Supplemental Appendix to "Results from Phase 1 Extension Study Assessing Pexidartinib Treatment in 6 cohorts with Solid Tumors including TGCT, and Abnormal CSF1 Transcripts in TGCT"

Tenosynovial Giant Cell Tumor Extension Cohort Study

In the part 2 Extension phase of this study, 6 cohorts comprising patients with 1) mucoepidermal carcinoma (MEC) of the salivary gland, 2) tenosynovial giant cell tumor (TGCT), 3) gastrointestinal stromal tumor (GIST), 4) anaplastic thyroid carcinoma (ATC), 5) solid tumors with documented malignant pleural or peritoneal effusions, and 6) miscellaneous tumor types were enrolled. These histological types were selected based on available scientific evidence supporting the involvement of CSF1/KIT signaling in tumorigenesis. More specifically, tumor-associated macrophage (TAM) count is strongly associated with tumor grade and stage of MEC of the salivary gland (1). In addition, a dose-escalation patient with MEC of the salivary gland had a pronounced and confirmed partial response (PR) during treatment with pexidartinib (2). TGCT is characterized by a proliferation of synoviocytes that attract histiocytes, hemosiderin-laden macrophages, and other inflammatory cells via a CSF-1-mediated landscaping effect (3). KIT is the major oncogenic driver of GIST. Pexidartinib is active against both primary (exon 9 and 11) and secondary (exon 13 and 14) mutants resistant to imatinib (4). Recent work has highlighted the role of TAMs in the progression of thyroid cancers; ATC, in particular, harbors abundant TAM infiltration (5). Malignant pleural effusions are associated with alternatively activated TAMs(6). The aforementioned dose-escalation patient with MEC of the salivary gland had a profound decrease in her pleural effusions.

Eligibility Criteria

Key eligibility criteria for the extension phase included measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and the ability to meet the following disease-specific criteria: 1) for advanced or recurrent MEC of the salivary gland, patients could not be candidates for curative surgery or radiotherapy; 2) for TGCT, patients had to have a histologically confirmed diagnosis of inoperable progressive or relapsing TGCT, or resectable tumor requiring extensive surgery, as well as demonstrated progressive disease in the last 12 months; 3) for GIST, patients had to have progressed on previous therapy with imatinib and sunitinib, and patients with known platelet-derived growth factor receptor (PDGFR) mutations were excluded, but mutation testing was not required for study entry; 4) for ATC, patients had to have histologically or cytologically diagnosed advanced ATC; 5) for metastatic solid tumors with documented malignant pleural, pericardial, and/or peritoneal effusions, patients must not have been receiving specific therapy for the effusion (other than periodic drainage by needle) or have an indwelling drain; 6) other solid tumor types could be included in the miscellaneous cohort, provided there was a clear scientific rationale for treatment with pexidartinib and upon approval by the Medical Monitor.

Statistical Analysis

For each extension cohort, we planned to test the hypothesis of no clinical benefit against the hypothesis that at least 30% of patients achieved a clinical benefit. With a sample size of 10 patients per group, we would have 85% power at a 0·10 significance level to declare pexidartinib worthy of further study if at least 2 patients achieved clinical benefit. Clinical benefit was defined as either a complete response (CR) or PR, or progression-free survival (PFS) for at least

6 months. If fewer than 2 patients achieved clinical benefit within a disease group, pexidartinib would not be further studied within that disease. Depending on the response in the 10-patient cohort, the sample size for a specific cohort could be increased by 30 additional patients (to approximately 40 patients total) if those data were determined to be necessary to design additional studies in that indication.

For the miscellaneous extension cohort, a sample size of 20 patients was used, as the tumor types were anticipated to be rare and the group heterogeneous. The sample size was not determined by any statistical power considerations. Accordingly, the potential clinical benefit was evaluated on a per-patient basis. If 1 or more PRs were observed in patients in the miscellaneous cohort, up to 20 total additional patients could be recruited if needed to profile the tumor responses in the specific (or related) indications.

For the extension phase of the study, the safety set included all patients who receive at least 1 dose of study medication, regardless of their duration of treatment. For tumor response analysis, patients were included if a baseline scan and at least 1 post-treatment scan were evaluable by RECIST 1.1 or the tumor volume score (TVS); exact binomial 95% CIs (two-sided) were provided for each category response. The tumor response rate of pexidartinib was compared with that of imatinib using χ square test with Yates correction. A noncompartmental method of analysis was used to analyze the plasma concentrations of pexidartinib. Pharmacokinetic parameters were estimated using actual sampling times relative to study drug administration. No formal statistical analysis of data from the Patient Reported Outcome (PRO) instruments was performed.

Tumor Volume Score

For patients with TGCT, tumor response was also assessed using a new TVS specifically developed for this disease. To determine the TVS, MRI data were analyzed centrally by 2 independent radiologists for tumor size; the TVS was then calculated as a percentage of the entire synovial cavity or tendon sheath. Radiologists performing TVS were blinded to visit order, whereas investigators performing RECIST were aware of visit order.

Patient-Reported Outcomes

The PRO instrument contains an 11-point scale for patients to: 1) rate their symptoms—e.g., for pain, from 0 (no pain) to 10 (worst pain imaginable)—and 2) indicate which symptoms improved with pexidartinib treatment.

Safety

Safety and tolerability were assessed by adverse events, laboratory assessments (hematology, serum chemistry, and urinalysis), physical examinations, vital signs, 12-lead electrocardiograms, and Eastern Cooperative Oncology Group (ECOG) performance status.

Supplementary Table S1. Treatment-Related Treatment-Emergent Adverse Events (>10% Incidence in Either Patient Group)—Safety Population

	Treatment-Related TEAEs				
	Patients with TGCT (N = 39)		Non-TGCT Patients[a] (N = 52)		All Patients (N = 91)
Preferred Term, n (%)	**Overall**	**≥ Grade 3**	**Overall**	**≥ Grade 3**	**Overall**
Patients Reporting at least 1 AE	39 (100%)	14 (36%)	45 (87%)	18 (35%)	84 (92%)
Fatigue	29 (74%)	1 (3%)	21 (40%)	3 (6%)	50 (55%)
Hair color changes	28 (72%)	0	16 (31%)	0	44 (48%)
Nausea	22 (56%)	0	17 (33%)	0	39 (43%)
Decreased appetite	8 (21%)	0	20 (39%)	1 (2%)	28 (31%)
Dysgeusia	14 (36%)	0	6 (12%)	0	20 (22%)
Periorbital oedema	15 (39%)	0	3 (6%)	0	18 (20%)
Diarrhea	9 (23%)	1 (3%)	9 (17%)	0	18 (20%)
Vomiting	8 (21%)	0	10 (19%)	0	18 (20%)
Pruritus	12 (31%)	0	3 (6%)	0	15 (17%)
Rash	9 (23%)	0	4 (8%)	0	13 (14%)
Hypophosphatemia	9 (23%)	4 (10%)	3 (6%)	2 (4%)	12 (13%)
Insomnia	4 (10%)	0	7 (14%)	1 (2%)	11 (12%)
Aspartate aminotransferase increased	7 (18%)	3 (8%)	4 (8%)	2 (4%)	11 (12%)
Alanine aminotransferase increased	7 (18%)	4 (10%)	3 (6%)	1 (2%)	10 (11%)
Anemia	6 (15%)	1 (3%)	5 (10%)	0	11 (12%)
Edema peripheral	7 (18%)	0	2 (4%)	0	9 (10%)
Headache	8 (21%)	0	1 (2%)	0	9 (10%)
Face edema	6 (15%)	0	2 (4%)	0	8 (9%)
Rash maculo-papular	7 (18%)	0	1 (2%)	0	8 (9%)
Skin hypopigmentation	6 (15%)	0	2 (4%)	0	8 (9%)
Cognitive disorder	7 (18%)	0	0	0	7 (8%)
Mucosal inflammation	5 (13%)	0	2 (4%)	0	7 (8%)
Dry mouth	4 (10%)	0	2 (4%)	0	6 (7%)
Dry skin	5 (13%)	0	0	0	5 (6%)
Blood alkaline phosphatase increased	4 (10%)	0	1 (2%)	1 (2%)	5 (6%)
Hypertension	4 (10%)	0	1 (2%)	0	5 (6%)
Arthralgia	4 (10%)	0	0	0	4 (4%)
Dizziness	4 (10%)	0	0	0	4 (4%)
Dyspepsia	4 (10%)	0	0	0	4 (4%)
Gastroesophageal Reflux Disease	4 (10%)	0	0	0	4 (4%)
Memory impairment	4 (10%)	0	0	0	4 (4%)
Weight increased	4 (10%)	0	0	0	4 (4%)

Note: At each level of summation (Overall, ≥ Grade 3, and Preferred Term), patients reporting more than 1 AE are counted only once.
Note:Percentages are based on the number of patients in each group, (i.e., N, unless otherwise specified).
Abbreviations: AE = adverse event; ATC = anaplastic thyroid carcinoma; GIST = gastrointestinal stromal tumor; MEC = mucoepidermal carcinoma; TEAE = treatment-emergent adverse event; TGCT = tenosynovial giant cell tumor.

[a]Non-TGCT Patients = The 5 non-TGCT cohorts include the following tumor types: ATC (n = 9); GIST (n = 11); malignant effusion (n = 8); MEC (n = 4); and other tumor types (n = 20).

Supplementary Table S2. Treatment-Emergent Adverse Events (Reported in ≥ 20% of Patients in Either Patient Group)

Preferred Term, n (%)	TEAEs		
	Patients with TGCT (N = 39)	Non-TGCT Patients[a] (N = 52)	All Patients (N = 91)
Fatigue	36 (92%)	32 (62%)	68 (75%)
Nausea	26 (67%)	22 (42%)	48 (53%)
Hair color changes	28 (72%)	16 (31%)	44 (48%)
Decreased appetite	9 (23%)	21 (40%)	30 (33%)
Diarrhea	14 (36%)	13 (25%)	27 (30%)
Constipation	11 (28%)	16 (31%)	27 (30%)
Arthralgia	24 (62%)	5 (10%)	29 (32%)
Vomiting	12 (31%)	14 (27%)	26 (29%)
Dysgeusia	14 (36%)	8 (15%)	22 (24%)
Edema peripheral	14 (36%)	8 (15%)	22 (24%)
Periorbital edema	15 (39%)	5 (10%)	20 (22%)
Pruritus	14 (36%)	6 (12%)	20 (22%)
Headache	13 (33%)	6 (12%)	19 (21%)
Rash	12 (31%)	5 (10%)	17 (19%)
Hypophosphatemia	9 (23%)	6 (12%)	15 (17%)
Cough	8 (21%)	7 (14%)	15 (17%)
Dyspnea	2 (5%)	13 (25%)	15 (17%)
Dizziness	11 (28%)	4 (8%)	15 (17%)
Pain in extremity	10 (26%)	4 (8%)	14 (15%)
Hypertension	8 (21%)	5 (10%)	13 (14%)
Rash maculo-papular	8 (21%)	1 (2%)	9 (10%)
Erythema	8 (21%)	0	8 (9%)

Abbreviations: ATC = anaplastic thyroid carcinoma; GIST = gastrointestinal stromal tumor; MEC = mucoepidermal carcinoma; TEAE = treatment-emergent adverse event; TGCT = tenosynovial giant cell tumor.

[a]Non-TGCT Patients = The 5 non-TGCT cohorts include the following tumor types: anaplastic thyroid carcinoma (ATC) (n = 9); gastrointestinal stromal tumor (GIST) (n = 11); malignant effusion (n = 8); mucoepidermal carcinoma (MEC) (n = 4); and other tumor types (n = 20).

Supplementary Table S3. Non-TGCT Patients Who Received Treatment for More Than 6 Months

Tumor Category	Number of Treatment Days	Duration of Response[a] (Days)	Progression-Free Survival[b] (Days)	Best Overall Tumor Response[c]
MEC	350	—	324	SD
GIST	345	—	344	SD
Malignant Effusion[d]	263	—	237	SD
Other Tumor Type[e]	187–494	115	142–504	SD, PR

CR = complete response; GIST = gastrointestinal stromal tumor; Malignant Effusion = solid tumors with documented malignant pleural or peritoneal effusions; MEC = mucoepidermal carcinoma; PR = partial response; SD = stable disease; TGCT = tenosynovial giant cell tumor.

[a]Duration of Response is defined for patients with a response to therapy as the number of days from the date of initial response (CR or PR) to the date of first documented disease progression or death, whichever occurs first. Patients without a post-baseline tumor response evaluation have their event censored on the first date of study drug with a duration of 1 day.
[b]Progression-Free Survival is defined as the number of days from the first day of treatment to the first documented disease progression or date of death, whichever occurs first.
[c]Best overall tumor response is derived using RECIST 1.1 criteria. The minimum interval for confirmation of CR and PR is 4 weeks. The minimum interval for confirmation of SD for the PVNS cohort is 22 weeks for other cohorts is 8 weeks.
[d]Mesothelioma
[e]n = 4; 3 patients with SD (Pancreatic neuroendocrine tumor, Familial Schwannomatosis, Neurofibromatosis) and 1 with PR (Erdheim-Chester disease). Values provided as ranges where applicable.

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