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Supplemental Tables for:
Pexidartinib long-term hepatic safety profile in TGCT patients
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Table S1. Summary of non-TGCT studies of pexidartinib

Study	No. of Patients	Population
Safety Data From Studies of Pexidartinib Monotherapy in Cancer Subjects		
PLX108-01 (non-TGCT cohort)	93	Non-TGCT solid tumor
PLX108-03	20	Hodgkin's lymphoma
PLX108-04	38	Glioblastoma multiforme
PLX108-05	90	AML
PLX108-06	6	Prostate cancer
PLX108-13	6	KIT-mutant melanoma
PL3397-A-A103	11	Solid tumors, 1 TGCT subject
Safety Data From Combination Therapy Studies		
PLX108-07 (+ paclitaxel)	74 (68 with pexidartinib)	Solid tumors
PLX108-08 (+ temozolomide, radiotherapy)	65	Glioblastoma multiforme
PLX108-09 (+ vemurafenib)	13	BRAF mutant melanoma
PLX108-14 (+ pembrolizumab)	78	Solid tumors
PLX121-01 (+ PLX9486)	12	Solid tumors
Other Pexidartinib Studies		
Investigator-initiated studies (8 studies)	138	Solid and hematologic tumors

Abbreviations: AML, acute myeloid leukemia; BRAF, murine sarcoma viral oncogene homolog B; KIT, proto-oncogene receptor tyrosine kinase; TGCT, tenosynovial giant cell tumor.

Table S2. Hepatic laboratory abnormalities (≥10% All Grades 1, 2, ≥3) in patients receiving pexidartinib

	ENLIVEN Randomized (1000 mg/d) n = 61			**ENLIVEN Crossover (800 mg/d)[a]** n = 30			**PLX108-01 TGCT Cohort (1000 mg/d)[a]** n = 39			**Other Phase 1 (600 or 800 mg/d)[a]** n = 10			**Pooled N = 140**		
Laboratory Abnormality[b]	**Grade 1 (%)**	**Grade 2 (%)**	**Grade ≥ 3 (%)**	**Grade 1 (%)**	**Grade 2 (%)**	**Grade ≥ 3 (%)**	**Grade 1 (%)**	**Grade 2 (%)**	**Grade ≥ 3 (%)**	**Grade 1 (%)**	**Grade 2 (%)**	**Grade ≥ 3 (%)**	**Grade 1 (%)**	**Grade 2 (%)**	**Grade ≥ 3 (%)**
Increased GGT[c]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	11	11	N/A	N/A	N/A
Decreased albumin	0	3	0	0	0	0	13	3	0	10	0	0	4	2	0
Increased PTT[d]	14	0	0	7	0	0	N/A	N/A	N/A	0	0	0	13	0	0
Increased INR[e]	10	0	0	14	0	0	N/A	N/A	N/A	0	0	0	11	0	0

[a]Pexidartinib starting dose.

[b]Graded per NCI CTCAE v. 4.03

[c]Routinely collected only in study 'PL3397-A-U126'. The number of patients who have ≥1 post-baseline value = 9.

[d]Not collected in study 'PLX108-01'. The number of subjects who have ≥1 baseline and post-baseline value = 65.

[e]Not collected in study 'PLX108-01'. The number of subjects who have ≥1 baseline and post-baseline value = 64.

Abbreviations: GGT, gamma-glutamyl transferase; INR, international normalized ratio; N/A, not applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PTT, partial thromboplastin time; TGCT, tenosynovial giant cell tumor.

Table S3. Serious Hepatic Adverse Reactions in Non-TGCT Patients

Non-TGCT Cases (study)	Pexidartinib Starting Dose (Onset)	Type of Hepatic Injury R value[a]	Outcome
60-year-old female with breast cancer (I-SPY2)	1200 mg/d combined with paclitaxel (Day 18)	Cholestatic hepatotoxicity w/vanishing bile duct syndrome (cholestasis with duct damage and duct loss; severe steatosis) R value <2 = cholestatic	Liver transplant at 20 months
66-year-old female with vaginal melanoma (PLX108-13)	1000 mg/d (Day 21)	Cholestasis with hyperbilirubinemia R value >5 = hepatocellular	Death in context of progressing melanoma and cachexia 3 months after pexidartinib discontinuation
58-year-old female with advanced breast cancer (IST3397-001)	1000 mg/d combined with eribulin (Day 28)	Cholestasis and vanishing bile duct syndrome R value 2.8 = mixed cholestatic	Significant worsening of breast cancer on last PET-CT. Recovered after 5 months
61-year-old female with ovarian cancer (PLX108-07)	600 mg/d combined with paclitaxel (Day 28)	Cholestatic hepatotoxicity (bland cholestasis) R value 3 = mixed cholestatic	Prolonged case. Last ALP at 28 days after onset still 8 × ULN. Died due to underlying cancer progression
73-year-old female with fallopian tube cancer (PLX108-14)	600 mg/d combined with pembrolizumab (Day 28)	Cholestatic hepatotoxicity R value <2 = cholestatic	Progressive fallopian tube cancer. Recovered after 2 months

[a]R value is at the time of initial event.

Abbreviations: ALP, alkaline phosphatase; d, day; PET-CT, positron emission tomography-computed tomography; R, ratio; TGCT, tenosynovial giant cell tumor; ULN, upper limit of normal.

Table S4. Liver test abnormalities meeting criteria for pexidartinib dose modifications

Clinical Parameter	ENLIVEN Randomized (1000 mg/d)[a] *n* = 61	ENLIVEN Crossover (800 mg/d)[a] *n* = 30	PLX108-01 TGCT Cohort (1000 mg/d)[a] *n* = 39	Other Phase 1[b] (600 or 800 mg/d)[a] *n* = 10	Total *N* = 140
Increased ALT and/or AST, *n* (%)					
>3 to 5 × ULN	7 (12)	4 (13)	4 (10)	1 (10)	16 (11)
>5 to 10 × ULN	9 (15)	2 (7)	2 (5)	1 (10)	14 (10)
>10 × ULN	5 (8)	1 (3)	3 (8)	1 (10)	10 (7)
Increased ALP and GGT[c], n (%)					
ALP >2 × ULN	8 (13)	1 (3)	4 (10)	1 (10)	14 (10)
ALP >2 × ULN and GGT >2 × ULN[a]	N/A	N/A	N/A	1 (11)[c]	1 (11)
Increased bilirubin, *n* (%)					
TBIL >ULN to <2 × ULN	4 (7)	1 (3)	3 (8)	0	8 (6)
TBIL >ULN to <2 × ULN or DBIL >ULN to <1.5 × ULN	6 (10)	2 (7)	4 (10)	0	12 (9)
TBIL ≥2 × ULN	3 (5)	0	2 (5)	1 (10)	6 (4)
TBIL ≥2 × ULN or DBIL >1.5 × ULN	7 (12)	1 (3)	6 (15)	1 (10)	15 (11)

[a] Pexidartinib starting dose.

[b] Includes one patient with a single timepoint elevation of TBIL considered unrelated to treatment.

[c] GGT was routinely collected only in study 'PL3397-A-U126'. Calculation for ALP >2 × ULN and GGT >2 × ULN in Other Phase 1 Studies is using only U126 TGCT patients (*n* = 9).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, gamma glutamyl transferase; TBIL, total bilirubin; TGCT, tenosynovial giant cell tumor; ULN, upper limit of normal.

Table S5. Recommended dosage modifications for pexidartinib dependent on adverse reaction [17]

Adverse Reaction	Severity	Pexidartinib Dosage Modifications
Hepatotoxicity		
Increased ALT and/or AST	>3 to 5 × ULN	• Withhold and monitor liver tests weekly. • If AST and ALT are ≤3 × ULN within 4 weeks, resume at reduced dose. • If AST or ALT is not ≤3 × ULN in 4 weeks, permanently discontinue pexidartinib.
	>5 to 10 × ULN	• Withhold and monitor liver tests twice weekly. • If AST and ALT are ≤3 × ULN within 4 weeks, resume at reduced dose. • If AST or ALT is not ≤3 × ULN in 4 weeks, permanently discontinue pexidartinib.
	>10 × ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until AST or ALT is ≤5 × ULN, then weekly until ≤3 times ULN.
Increased ALP[a] and GGT	ALP >2 × ULN with GGT >2 × ULN	• Permanently discontinue pexidartinib. Monitor liver tests twice weekly until ALP is ≤5 × ULN, then weekly until ≤2 × ULN.
Increased bilirubin	TBIL greater than ULN to less than 2 × ULN or DBIL > ULN and <1.5 × ULN	• Withhold and monitor liver tests twice weekly. • If an alternate cause for increased bilirubin is confirmed and bilirubin is < ULN within 4 weeks, resume at reduced dose. • If bilirubin is not < ULN in 4 weeks, permanently discontinue pexidartinib.
	TBIL ≥2 × ULN or DBIL >1.5 × ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until bilirubin is ≤ ULN.
Adverse Reactions or Other Laboratory Abnormalities		
Any	Severe or intolerable	• Withhold until improvement or resolution. • Resume at a reduced dose upon improvement or resolution.

[a] Confirm ALP elevations as liver isozyme fraction.

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, gamma-glutamyl transferase; TBIL, total bilirubin; ULN, upper limit of normal.