#401 A Phase 1/2 Dose Escalation and Expansion Study of Cabiralizumab (FPA008), an anti-CSF1R antibody, in Tenosynovial Giant Cell Tumor (TGCT, Diffuse Pigmented Villonodular Synovitis D-PVNS)

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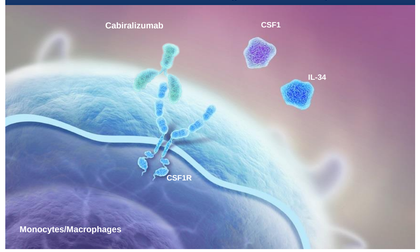
PVNS Background

- Tenosynovial giant-cell tumor is a proliferative, neoplastic joint disease that presents as single nodule (local) or multiple nodules (diffuse-type; also known as PVNS).
- In PVNS, overexpression of colony stimulating factor 1 (CSF1) by a minority of cells leads to recruitment of CSF1 receptor (CSF1R)-expressing cells such as monocytes and macrophages that make up the bulk of the tumor mass.
  - CSF1R signaling plays a fundamental role in the differentiation, maintenance, and function of monocytes and macrophages.[1]
- PVNS is a chronic disease associated with significant pain and debilitation.
- Currently, no therapies are approved for the treatment of PVNS.

Cabiralizumab (FPA008) Antibody Inhibits CSF1R and Blocks the Activation and Survival of Macrophages and Monocytes

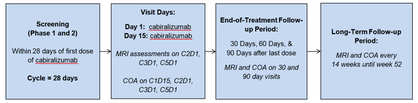


Cabiralizumab Mechanism of Action

Study Design

- This Phase 1/2 clinical trial is an open-label, dose escalation and dose expansion study designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of cabiralizumab in patients with PVNS.
- Phase 1 consisted of a 3+3 dose escalation at dose levels of 1, 2, and 4 mg/kg given intravenously (IV) every two weeks (Q2W).
- Phase 2 is ongoing and as of 07Mar2017 had enrolled 29 patients at the Recommended Dose (RD) of 4 mg/kg Q2W.
- Cabiralizumab inhibits Kupffer cells, a known class effect of anti-CSF1Rs, leading to decreased clearance of creatine kinase (CK).
  - In 3 of the first 11 patients enrolled at the RD (in Phase 1 and 2), asymptomatic elevations in serum CK led to protocol-mandated discontinuation of study drug.
  - The protocol was amended to allow for continued treatment with cabiralizumab despite asymptomatic CK elevations and an additional 21 patients were enrolled at 4 mg/kg between 09Nov2016 and 07Mar2017.

Study Schema



MRI = Magnetic Resonance Imaging
COA = Clinical Outcomes Assessments

- Maximum number of doses is 12 (approximately 160 days).
- Efficacy evaluation by MRI and COA continue up to approximately 12 months in the absence of radiographic disease progression, even if drug is discontinued.

Key Eligibility Criteria

- Inclusion
  - Histologically confirmed diagnosis of inoperable PVNS/dt-TGCT or potentially resectable tumor that would result in unacceptable functional loss or morbidity
  - Measurable PVNS/dt-TGCT by RECIST 1.1 on MRI
  - Age ≥18 years
  - ECOG performance status ≤1
- Exclusion
  - Prior anti-CSF1R antibody
  - Prior PLX3397 unless discontinued for intolerance; prior imatinib or nilotinib allowed
  - Any condition known to elevate serum CK levels
  - NYHA > Class 2
  - Metastatic PVNS/dt-TGCT

Study Endpoints

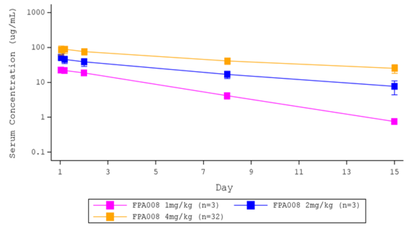
- Primary
  - Phase 1: Incidence of Grade 3 and Grade 4 adverse events (AEs) and clinical laboratory abnormalities defined as DLTs
    - DLTs were defined as any Grade ≥ 3 related AE that occurred during the first 28 days (1 cycle) of treatment, except pre-specified changes in AST, ALT, and/or CK.
  - Phase 2: Objective responses per RECIST v1.1
    - Efficacy evaluable population was defined as patients with at least 1 post-baseline MRI assessment, per Investigator assessment.
- Key Secondary
  - PK parameters: AUC, C_{max}, C_{min}, CL, V_{ss}
  - Incidence of AEs
- Key Exploratory
  - PD parameters: level of non-classical monocytes in peripheral blood
  - Clinical Outcomes Assessments (COA) as measured by Ogilvie-Harris score comprising four Investigator-assessed parameters of pain, synovitis, functional status and stiffness
    - Each parameter is measured on a scale of 0 to 3, with 3 being the best score.
    - The Total Score represents a composite of each individual parameter (0-12).
    - Study protocol did not require patients to be symptomatic prior to enrollment.

Demographics and Prior Tyrosine Kinase Inhibitor Therapy of All Enrolled Patients (N=38)

	Phase 1 (N = 9)	Phase 2 (N = 29)
Age		
Median	35	37
Range	24 – 67	20 – 75
Gender		
Male	2 (22%)	8 (28%)
Female	7 (78%)	21 (72%)
Race		
White	7 (78%)	17 (59%)
Asian	1 (11%)	5 (17%)
Other	0	7 (24%)
Prior Tyrosine Kinase Inhibitor Therapy		
Imatinib	2 (22%)	5 (17%)
Nilotinib	1 (11%)	0

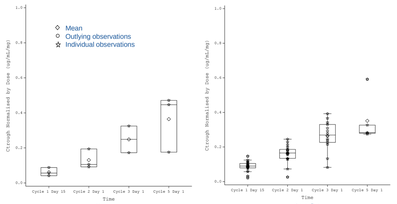
PK of Cabiralizumab Has Non-Linear Clearance and Supports Q2W or Less Frequent Dosing

Figure 1: PK following first dose



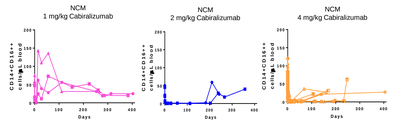
Accumulation Was Observed with Q2W Dosing at ≥ 2 mg/kg

Figure 2: Dose Normalized C_{trough} for Different Cycles



Maximum Reduction of Nonclassical CD16⁺ Monocytes was Observed at Doses ≥ 2 mg/kg Q2W

Figure 3: Nonclassical Monocyte (NCM) Concentrations at 1, 2, and 4 mg/kg



- 4 mg/kg was selected as RD based on:
  - Maximum reduction of NCM between dose intervals
  - No DLT
  - Early signal of clinical efficacy
- Patients that show an increase in non-classical monocytes after maximum reduction discontinued study drug prior to increase

RESULTS

Safety of All Treated Patients (N=38)

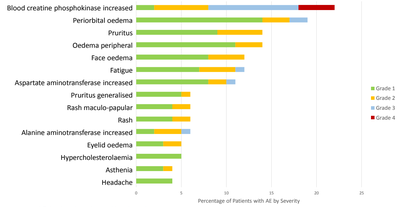
- No DLTs observed.
- Treatment-related serious adverse events (SAEs) were reported in 4 patients:
  - Grade 2 hypertension
  - Grade 2 myocarditis based on symptoms and MRI. No reduction in ejection fraction by echocardiogram. Event resolved without sequelae.
  - Grade 3 viral infection
  - Grade 3 pyrexia with Grade 4 increase in transaminases. Also associated with a concomitant increase in bilirubin and a right cerebellar infarct that resolved with high dose corticosteroids.
- AEs leading to treatment discontinuation occurred in 11 patients – all at 4 mg/kg.

Adverse Event	Grade 1-2 N (%)	Grade 3-4 N (%)
Total	**6 (16)**	**5 (13)**
Skin and Subcutaneous Tissue Disorders		
Skin disorder	2 (5)	0
Urticaria	0	1 (3)
Pain of skin	0	1 (3)
Rash pruritic	0	1 (3)
Eye Disorders		
Periorbital oedema	2 (5)	0
General Disorders and Administration Site Conditions		
Face oedema	3 (8)	0
Oedema peripheral	1 (3)	0
Investigations		
Blood creatine phosphokinase increased	0	3 (8)
Transaminases increased	0	1 (3)
Cardiac Disorders		
Myocarditis[1]	1 (3)	0
Musculoskeletal and Connective Tissue Disorders		
Rhabdomyolysis[2]	0	1 (3)

1 – Resolved after treatment discontinuation; did not result in ejection fraction decrease
2 – Based on CK elevation, not associated with renal dysfunction or myoglobinuria

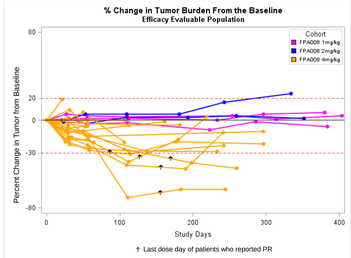
Most Treatment-Related AEs were Grades 1 and 2

Table 1: Treatment-related Adverse Events in ≥ 10% of All Treated Patients (N = 38)*



* Subject incidence by worst toxicity grade

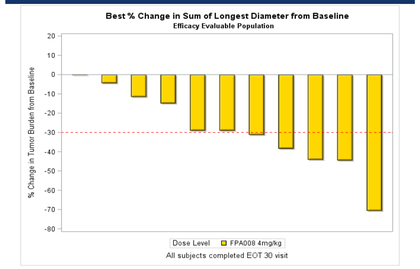
5 of 11 Efficacy Evaluable* Patients at the 4 mg/kg Dose Enrolled Prior to the Amendment Had a PR (4 Confirmed)



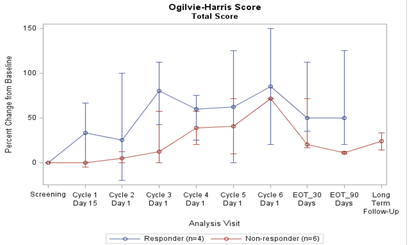
*Efficacy Evaluable defined as patients with at least 1 post-baseline MRI assessment, per Investigator assessment

- No responses observed at the 1 mg/kg and 2 mg/kg dose levels (n=6)
- 5 PRs (4 confirmed) were observed at the 4 mg/kg dose level (n=11)
- Median duration of treatment for the patients at 4mg/kg was 18 weeks (range 0.1 to 26 weeks)
- 12 additional patients enrolled after the amendment were considered efficacy evaluable with evidence of early shrinkage in tumor, but too early to assess overall response
  - Median duration of treatment for these 12 patients is short at 5.4 weeks (range 4 to 14 weeks) with no PRs reported as of 07March 2017.

Most Patients Enrolled at the 4 mg/kg Dose Prior to the Amendment Experienced Tumor Reduction

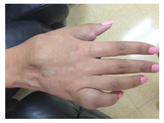


Improvement in Median Ogilvie-Harris Composite Score Was Reported in Responders and Non-Responders (per RECIST v1.1 on MRI)

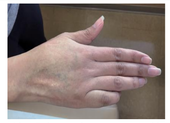


10 of 11 Efficacy evaluable patients including 4 of 5 patients with PR had baseline Ogilvie-Harris score

29-year-old Female with PVNS of Right Hand Demonstrating Dose-Related Clinical Improvement



During initial treatment with cabiralizumab at 1 mg/kg Q2W



After 5 doses of retreatment* with cabiralizumab at 4 mg/kg Q2W

*Up to 5 patients who received either the 1 or 2 mg/kg dose in Phase 1 were eligible for re-treatment at the RD in phase 2.

Patient With 10% Tumor Reduction by MRI Showed No Viable Tumor Cells by Pathology After 8 Doses

Figure 4: Pre-treatment MRI[2]

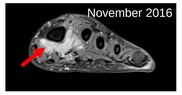


Figure 5: Post-treatment MRI[2]

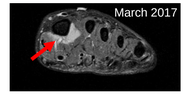


Figure 6: Pre-treatment biopsy (H&E 400x)[3]

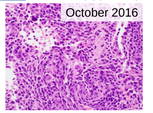
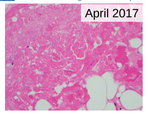


Figure 7: Post-treatment surgical resection (H&E 400x)[3]



- 41-year-old female patient had a pre-treatment biopsy approximately one month prior to receiving first study treatment. Pathology indicated a cellular proliferation composed of epithelioid histiocytic cells, admixed with lymphocytes and scattered multinucleated giant cells consistent with tenosynovial giant-cell tumor (diffuse-type) (Figure 6). Baseline MRI showed single target lesion in left foot measuring 50 mm in the longest dimension (Figure 4).
- Patient received no PVNS-specific treatment between pre-treatment biopsy and start of cabiralizumab.
- Patient experienced 10% reduction in tumor size by MRI after 8 doses of cabiralizumab (Figure 5). She subsequently was able to undergo a complete resection of the remaining mass in which no viable tumor cells were observed (Figure 7). Pathology indicated presence of amorphous eosinophilic material and what appeared to be necrotic "ghost" cells.

Conclusions

- PK and PD of cabiralizumab support dosing at 4 mg/kg Q2W or less frequently
- No DLTs were observed at doses up to 4mg/kg Q2W
- Most frequently reported AEs of periorbital and eyelid edema, rash and pruritus are similar to reports with other agents in this class[4]
  - 3 out of 11 patients enrolled prior to the protocol amendment discontinued drug due to asymptomatic laboratory elevations of CK
- Cabiralizumab demonstrates clinical benefit in patients with PVNS at 4mg/kg Q2W
  - Most patients enrolled at the 4 mg/kg dose prior to the amendment experienced tumor reduction
  - 5 out of 11 patients had a radiographic response (4 confirmed)
  - Improvement in median Ogilvie-Harris composite score was reported in both responders and non-responders (per RECIST v1.1 on MRI)

References and Acknowledgements

1. Hamilton, JA and Achuthan A. Colony Stimulating Factors and Myeloid Cell Biology in Health and Disease. *Trends in Immunology.* 2013; 34(2): 81-89.
2. MRI images courtesy of Dr. Andrew Thierry, Beverly Hill Cancer Center, Los Angeles, CA
3. Pathology images courtesy of Dr. Scott D Nelson, UCLA Santa Monica and Orthopaedic Hospital, Santa Monica, CA
4. Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R Inhibition with Emactuzumab in Locally Advanced Diffuse-Type Tenosynovial Giant Cell Tumours of the Soft Tissue: a Dose-Escalation and Dose-Expansion Phase 1 Study. *Lancet Oncology.* 2015; 16(8): 949-56.

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