Phase 1/2 Study of Epacadostat in Combination With Ipilimumab in Patients With Unresectable or Metastatic Melanoma

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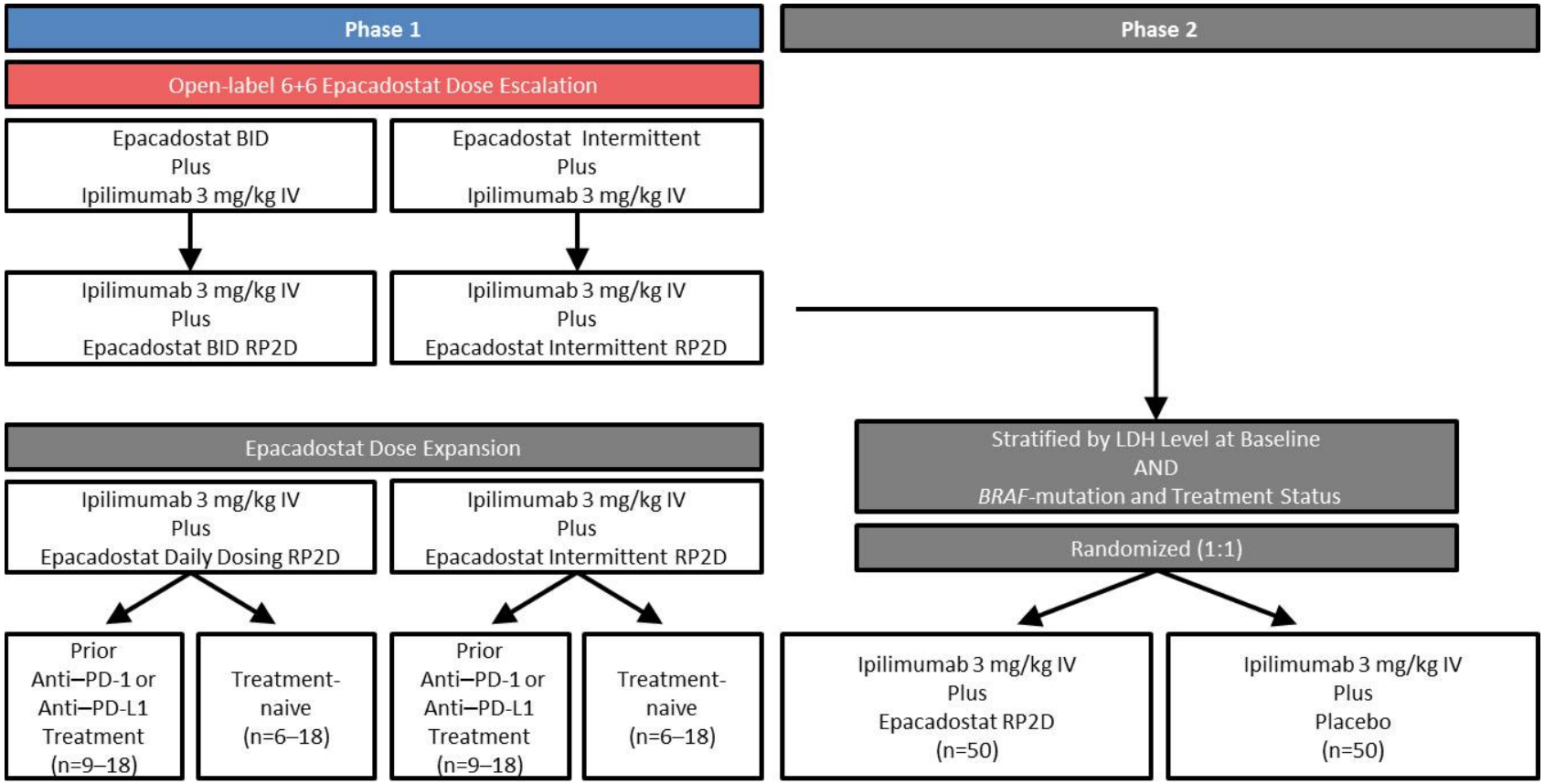
SUPPLEMENTARY MATERIALS

Supplementary Figure S1. Study Design



BID, twice daily; IV, intravenous; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RP2D, recommended phase 2 dose.
Note: Phase 1 expansion cohorts and phase 2 were not conducted.

Supplementary Table S1. Epacadostat and Ipilimumab Treatment Exposure

	25 mg BID (n=8)	50 mg BID Cont' (n=18)	50 mg BID Int' (n=9)	75 mg Total Daily (n=7)	100 mg BID* (n=1)	300 mg BID* (n=7)	Total (N=50)
Median (range) days of exposure to epacadostat	239 (9–1352)	79 (10–1019)	109 (7–941)	211 (24–739)	1 (1–1)	41 (30–75)	84 (1–1352)
Median (range) average daily dose of epacadostat, mg	48 (39–50)	100 (50–100)	71 (54–100)	75 (27–75)	100 (100–100)	332 (296–600)	76 (27–600)
Patients by total ipilimumab dose received, n							
0 dose	0	0	0	0	1†	0	1†
1 dose	1	1	1	0	0	0	3
2 doses	1	3	1	1	0	5	11
3 doses	1	3	1	1	0	1	7
4 doses	5	11	6	5	0	1	28

BID, twice daily; cont', continuous; int', intermittent.

* Epacadostat 100-mg BID and 300-mg BID dose cohorts were not re-explored in this study after protocol amendment to evaluate lower doses of epacadostat.

† The 1 patient in the 100-mg BID dose cohort discontinued study after 1 day of treatment with epacadostat and did not receive ipilimumab.

Supplementary Table S2. Dose-Limiting Toxicities

Epacadostat Dose Cohort	Number of Patients With DLT/ Number of Evaluable Patients	DLT Description
25 mg BID	1/8	Grade 3 AST elevation (n=1)*
50 mg BID cont'	4/18	Grade 3 ALT/AST elevation (n=1) Grade 3 colitis (n=1) Grade 3 diarrhea (n=1) Grade 3 pneumonitis (n=1)
50 mg BID int'	1/9	Grade 3 colitis (n=1)
75 mg total daily	1/7	Grade 3 rash (n=1)
100 mg BID†	0/1	–
300 mg BID†	4/7	Grade 4 ALT/AST elevation (n=1) Grade 3 ALT elevation/grade 2 AST elevation (n=1) Grade 3 ALT elevation (n=2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; cont', continuous; DLT, dose-limiting toxicity; int', intermittent.

* Patient experienced with progression of prior extensive liver metastases.

† Epacadostat 100-mg BID and 300-mg BID dose cohorts were not re-explored in this study after protocol amendment to evaluate lower doses of epacadostat.

Supplementary Table S3. Epacadostat Steady-State Pharmacokinetic Parameters (Cycle 1, Day 10)

Parameter	25 mg BID (n=10)*	50 mg BID Cont' (n=13)	50 mg BID Int' (n=7)	300 mg BID* (n=6)
C_{max}, μM	0.3±0.1 (0.3)	0.5±0.2 (0.4)	0.6±0.1 (0.5)	2.6±0.7 (2.6)
t_{max}, h	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–2.2)	2.0 (1.0–2.0)
C_{min}, μM	0.03±0.03 (NC)	0.06±0.05 (NC)	0.06±0.04 (NC)	0.3±0.2 (0.2)
$AUC_{0–12h}$, μM·h	1.1±0.7 (0.9)	1.9±0.8 (1.8)	2.2±0.7 (2.1)	9.5±3.0 (9.2)
$t_{½}$, h	9.1±6.1 (7.4)	7.1±5.5 (5.9)	5.1±2.9 (4.5)	6.2±3.5 (5.4)
CL/F, L/h	68.9±32.1 (61.3)	69.7±29.8 (64.2)	57.6±21.7 (54.4)	77.6±22.2 (74.8)
V_z/F, L/h	891±840 (592)	722±547 (568)	400±229 (342)	709±512 (579)

Values are expressed as mean ± SD (geometric mean) except t_{max}, which is expressed as median (range).
AUC_{0-12h}, area under the concentration time curve from time 0–12 hours after dosing; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CL/F, oral dose clearance; n, number of patients with AUC calculable; NC, not calculated; t_{max}, time to maximum plasma concentration; $t_{½}$, elimination half-life; V_z/F, volume of distribution.
* Two patients from the 50-mg BID cohort received epacadostat 25 mg BID at the time of the pharmacokinetic sample blood draw at the steady-state visit.

Supplementary Table S4. Whole Blood Kynurenine Pharmacodynamic Analysis

Dose	Patients, n	Inhibition Maximal,* %	Average Inhibition (0–6 h),* %	Inhibition Trough,* %
25 mg BID	4	60±15 (40–77)	70±9 (31–79)	48±29 (8–76)
50 mg BID cont’	14	87±12 (58–100)	70±20 (29–99)	46±38 (0–98)
50 mg BID int’	1	86	59	14
75 mg total daily	5	71±36 (7–90)	46±24 (7–69)	6±10 (0–22)
300 mg BID	3	98±2 (96–100)	85±17 (65–97)	67±23 (40–81)

BID, twice daily.

* All values are mean ± SD (range).