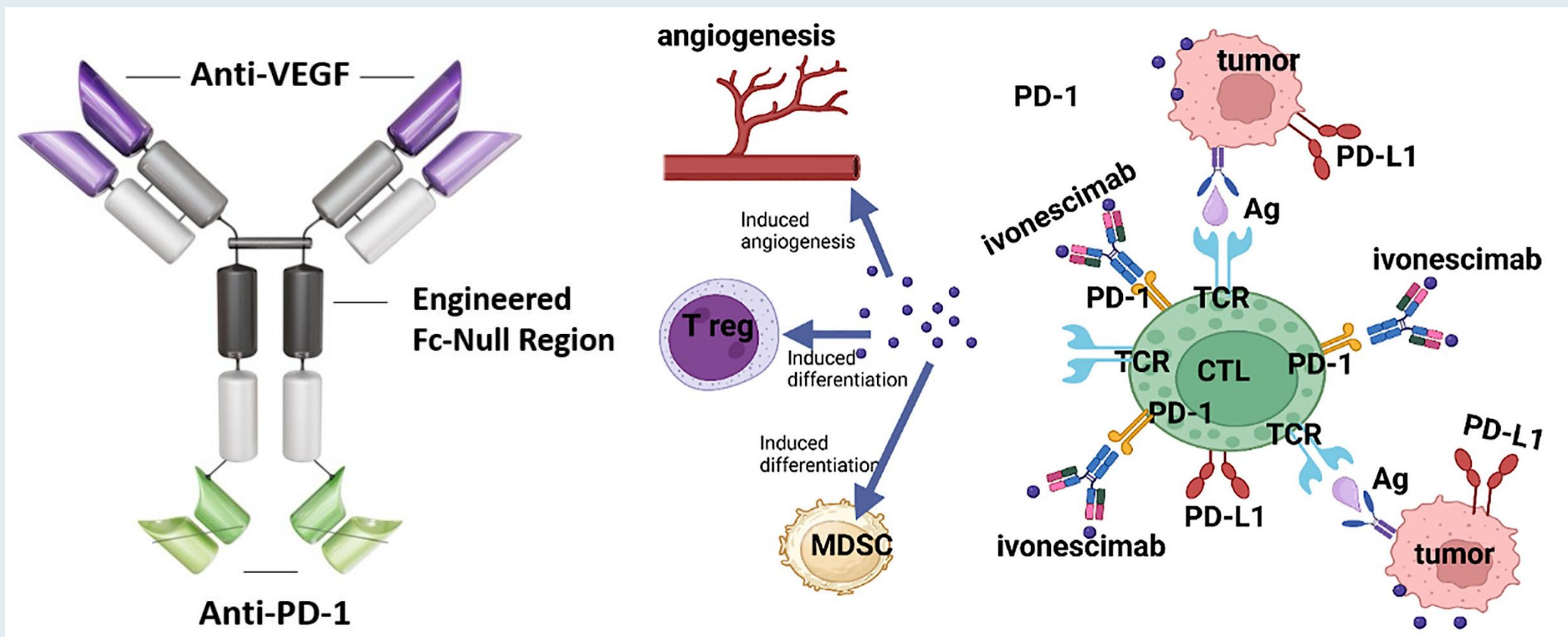
Module 3: Other Novel PD-1/PD-L1 x VEGF Bispecific Antibodies Under Investigation

Rationale for Dual Targeting of PD-1/PD-L1 and VEGF



- By blocking both PD-1/PD-L1 and VEGF in the tumor microenvironment (TME), bispecific antibodies have the potential to drive synergistic antitumor activity through higher binding affinity and increased activity of T cells
- In vitro studies have demonstrated that the presence of VEGF increased PD-1 binding strength more than tenfold

Ivonescimab Mechanism of Action



Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced squamous non-small-cell lung cancer (HARMONi-6): a randomised, double-blind, phase 3 trial

Zhiwei Chen*, Fang Yang*, Zhou Jiang*, Longhua Sun*, Lin Wu*, Zhengxiang Han, Yun Fan, Yanqiu Zhao, Xingya Li, Haipeng Xu, Xiangjiao Meng, Ying Liu, Zhiye Zhang, Hui Luo, Xuelei Ma, Xuezhen Ma, Qin Shi, Zhongmin Zhang, Runxiang Yang, Pingli Wang, Pinhua Pan, Xiaohong Ai, Jie Li[†], Xingxiang Pu, Zhiwu Wang, Jian Fang, Ming He, Yong He, Shuliang Guo, Juan Li, Hongbiao Wang, Junaiana Zhang, Qian Chu, Xuwen Liu, Shenpeng Ying, Hongcheng Wu, Hongmei Sun, Yinghua Ji, Ming Zhou, Jianya Zhou, Hongzhong Yang, Yingying Du, Hui Yang, Jian Shi, Hualin Baiyong Li, Michelle Xia, Shun Lu

Lancet 2025;406:2078-88.

2026 ASCO[®]
ANNUAL MEETING

Abstract LBA4

Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy in previously untreated advanced squamous non-small cell lung cancer: Overall survival results of the Phase 3 HARMONi-6 trial

Presented by: Shun Lu, MD, PhD

Chen Zhiwei¹, Fang Yang², Yongzhong Luo³, Longhua Sun⁴, Lin Wu³, Zhengxiang Han⁵, Yun Fan⁶, Yanqiu Zhao⁷, Xingya Li⁸, Haipeng Xu⁹, Xiangjiao Meng¹⁰, Ying Liu¹¹, Zhiye Zhang¹², Hui Luo¹³, Qin Shi¹⁴, Xuelei Ma¹⁵, Xuezhen Ma¹⁶, Zhongmin Zhang¹⁷, Michelle Y. Xia¹⁸, Shun Lu¹

What's Old is New Again

VEGF inhibition's role with immunotherapy for squamous NSCLC

Julie R Brahmer, MD, MSc, FASCO, FAIO

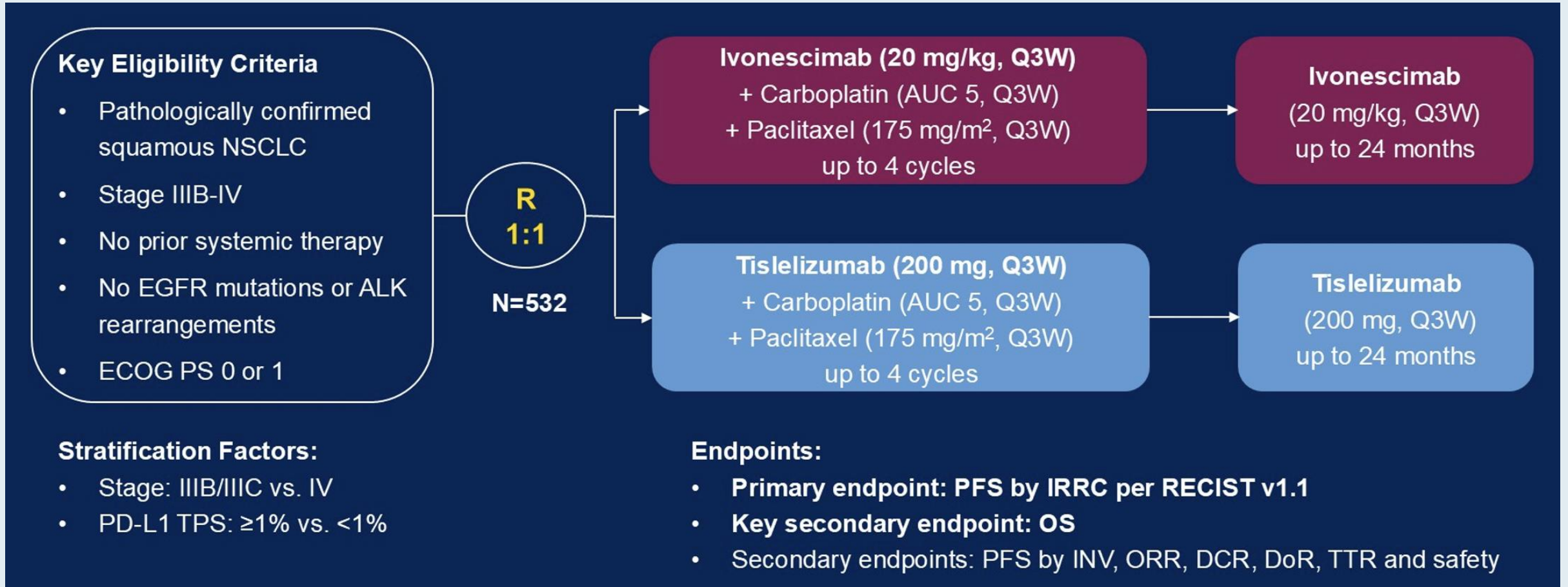
The Marilyn Meyerhoff Professor of Thoracic Oncology

Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland

Will PD-1/VEGF Bispecific Antibodies Replace Immune Checkpoint Inhibitors for Some, Many or All Patients?

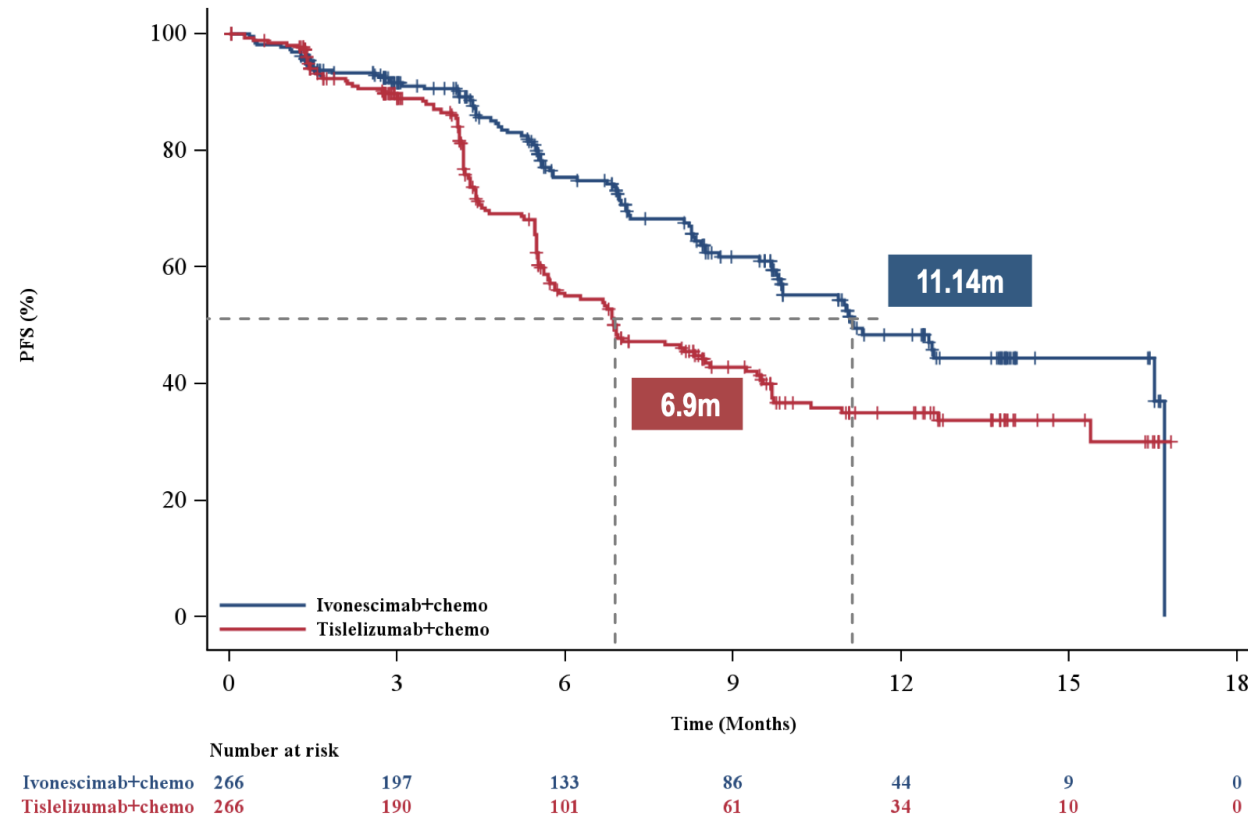
Immune checkpoint inhibitor	Approval date
Nivolumab	2015
Pembrolizumab	2015
Atezolizumab	2016
Durvalumab	2018
Ipilimumab	2020
Cemiplimab	2021
Tremelimumab	2022

HARMONi-6 Chinese Phase III Study Design



HARMONi-6: Progression-Free Survival (PFS) Outcomes

Ivonescimab + chemo demonstrated a statistically significant improvement in PFS vs. tislelizumab + chemo with HR = 0.60, representing a 4.2-month improvement in mPFS.



	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
mPFS, months (95% CI)	11.14 (9.86, NE)	6.90 (5.82, 8.57)
Stratified HR (95% CI)	0.60 (0.46, 0.78)	
p-value	<0.0001	

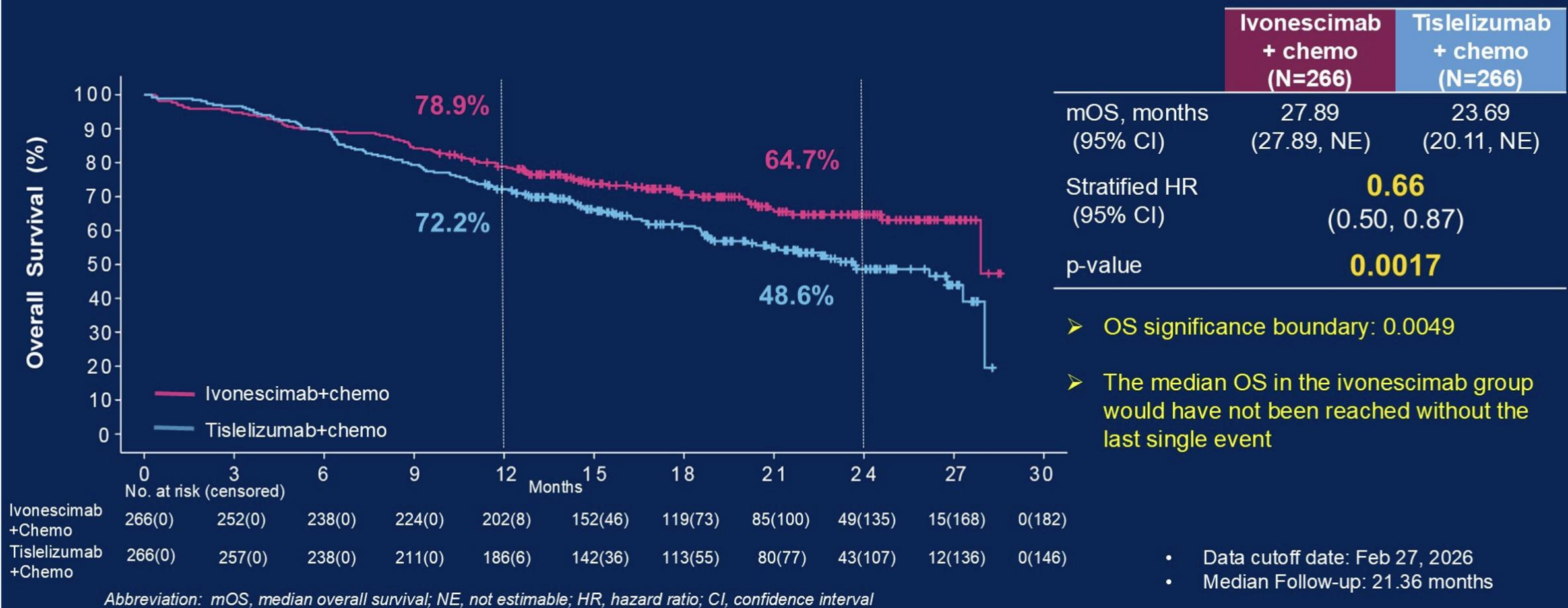
Median Follow-up: 10.28 months

Consistent PFS benefit by investigator-assessment: HR = 0.64 (95% CI: 0.50, 0.84)

mPFS = median PFS

HARMONi-6: Interim Overall Survival (OS) Analysis

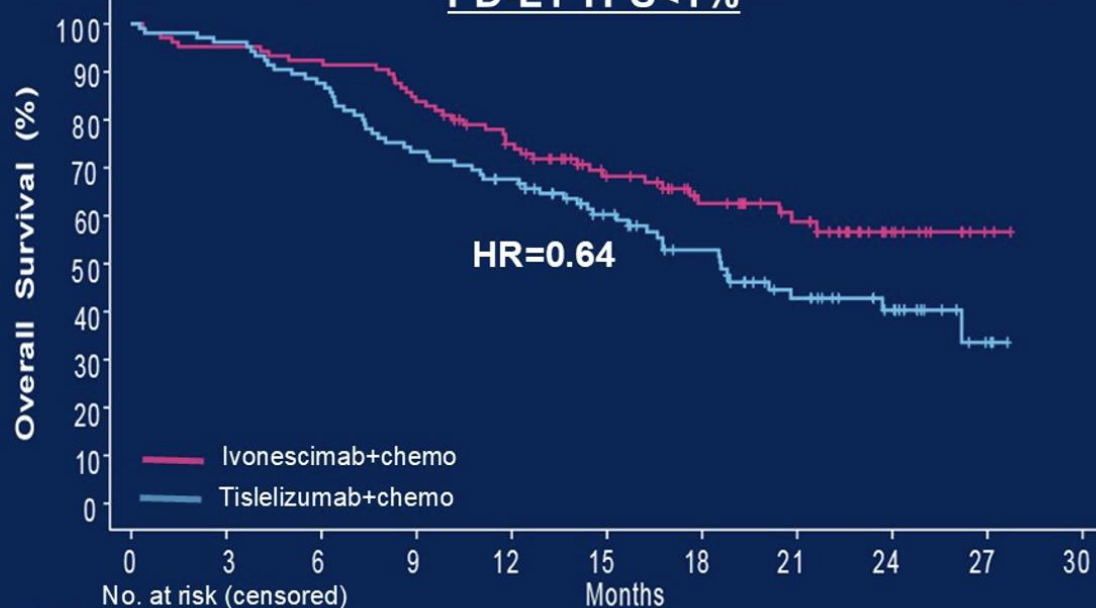
✓ Ivonescimab with chemotherapy significantly improved OS



HARMONi-6: OS by PD-L1 Expression Levels

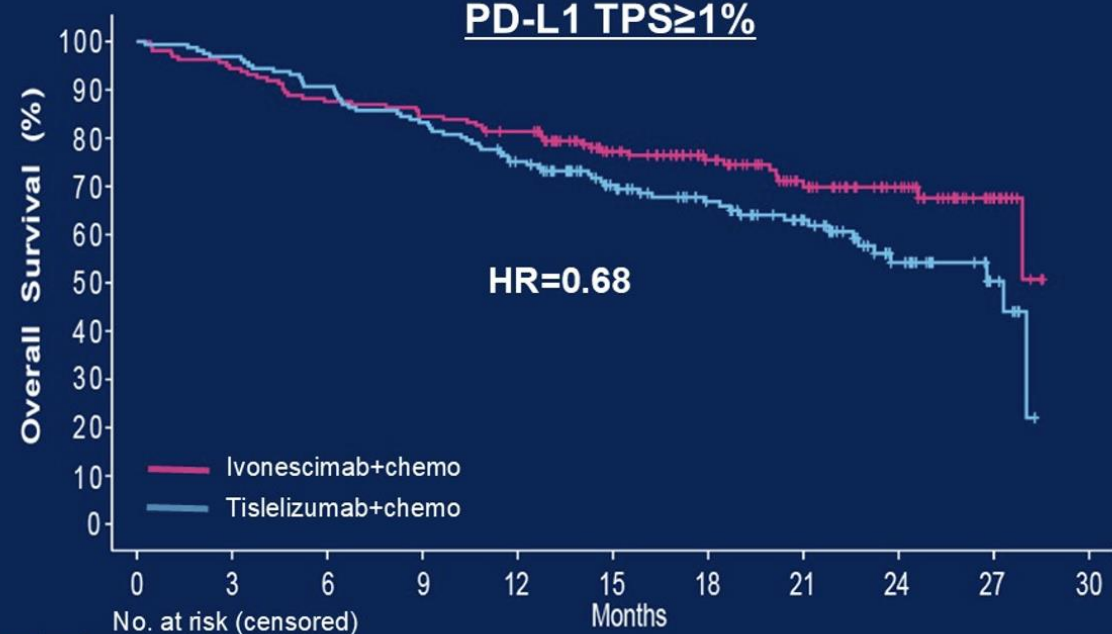
- ✓ **Ivonescimab with chemotherapy showed consistent OS improvement across PD-L1 expression subgroups**

PD-L1 TPS<1%



	No. at risk (censored)									
Ivonescimab+Chemo	105(0)	100(0)	97(0)	88(0)	73(6)	54(19)	40(29)	30(37)	12(54)	3(63)
Tislelizumab+Chemo	105(0)	101(0)	92(0)	77(0)	69(2)	52(12)	40(18)	25(26)	15(35)	3(46)

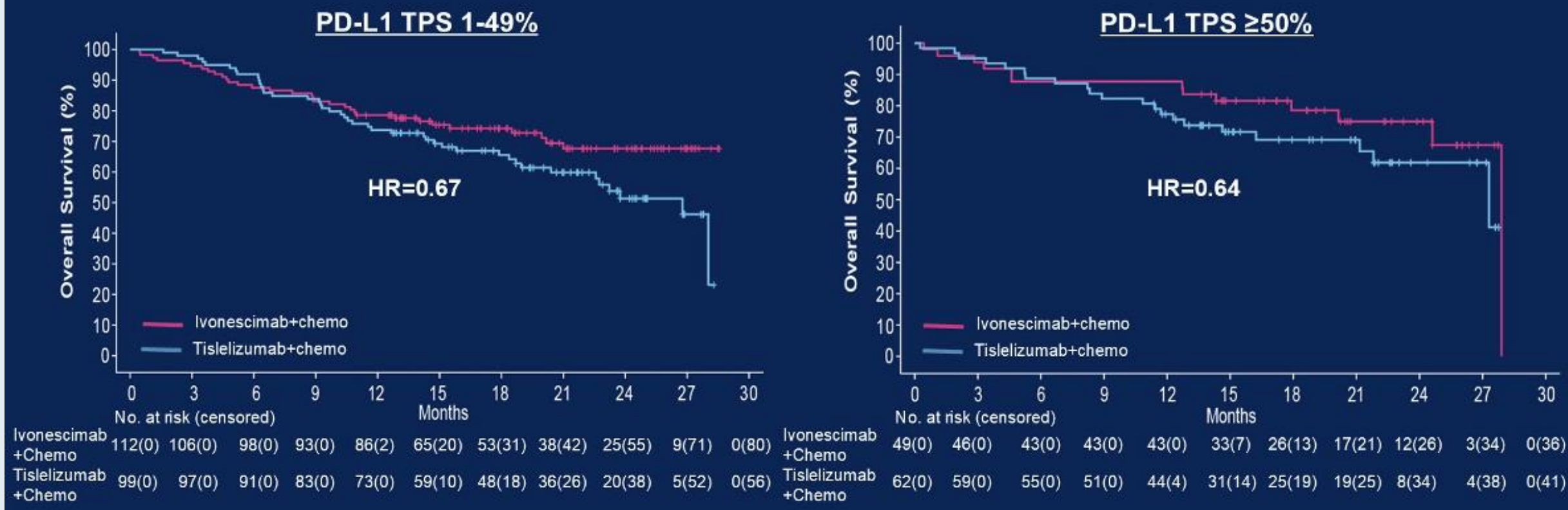
PD-L1 TPS≥1%



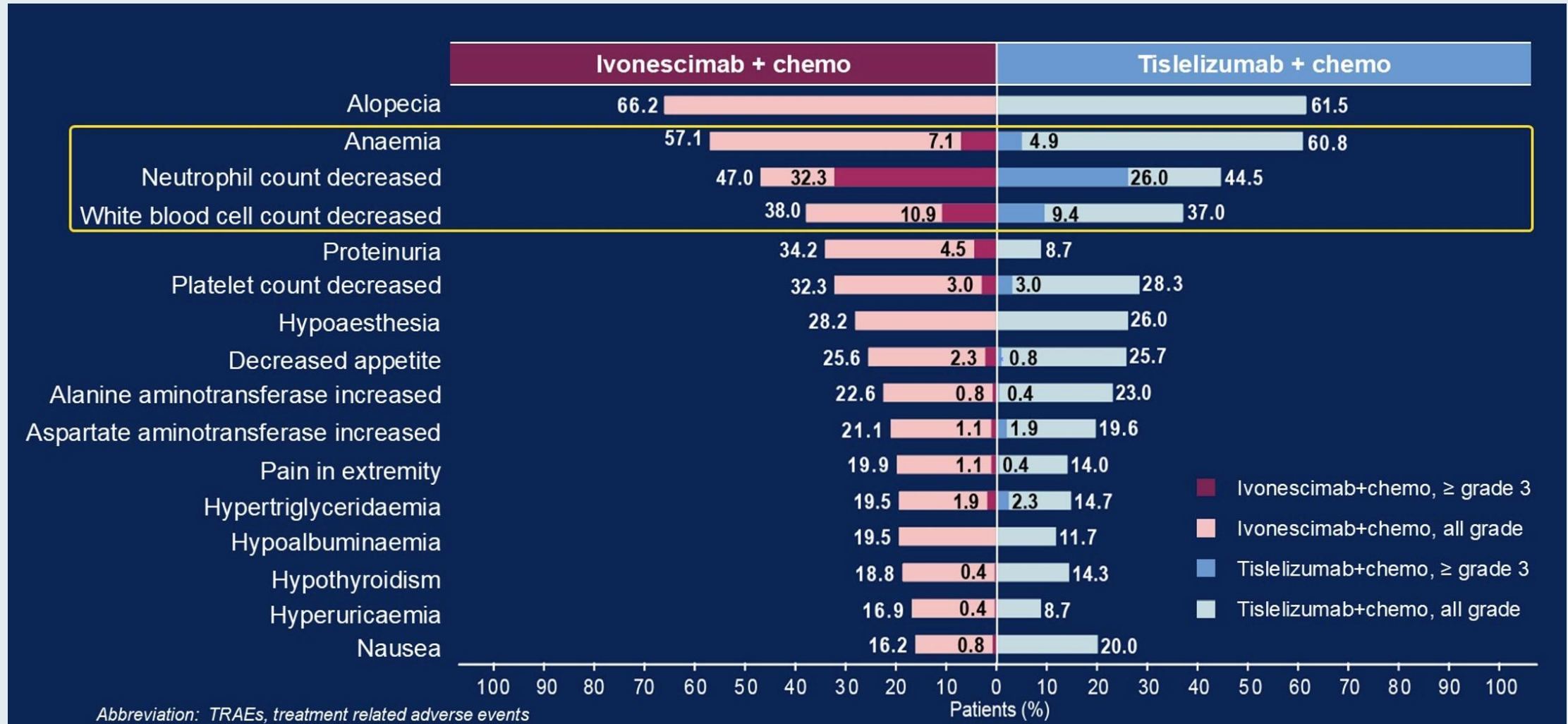
	No. at risk (censored)									
Ivonescimab+Chemo	161(0)	152(0)	141(0)	136(0)	129(2)	98(27)	79(44)	55(63)	37(81)	12(105)
Tislelizumab+Chemo	161(0)	156(0)	146(0)	134(0)	117(4)	90(24)	73(37)	55(51)	28(72)	9(90)

HARMONi-6: OS by PD-L1 Expression Levels

- ✓ Ivonescimab with chemotherapy showed consistent OS improvement across PD-L1 expression subgroups



HARMONi-6: Safety Profile



- Grade ≥3 immune-related adverse events (AEs) were observed in 34 (14%) of patients receiving ivonescimab/chemotherapy and in 36 (14%) of patients receiving tislelizumab/chemotherapy.

HARMONi-6: Possibly VEGF-Related Adverse Events (AEs)

- Possibly VEGF-related AEs occurred more frequently in the ivonescimab arm, most of which were grade 1-2

Possibly VEGF-Related AEs [#]	Ivonescimab + chemo (N=266)				Tislelizumab + chemo (N=265)			
	Any Grade	Grade 1	Grade 2	Grade ≥3	Any Grade	Grade 1	Grade 2	Grade ≥3
Proteinuria	113 (42.5)	35 (13.2)	60 (22.6)	18 (6.8)	34 (12.8)	26 (9.8)	8 (3.0)	0
Haemorrhage	66 (24.8)	39 (14.7)	20 (7.5)	7 (2.6)	32 (12.1)	24 (9.1)	6 (2.3)	2 (0.8)
Hypertension	39 (14.7)	7 (2.6)	22 (8.3)	10 (3.8)	15 (5.7)	3 (1.1)	7 (2.6)	5 (1.9)
Arterial thromboembolism	4 (1.5)	1 (0.4)	0	3 (1.1)	0	0	0	0
Venous thromboembolism	2 (0.8)	0	2 (0.8)	0	3 (1.1)	0	2 (0.8)	1 (0.4)
Fistula	1 (0.4)	0	1 (0.4)	0	0	0	0	0

- # AE terms were grouped terms
- Data are n (%)

Key Takeaway Points

Ivonescimab plus taxane/carboplatin chemotherapy is effective for Chinese patients with advanced squamous NSCLC based on the interim overall survival advantage.

Ivonescimab results in VEGF-related AEs, and there is some uncertainty regarding patient selection.

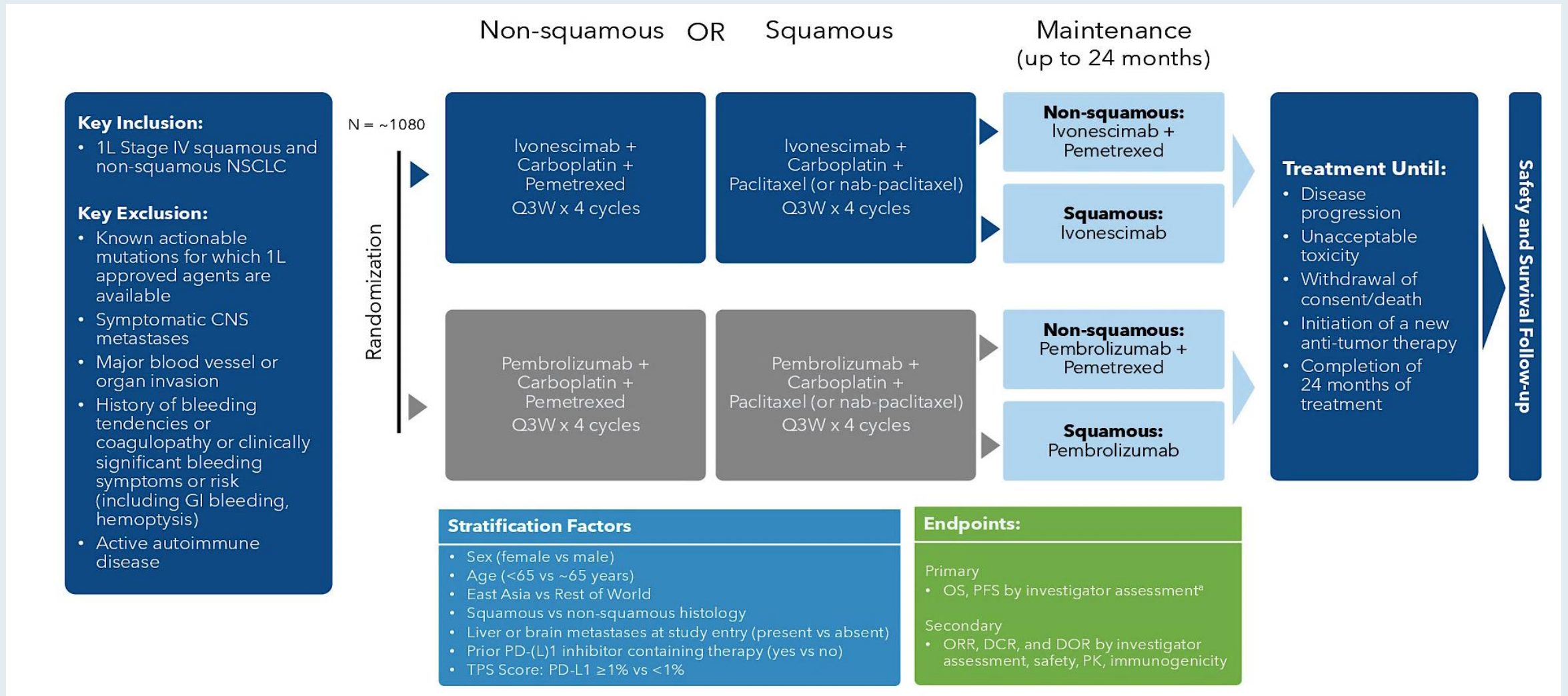
Applicability to the global, generally older, squamous lung cancer population is unclear.

“We have to wait and see if ivonescimab will be approved in squamous cell. If they approve it in the EU based on HARMONi-6 and we don’t, and then years down the line, it turns out to be the same in the US, we will regret that, and our patients would have been getting inferior care, which has never happened. We’re always the first, so how can we be the last? So that’s a big deal.”

Stephen V Liu, MD

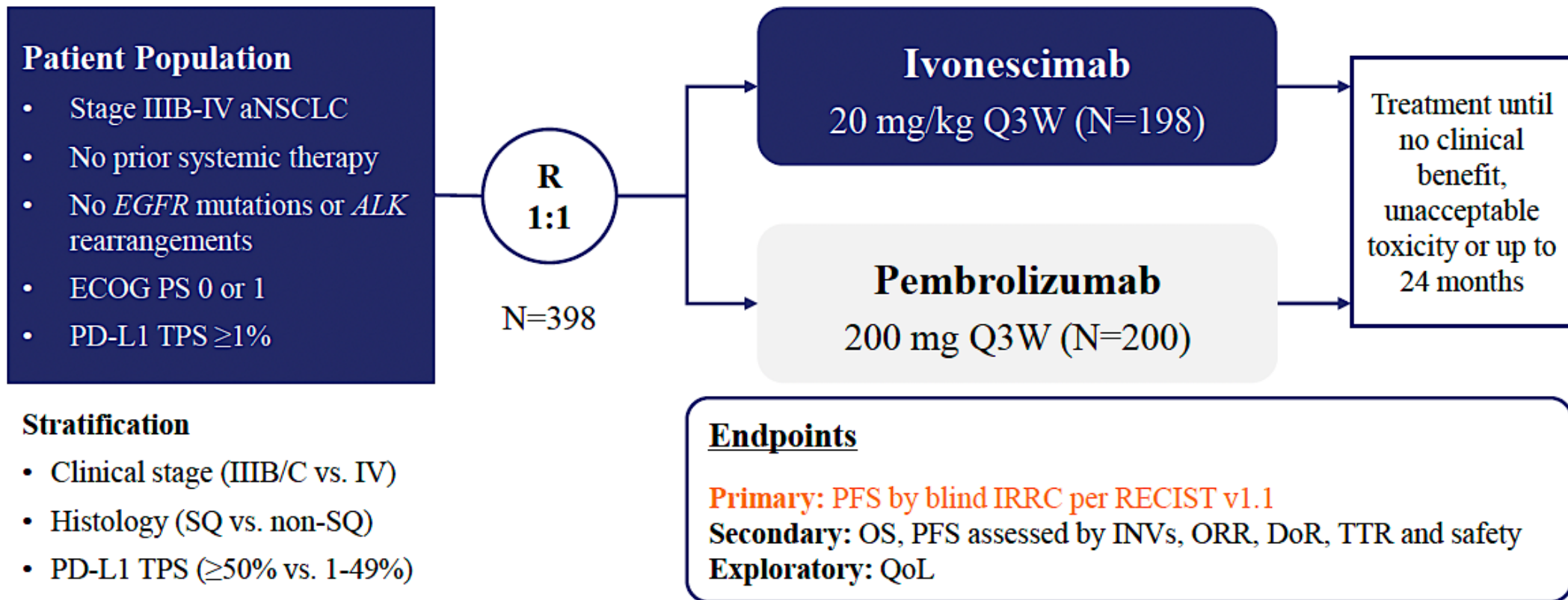
Oncology Today Podcast with Dr Neil Love

HARMONi-3: An Ongoing Phase III Study of Ivonescimab/Chemotherapy versus Pembrolizumab/Chemotherapy for Previously Untreated mNSCLC

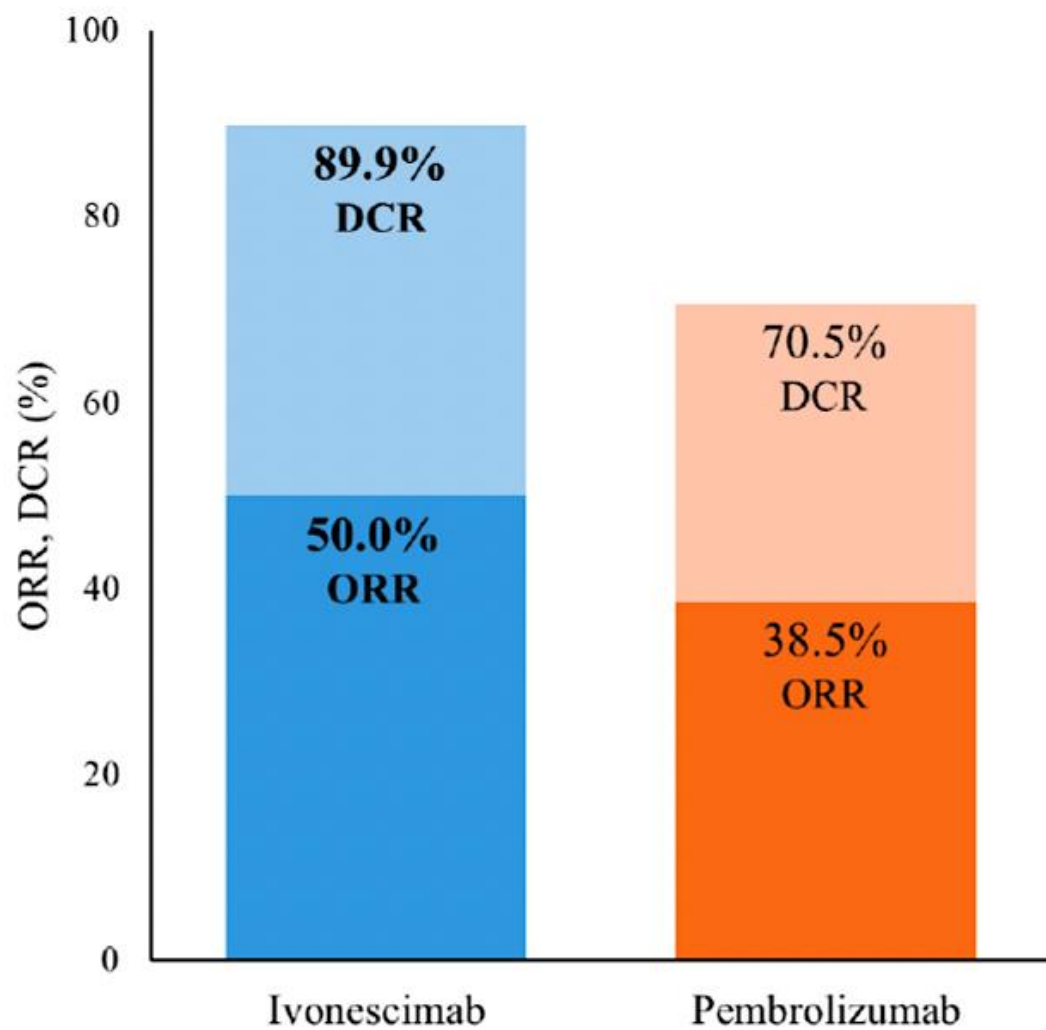


HARMONi-2 Chinese Phase III Study Design

A randomized, double-blind, phase 3 study^a



HARMONi-2: Response Data

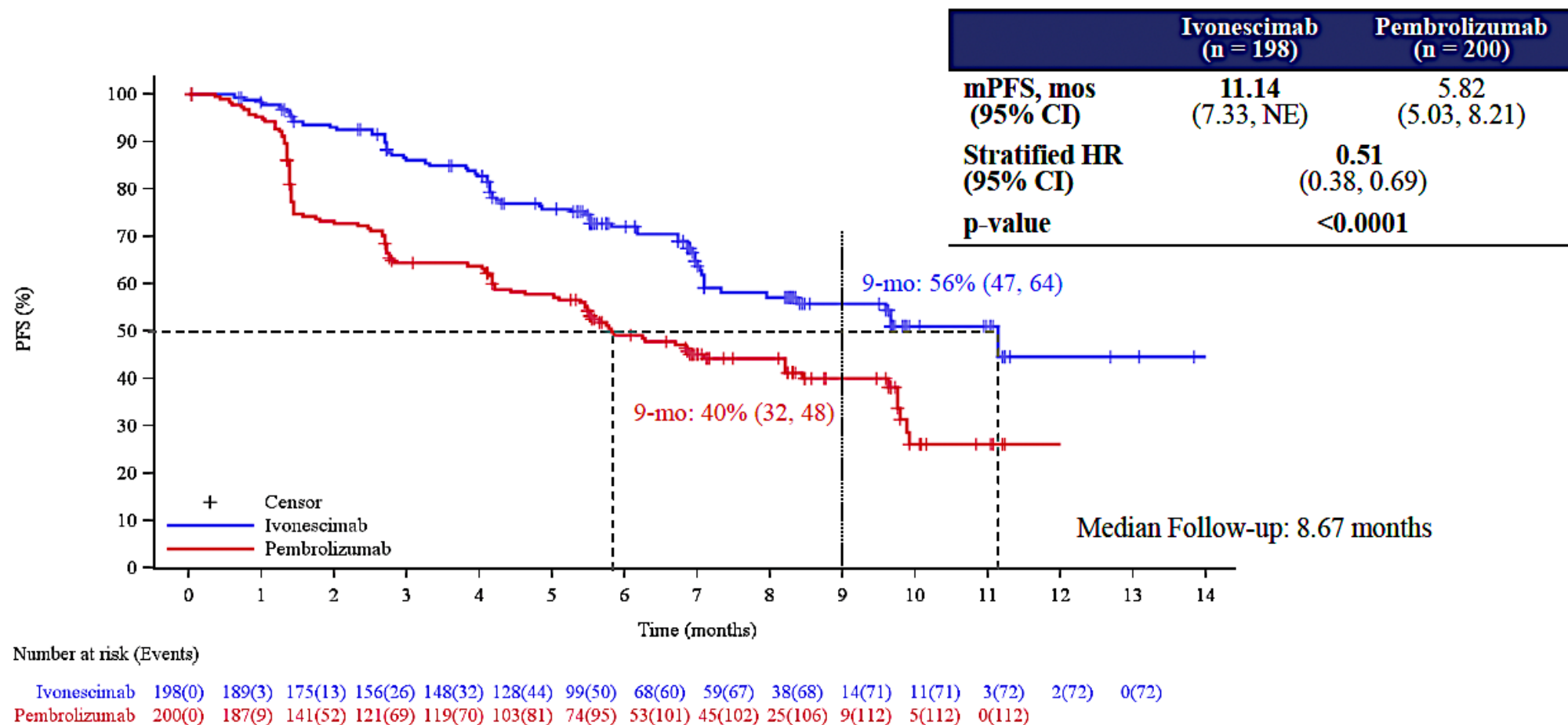


	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
ORR, % (95% CI)	50.0 (42.8, 57.2)	38.5 (31.7, 45.6)
DCR, % (95% CI)	89.9 (84.8, 93.7)	70.5 (63.7, 76.7)
Median DoR, mos (95% CI)	NR (NE, NE)	NR (8.28, NE)

ORR and DCR were higher with ivonescimab vs. pembrolizumab.

ORR = objective response rate; DCR = disease control rate; DoR = duration of response

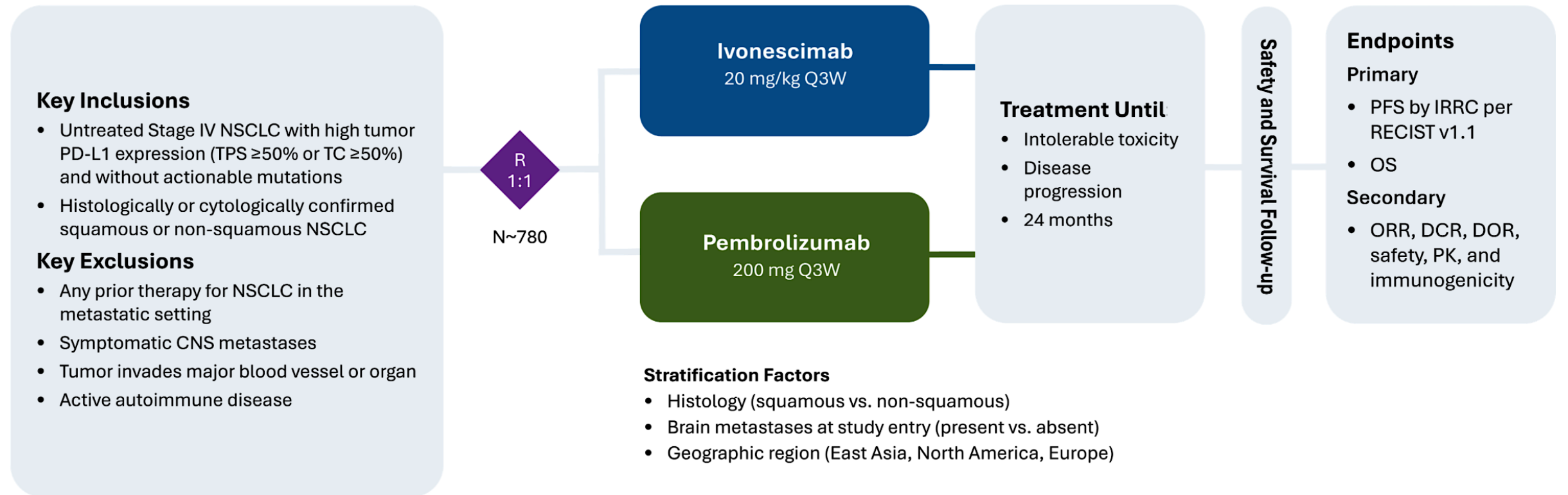
HARMONi-2: PFS Outcomes



Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

HARMONi-7: An Ongoing Phase III Study of Ivonescimab versus Pembrolizumab for mNSCLC with High PD-L1 Expression

Monotherapy Ivonescimab vs. Pembrolizumab



Do you anticipate that ivonescimab/chemotherapy will yield superior efficacy outcomes compared to pembrolizumab/chemotherapy in previously untreated advanced NSCLC in a global population?



Dr Baik

Yes



Dr Goldman

Yes



Dr Paik

Yes



Prof Passaro

I'm not sure



Dr Piotrowska

Yes



Dr Rotow

Yes



Dr Villaruz

Yes

Do you anticipate that ivonescimab monotherapy will yield superior efficacy outcomes compared to pembrolizumab monotherapy in previously untreated advanced NSCLC with high PD-L1 expression in a global population?



Dr Baik

Yes



Dr Goldman

Yes



Dr Paik

Yes



Prof Passaro

I'm not sure



Dr Piotrowska

Yes



Dr Rotow

Yes



Dr Villaruz

Yes

According to clinical trial data and/or your clinical experience, how much of a concern are treatment-related adverse events for patients receiving ivonescimab?



Dr Baik

A minor concern; the majority of patients experience low-grade side effects related to VEGF pathway inhibition



Dr Goldman

A minor concern; the majority of patients experience low-grade side effects related to VEGF pathway inhibition



Dr Paik

A minor concern; the majority of patients experience low-grade side effects related to VEGF pathway inhibition



Prof Passaro

Minimal concern; the majority of patients experience no side effects



Dr Piotrowska

A minor concern; the majority of patients experience low-grade side effects related to VEGF pathway inhibition



Dr Rotow

A minor concern; the majority of patients experience low-grade side effects related to VEGF pathway inhibition



Dr Villaruz

A minor concern; the majority of patients experience low-grade side effects related to VEGF pathway inhibition

How would you indirectly compare the spectrum and severity of VEGF-related toxicities associated with ivonescimab to those experienced by patients with NSCLC receiving VEGF/VEGFR-targeted monoclonal antibodies?



Dr Baik

VEGF-related toxicities are about the same



Dr Goldman

VEGF-related toxicities are more common/severe with VEGF/VEGFR-targeted monoclonal antibodies



Dr Paik

VEGF-related toxicities are more common/severe with VEGF/VEGFR-targeted monoclonal antibodies



Prof Passaro

VEGF-related toxicities are about the same



Dr Piotrowska

VEGF-related toxicities are more common/severe with VEGF/VEGFR-targeted monoclonal antibodies



Dr Rotow

VEGF-related toxicities are about the same



Dr Villaruz

Not enough available data to tell

How would you indirectly compare the spectrum and severity of immune-related toxicities associated with ivonescimab to those experienced by patients with NSCLC receiving PD-1/PD-L1-targeted monoclonal antibodies?



Dr Baik

Immune-related toxicities are about the same



Dr Goldman

Immune-related toxicities are about the same



Dr Paik

Immune-related toxicities are more common/severe with PD-1/PD-L1-targeted monoclonal antibodies



Prof Passaro

Immune-related toxicities are about the same



Dr Piotrowska

Immune-related toxicities are about the same



Dr Rotow

Immune-related toxicities are about the same



Dr Villaruz

Not enough available data to tell

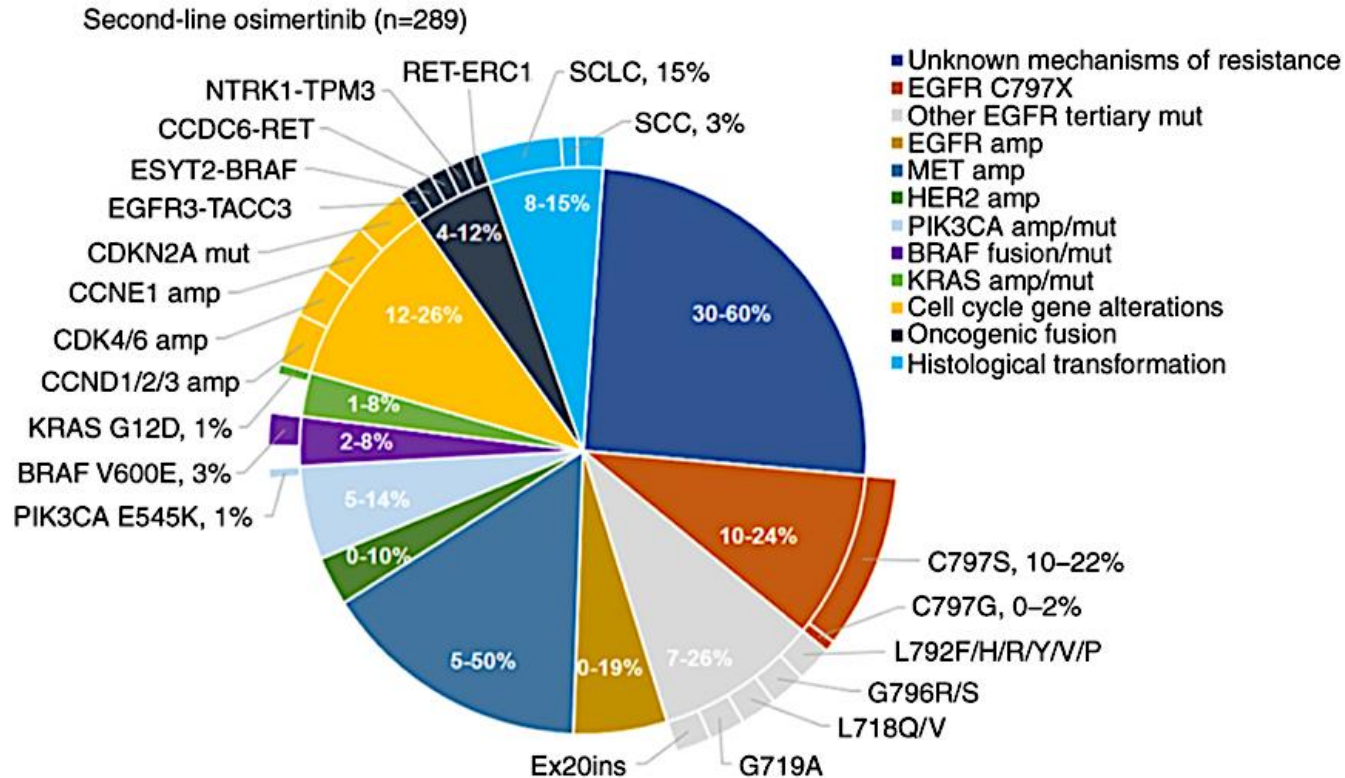
Agenda

Module 1: Ivonescimab for Previously Untreated Metastatic Non-Small Cell Lung Cancer (mNSCLC)

Module 2: Ivonescimab for Relapsed/Refractory EGFR-Mutated mNSCLC

Module 3: Other Novel PD-1/PD-L1 x VEGF Bispecific Antibodies Under Investigation

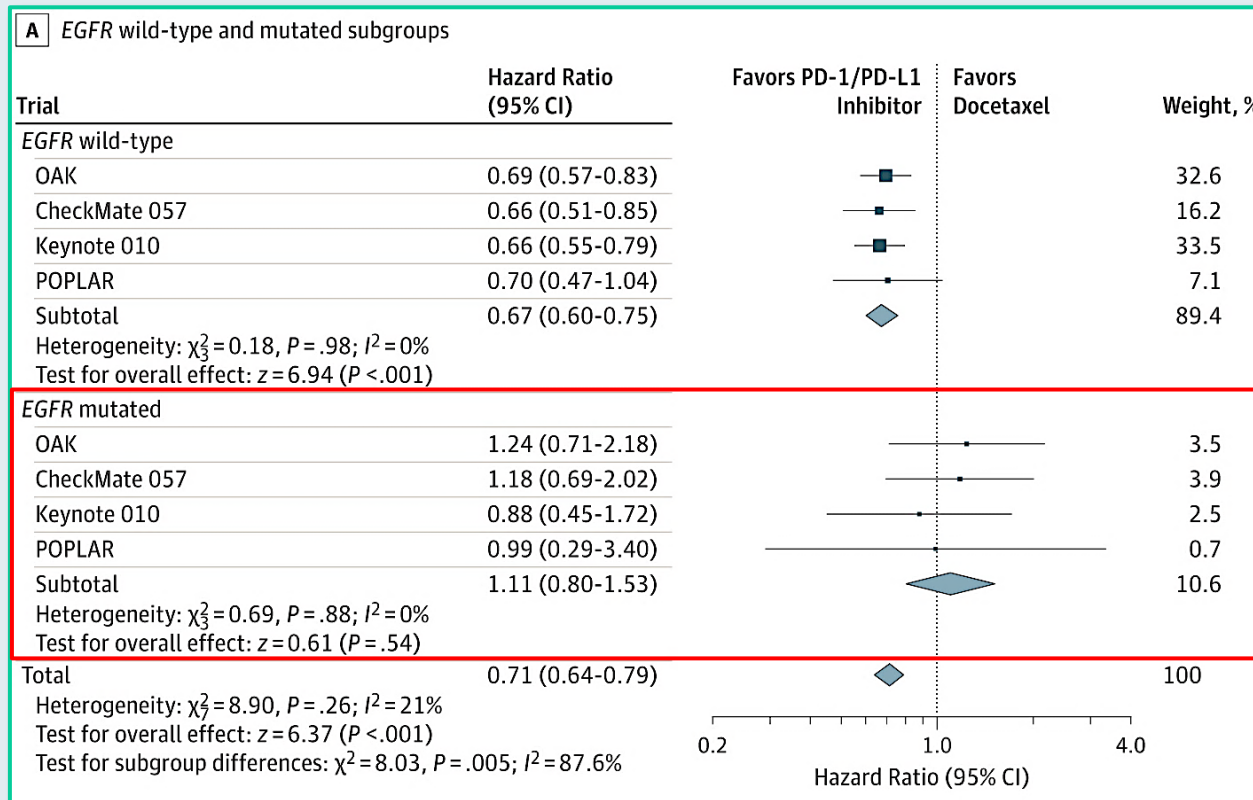
Acquired Resistance in EGFR-Mutated NSCLC



- The occurrence of acquired resistance is inevitable, and the mechanisms of third-generation EGFR tyrosine kinase inhibitor (TKI) resistance are complex and incompletely understood
- The mechanisms of acquired resistance to third-generation EGFR TKIs include an altered EGFR signaling pathway, aberrant activation of bypass and downstream signaling pathways and histological transformation

Poor Immunotherapy Response in EGFR-Mutated NSCLC

Overall survival hazard ratios



Mechanisms

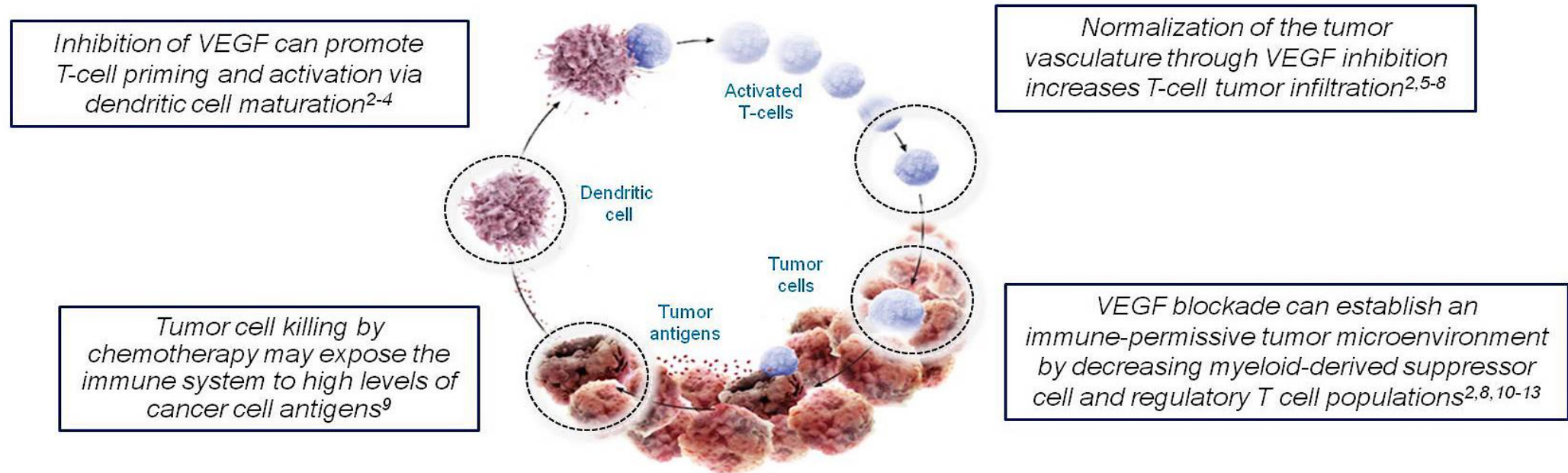
- Low tumor mutational burden
- Immunosuppressive tumor microenvironment
- Disrupted helper T-cell signaling
- EGFR-mediated suppression of IFN- γ
- TGF- β upregulation

Content courtesy of Jonathan Goldman, MD

Lee et al. *JAMA Oncology* 2018. Yang et al. *J Clin Oncol* 2024. Mok et al. *J Clin Oncol* 2024. Lu et al. *Lancet Oncol* 2022 and *Lancet Respir Med* 2023. Shi et al. *Cancer Medicine* 2021.

Rationale for the Combination of Atezolizumab + Bevacizumab + Chemotherapy

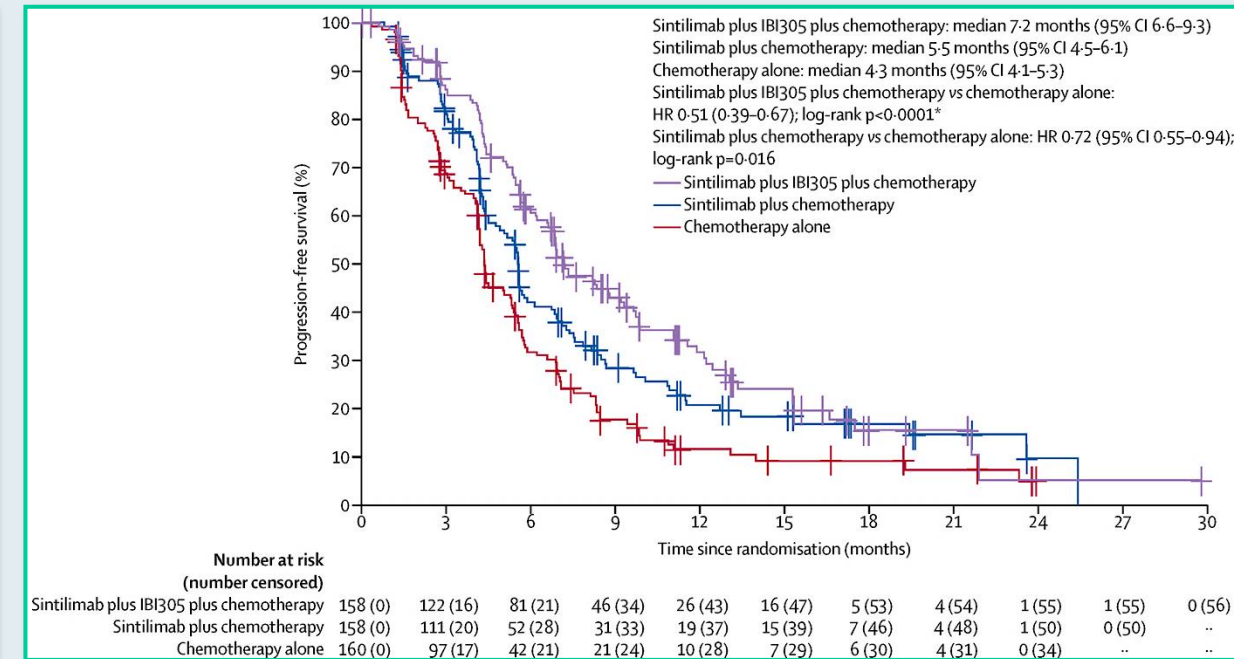
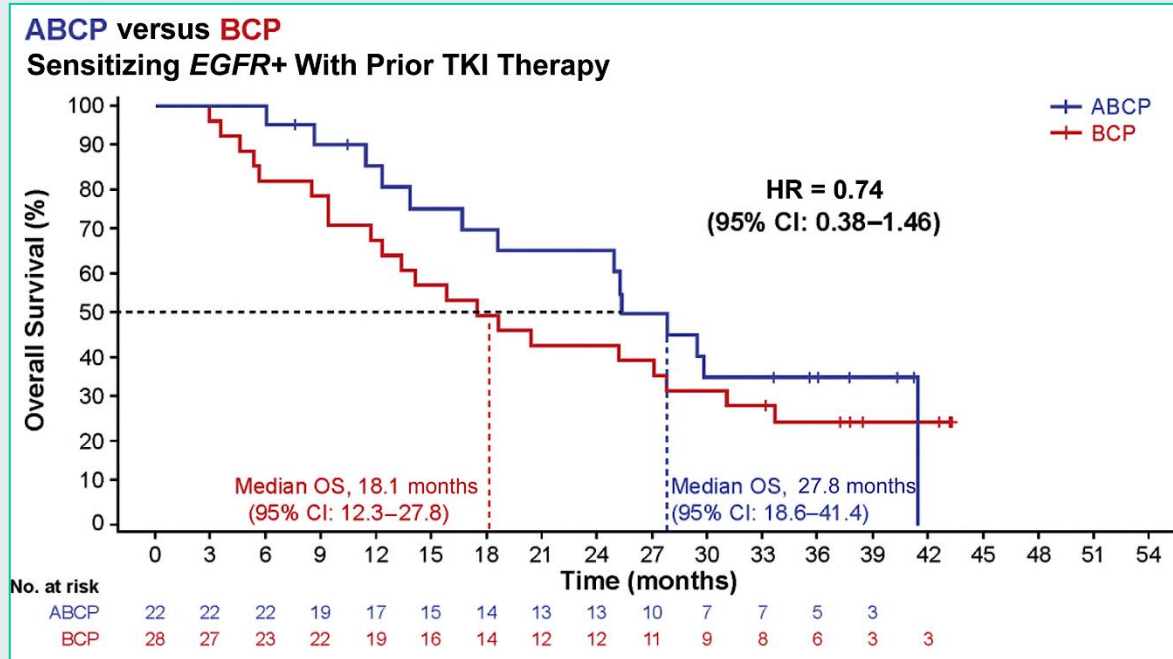
- In addition to its known anti-angiogenic effects¹, bevacizumab's inhibition of VEGF has immune modulatory effects²



- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Ferrara N, et al. *Nat Rev Drug Discov*, 2004. 2. Hegde PS, et al. *Semin Cancer Biol*, 2017. 3. Gabrilovich DI, et al. *Nat Med*, 1996. 4. Oyama T, et al. *J Immunol*, 1998. 5. Goel S, et al. *Physiol Rev*, 2011. 6. Motz GT, et al. *Nat Med*, 2014. 7. Hodi FS, et al. *Cancer Immunol Res*, 2014. 8. Wallin JJ, et al. *Nat Commun*, 2016. 9. Zitvogel L, et al. *Immunity*, 2013. 10. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 11. Roland CL, et al. *PLoS One*, 2009. 12. Facciabene A, et al. *Nature*, 2011. 13. Voron T, et al. *J Exp Med*, 2015. Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

Combination Chemotherapy with VEGF Inhibition and Immunotherapy (IO)



IMpower150 trial: Chemo + VEGFi vs chemo + VEGFi + IO

- Exploratory analysis in 123 patients with EGFRm.
For all pt, OS HR 0.60.
For those treated with previous TKI, HR 0.74.

ORIENT-31 trial: Chemo vs chemo + IO vs chemo + VEGFi + IO

- PFS 4.3 vs 5.5 vs 7.2 months.
- OS curves are overlapping.

HARMONi-A Chinese Phase III Study Design

Key Eligibility Criteria

- nsq-NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- EGFR sensitive mutation positive
- ECOG PS 0 or 1
- Regardless PD-L1 expression

Stratification Factors:

- Exposure to 3rd EGFR-TKI before (yes vs. no)
- Brain metastases (yes vs. no)

R
(1:1)

Ivonescimab
20mg/kg
+
Pemetrexed 500 mg/m²
Carboplatin AUC5
Q3W for 4 cycles

Ivonescimab
20mg/kg Q3W
+
Pemetrexed 500
mg/m² Q3W

Placebo
+
Pemetrexed 500 mg/m²
Carboplatin AUC5
Q3W for 4 cycles

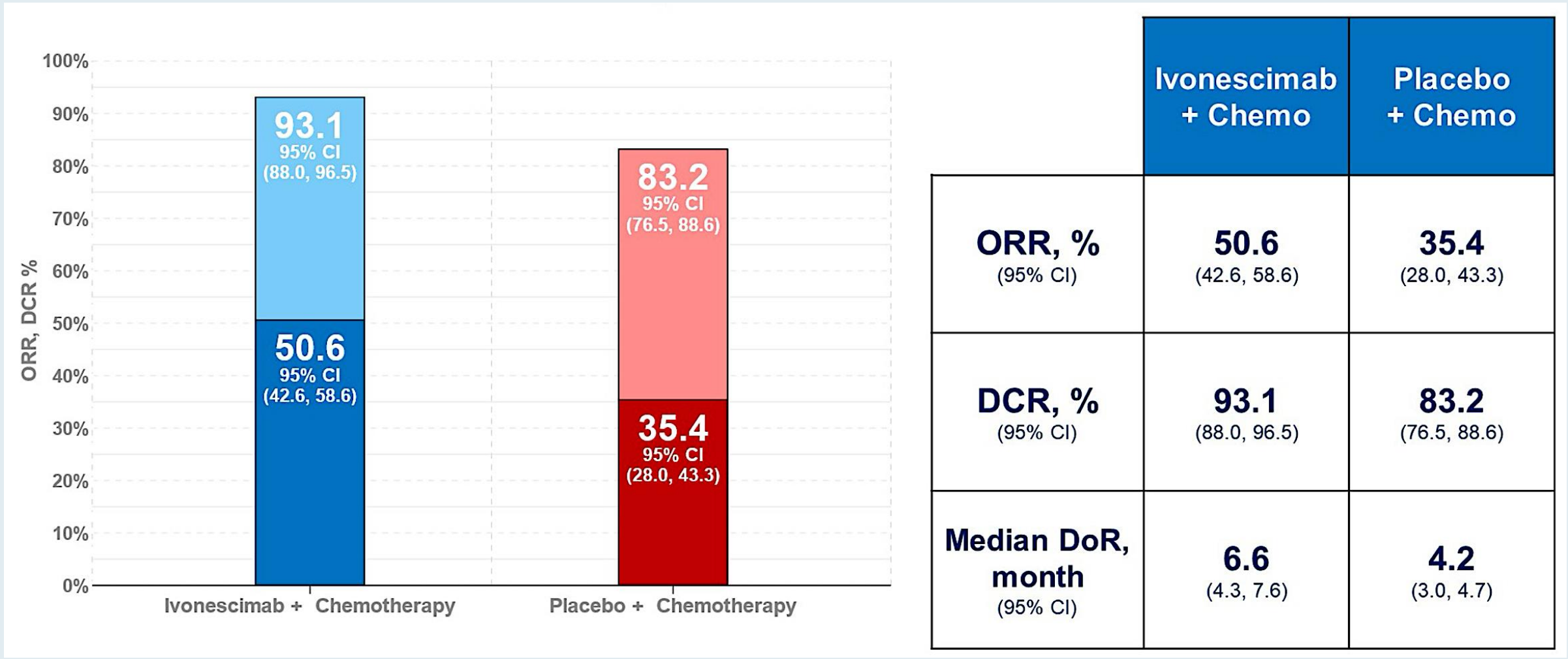
Placebo
Q3W
+
Pemetrexed 500
mg/m² Q3W

Treatment until:

- Intolerable toxicity
- No clinical benefit
- Initiation of new anti-tumor therapy

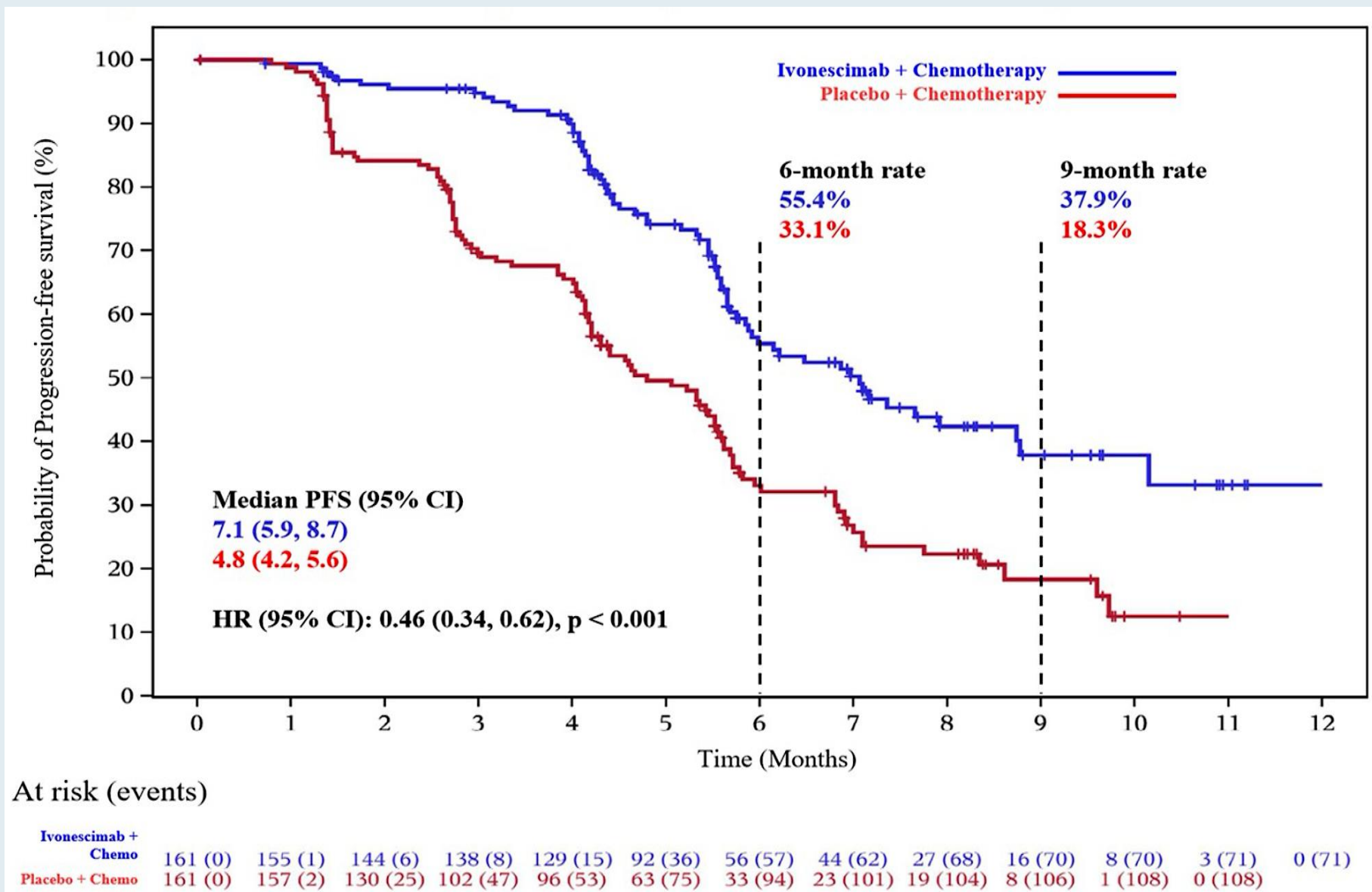
Up to 24 months

HARMONi-A: Response Data



ORR = objective response rate; DCR = disease control rate; DoR = duration of response

HARMONi-A: PFS Outcomes



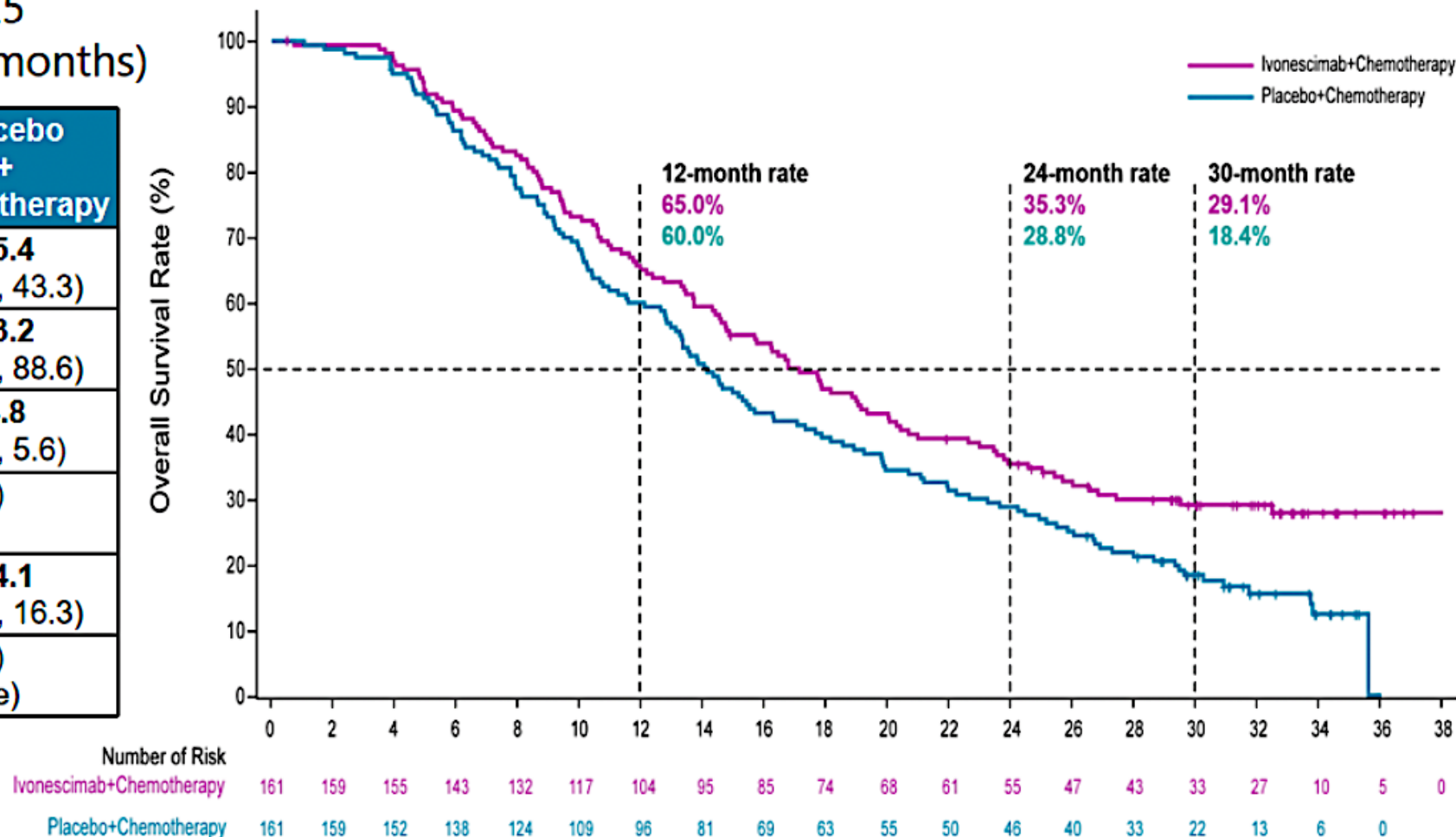
HARMONi-A: Final OS Analysis

Data cut-off date: April 2025
(median follow-up of 32.5 months)

	Ivonescimab + chemotherapy	Placebo + chemotherapy
ORR¹, % (95% CI)	50.6 (42.6, 58.6)	35.4 (28.0, 43.3)
DCR¹, % (95% CI)	93.1 (88.0, 96.5)	83.2 (76.5, 88.6)
mPFS¹, months (95% CI)	7.1 (5.9, 8.7)	4.8 (4.2, 5.6)
PFS HR¹ (95% CI)	0.46 (0.34, 0.62) p<0.001	
mOS², months (95% CI)	16.8 (14.5, 20.0)	14.1 (12.8, 16.3)
OS HR² (95% CI)	0.74 (0.58, 0.95) p=0.019 (two-side)	

¹Interim analysis

²Final analysis



HARMONi Study Design (Asia and Western Populations)

Key Eligibility Criteria

Locally advanced or metastatic NSCLC:

- EGFR sensitizing mutation+
- Progressed on 3rd gen EGFR-TKI
- ECOG 0 or 1
- Any PD-L1 expression

Stratification factor by geographic region:

- Brain metastases (yes or no)



N=438

**Ivonescimab +
Chemotherapy**
(N = 219)

**Placebo +
Chemotherapy**
(N = 219)

Ivonescimab: 20 mg/kg Q3W

Chemotherapy:

- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m² Q3W

Endpoints:

Primary

- OS, PFS by IRRC per RECIST 1.1

Secondary

- ORR by IRRC, DoR, safety and tolerability

Planned Efficacy Analyses

- PFS primary (at ~231 events) & OS interim analyses
- OS final analysis (at ~261 events)

FPI: Jan 2022 (overall)

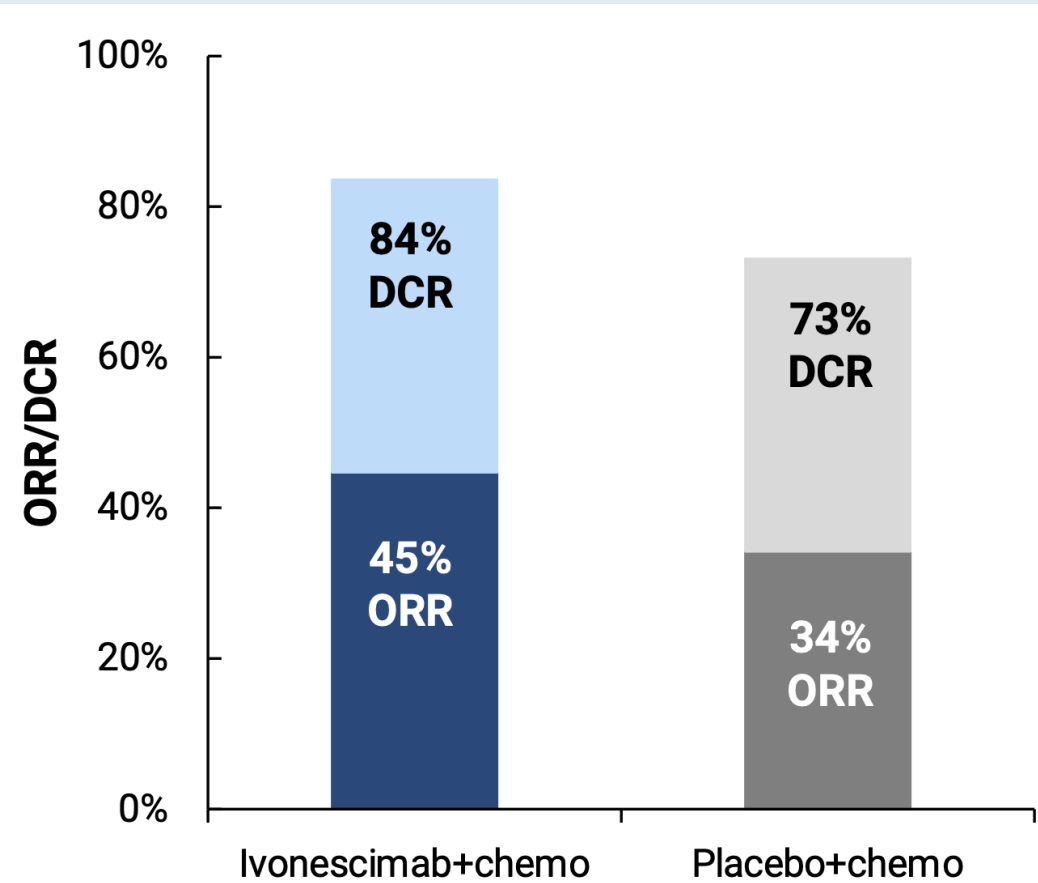
LPI Asia: Nov 2022

LPI NA & EU (and overall): Oct 2024

Note: Positive outcomes were reported from the single-region (Asia) study HARMONi-A, with PFS as the primary endpoint.

DoR=duration of response; ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; EU=Europe; FPI=first patient in; IRRC= independent radiology review committee; LPI=last patient in; mets=metastases; NA=North America; ORR=overall response rate; OS=overall survival; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitor; PD-L1= programmed cell death ligand; PFS=progression-free survival; Q3W=every 3 weeks; RECIST=response evaluation criteria in solid tumors.

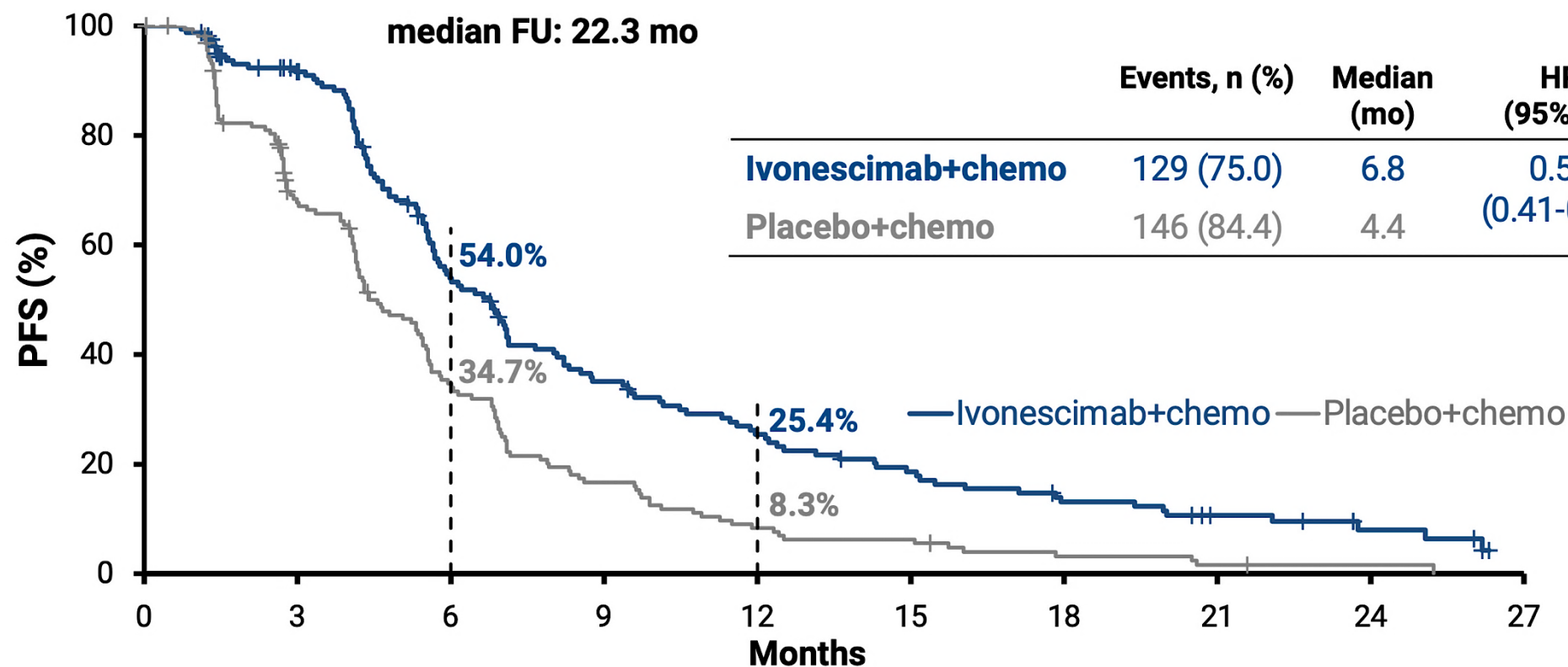
HARMONi: Response Data



DoR (mo)	Ivonescimab + chemo	Placebo + chemo
n	98	75
Median (95% CI)	7.6 (5.5-10.6)	4.2 (2.9-4.7)

ORR = overall response rate

HARMONi: PFS Outcomes



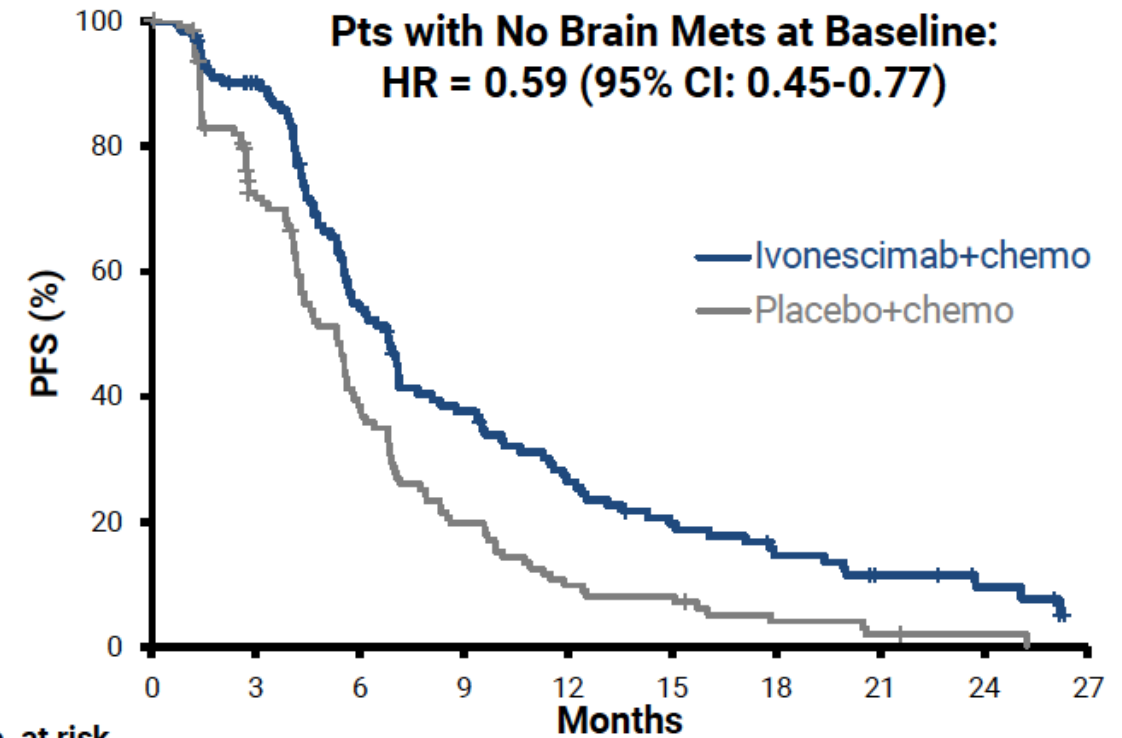
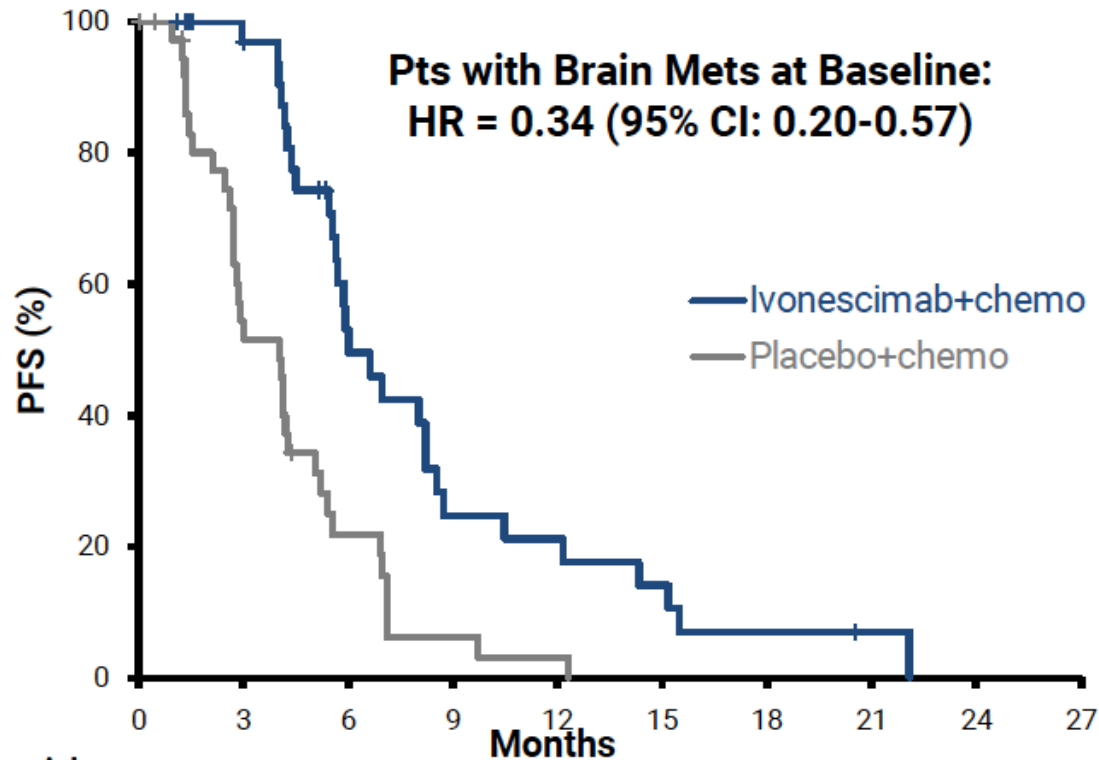
No. at risk

Ivonescimab+chemo 172 134 76 48 34 24 16 10 5 0

Placebo+chemo 173 100 50 24 12 9 4 2 1 0

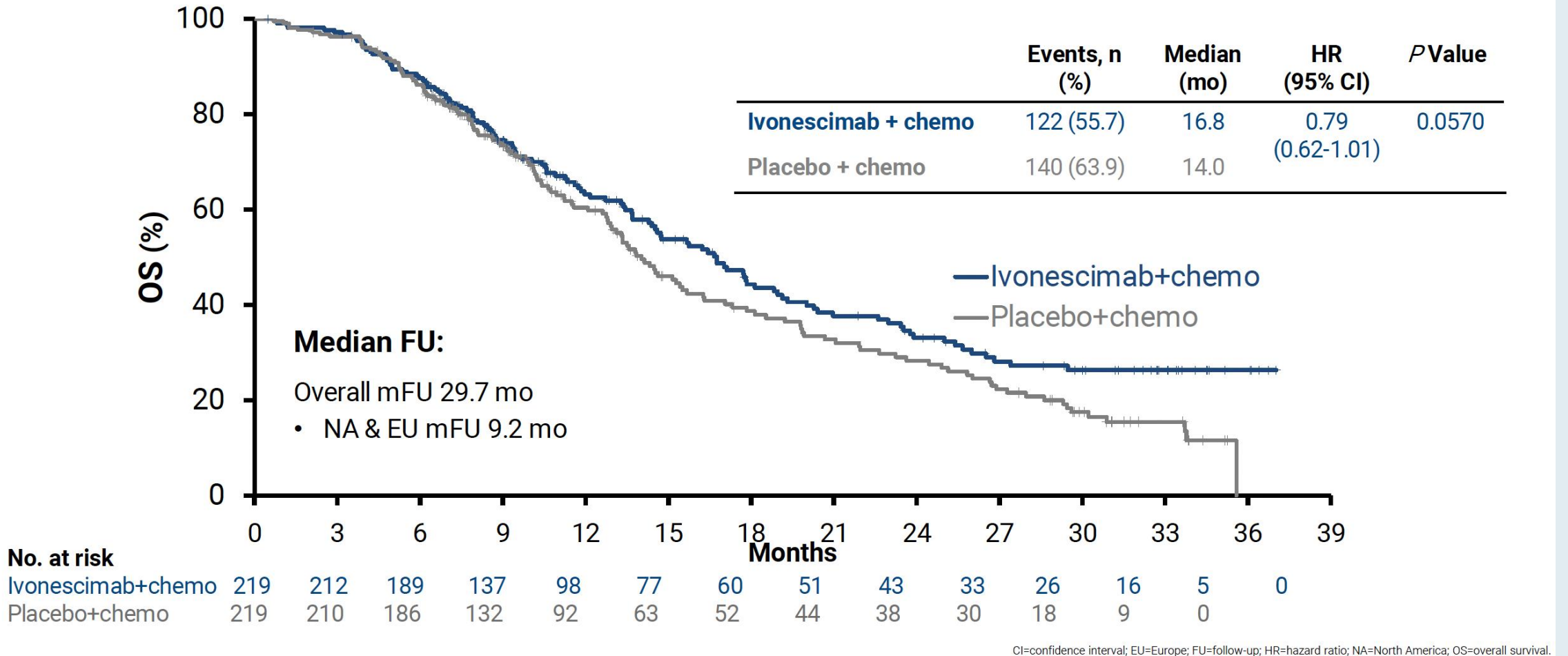
Consistent PFS benefit by investigator: HR = 0.58 (95% CI: 0.45-0.73)

HARMONi: PFS by Brain Metastases Status



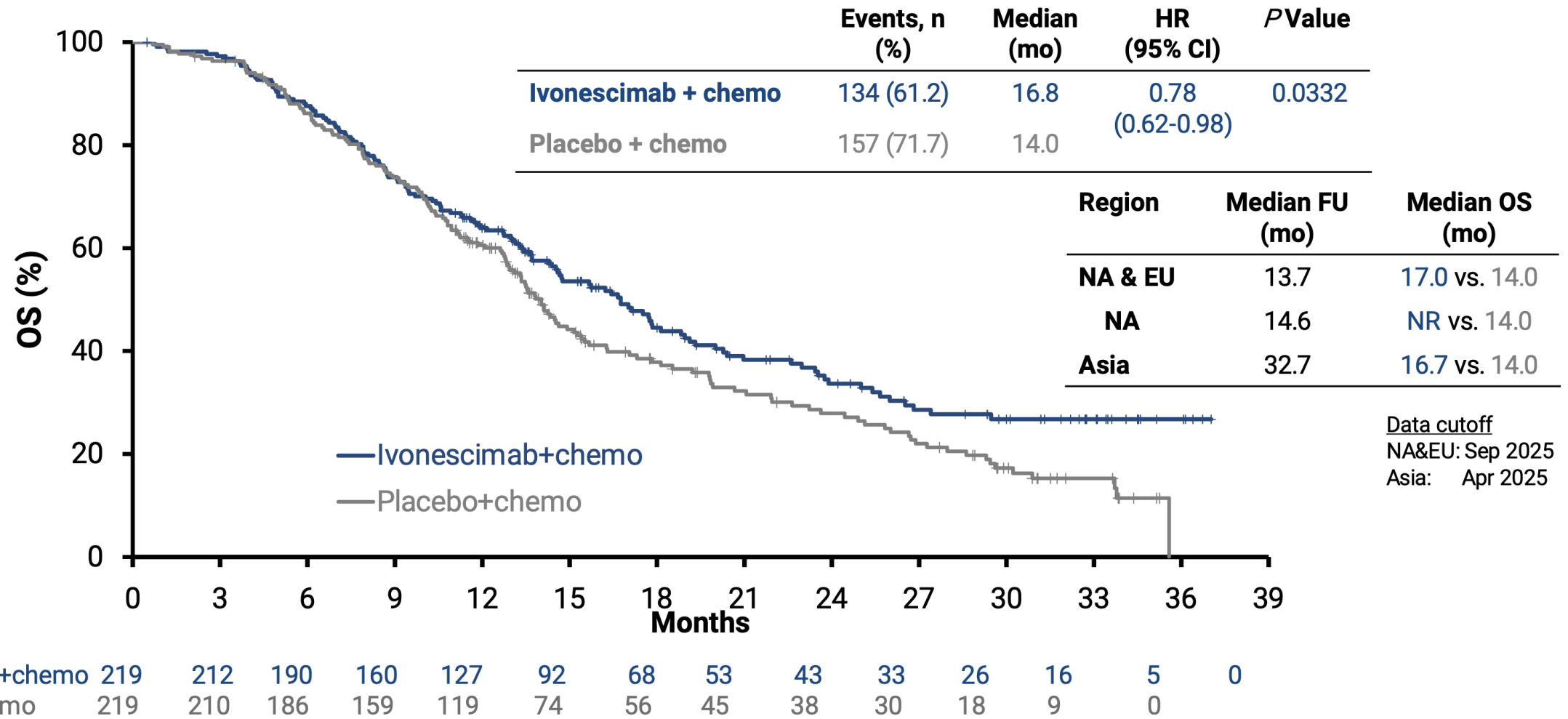
HARMONi: OS Outcomes

Favorable Trend Observed; NA & EU Follow-up Not Yet Mature



HARMONi: OS Outcomes

OS stable with longer term Western data, nominal p=0.0332



Ivonescimab with Chemotherapy Demonstrates Consistent, Favorable Overall Survival Results for Western and Asian Patients in an Updated Analysis from the Global Phase III HARMONi Study

Press Release: July 22, 2026

“[The manufacturer] announced results of an updated overall survival (OS) analysis from the global Phase III HARMONi clinical trial featuring ivonescimab. Ivonescimab plus platinum-doublet chemotherapy in this trial continues to show a positive OS trend and a consistent efficacy and safety profile in Asian and western patients when compared to chemotherapy alone.

	<i>Western Subgroup of Overall Survival Analyses at Each Data Cut-Off</i>					
	<i>DCO: Apr 2025</i>		<i>DCO: Sept 2025</i>		<i>DCO: June 2026*</i>	
	Ivonescimab + Chemo (n=83)	Placebo + Chemo (n=82)	Ivonescimab + Chemo (n=83)	Placebo + Chemo (n=82)	Ivonescimab + Chemo (n=83)	Placebo + Chemo (n=82)
Hazard Ratio, Western pts	0.98		0.84		0.76	
Median follow-up time	9.2 months		13.7 months		23.2 months	

*Note: Additional information, including median OS, confidence intervals for hazard ratios, etc., are intended to be presented at an upcoming medical conference”

FDA Acceptance of Biologics License Application Seeking Approval for Ivonescimab in Combination with Chemotherapy in the Treatment of EGFR-Mutated NSCLC After Tyrosine Kinase Inhibitor Therapy

Press Release: January 29, 2026

“The US Food & Drug Administration (FDA) has accepted for filing a Biologics License Application (BLA) seeking approval for ivonescimab in combination with chemotherapy in patients with epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) post-tyrosine kinase inhibitor (TKI) therapy.

The FDA provided a Prescription Drug User Fee Act (PDUFA) goal action date of **November 14, 2026**.

The BLA was submitted based on the overall results of the Phase III HARMONi trial, which evaluated ivonescimab plus platinum-doublet chemotherapy compared to placebo plus platinum-doublet chemotherapy in patients with EGFR-mutated, locally advanced or metastatic NSCLC who were previously treated with a 3rd generation EGFR TKI.”

Do you believe VEGF inhibition yields enhanced antitumor activity in EGFR-mutant NSCLC relative to EGFR wild-type disease?



Dr Baik

Yes



Dr Goldman

Yes



Dr Paik

Yes



Prof Passaro

I'm not sure



Dr Piotrowska

Yes



Dr Rotow

No



Dr Villaruz

Yes

Do you believe the risk-benefit ratio with ivonescimab/chemotherapy in previously treated EGFR-mutated NSCLC supports its clinical use?



Dr Baik

Yes, for select patients for whom chemotherapy makes sense



Dr Goldman

Yes



Dr Paik

I'm not sure



Prof Passaro

Yes



Dr Piotrowska

I'm not sure



Dr Rotow

Yes



Dr Villaruz

Yes

Would you like to be able to access ivonescimab/chemotherapy today for your patients with previously treated EGFR-mutated NSCLC?

	Dr Baik	No
	Dr Goldman	Yes
	Dr Paik	I'm not sure
	Prof Passaro	Yes
	Dr Piotrowska	Yes
	Dr Rotow	Yes
	Dr Villaruz	Yes

In what line of therapy do you envision ivonescimab/chemotherapy will be employed for patients with EGFR-mutated NSCLC?



Dr Baik

Third line or later



Dr Goldman

Second line and beyond, but most likely in third line



Dr Paik

Probably around fourth line



Prof Passaro

Second-line setting



Dr Piotrowska

Possibly in second line for patients with a smoking history, higher PD-L1 status and limited benefit from EGFR TKIs



Dr Rotow

Second-line platinum doublet competing with COMPEL and MARIPOSA-2



Dr Villaruz

Second to third line

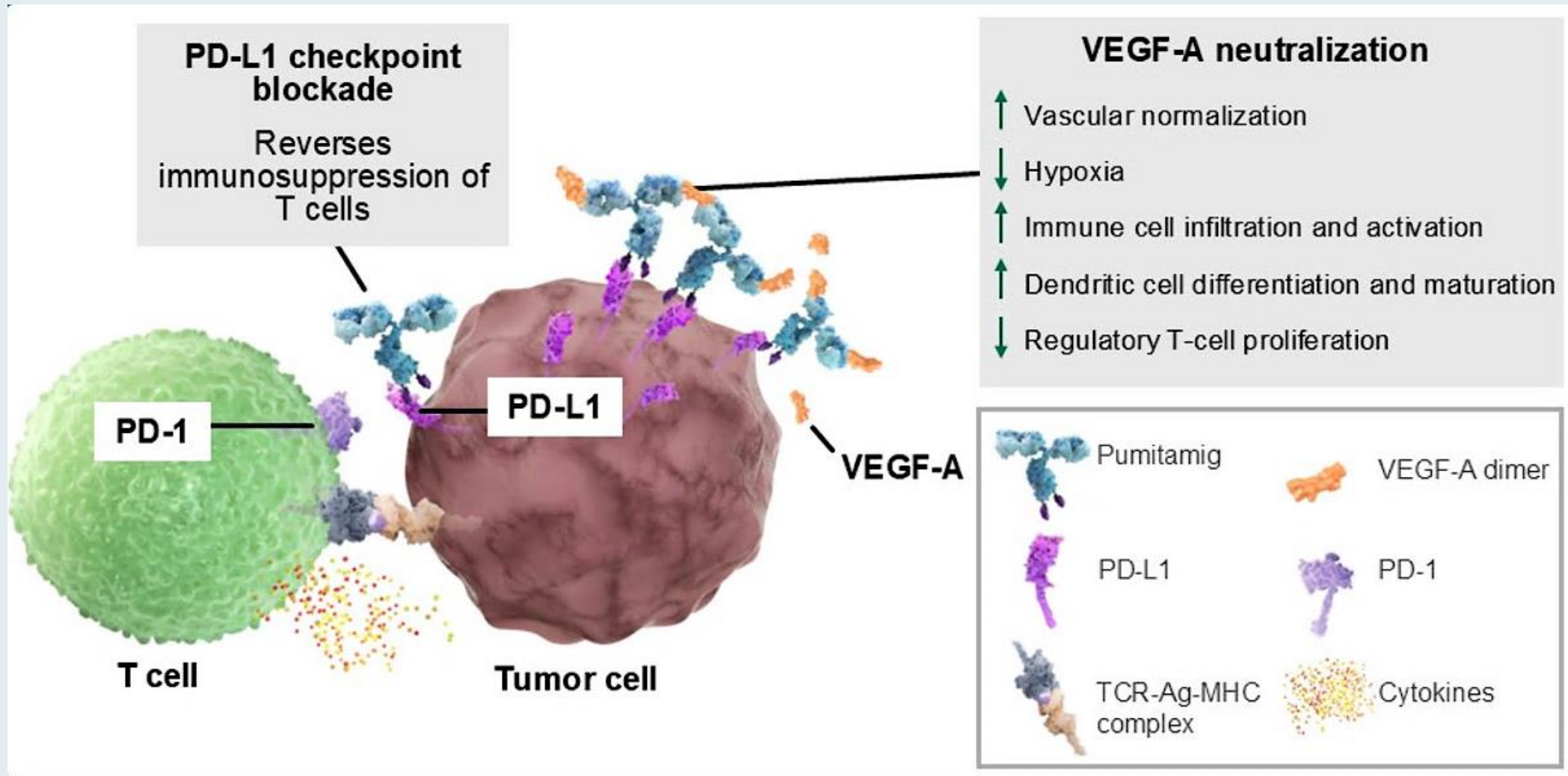
Agenda

Module 1: Ivonescimab for Previously Untreated Metastatic Non-Small Cell Lung Cancer (mNSCLC)

Module 2: Ivonescimab for Relapsed/Refractory EGFR-Mutated mNSCLC

Module 3: Other Novel PD-1/PD-L1 x VEGF Bispecific Antibodies Under Investigation

Pumitamig Mechanism of Action





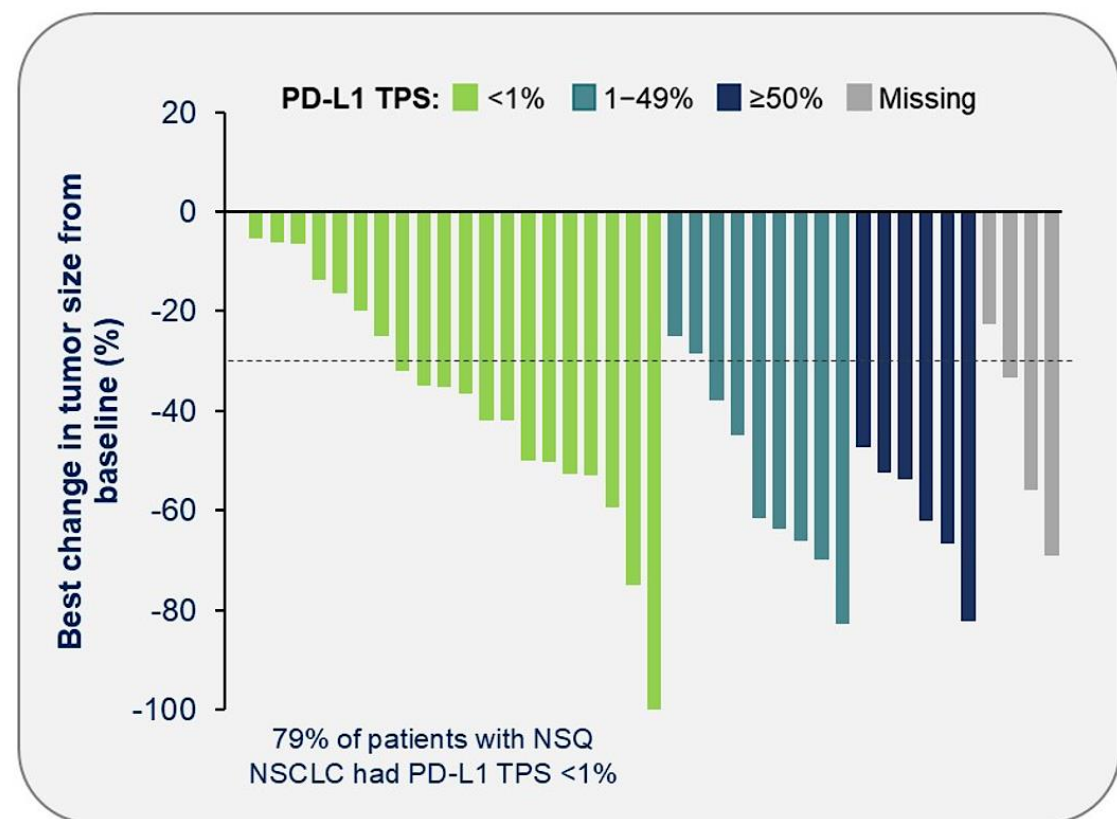
Phase 2 data from ROSETTA Lung-02

**A global, randomized, phase 2/3 trial of pumitamig (PD-L1 × VEGF-A bsAb)
+ chemotherapy in 1L NSCLC**

Solange Peters,¹ Youngjoo Lee,² Mustafa Erman,³ Stephen V. Liu,⁴ Benjamin Solomon,⁵ Terufumi Kato,⁶ Shun Lu,⁷ Sanjay Popat,⁸ Ulug Mutlu Gunaydin,⁹ René Bartz,¹⁰ Vikesh Patel,¹¹ Kevin Tsai,⁹ Li Li,⁹ Uchechukwu Dimkpa,¹⁰ Claudia-Nanette Gann,¹⁰ Aurora O'Brate,¹² Ilhan Celik,¹⁰ Özlem Türeci,¹⁰ Ugur Sahin,¹⁰ Byoung Chul Cho¹³

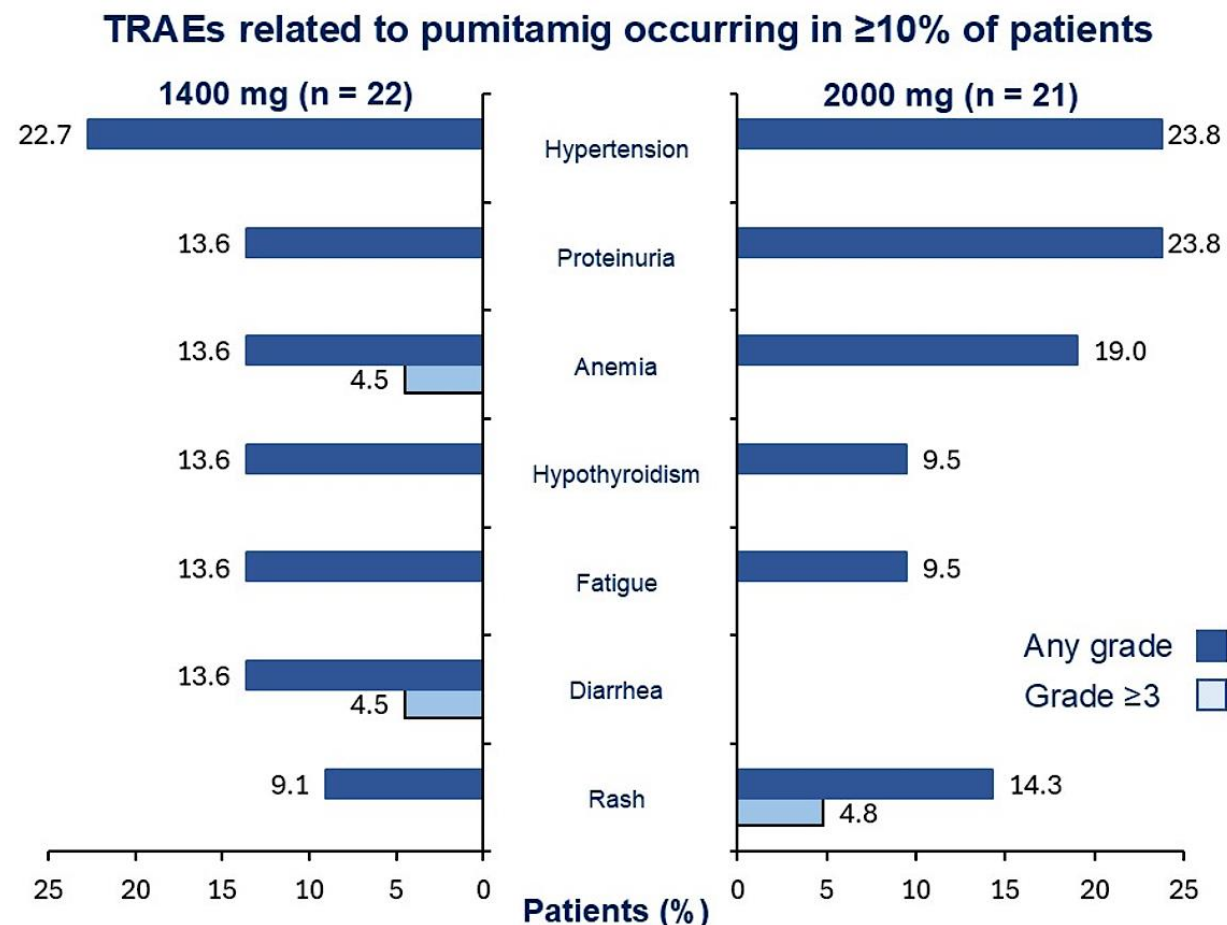
ROSETTA Lung-02: Response Data

	Overall NSCLC (NSQ + SQ)				
	TPS <1% (n = 21)	TPS 1–49% (n = 9)	TPS ≥50% (n = 6)	Missing* (n = 4)	Overall (N = 40)
uORR, % (95% CI)	61.9 (38.4–81.9)	77.8 (40.0–97.2)	100.0 (54.1–100.0)	75.0 (19.4–99.4)	72.5 (56.1–85.4)
cORR, % (95% CI)	47.6 (25.7–70.2)	77.8 (40.0–97.2)	100.0 (54.1–100.0)	50.0 (6.8–93.2)	62.5 (45.8–77.3)
cBOR, n (%)					
CR	0	1 (11.1)	0	0	1 (2.5)
PR	10 (47.6)	6 (66.7)	6 (100.0)	2 (50.0)	24 (60.0)
SD	11 (52.4)	2 (22.2)	0	2 (50.0)	15 (37.5)

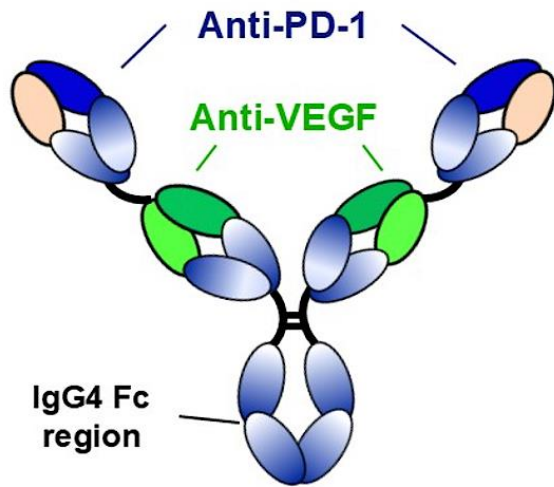


ROSETTA Lung-02: Safety Summary

	NSQ (n = 22)	SQ (n = 21)	Overall (N = 43)
Any TRAE, n (%)	19 (86.4)	21 (100.0)	40 (93.0)
Grade ≥3	8 (36.4)	13 (61.9)	21 (48.8)
Pumitamig-related TRAE, n (%)	14 (63.6)	19 (90.5)	33 (76.7)
Grade ≥3	4 (18.2)	6 (28.6)	10 (23.3)
TRAE leading to discontinuation, n (%)	3 (13.6)	5 (23.8)	8 (18.6)
Pumitamig-related	1 (4.5)	3 (14.3)	4 (9.3)
TRAE leading to death, n (%)	0	1 (4.8)*	1 (2.3)*
Pumitamig-related	0	1 (4.8)*	1 (2.3)*
Any irAE TEAE , n (%)	8 (36.4)	8 (38.1)	16 (37.2)
Grade ≥3	1 (4.5)	1 (4.8)	2 (4.7)
VEGF-related TEAEs, n (%)	10 (45.5)	14 (66.7)	24 (55.8)
Grade ≥3	1 (4.5)	1 (4.8)	2 (4.7)
Hemorrhage/bleeding TEAEs, n (%)	2 (9.1)	7 (33.3)	9 (20.9)
Grade ≥3	0	1 (4.8)‡	1 (2.3)‡



SSGJ-707 (PF-08634404) Mechanism of Action



PF-08634404

**Bispecific Antibody with Unique
Tetravalent Structure:**

VEGF and PD-1 binding arms in
linear, stacked orientation

**Simultaneous Binding of PD-1 and VEGF Amplifies
Therapeutic Potential Through:**

Cooperative binding and Improved PD-1 Inhibition¹

In the presence of VEGF, PF'4404 forms multimers to enhance
binding and inhibition of PD-1

Augmented VEGF Inhibition¹

Functionally enhanced VEGF Fab arm normalizes tumor vasculature
and reduces VEGF-related immune suppression

IgG4 backbone^{2,3}

IgG4 backbone is consistent with approved anti-PD-1 therapeutics

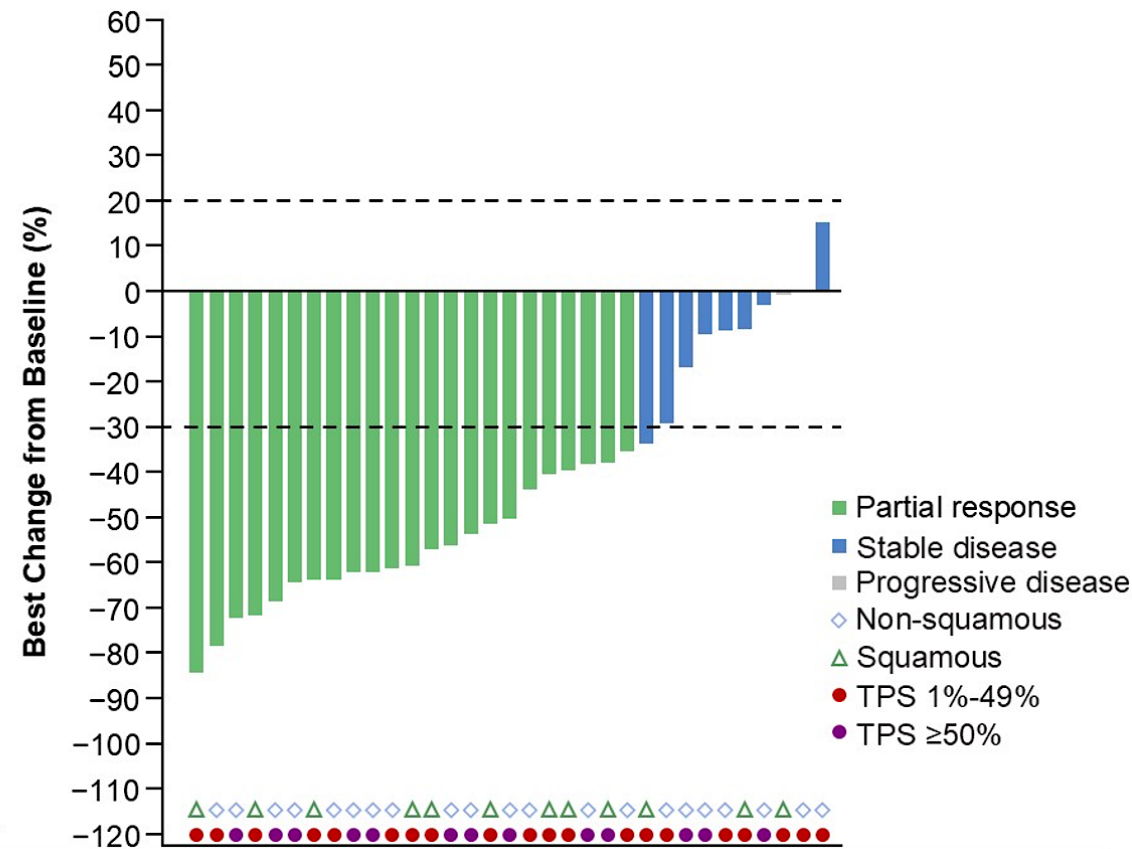
A phase 2 trial of PF-08634404 (SSGJ-707), a PD-1/VEGF bispecific antibody, as monotherapy in patients with advanced non-small cell lung cancer: updated results

Lin Wu,¹ Jun Yao,² Yulan Sun,³ Ruoyu Wang,⁴ Xiang Li,⁴ Bolin Chen,¹ Qian Chu,⁵ Qing Bu,⁶ Yong Fang,⁷ Jun Zhao,⁸ Weizhen Huang,⁹ Jin Zhou,¹⁰ Qiming Wang,¹¹ Jie Li,¹² Yongzhong Luo,¹ Yan Yu,¹³ Michael Burns,¹⁴ Tienan Yi¹⁵

A Phase II Study of SSGJ-707 (PF-08634404) Monotherapy for PD-L1-Positive mNSCLC – Response Data

Endpoint	10 mg/kg (n=34)
Confirmed ORR, % (95% CI)	67.6 (49.5-82.6)
Best overall response, n (%)	
Partial response	23 (67.6)
Stable disease	10 (29.4)
Progressive disease	1 (2.9)
Disease control rate, % (95% CI)	97.1 (84.7-99.9)
Duration of response, median (95% CI), months	18.0 (10.9-NE)

CI, confidence interval; cORR, confirmed objective response rate; NE, not estimable; Q3W, every 3 weeks; TPS, tumor proportion score.

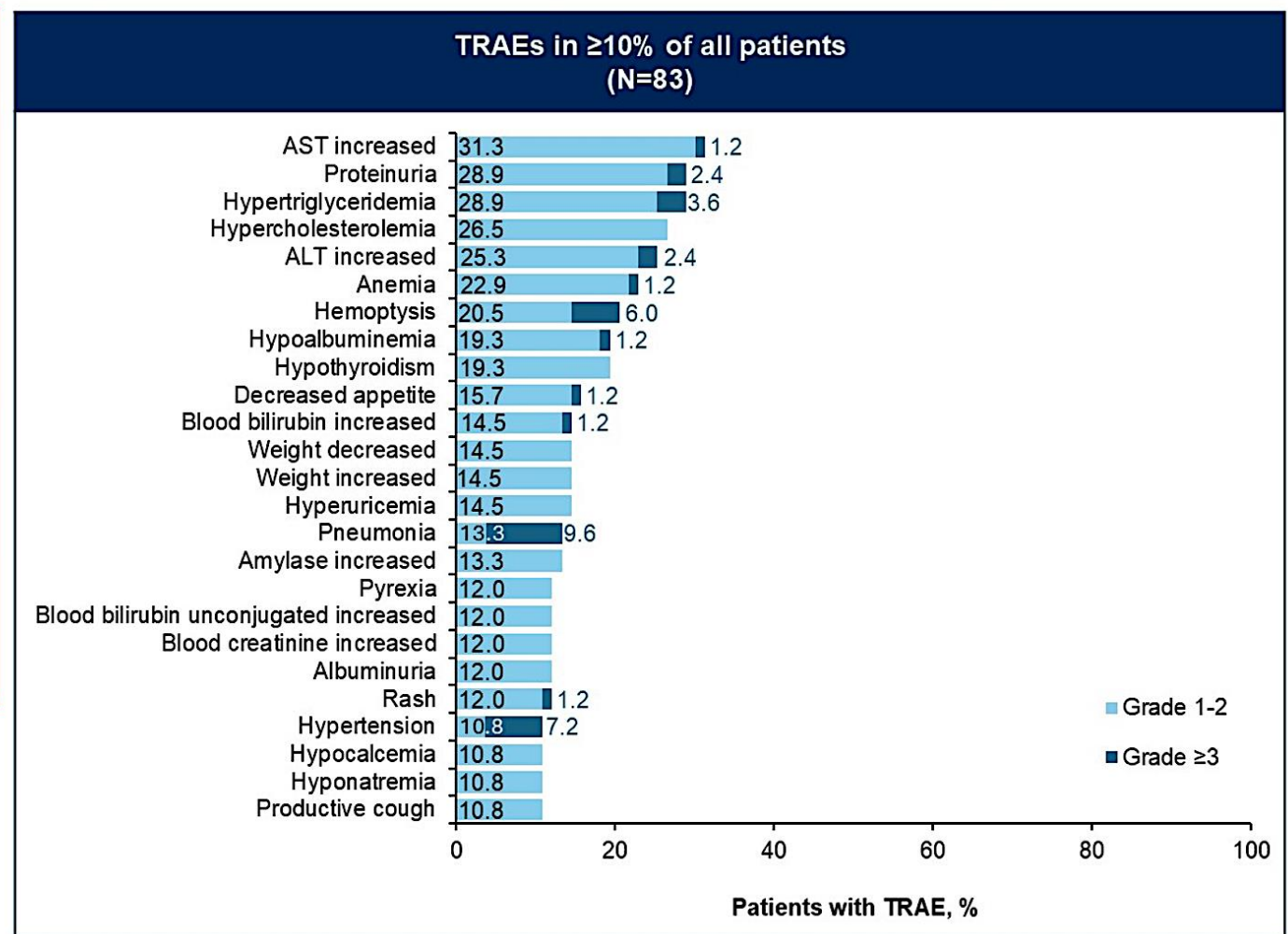


A Phase II Study of SSGJ-707 (PF-08634404) Monotherapy for PD-L1-Positive mNSCLC – Safety Summary

	All patients (N=83)	10 mg/kg (n=34)
TRAEs, n (%)^a		
Any grade	77 (92.8)	34 (100)
Grade ≥3	36 (43.4)	15 (44.1)
Grade 5	2 (2.4) ^b	0
SAE	31 (37.3)	10 (29.4)
Leading to discontinuation	7 (8.4) ^c	1 (2.9) ^d
VEGF-related AEs, n (%)^e		
Any grade	52 (62.7)	25 (73.5)
Grade ≥3	15 (18.1)	5 (14.7)
irAEs, n (%)^f		
Any grade	32 (38.6)	17 (50.0)
Grade ≥3	7 (8.4)	2 (5.9) ^g

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; VEGF, vascular endothelial growth factor.

^aDefined as a TEAE that was "related" to PF4404, "most possibly related" to PF4404, or "possibly related" to PF4404, or for which relationship to PF4404 was missing. ^bGrade 5 TRAEs consisted of hemoptysis (n=1) and death from unknown cause (n=1). No grade 4 events occurred. ^cHemoptysis (n=4), pneumonia (n=1), increased alanine transferase (n=1), diabetic ketoacidosis (n=1). ^dHemoptysis. ^eDefined as gastrointestinal perforation and fistula, hemorrhage, thromboembolic event, hypertension, or proteinuria. ^fDefined as any TEAE that was potentially immune mediated and categorized as "related," "most possibly related," or "possibly related" to PF4404. ^gAbnormal hepatic function (n=1), rash (n=2).



Thank you for your attention!

Questions?

Access CME credit form and download slides

