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# Ivonescimab vs Placebo Plus Chemo, Phase 3 in Patients with EGFR+ NSCLC Progressed with 3rd gen EGFR-TKI Treatment: HARMONi

**Jonathan W. Goldman[1], Antonio Passaro[2], Janessa Laskin[3], Delvys Rodrigues-Abreu[4], Antonio Calles[5], Lyudmila Bazhenova[6], Giuseppe Lo Russo[7], Natasha Leighl[8], Federico Cappuzzo[9], Nicolas Girard[10], Sanjay Popat[11], Wenfeng Fang[12], Yongzhong Luo[13], Runxiang Yang[14], Wenting Li[15], Jianling Li[16], Lori Styles[16], Benjamin Thompson[16], Li Zhang[17], Xiuning Le[18].**

[1]UCLA Health, Santa Monica, CA, USA; [2]European Institute of Oncology, Milan, Italy; [3]British Columbia Cancer Research Institute, Vancouver, Canada; [4]Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [6]UC San Diego Moores Cancer Center, San Diego, CA, USA; [7]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [8]Princess Margaret Cancer Centre University of Toronto, Toronto, Ontario, Canada; [9]Regina Elena National Cancer Institute, Rome, Italy; [10]Institut Curie, Paris, France; [11]Lung Unit, Royal Marsden Hospital, London, UK; [12]Sun Yat-sen University Cancer Center, Guangzhou, China; [13]Hunan Cancer Hospital, Changsha, China; [14]Yunnan Cancer Hospital, Kunming, China; [15]Akeso Biopharma, Inc., Zhongshan, China; [16]Summit Therapeutics, Menlo Park, CA, USA; [17]Sun Yat-sen University Cancer Center, Guangzhou, China; [18]The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Ivonescimab is an investigational therapy not presently approved by any regulatory authority other than China’s National Medical Products Administration (NMPA).

# Phase 3 Study Design

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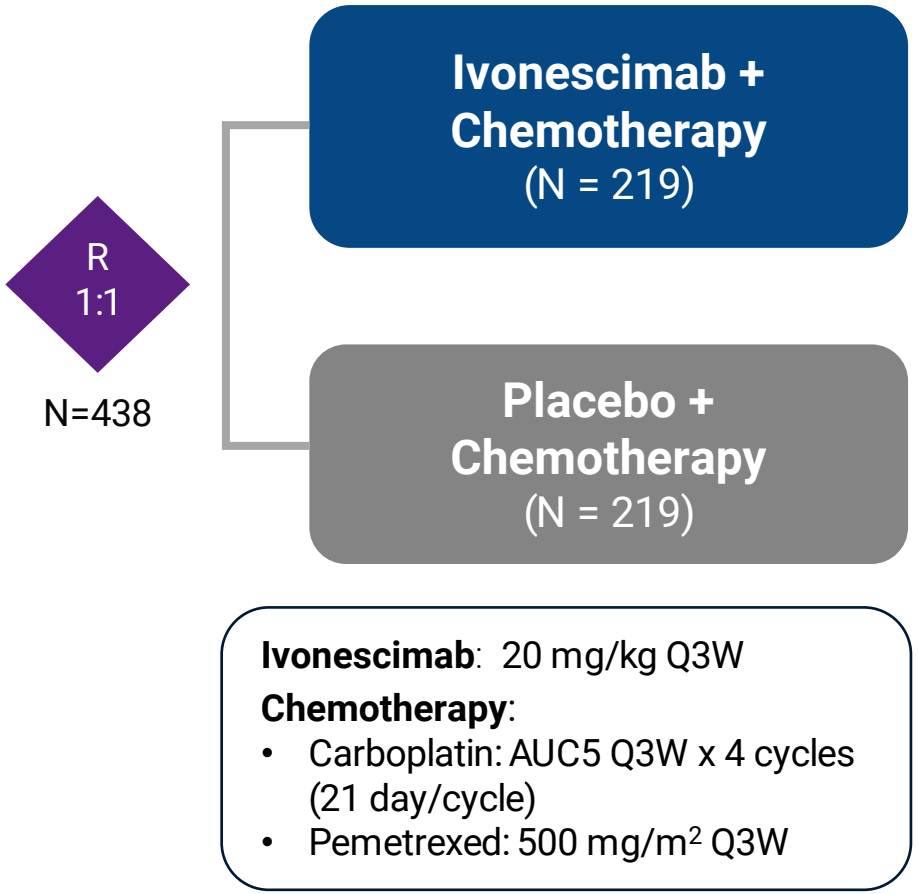
## Key Eligibility Criteria

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)




**Ivonescimab**: 20 mg/kg Q3W

**Chemotherapy**:

- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m$^2$ 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.

# Demographic and Baseline Characteristics

## Arms were well-balanced; majority were females, ECOG 1, never smokers; 25% with brain mets

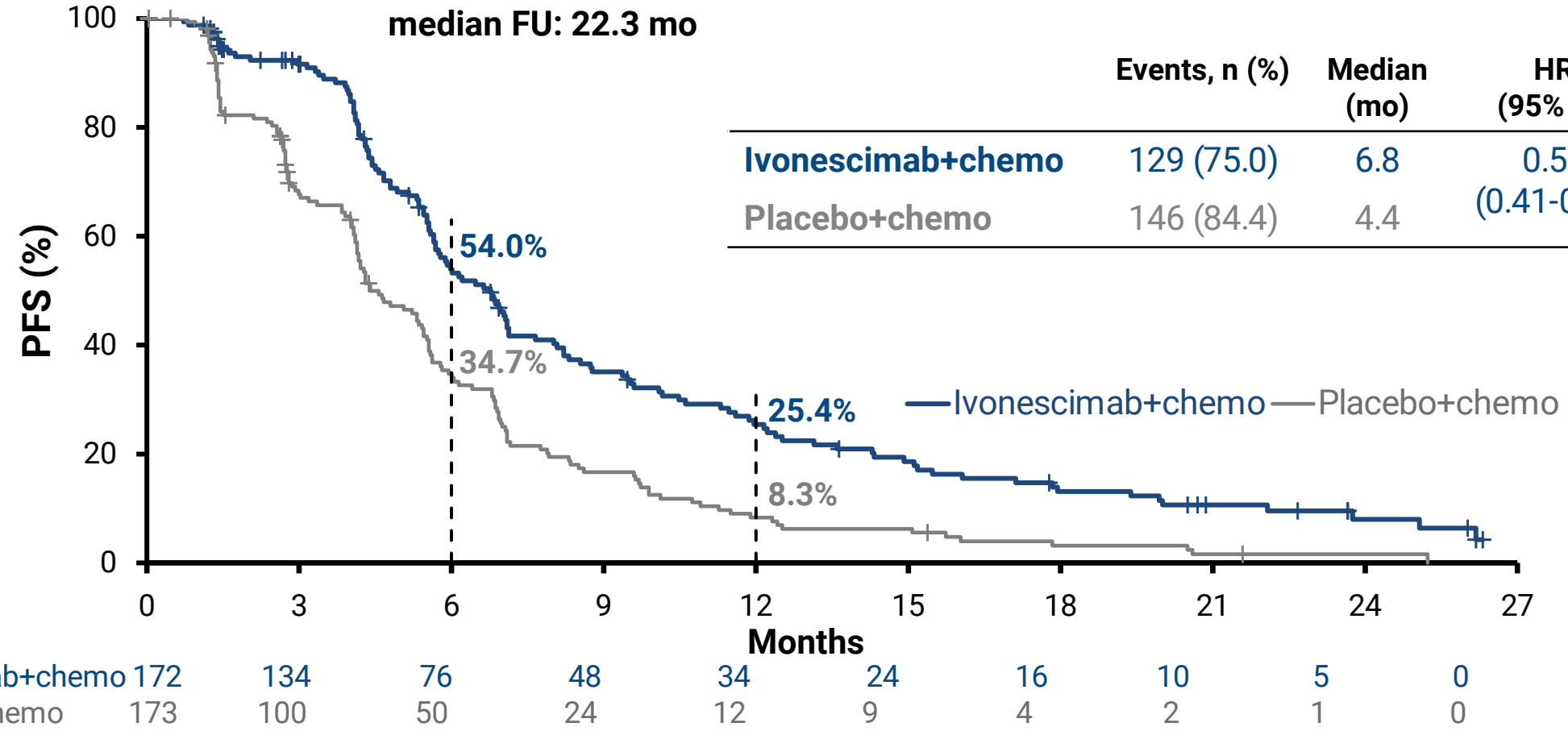
| Characteristic, n (%) | Ivonescimab+chemo (N=219) | Placebo+chemo (N=219) |
|---|---|---|
| **Age – Median (range)** | 62 (32-84) | 60 (36-84) |
| ≥65 yr | 83 (37.9) | 88 (40.2) |
| **Female** | 130 (59.4) | 127 (58.0) |
| **Region – NA & Europe** | 83 (37.9) | 82 (37.4) |
| **Asia** | 136 (62.1) | 137 (62.6) |
| **Race – Asian** | 153 (69.9) | 153 (69.9) |
| **White** | 51 (23.3) | 54 (24.7) |
| **ECOG - 1** | 162 (74.0) | 157 (71.7) |
| **Smoking - Never** | 143 (65.3) | 155 (70.8) |
| **Stage - IV** | 215 (98.2) | 214 (97.7) |
| **Brain metastasis** | 54 (24.7) | 54 (24.7) |
| **Liver metastasis** | 32 (14.6) | 23 (10.5) |
| **Prior line of systemic cancer therapy (median)** | 1.0 | 1.0 |
| **Prior EGFR-TKI** | | |
| 1st/2nd generation | 95 (43.4) | 92 (42.0) |
| 3rd generation | 219 (100) | 218 (99.5) |
| 4th generation | 1 (0.5) | 0 |
| **EGFR Mutation** | | |
| 19del | 131 (59.8) | 118 (53.9) |
| L858R | 74 (33.8) | 90 (41.1) |
| Non-19del/L858R* | 15 (6.8) | 11 (5.0) |

* Non-19del/L858R mutations include G719X, L861Q, S768I, etc.

ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; TKI=tyrosine kinase inhibitor.

# Primary Endpoint: PFS by IRRC

## Statistically significant and clinically meaningful benefit with ivonescimab




| | Events, n (%) | Median (mo) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| **Ivonescimab+chemo** | 129 (75.0) | 6.8 | 0.52 (0.41-0.66) | <0.0001 |
| **Placebo+chemo** | 146 (84.4) | 4.4 | | |

**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 |

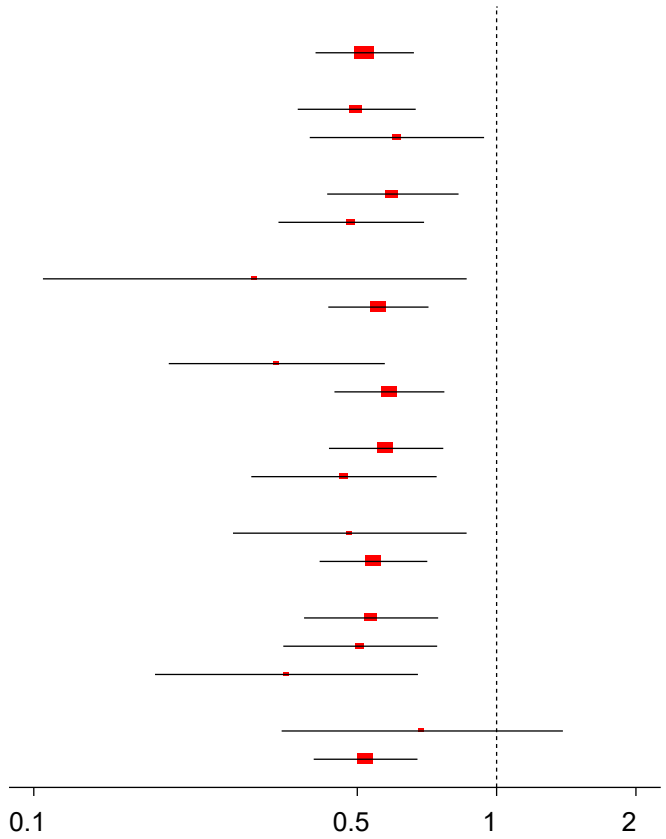
**Consistent PFS benefit by investigator: HR = 0.58 (95% CI: 0.45-0.73)**

CI=confidence interval; FU=follow-up; HR=hazard ratio; IRRC= independent radiology review committee; PFS=progression-free survival.

# PFS by IRRC – Subgroup Analysis

## Consistent across pre-defined subgroups

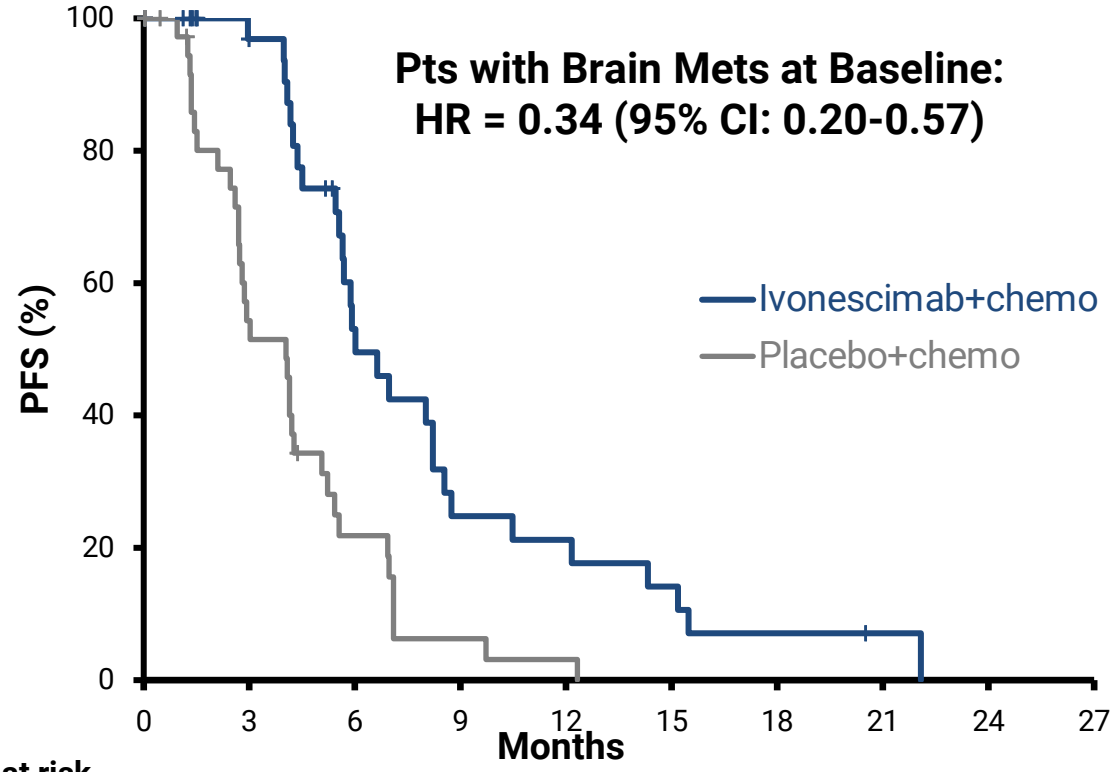
| | Ivonescimab + chemo (Events/N) | Placebo + chemo (Events/N) | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Overall population** | 129/172 | 146/173 | 0.52 (0.41-0.66) |
| **Age** | | | |
| <65 years | 89/115 | 101/110 | 0.50 (0.37-0.67) |
| >=65 years | 40/57 | 45/63 | 0.61 (0.39-0.94) |
| **Sex** | | | |
| Female | 74/97 | 74/92 | 0.60 (0.43-0.83) |
| Male | 55/75 | 72/81 | 0.49 (0.34-0.70) |
| **Geographic region** | | | |
| NA & EU | 6/36 | 12/36 | 0.30 (0.10-0.86) |
| Asia | 123/136 | 134/137 | 0.56 (0.43-0.71) |
| **Brain metastases prior to study entry** | | | |
| Present | 28/41 | 34/42 | 0.34 (0.20-0.57) |
| Absent | 101/131 | 112/131 | 0.59 (0.45-0.77) |
| **Smoking history** | | | |
| Never | 95/117 | 101/121 | 0.58 (0.43-0.77) |
| Former/Current | 34/55 | 45/52 | 0.47 (0.30-0.74) |
| **Baseline ECOG performance status** | | | |
| 0 | 19/35 | 33/43 | 0.48 (0.27-0.86) |
| 1 | 110/137 | 113/130 | 0.54 (0.41-0.71) |
| **Baseline EGFR mutation** | | | |
| 19Del | 77/104 | 69/86 | 0.54 (0.38-0.75) |
| L858R | 45/56 | 73/78 | 0.51 (0.35-0.74) |
| T790M | 25/27 | 17/21 | 0.35 (0.18-0.68) |
| **Liver metastases prior to study entry** | | | |
| Present | 19/26 | 15/20 | 0.69 (0.34-1.39) |
| Absent | 110/146 | 131/153 | 0.52 (0.40-0.67) |



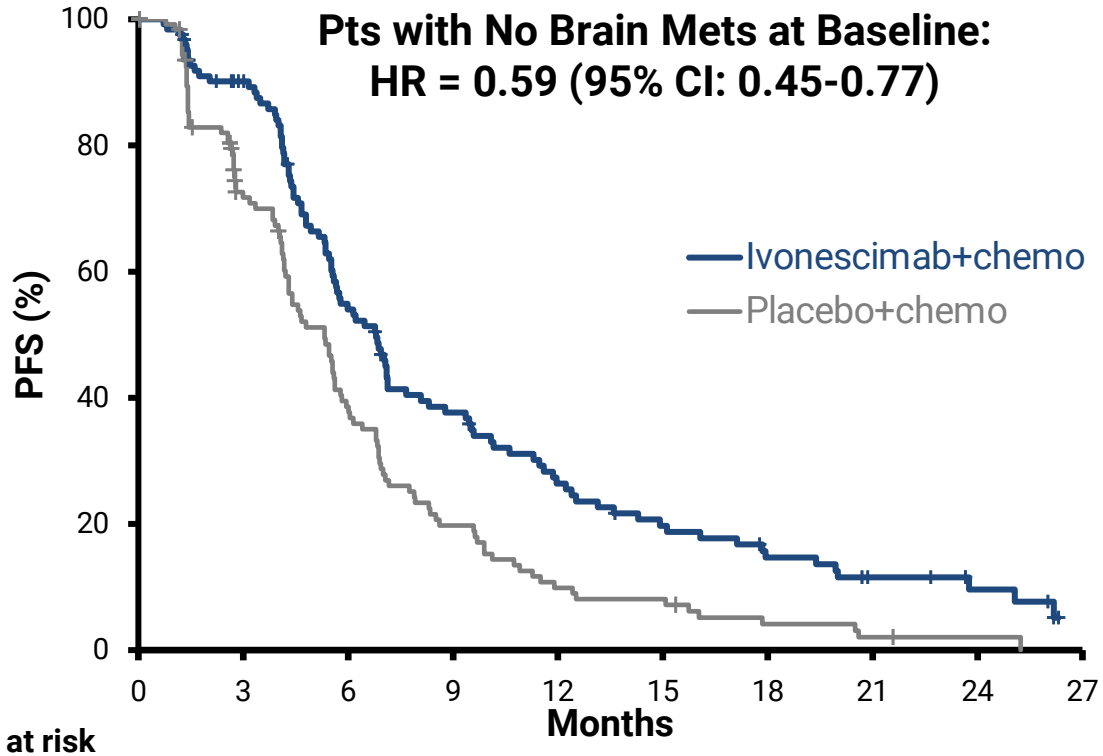

ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; IRRC= independent radiology review committee; PFS=progression-free survival; PS=performance status; TKI=tyrosine kinase inhibitor.

# PFS by Presence or Absence of Brain Mets

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| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ivonescimab +chemo | 41 | 30 | 15 | 7 | 6 | 4 | 2 | 1 | 0 |
| Placebo +chemo | 42 | 19 | 7 | 2 | 1 | 0 | | | |

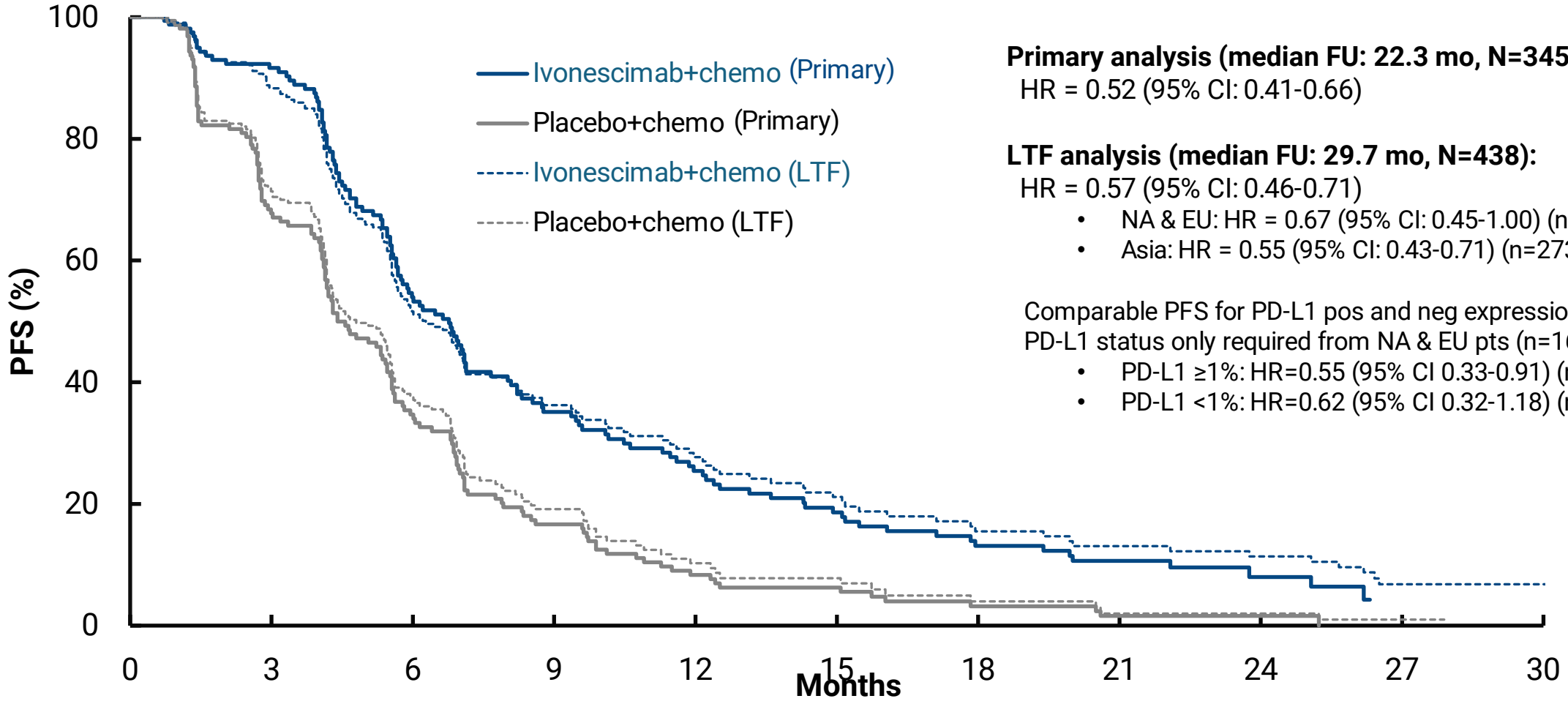



| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ivonescimab +chemo | 131 | 104 | 61 | 41 | 28 | 20 | 14 | 9 | 5 | 0 |
| Placebo +chemo | 131 | 81 | 43 | 22 | 11 | 9 | 4 | 2 | 1 | 0 |

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival; pts=patients.

# PFS by IRRC: Primary Analysis vs Longer Term Follow-Up (LTF)

## Consistent PFS between primary and LTF including all NA & EU patients




**Primary analysis (median FU: 22.3 mo, N=345):**
HR = 0.52 (95% CI: 0.41-0.66)

**LTF analysis (median FU: 29.7 mo, N=438):**
HR = 0.57 (95% CI: 0.46-0.71)

- NA & EU: HR = 0.67 (95% CI: 0.45-1.00) (n=165)
- Asia: HR = 0.55 (95% CI: 0.43-0.71) (n=273)

Comparable PFS for PD-L1 pos and neg expression.
PD-L1 status only required from NA & EU pts (n=160):

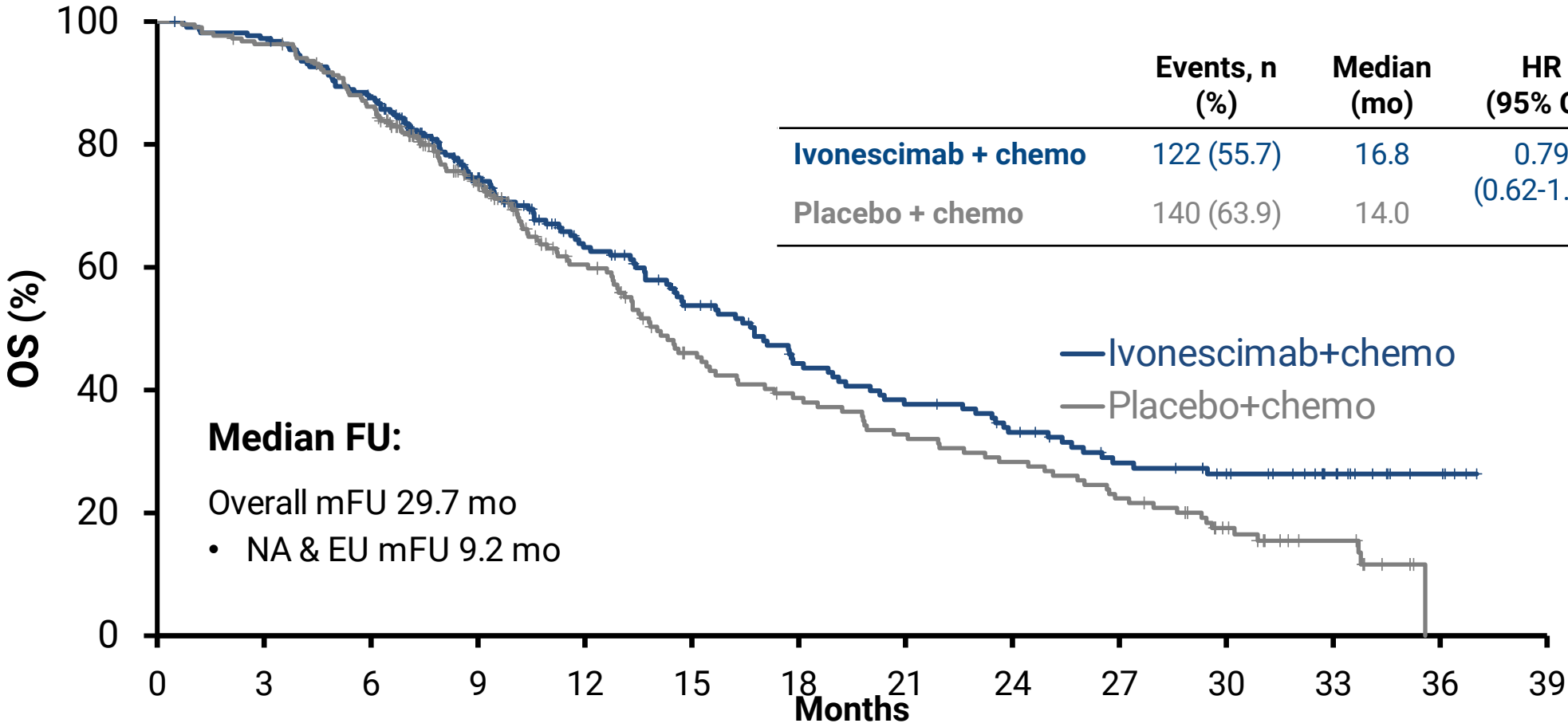
- PD-L1 ≥1%: HR=0.55 (95% CI 0.33-0.91) (n=106)
- PD-L1 <1%: HR=0.62 (95% CI 0.32-1.18) (n=54)

CI=confidence interval; EU=Europe; FU=follow-up; HR=hazard ratio; IRRC=independent radiographic review committee; NA=North America; PD-L1= programmed cell death ligand; PFS=progression-free survival.

# Primary Endpoint: Overall Survival

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

| | Events, n (%) | Median (mo) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| **Ivonescimab + chemo** | 122 (55.7) | 16.8 | 0.79 (0.62-1.01) | 0.0570 |
| **Placebo + chemo** | 140 (63.9) | 14.0 | | |




**No. at risk**

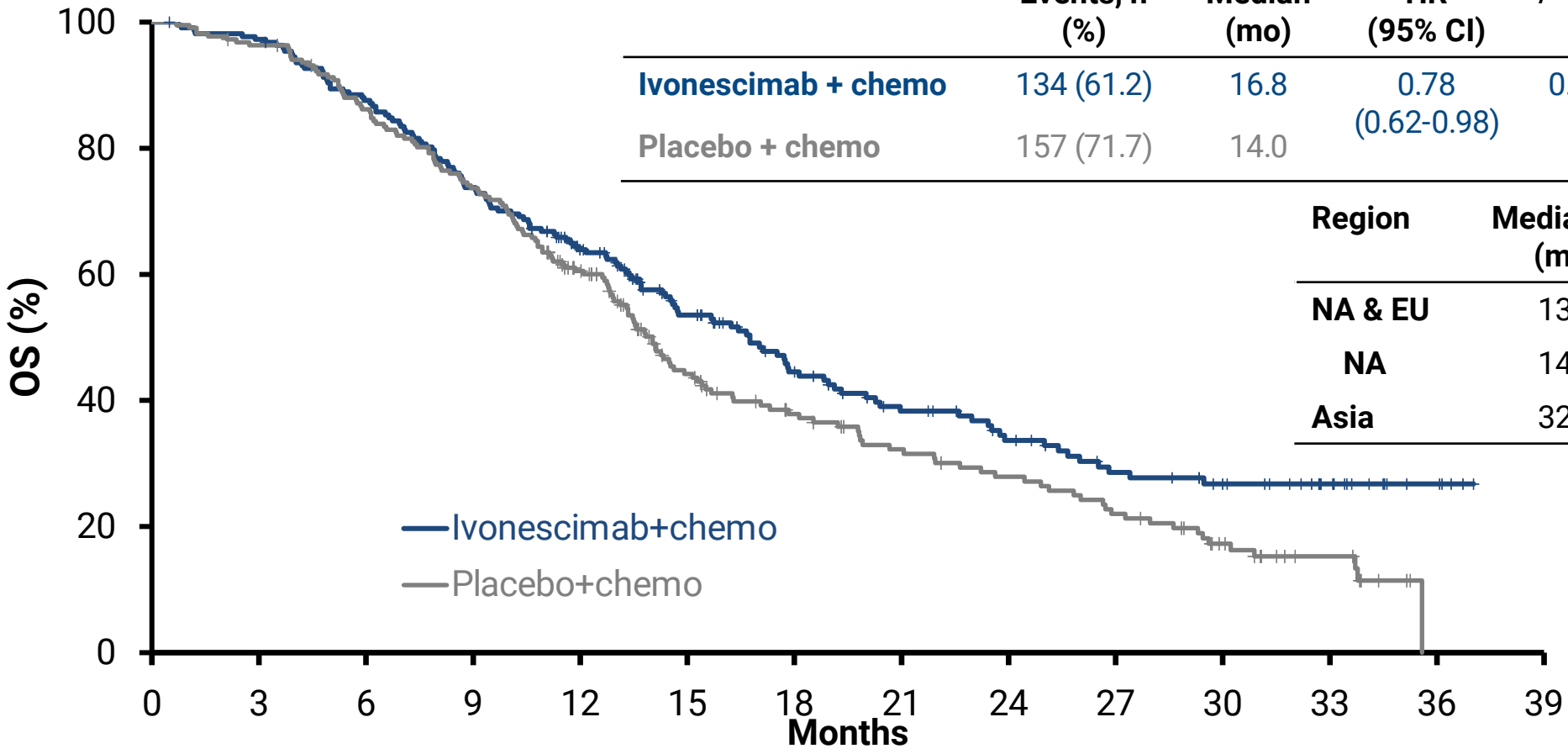
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ivonescimab+chemo | 219 | 212 | 189 | 137 | 98 | 77 | 60 | 51 | 43 | 33 | 26 | 16 | 5 | 0 |
| Placebo+chemo | 219 | 210 | 186 | 132 | 92 | 63 | 52 | 44 | 38 | 30 | 18 | 9 | 0 | |

CI=confidence interval; EU=Europe; FU=follow-up; HR=hazard ratio; NA=North America; OS=overall survival.

# Overall Survival: Longer Term Western Follow-up

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

| | Events, n (%) | Median (mo) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| **Ivonescimab + chemo** | 134 (61.2) | 16.8 | 0.78 (0.62-0.98) | 0.0332 |
| **Placebo + chemo** | 157 (71.7) | 14.0 | | |




| Region | Median FU (mo) | Median OS (mo) |
|---|---|---|
| **NA & EU** | 13.7 | 17.0 vs. 14.0 |
| **NA** | 14.6 | NR vs. 14.0 |
| **Asia** | 32.7 | 16.7 vs. 14.0 |

Data cutoff
NA&EU: Sep 2025
Asia: Apr 2025

**No. at risk**

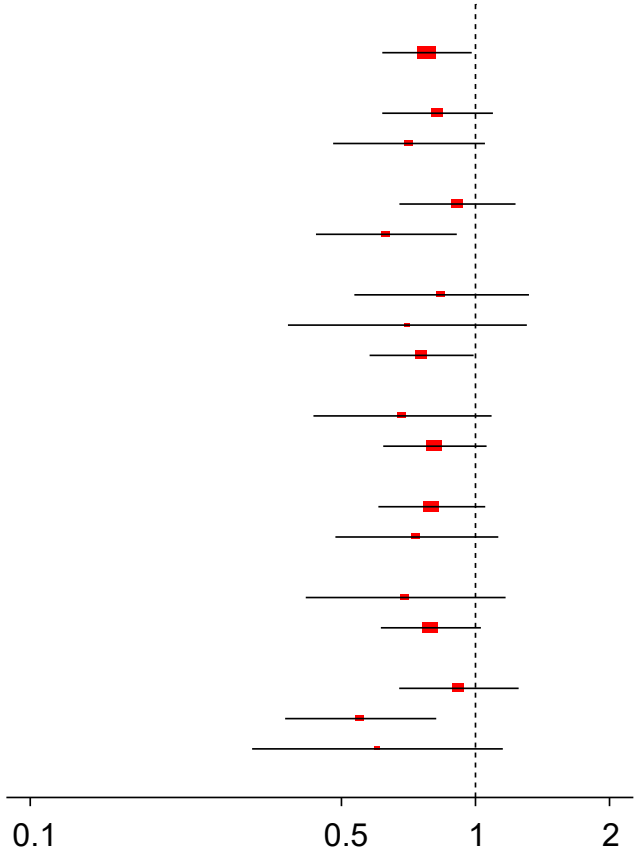
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ivonescimab+chemo | 219 | 212 | 190 | 160 | 127 | 92 | 68 | 53 | 43 | 33 | 26 | 16 | 5 | 0 |
| Placebo+chemo | 219 | 210 | 186 | 159 | 119 | 74 | 56 | 45 | 38 | 30 | 18 | 9 | 0 | |

CI=confidence interval; EU=Europe; FU=follow-up; HR=hazard ratio; NA=North America; OS=overall survival; mo=months.

# Overall Survival Subgroup Analysis – Longer Term FU

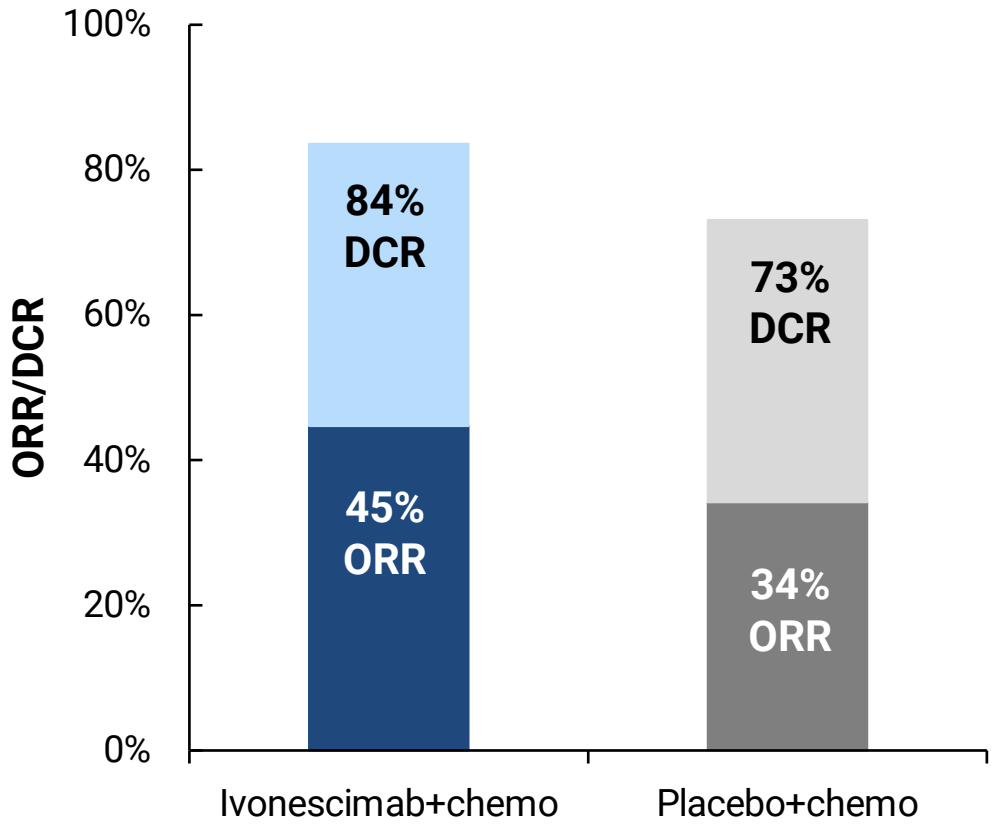
## Consistent across pre-defined subgroups

| | Ivonescimab + chemo (Events/N) | Placebo + chemo (Events/N) | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Overall population** | 134/219 | 157/219 | 0.78 (0.62-0.98) |
| **Age** | | | |
| <65 years | 90/136 | 99/131 | 0.82 (0.62-1.09) |
| >=65 years | 44/83 | 58/88 | 0.71 (0.48-1.05) |
| **Sex** | | | |
| Female | 84/130 | 87/127 | 0.91 (0.67-1.23) |
| Male | 50/89 | 70/92 | 0.63 (0.44-0.91) |
| **Geographic region** | | | |
| NA & EU | 36/83 | 40/82 | 0.84 (0.53-1.32) |
| NA | 17/43 | 25/50 | 0.70 (0.38-1.30) |
| Asia | 98/136 | 117/137 | 0.76 (0.58-0.99) |
| **Brain metastases prior to study entry** | | | |
| Present | 33/54 | 41/54 | 0.69 (0.43-1.09) |
| Absent | 101/165 | 116/165 | 0.81 (0.62-1.06) |
| **Smoking history** | | | |
| Never | 92/143 | 112/155 | 0.80 (0.61-1.05) |
| Former/Current | 42/76 | 45/64 | 0.74 (0.48-1.13) |
| **Baseline ECOG performance status** | | | |
| 0 | 24/57 | 36/62 | 0.70 (0.42-1.17) |
| 1 | 110/162 | 121/157 | 0.79 (0.61-1.03) |
| **Baseline EGFR mutation** | | | |
| 19Del | 84/131 | 78/118 | 0.92 (0.67-1.25) |
| L858R | 39/74 | 73/90 | 0.55 (0.37-0.82) |
| T790M | 19/29 | 18/25 | 0.60 (0.31-1.15) |




FU=follow-up; ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor;; NA = North America, EU = Europe, PS=performance status; TKI=tyrosine kinase inhibitor.

# Overall Response Rate and Duration of Response
## By IRRC




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

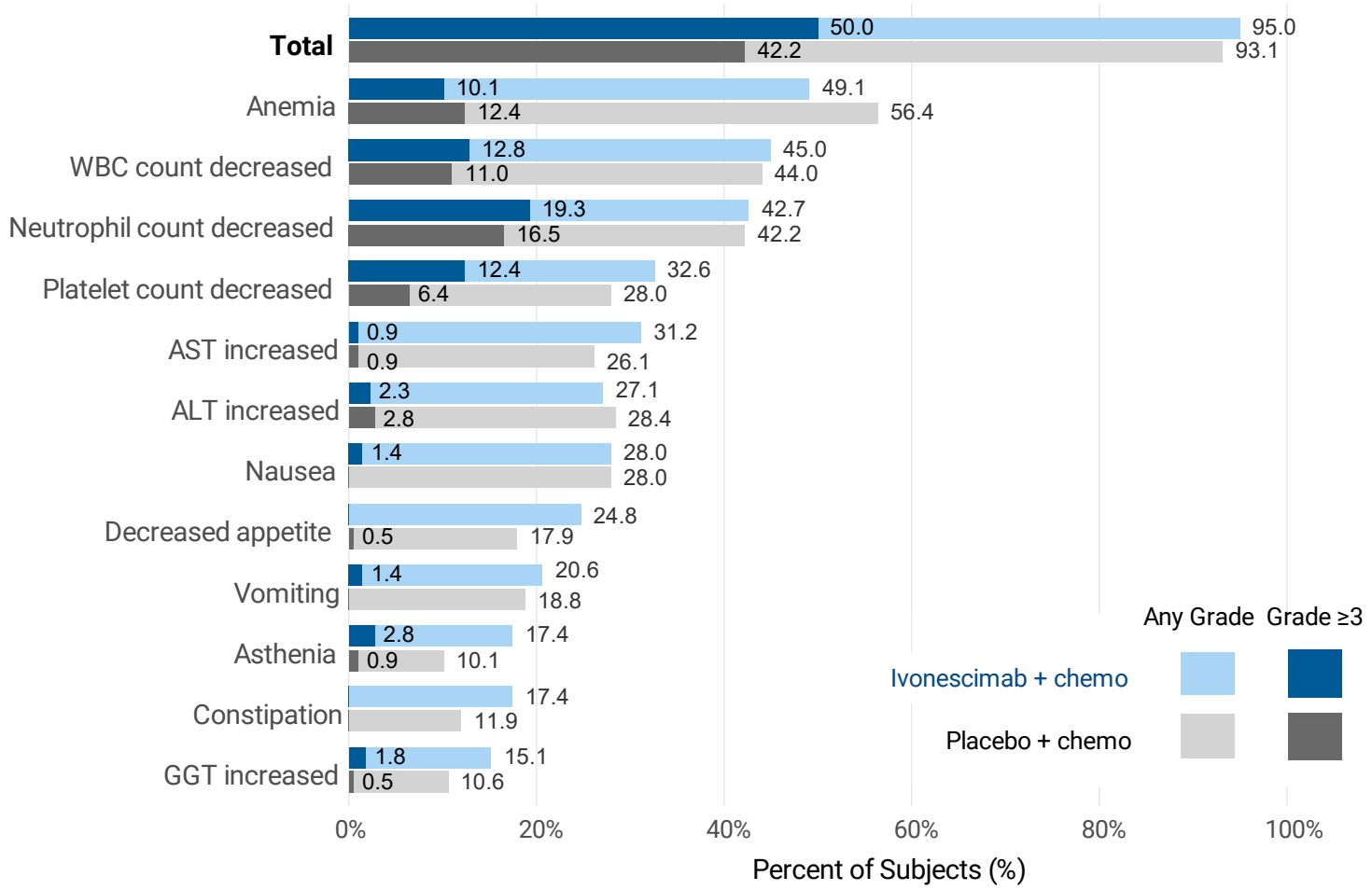
CI=confidence interval; DCR=disease control rate; DoR=duration of response; ORR=overall response rate; IRRC= independent radiographic review committee.

# Treatment-Related Adverse Events (TRAEs)

## Most common were lab abnormalities, nausea, decreased appetite

| TRAE, n(%) | Ivonescimab + chemo (N=218) | Placebo + chemo (N=218) |
|---|---|---|
| **Any Grade** | 207 (95.0) | 203 (93.1) |
| **Grade ≥3** | 109 (50.0) | 92 (42.2) |
| **Serious** | 61 (28.0) | 33 (15.1) |
| **Led to d/c of ivonescimab/placebo** | 16 (7.3) | 11 (5.0) |
| **Led to death** | 4 (1.8) | 5 (2.3) |
| **Grade ≥3 irAE** | 21 (9.6) | 13 (6.0) |
| **Grade ≥3 VEGF-related** | 16 (7.3) | 7 (3.2) |

One patient in each treatment arm did not receive study drug



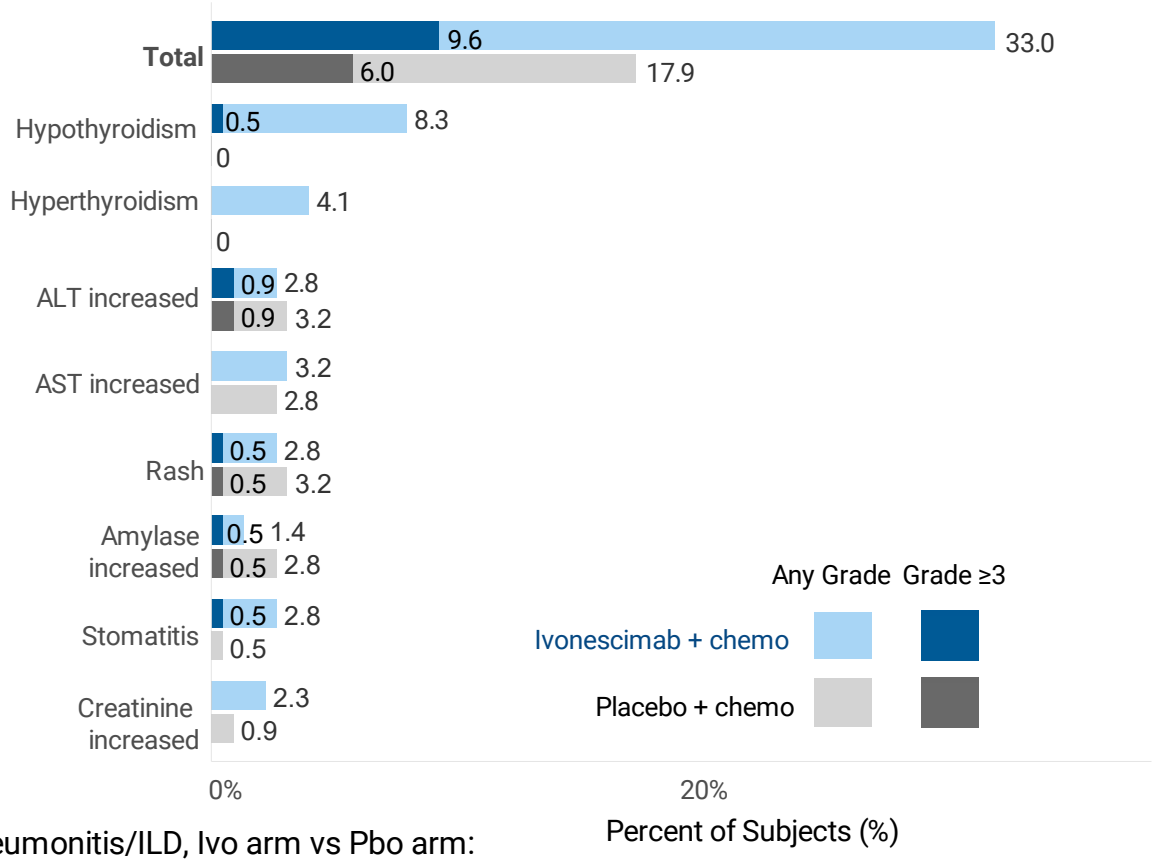

d/c=discontinuation; irAE=immune-related adverse events; VEGF= vascular endothelial growth factor.

Ivonescimab is an investigational therapy not presently approved by any regulatory authority other than China's National Medical Products Administration (NMPA).

# Immune-related and VEGF-related TRAEs

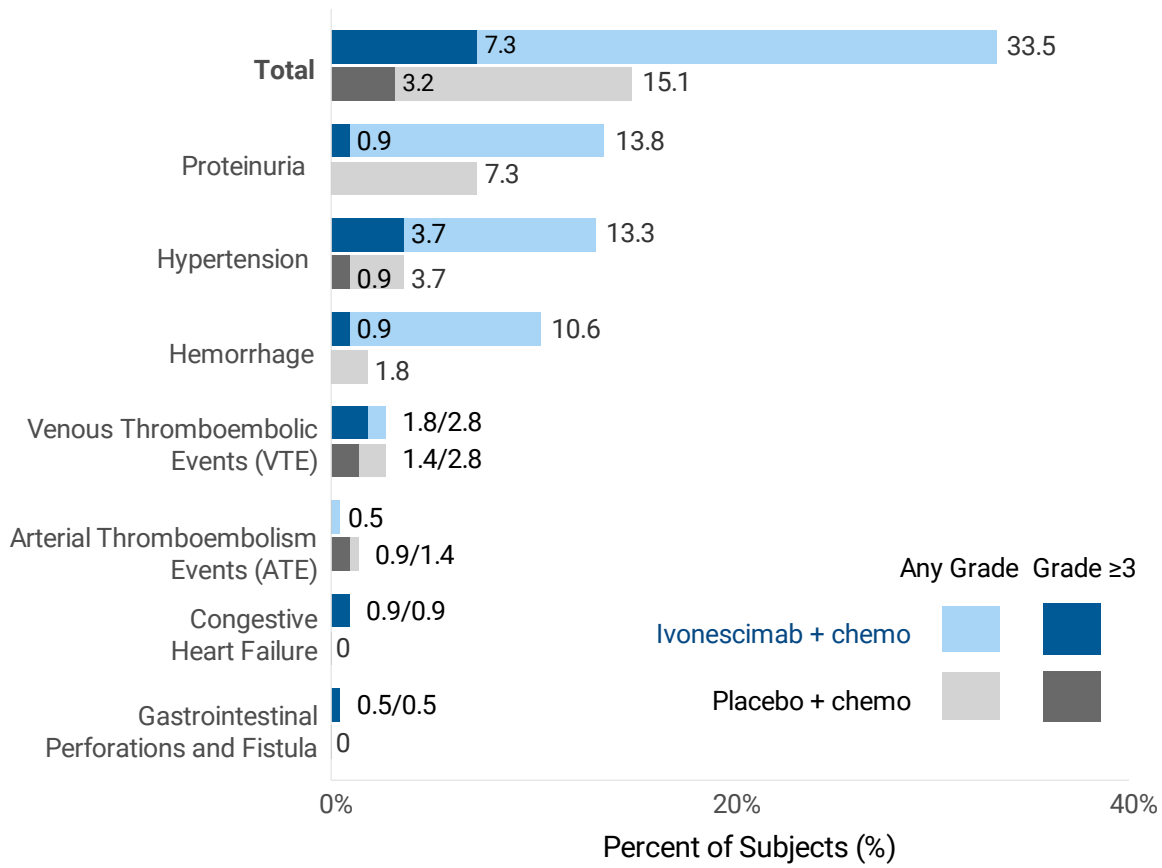
**Most common irAEs: hypo/hyperthryroidism, transaminase elevation, rash; mostly low grade**
**Most common VEGF-related TRAEs: proteinuria, hypertension, hemorrhage; mostly low grade**

## irAE




Pneumonitis/ILD, Ivo arm vs Pbo arm:
**2.8%** (1.4% Grade ≥3) vs **1.8%** (1.4% Grade ≥3)

## VEGF-related




d/c=discontinuation; ILD=interstitial lung disease; irAE=immune-related adverse events; ivo=ivonescimab; pbo=pembrolizumab; TRAE=treatment-related adverse events; VEGF= vascular endothelial growth factor.

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# Summary




- Ivonescimab had a significant and clinically meaningful PFS benefit in NSCLC patients post-3rd gen TKI
  - Reduced risk of progression or death by 48% vs chemotherapy, HR=0.52
  - Consistent efficacy across pre-defined subgroups
  - Increased ORR and DoR
- OS final analysis showed favorable trend; HR=0.79 with p=0.0570
  - Longer-term follow-up of Western patients showed stable OS; HR=0.78 with nominal p=0.0332
  - Western patients' median OS was numerically higher by 3 months
- Ivonescimab well tolerated, with no new safety findings
  - <1% Grade 3+ bleeding and comparable rates of discontinuation and death between arms

DoR=duration of response; EGFRm+=epidermal growth factor receptor mutation positive; EU=Europe; gen=generation; NA=North America; ORR=overall response rate; OS=overall survival; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitor; PFS=progression-free survival.

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# Acknowledgements

*Thank you to everyone who made this trial possible:*

- *The patients and their families*
- *The personnel at all the clinical study sites*
- *The scientists, regulatory, operations, and other teams within Summit and Akeso who helped develop ivonescimab and supported the study*

*The study was supported by Summit Therapeutics and Akeso Biopharma.*