Epacadostat Plus Pembrolizumab Versus Pembrolizumab Alone in Patients With Unresectable or Metastatic Melanoma: Results of the Phase 3 ECHO-301/KEYNOTE-252 Study

Georgina V. Long,[1] Reinhard Dummer,[2] Omid Hamid,[3] Thomas Gajewski,[4] Christian Caglevic,[5] Stephane Dalle,[6] Ana Arance,[7] Matteo S. Carlino,[8] Jean-Jacques Grob,[9] Tae Min Kim,[10] Lev Demidov,[11] Caroline Robert,[12] James Larkin,[13] James R. Anderson,[14] Janet Maleski,[15] Mark Jones,[15] Scott J. Diede,[14] Tara C. Mitchell[16]

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]University Hospital Zürich, Zurich, Switzerland; [3]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [4]University of Chicago Medical Center, Chicago, IL, USA; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [9]Aix-Marseille University, Marseille, France; [10]Seoul National University Hospital, Seoul, South Korea; [11]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [12]Gustave Roussy Comprehensive Cancer Center, Villejuif, France; [13]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Incyte Corporation, Wilmington, DE, USA; [16]Abramson Cancer Center of the University of Philadelphia, Philadelphia, PA, USA.

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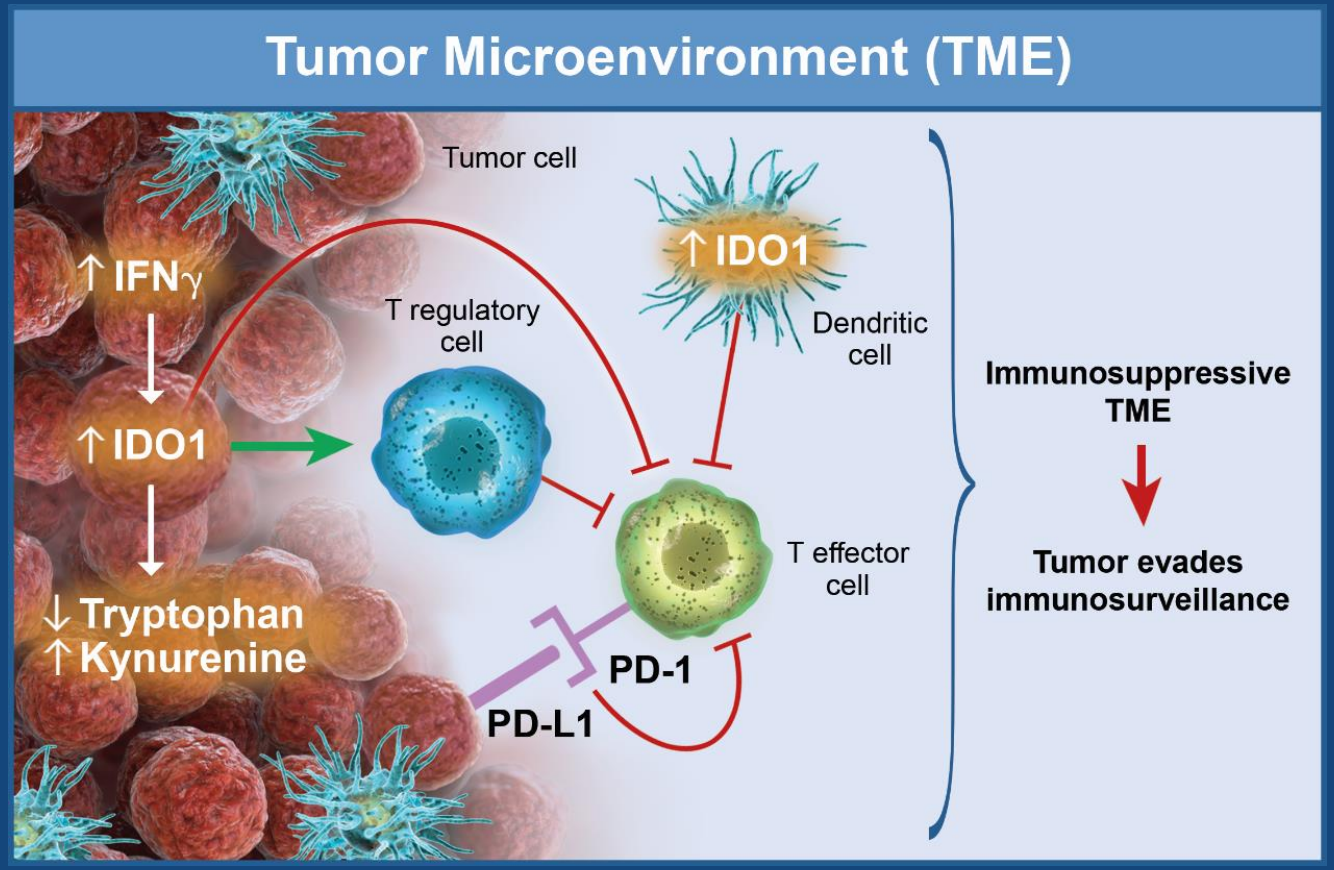
PRESENTED BY: Georgina V. Long

Background

- Upregulation of IDO1 is a potential mechanism to evade immunosurveillance
  - ↓ Tryptophan ↑ Kynurenine
  - ↓ T_{eff} and NK cells
  - ↑ T_{reg} cells, MDSCs, TAMs
- Epacadostat: IDO1 enzyme inhibitor
- Pembrolizumab: anti-PD-1 humanized antibody

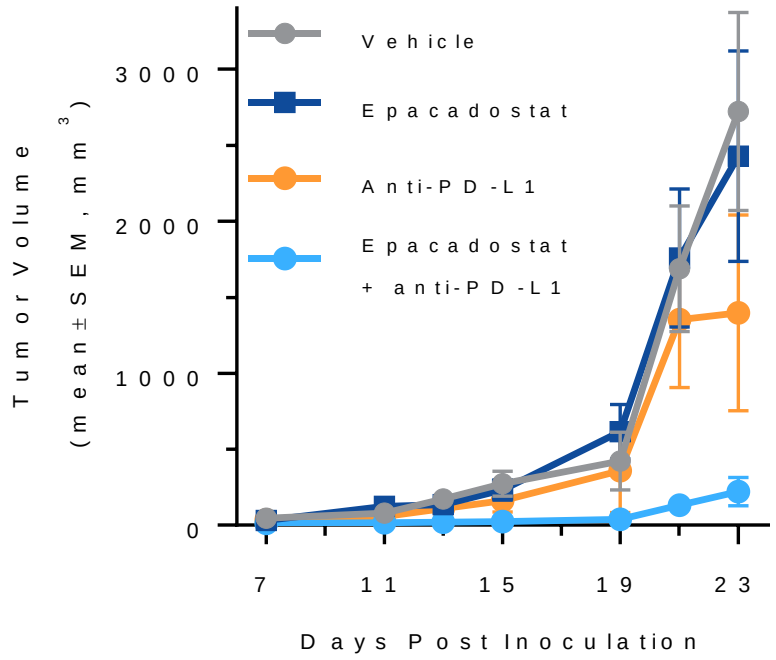


IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death ligand-1; TAM, tumor-associated macrophage; T_{eff}, effector T cell; T_{reg}, regulatory T cell.

Background: Rationale for Combination and Dosing

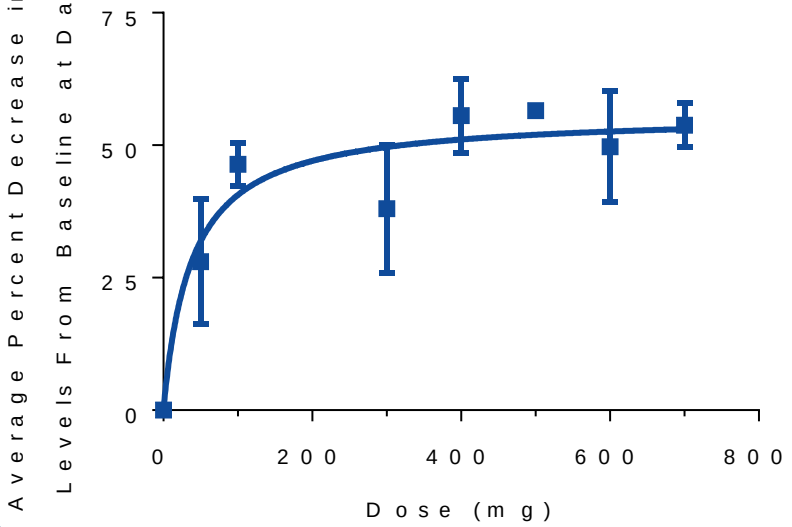
Preclinical Model[1,2]

- Marked synergy with anti-PD-L1 mAbs



Epacadostat Phase 1[3]

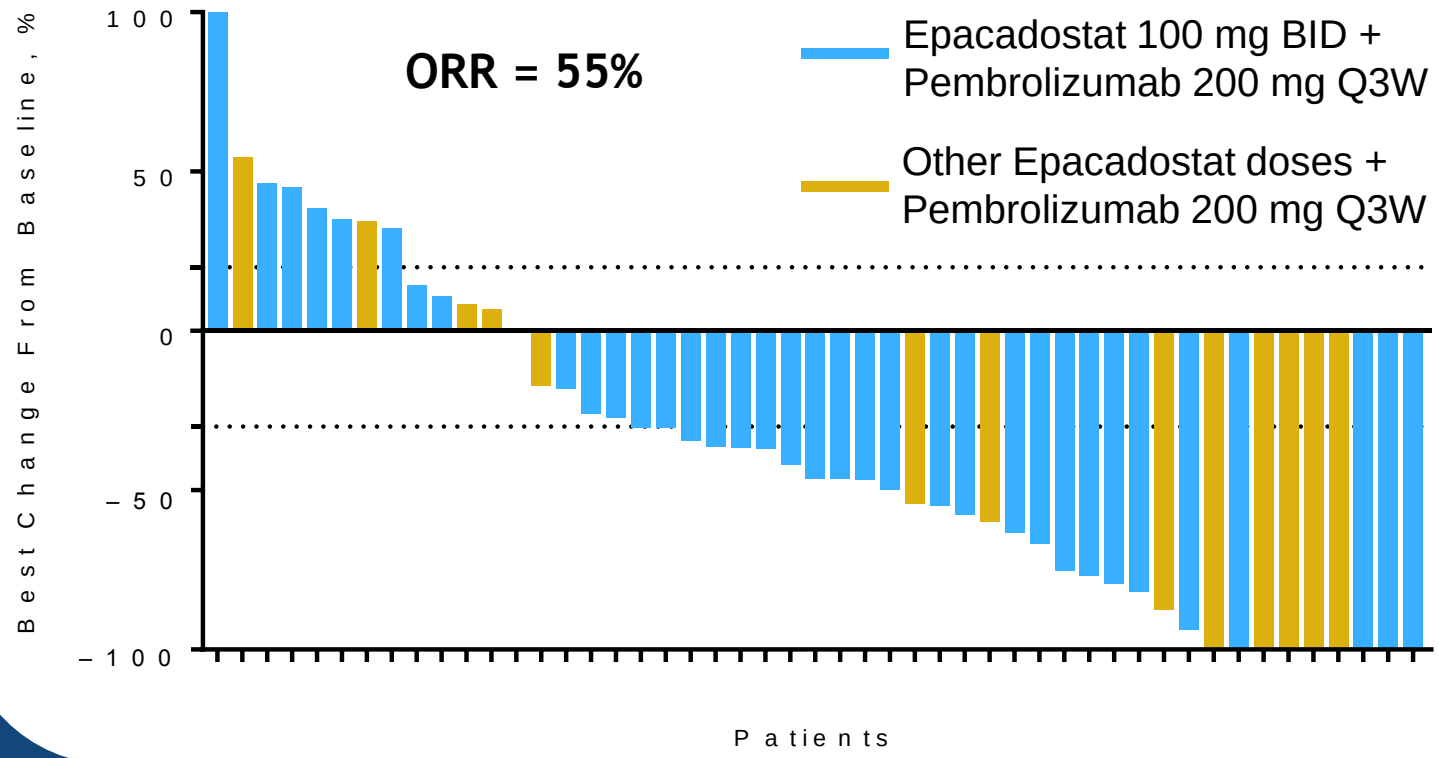
- Plasma Kyn near max inhibition at ≥100 mg BID
- >80% C_{min} inhibition of IDO1 ex vivo post stimulation



BID, twice daily; IDO1, indoleamine 2,3 dioxygenase 1; Kyn, kynurenine; mAb; monoclonal antibody; PD-L1, programmed death ligand-1.

1. WIPO #WO/2014/066834 https://patentscope.wipo.int/ Accessed August 2, 2017. **2.** Spranger S, et al. *J Immunother Cancer*. 2014;2:3. **3.** Beatty GL, et al. *Clin Cancer Res.* 2017;23:3269-3276, with permission from AACR.

Background: Rationale for Combination and Dosing



ECHO-202 / KEYNOTE-037

- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo (12.4 mo all melanoma)

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol*. 2017;28(suppl 5):1214O.

Study Design: Phase III Randomized Controlled Trial

Key Eligibility Criteria

- Unresectable stage III or IV melanoma, advanced/metastatic disease
  - Patients with *BRAF* mutation could have received prior BRAF/MEK therapy
  - Prior anti-CTLA-4 or interferon in adjuvant setting permitted
- ECOG performance status 0–1
- No active CNS metastases

N=706
R 1:1

Epacadostat 100 mg PO BID
+
Pembrolizumab 200 mg IV Q3W
n=354

Placebo
+
Pembrolizumab 200 mg IV Q3W
n=352

Stratification

- PD-L1 status (positive[a] vs negative)
- *BRAF* mutation status
  - Wild type
  - Mutant with prior *BRAF*-directed therapy
  - Mutant without prior *BRAF*-directed therapy

- **Primary endpoints:** PFS (RECIST v1.1) and OS
- **Secondary endpoints:** ORR (RECIST v1.1), DOR, safety

BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Assessments

- Tumor imaging at week 12; every 9 weeks thereafter
- Response by RECIST v1.1 (central review)
- AEs of special interest
  - Immune-related
  - Regardless of treatment attribution

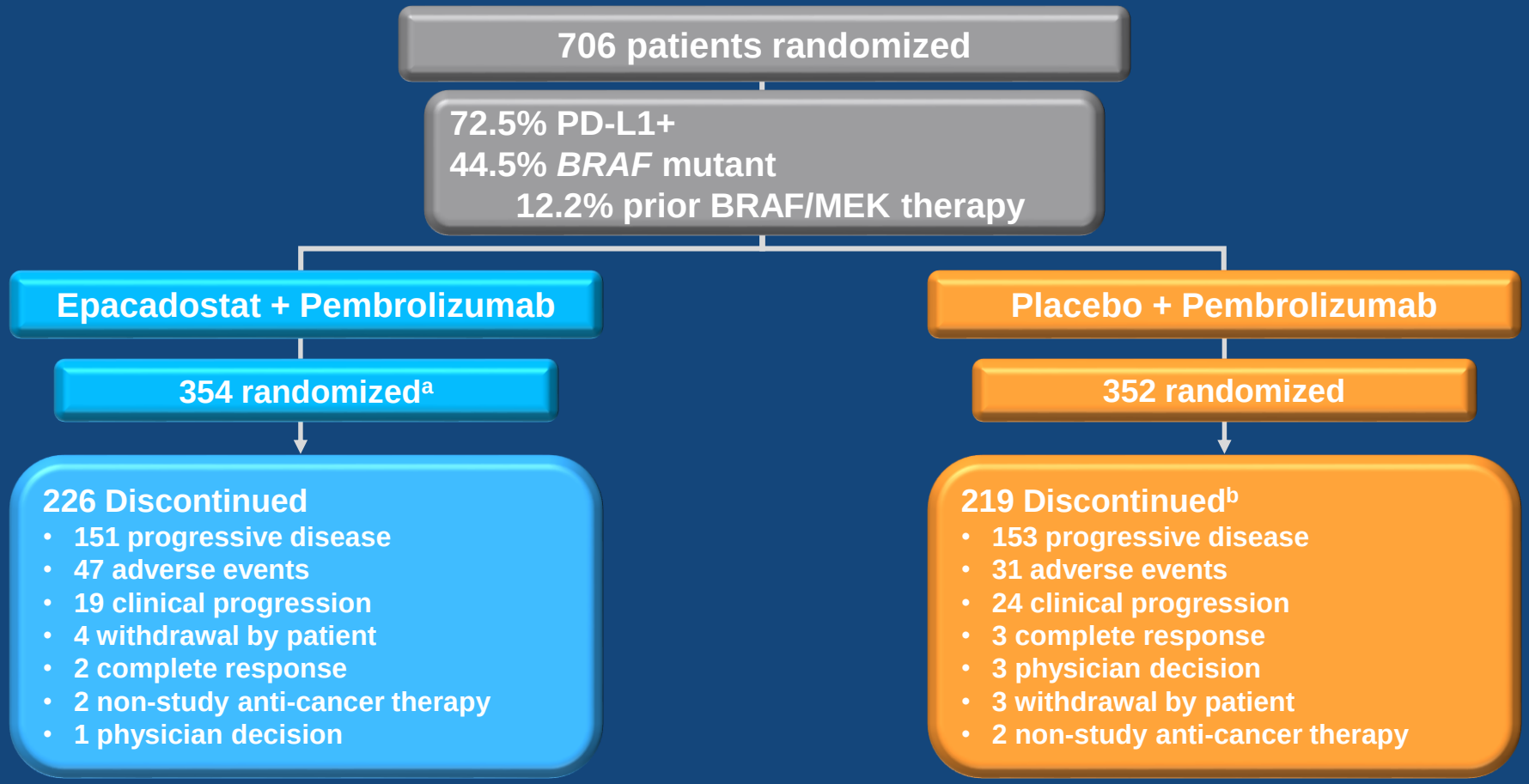
AE, adverse event; RECIST, Response Evaluation Criteria In Solid Tumors.

Statistical Considerations

- Data cutoff: January 8, 2018
- Analysis populations
  - Efficacy: randomized patients (ITT)
  - Safety: patients who received at least 1 dose of treatment
- Final analysis of PFS and interim analysis of OS
- PFS and OS stratified log-rank test; HR Cox regression

HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression-free survival.

Treatment Disposition



Median follow-up (range): 12.4 (0.3–18.6) months

PD-L1, programmed death ligand 1.
[a]One patient randomized to the epacadostat + pembrolizumab group did not receive treatment.
[b]2 additional patients discontinued placebo but continued receiving pembrolizumab.

Baseline Characteristics

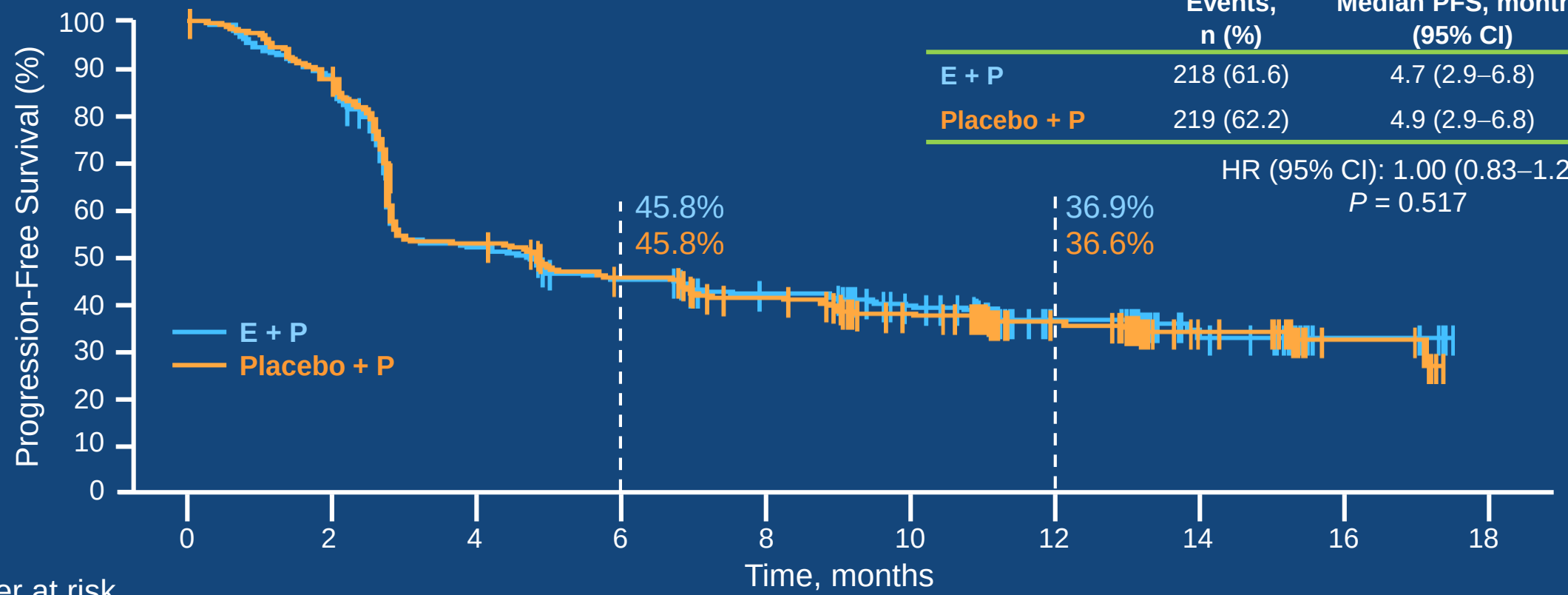
Patients, n (%)	Epacadostat + Pembrolizumab (n=354)	Placebo + Pembrolizumab (n=352)
Age, median (range), y	64 (20–88)	63 (23–91)
Male	217 (61.3)	206 (58.5)
ECOG PS		
0	261 (73.7)	267 (75.9)
1	93 (26.3)	85 (24.1)
Lactate dehydrogenase >ULN	123 (34.7)	113 (32.1)
>ULN but <2X ULN	99 (28.0)	93 (26.4)
≥2x ULN	24 (6.8)	20 (5.7)
M1c disease	228 (64.4)	214 (60.8)
Treated brain metastasis	19 (5.4)	14 (4.0)
Prior adjuvant/neoadjuvant therapy	34 (9.6)	23 (6.5)
Prior lines of therapy for advanced disease		
1	47 (13.3)	37 (10.5)
≥2	1 (0.3)	5 (1.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; ULN, upper limit of normal.

Progression-Free Survival (RECIST v1.1, BICR)

	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517



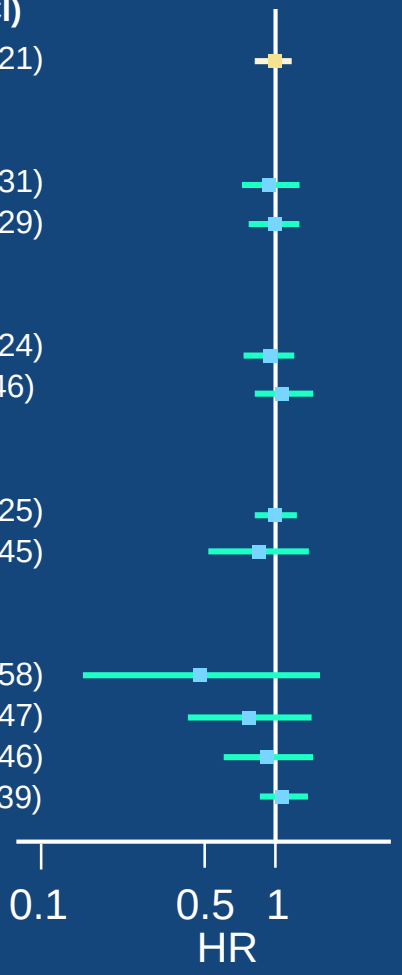
Number at risk

E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

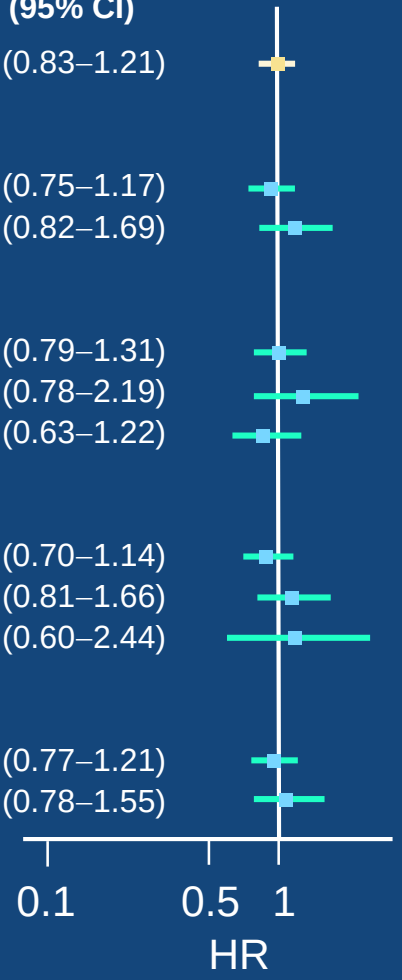
BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.
PFS defined as time from randomization to disease progression or death, whichever occurred first.

Progression-Free Survival by Subgroups

	# Events/N	HR (95% CI)
Overall	437/706	1.00 (0.83–1.21)
Sex		
Female	182/283	0.97 (0.73–1.31)
Male	255/423	1.01 (0.79–1.29)
Age		
<65	240/376	0.96 (0.74–1.24)
≥65	197/330	1.1 (0.83–1.46)
Race		
White	372/626	1.02 (0.83–1.25)
Non-white	65/79	0.87 (0.52–1.45)
Disease Stage		
III	18/26	0.47 (0.14–1.58)
IVM1a	44/82	0.79 (0.42–1.47)
IVM1b	82/152	0.94 (0.60–1.46)
IVM1c	291/442	1.11 (0.88–1.39)



	# Events/N	HR (95% CI)
Overall	437/706	1.00 (0.83–1.21)
Baseline ECOG PS		
0	318/528	0.94 (0.75–1.17)
1	119/178	1.18 (0.82–1.69)
BRAF Mutation Status		
BRAF wild type	240/392	1.02 (0.79–1.31)
BRAF mutant, prior *BRAF* trt	59/86	1.31 (0.78–2.19)
BRAF mutant, no prior *BRAF* trt	138/228	0.88 (0.63–1.22)
Baseline LDH		
≤ULN	268/463	0.89 (0.70–1.14)
>ULN but <2X ULN	126/192	1.16 (0.81–1.66)
≥2X ULN	39/44	1.21 (0.60–2.44)
PD-L1 Status		
PD-L1+	306/512	0.97 (0.77–1.21)
PD-L1-	131/194	1.10 (0.78–1.55)

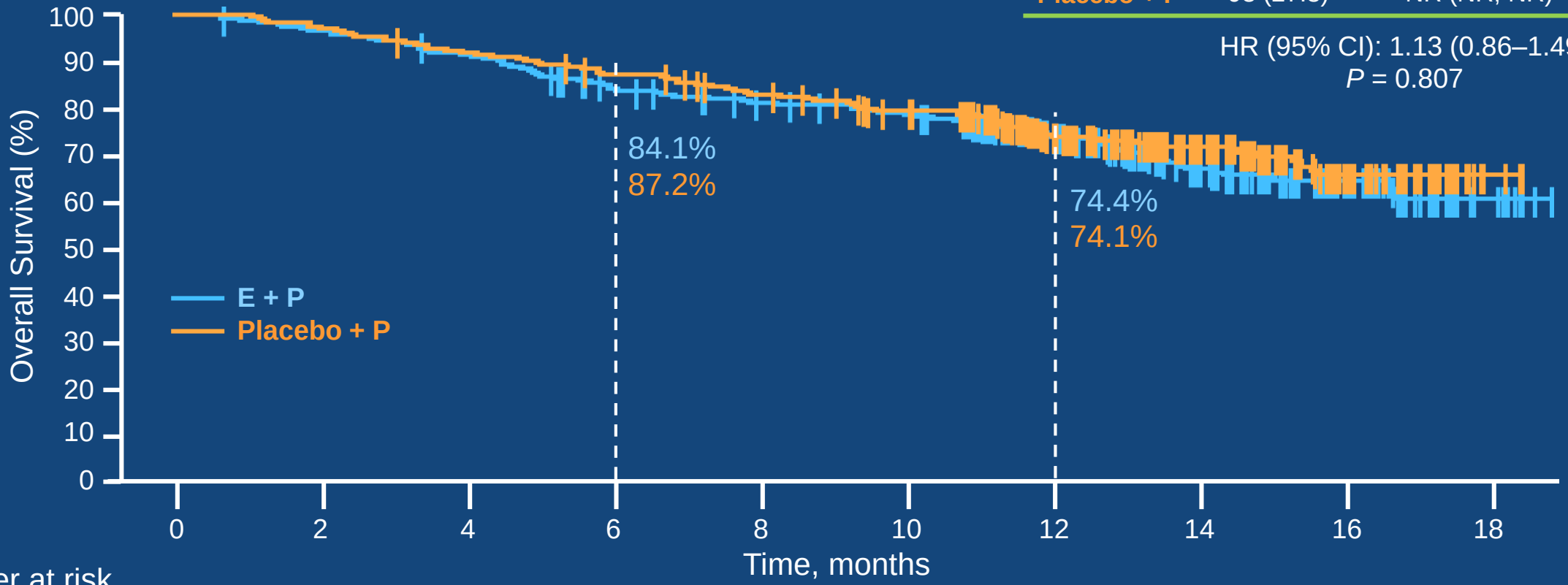


CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; trt, treatment; ULN, upper limit of normal.

Overall Survival

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807



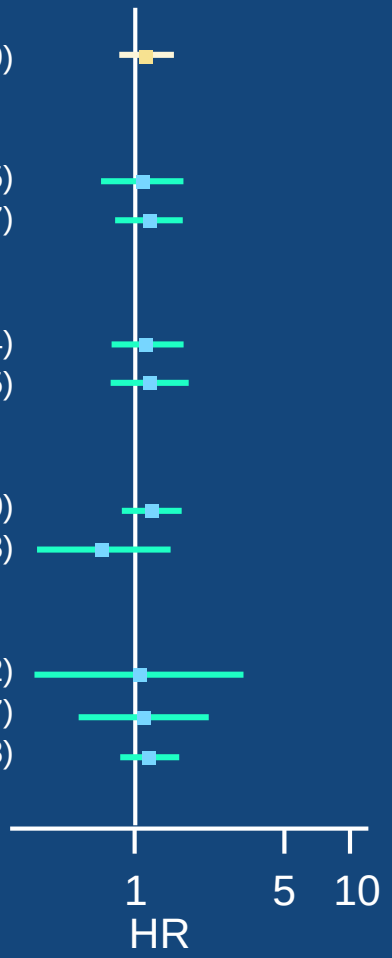
Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

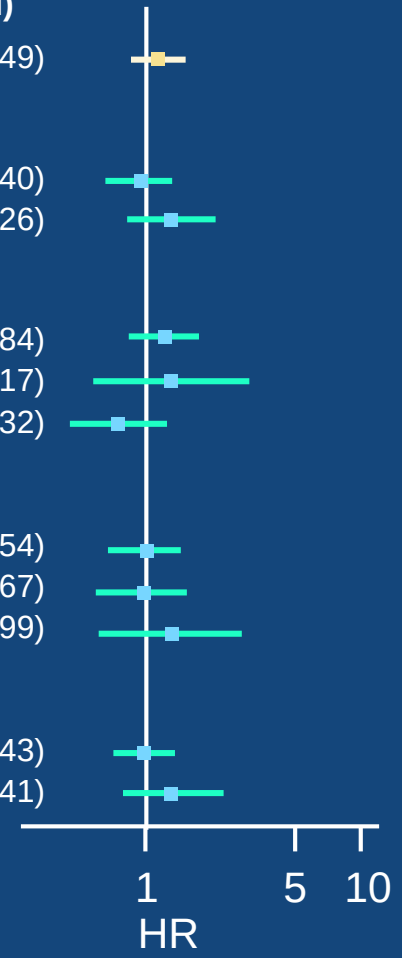
CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

Overall Survival by Subgroups

	# Events/N	HR (95% CI)
Overall	204/706	1.13 (0.86–1.49)
Sex		
Female	84/283	1.07 (0.70–1.65)
Male	120/423	1.16 (0.81–1.67)
Age		
<65	112/376	1.13 (0.78–1.64)
≥65	92/330	1.16 (0.77–1.75)
Race		
White	171/626	1.19 (0.88–1.60)
Non-white	33/79	0.70 (0.35–1.43)
Disease Stage		
IVM1a	14/82	1.03 (0.34–3.12)
IVM1b	33/152	1.09 (0.55–2.17)
IVM1c	154/442	1.15 (0.84–1.58)



	# Events/N	HR (95% CI)
Overall	204/706	1.13 (0.86–1.49)
Baseline ECOG PS		
0	131/528	0.99 (0.70–1.40)
1	73/178	1.41 (0.88–2.26)
BRAF Mutation Status		
BRAF wild type	123/392	1.29 (0.90–1.84)
BRAF mutant, prior *BRAF* trt	23/86	1.39 (0.61–3.17)
BRAF mutant, no prior *BRAF* trt	58/228	0.78 (0.47–1.32)
Baseline LDH		
≤ULN	104/463	1.05 (0.71–1.54)
>ULN but <2X ULN	65/192	1.02 (0.63–1.67)
≥2X ULN	33/44	1.38 (0.64–2.99)
PD-L1 Status		
PD-L1+	149/512	1.04 (0.75–1.43)
PD-L1-	55/194	1.41 (0.83–2.41)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; trt, treatment; ULN, upper limit of normal.

Best Objective Response (RECIST v1.1, BICR)

Response, n (%)	Epacadostat + Pembrolizumab (n=354)	Placebo + Pembrolizumab (n=352)
ORR	**121 (34.2)**	**111 (31.5)**
CR	14 (4.0)	15 (4.3)
PR	107 (30.2)	96 (27.3)
SD	59 (16.7)	68 (19.3)
DCR (CR+PR+SD)	180 (50.8)	179 (50.9)
PD	151 (42.7)	150 (42.6)
Non-CR/Non-PD	10 (2.8)	9 (2.6)
Not available or evaluable[a]	13 (3.7)	14 (4.0)
Median DOR (range), months	NR (0.0+ to 14.7+)	NR (0.0+ to 15.0+)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

[a]Patient had no post-baseline imaging or had post-baseline imaging and the best objective response was determined to be non-evaluable per RECIST 1.1.

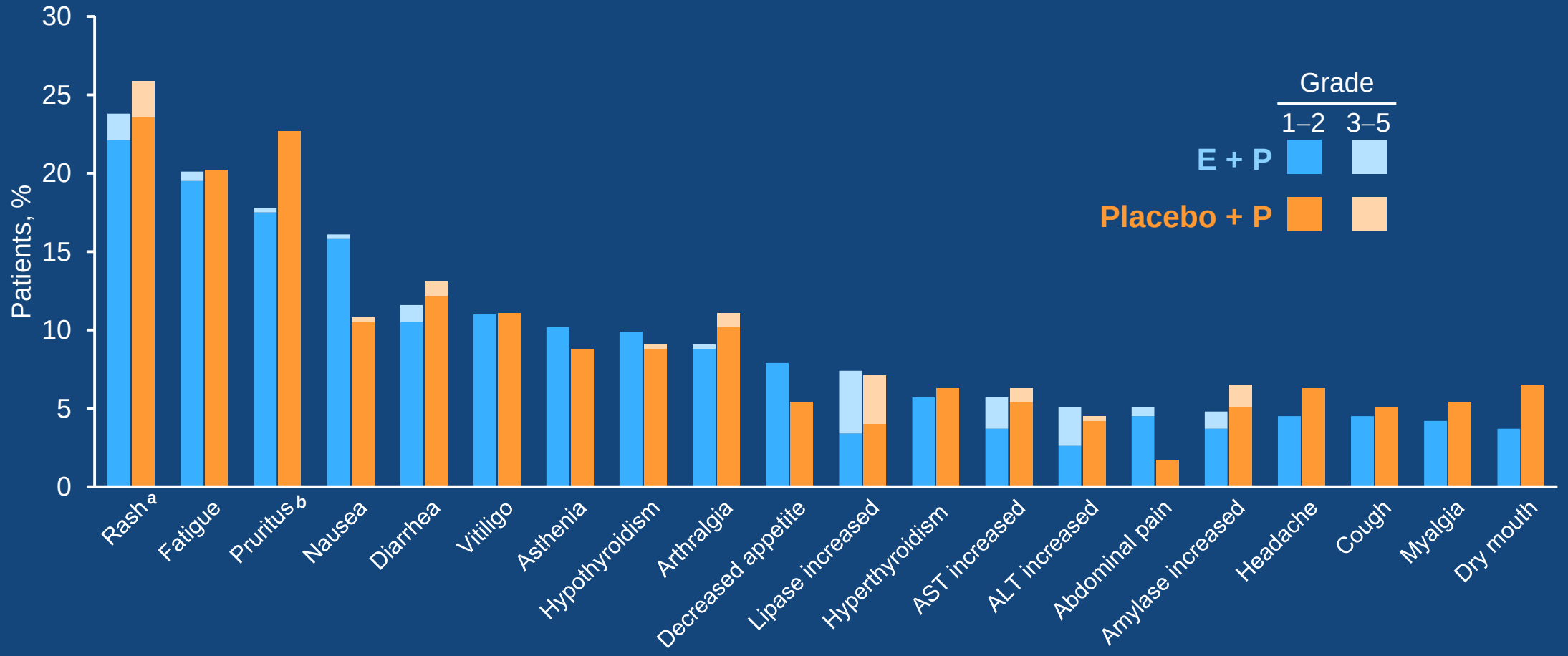
Summary of Adverse Events

Patients, n (%)	Epacadostat + Pembrolizumab (n=353)	Placebo + Pembrolizumab (n=352)
Treatment-related AEs[a]	280 (79.3)	285 (81.0)
Grade ≥3 treatment-related AEs	77 (21.8)	60 (17.0)
Serious treatment-related AEs	37 (10.5)	32 (9.1)
Discontinued drug due to a treatment-related AE	39 (11.0)	34 (9.7)
Dose reductions epacadostat/placebo due to AE	12 (3.4)	6 (1.7)
Dose interruptions (any treatment) due to AE	121 (34.3)	98 (27.8)

AE, adverse event.
[a]No patient died due to a treatment-related AE.

Treatment-Related Adverse Events

≥5% in Any Treatment Group

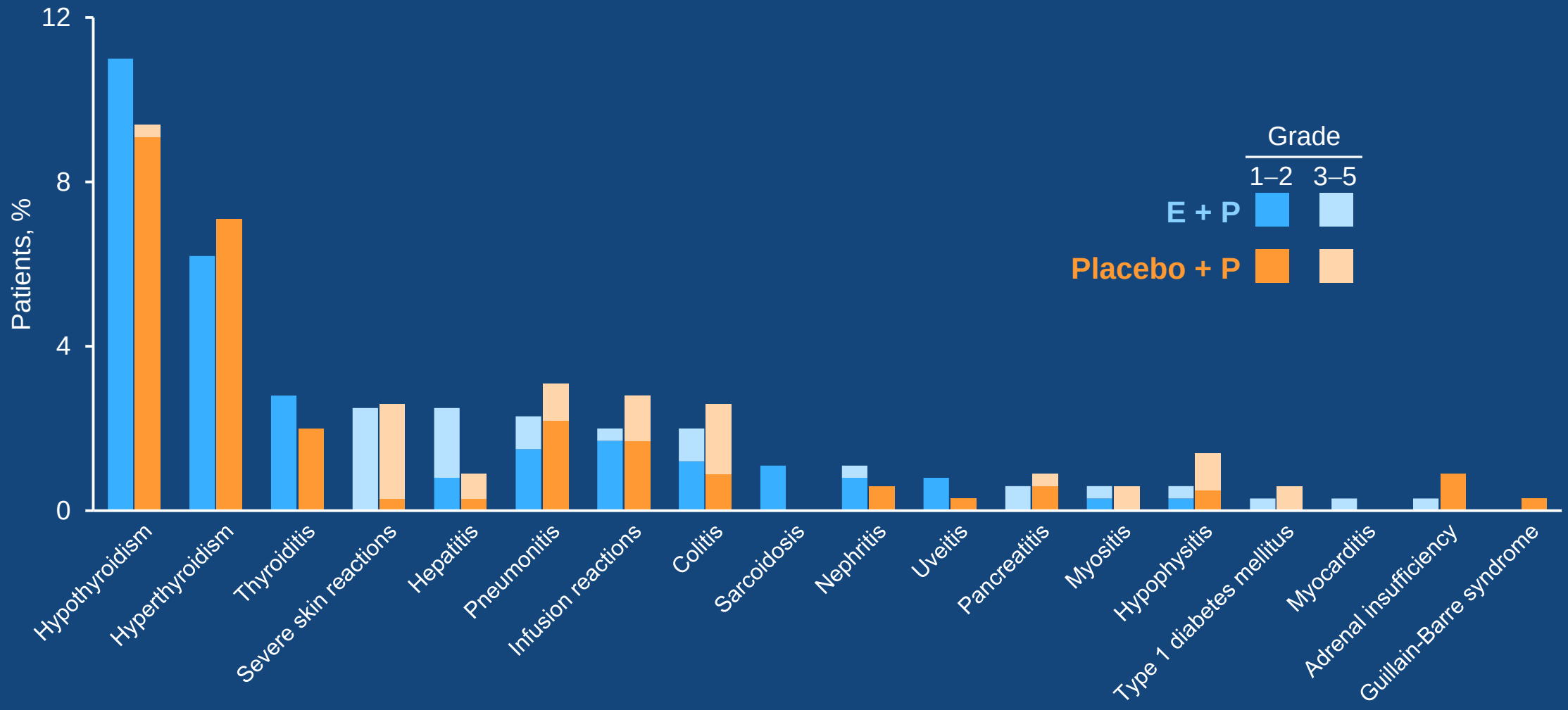


ALT, Alanine aminotransferase; AST, aspartate aminotransferase; E, epacadostat; P, pembrolizumab.

[a]Rash includes the following MedDRA preferred terms: dermatitis, dermatitis allergic, dermatitis exfoliative, drug eruption, drug reaction with eosinophilia and systemic symptoms, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin reaction.

[b]Pruritus includes the following MedDRA preferred terms: pruritus and pruritus generalized.

Adverse Events of Special Interest



E, epacadostat; P, pembrolizumab.

Conclusions

- The efficacy and safety of pembrolizumab in this study are consistent with KEYNOTE-006 (pembrolizumab vs ipilimumab for advanced melanoma)
- In patients with unresectable or metastatic melanoma, the addition of epacadostat to pembrolizumab did not result in greater clinical benefit than pembrolizumab alone
- External Data Monitoring Committee recommendation
  - Stop trial as study did not meet primary endpoint of PFS, and OS was not expected to reach statistical significance
- Additional analyses are underway to better understand these findings
  - IDO1 expression by RNAscope
  - Tumor mutation burden
  - RNAseq
  - Baseline Kyn and other blood-based markers

IDO1, indoleamine 2,3 dioxygenase 1; Kyn, kynurenine.

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