IASLC 2025 World Conference on Lung Cancer

SEPTEMBER 6-9, 2025 | BARCELONA, SPAIN

wclc.iaslc.org #WCLC25

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], Frederico 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.

Phase 3 Study Design

HARMONi

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)

R 1:1

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/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

HARMONi

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)

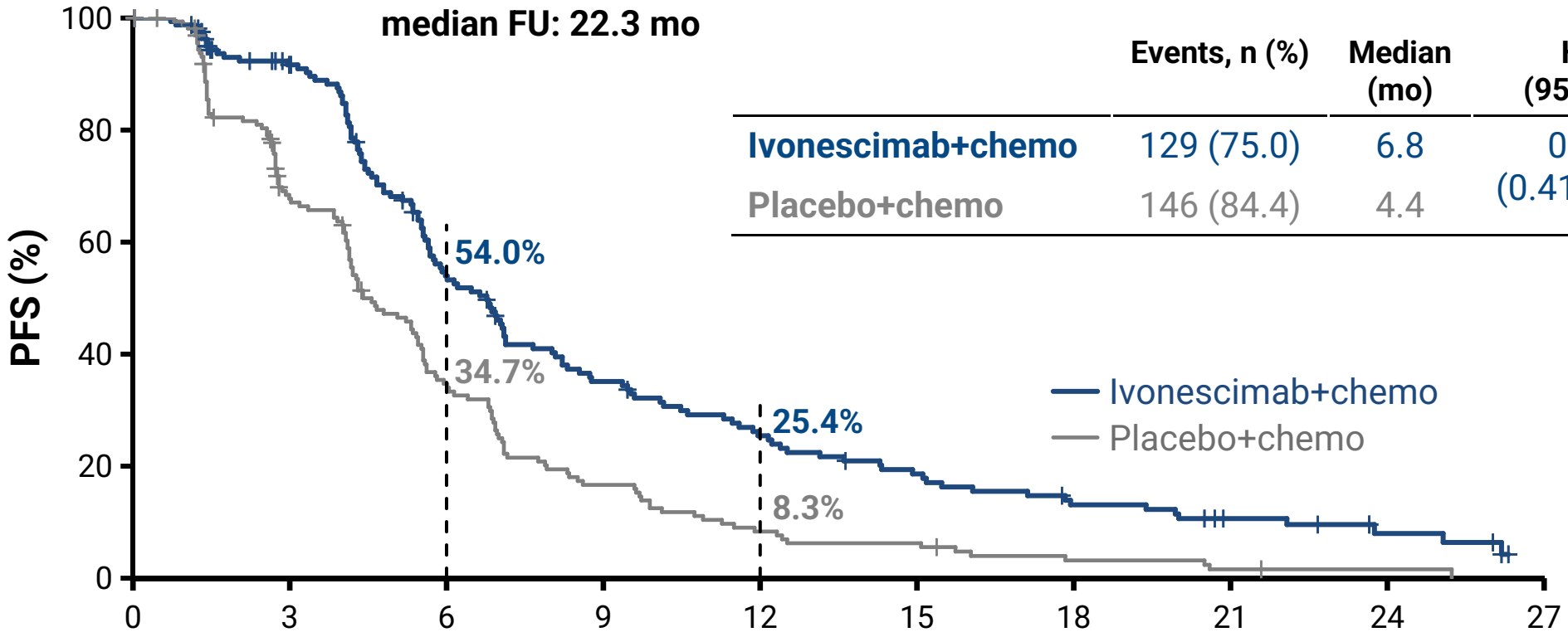
* Non-19del/L858R mutations include G719X, L861Q, S768I, etc.

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

Primary Endpoint: PFS by IRRC

HARMONi

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)

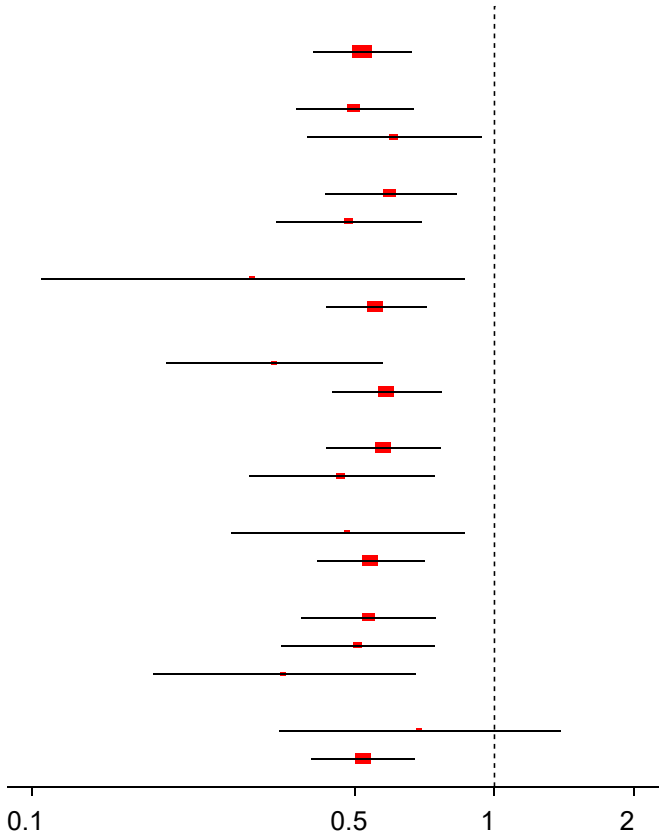
CI=confidence interval; FU=follow-up; HR=hazard ratio; IRRC= independent radiology review committee; PFS=progression-free survival.

PFS by IRRC – Subgroup Analysis

Consistent across pre-defined subgroups

HARMONi

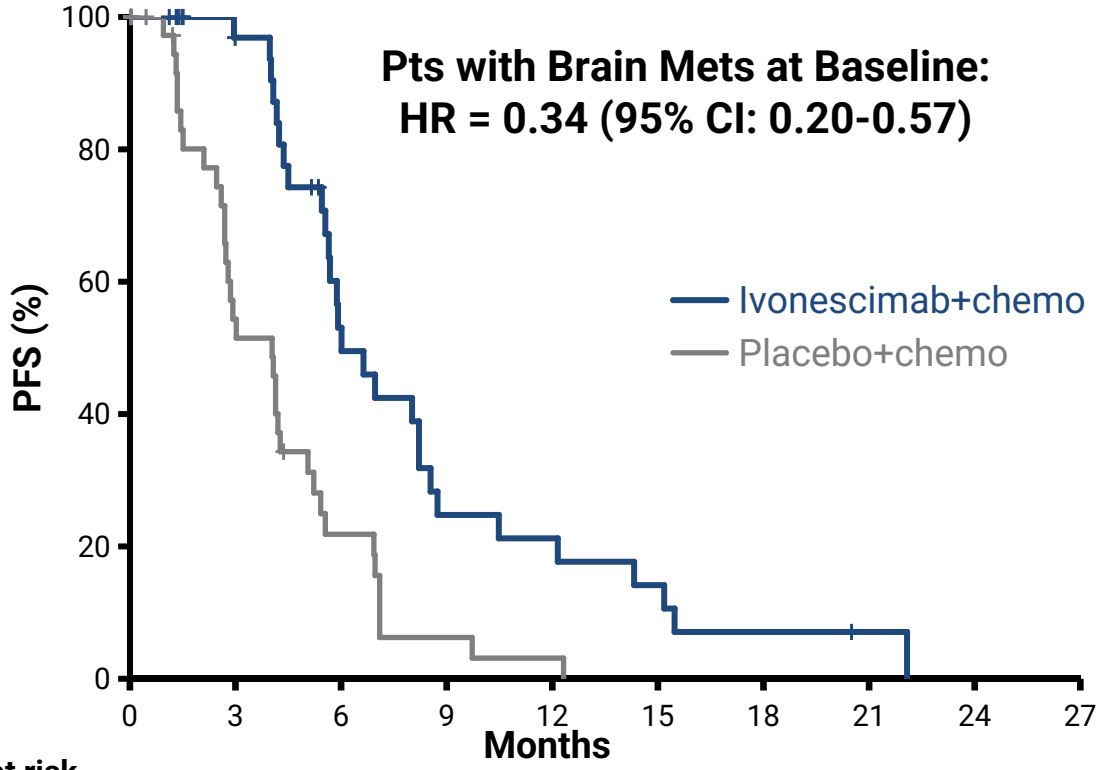
	Ivonescimab + chemo (Events/N)	Placebo + chemo (Events/N)	Hazard Ratio (95% CI)
Overall population	129/172	146/173	0.52 (0.41-0.66)
Age			
<65 years	89/115	101/110	0.50 (0.37-0.67)
>=65 years	40/57	45/63	0.61 (0.39-0.94)
Sex			
Female	74/97	74/92	0.60 (0.43-0.83)
Male	55/75	72/81	0.49 (0.34-0.70)
Geographic 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)



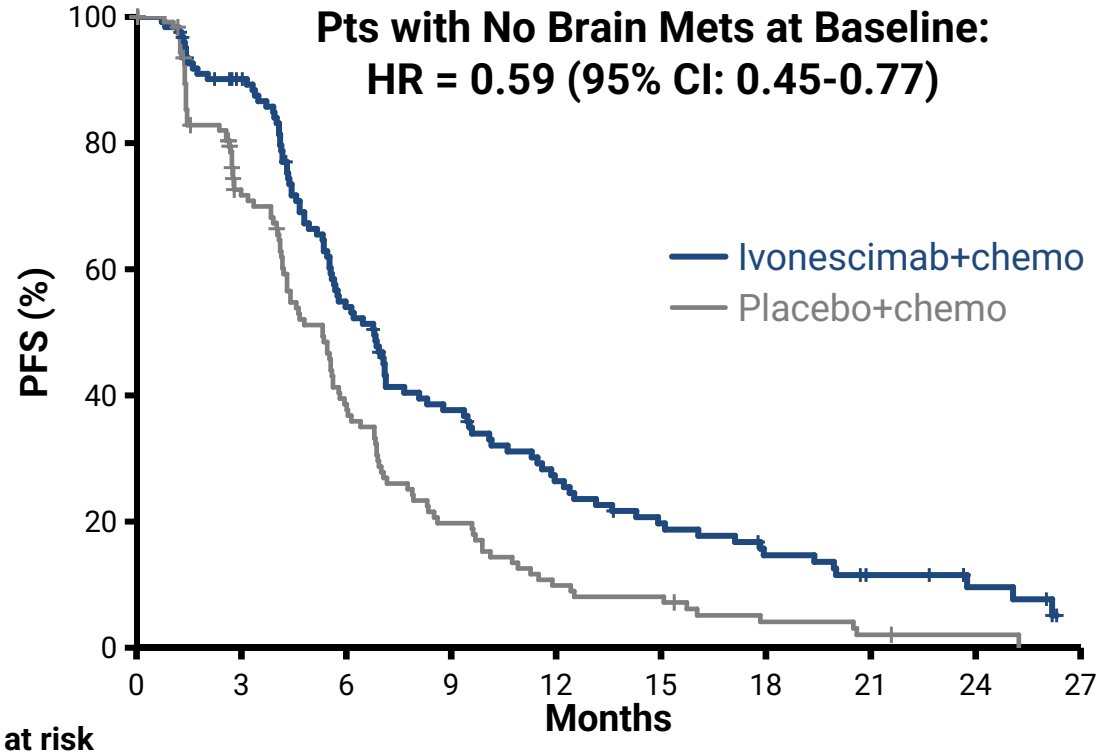
ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; IRRC= independent radiology review committee; PFS=progression-free survival; PS=performance status; TKI=tyrosine kinase inhibitor.

PFS by Presence or Absence of Brain Mets

HARMONi



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



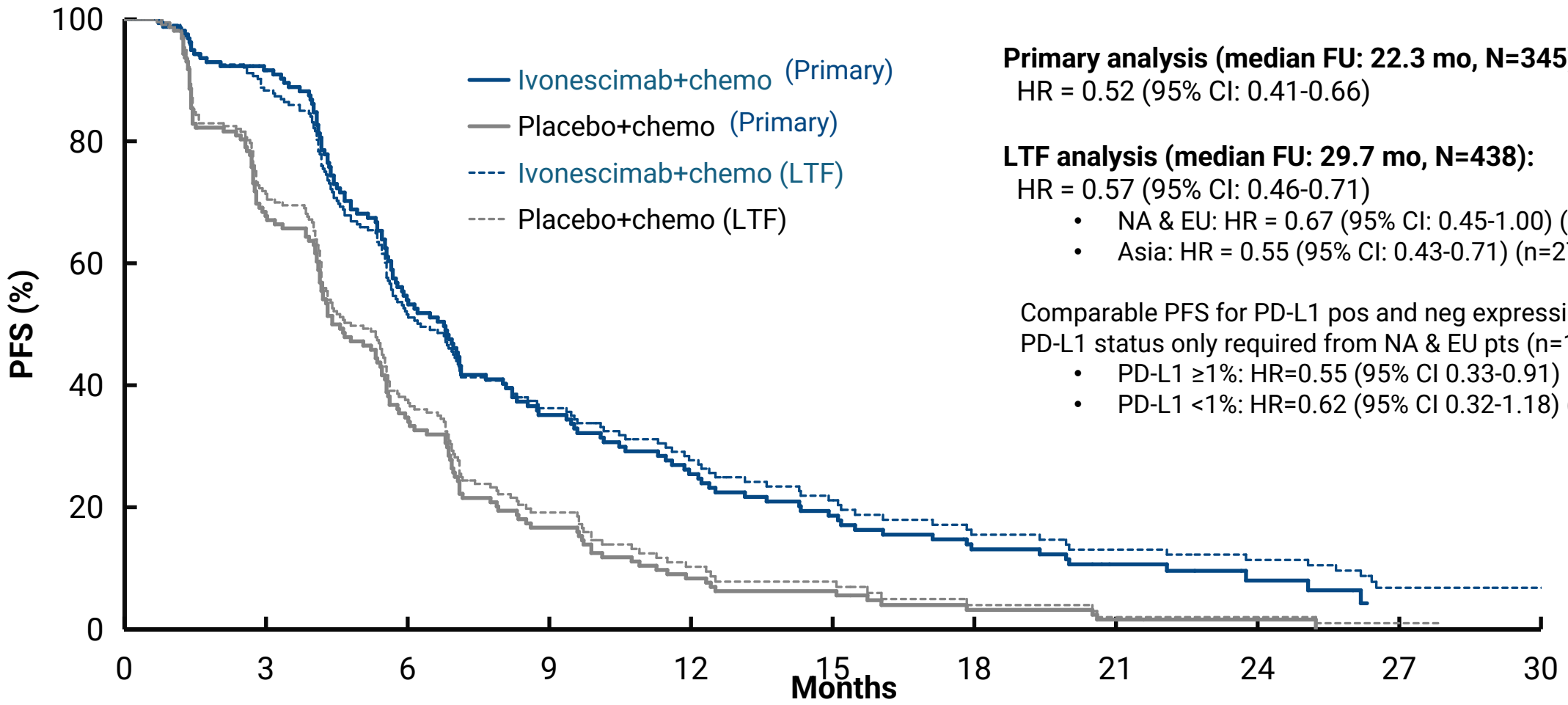
No. at risk										
Ivonescimab +chemo	131	104	61	41	28	20	14	9	5	0
Placebo +chemo	131	81	43	22	11	9	4	2	1	0

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

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

HARMONi

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)

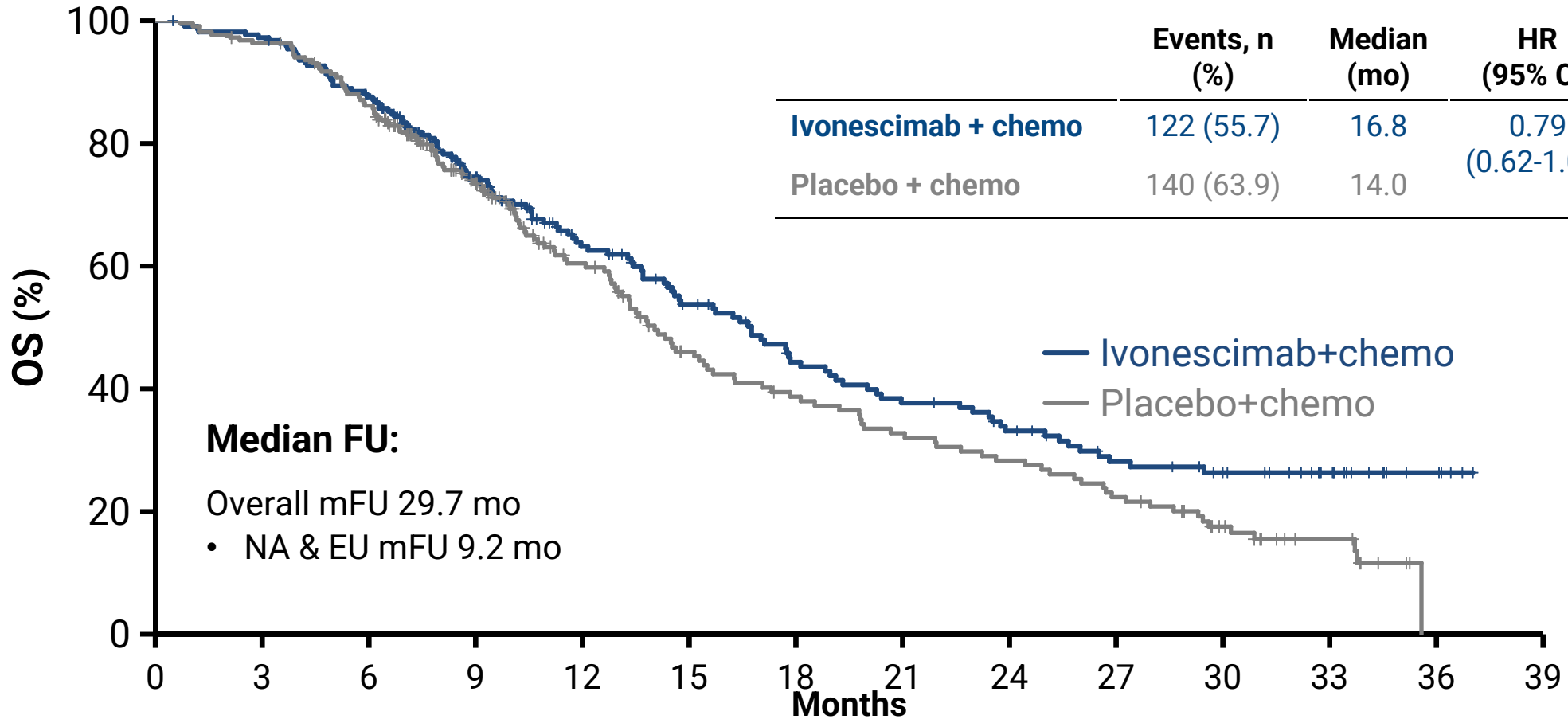
CI=confidence interval; EU=Europe; FU=follow-up; HR=hazard ratio; IRRC=independent radiographic review committee; NA=North America; PD-L1= programmed cell death ligand; PFS=progression-free survival.

Primary Endpoint: Overall Survival

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

HARMONi

	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		



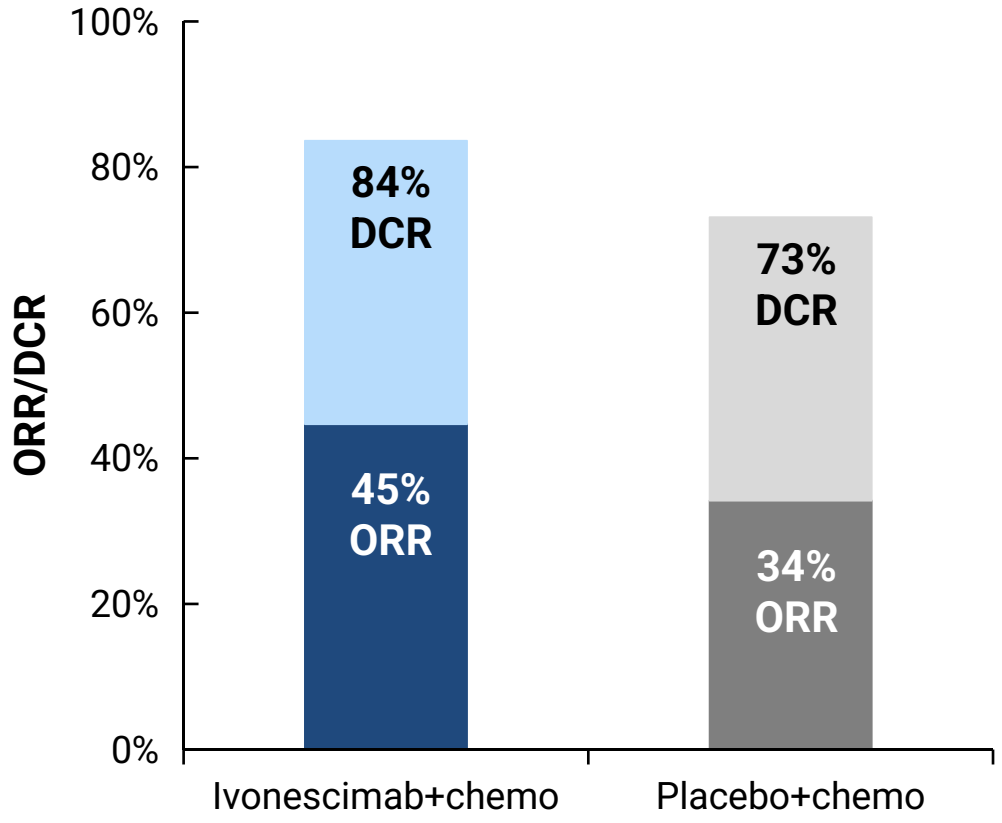
No. at risk

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 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.

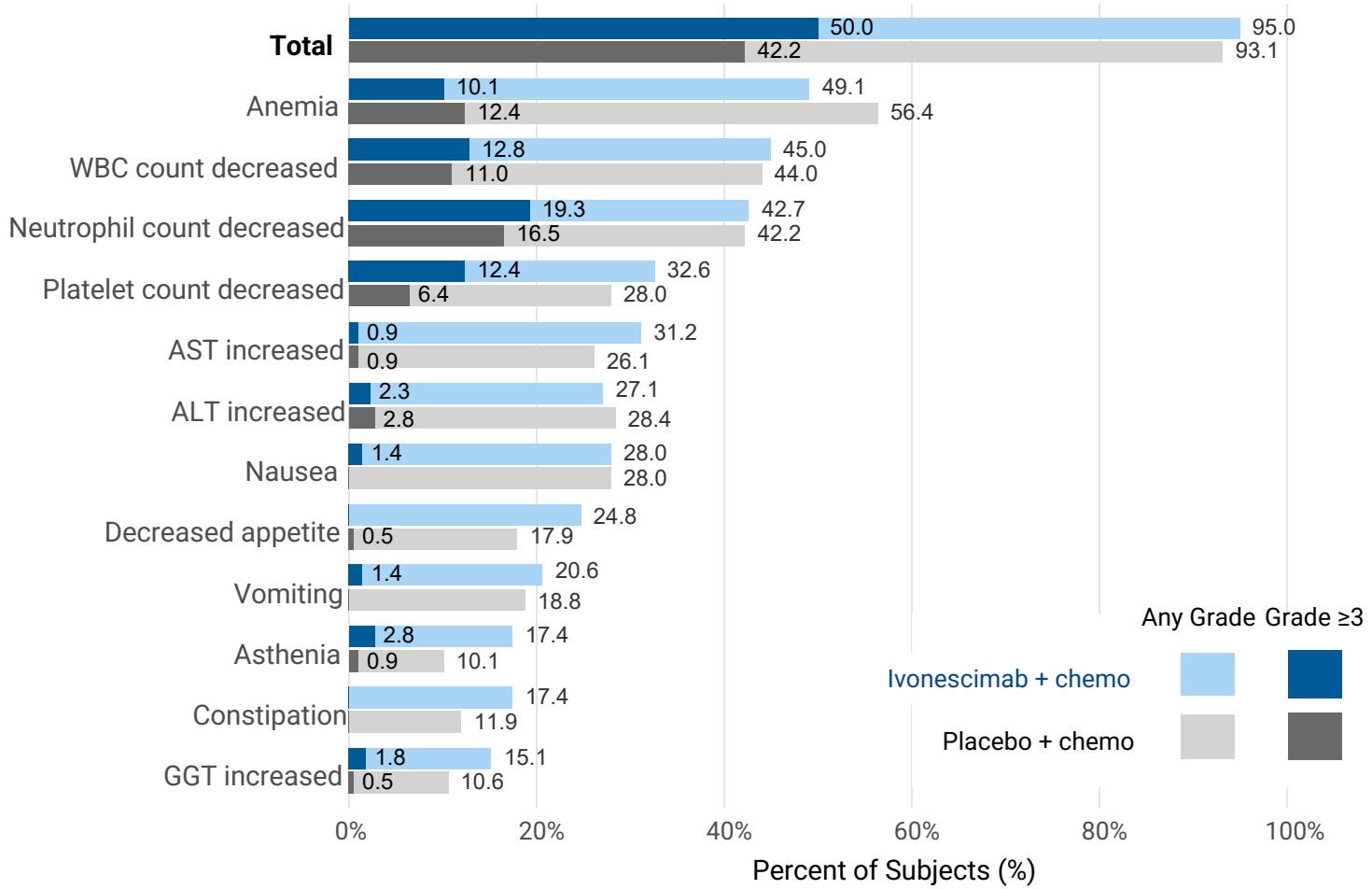
Treatment-Related Adverse Events (TRAEs)

HARMONi

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



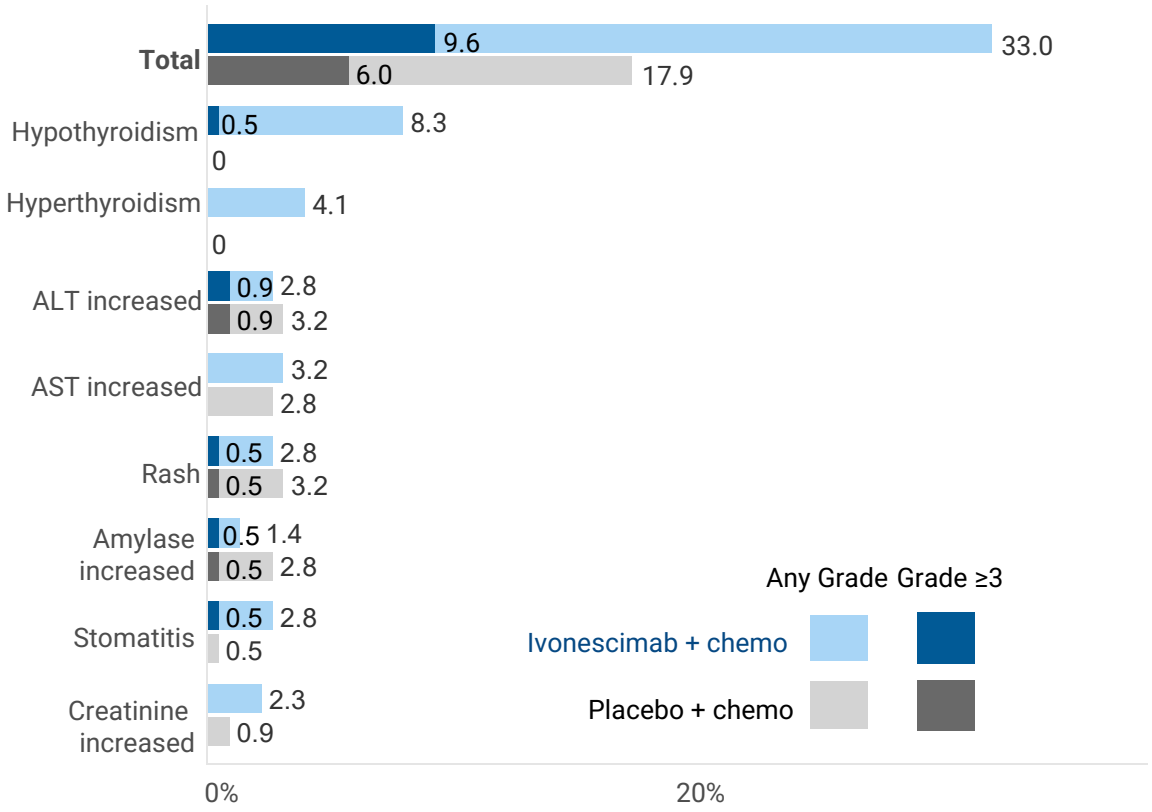
d/c=discontinuation; irAE=immune-related adverse events; VEGF= vascular endothelial growth factor.

Immune-related and VEGF-related TRAEs

HARMONi

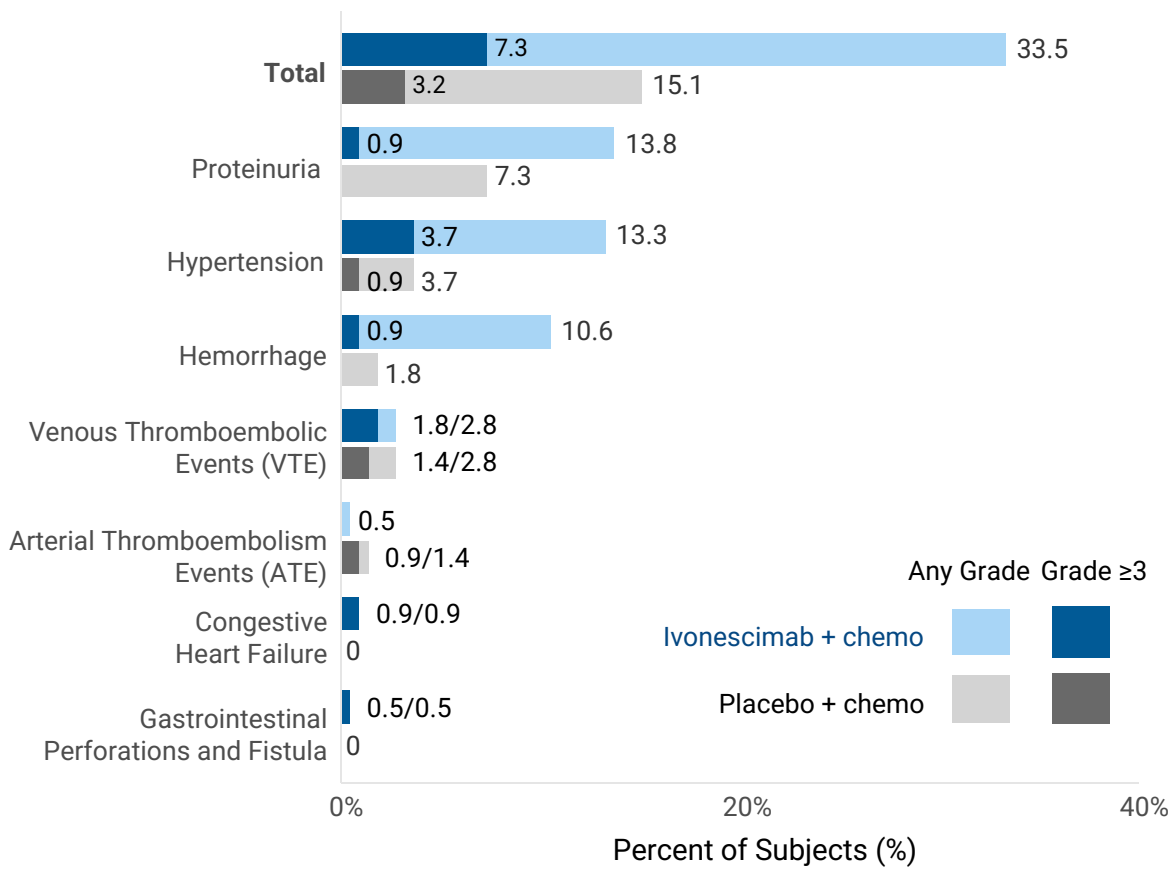
Most common irAEs: hypo/hyperthryroidism, transaminase elevation, rash; mostly low grade
Most common VEGF-related TRAEs: proteinuria, hypertension, hemorrhage; mostly low grade

irAE



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

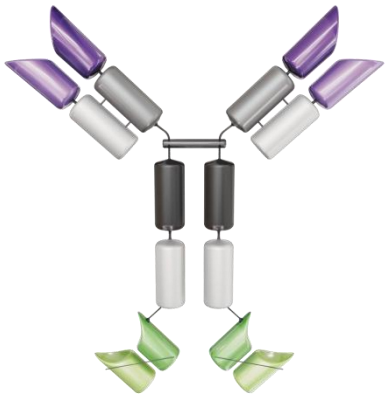
VEGF-related



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.

Summary

HARMONi



- Ivonescimab had a significant and clinically meaningful PFS benefit in EGFRm+ 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
  - OS improvement trend, HR=0.79
  - Increased ORR and DoR
- Ivonescimab well tolerated, with no new safety findings
  - <1% Grade 3+ bleeding and comparable rates of discontinuation and death between arms
- Analysis with longer OS follow-up to be performed
  - To increase maturity for NA & EU pts

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.

HARMONi

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.

Thank You