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A Phase I study of TGF-β inhibitor, Vactosertib, in Combination with Imatinib in Patients with Advanced Desmoid Tumor (Aggressive Fibromatosis)

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BACKGROUND

- Desmoid tumor (aggressive fibromatosis) is fibroproliferative neoplasm arising from deep connective tissues. TCGA pan-cancer analysis revealed high expression TGF-β responsive signature in desmoid tumor
- Vactosertib (TEW-7197), a highly selective and potent inhibitor of TGF-β receptor type 1
- Regarding the combination, Vactosertib and imatinib demonstrated synergistic effect in vitro and xenograft model. Compared to imatinib alone, administration of imatinib plus vactosertib in mice significantly delayed disease relapse and prolonged survival. Collectively, these results indicate that vactosertib plus imatinib may be a promising candidate for a new therapeutic strategy
- This phase I study assessed the safety, tolerability, and pharmacokinetics of the TGF-β inhibitor, vactosertib in combination with imatinib for desmoid tumor

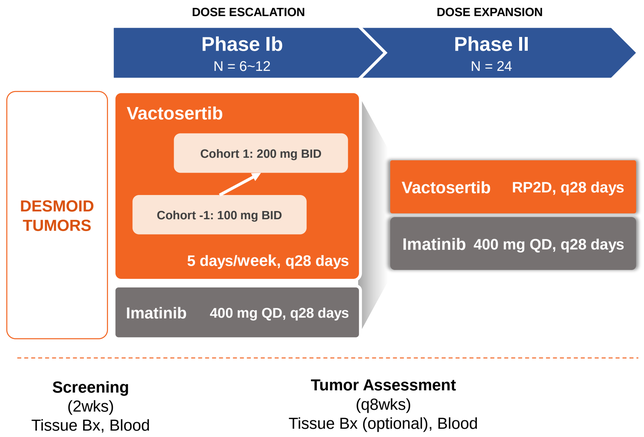
OBJECTIVES

Study Endpoints

- **Primary endpoint:**
  - ✓Phase I: To evaluate the safety and tolerability of vactosertib in combination with imatinib including estimation of the maximum tolerated dose (MTD) and/or characterization of DLTs
  - ✓Phase II : To evaluate antitumor activity : progression free rate at 16 weeks
- **Secondary endpoints:**
  - ✓To characterize the pharmacokinetics (PK) of vactosertib in combination with imatinib
    - Plasma concentration of vactosertib at specified time points for the following parameters: Area under the concentration time-curve (AUC), Maximum serum concentration (Cmax), Minimum serum concentration (Cmin), Clearance (CL), volume of distribution at steady state (Vss); Other parameters such as accumulation ratio, half-life, and dose proportionality may also be calculated
  - ✓Tumor response was assessed per RECIST v1.1
  - ✓Safety profile with CTCAE v4.03
- **Exploratory endpoints:**
  - ✓Tumor biomarkers including TGF-β signature and epithelial-to-mesenchymal transition (EMT) in serial tumor samples

STUDY DESIGN

This is a phase I/II, open-label, non-randomized, multicentre study to evaluate the clinical activity of vactosertib plus imatinib in desmoid tumor



INCLUSION/EXCLUSION CRITERIA

- **Inclusion criteria**
  - ✓Histologically confirmed desmoid tumor (aggressive fibromatosis) not available for local treatment (surgical resection or radiation therapy)
  - ✓Measurable lesion (RECIST 1.1)
  - ✓Eastern Cooperative Oncology Group performance status of 0-1
  - ✓Able to newly acquired tumor biopsy during screening (preferred) or provide an available tumor sample taken ≤3 years prior to screening
- **Exclusion criteria**
  - ✓Previous TGF-β inhibitor exposure
  - ✓Patient who has had chemotherapy, radiotherapy, or biological therapy within 2 weeks
  - ✓Unresolved chronic toxicity greater than CTC grade 2
  - ✓Uncontrolled intercurrent illness
  - ✓Uncontrolled or active CNS metastasis and/or carcinomatous meningitis

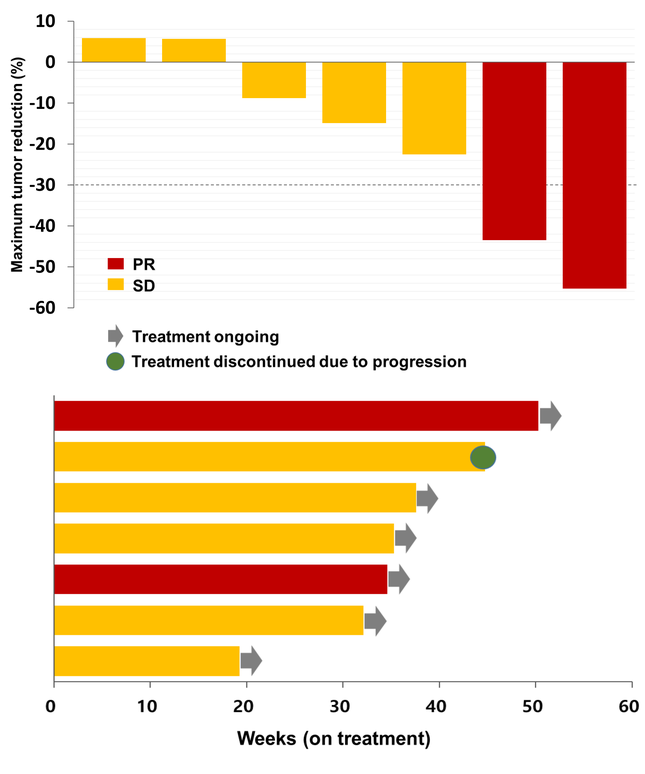
RESULTS

Baseline Characteristics

		Cohort -1 (n=4)	Cohort 1 (n=3)	Overall (n=7)
Age, years, median (range)		34 (32-59)	33 (21-35)	33 (21-59)
Sex, n (%)	Male	2 (50)	1 (33)	3 (42.9)
	Female	2 (50)	2 (67)	4 (57.1)
No. of Prior Anticancer Therapies (median range)		1 (0-2)	2 (0-2)	1 (0-2)
ECOG Performance Status, n (%)	0	2 (50)	3 (100)	5 (71.4)
	1	2 (50)	-	2 (28.6)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; n = number of subjects

Efficacy



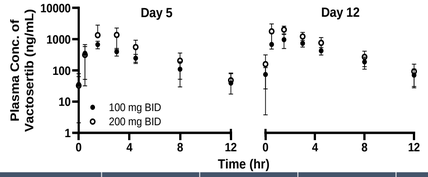
Safety

- There was no dose limiting toxicity (DLT) in cohort -1 (100 mg) & cohort 1 (200 mg) BID vactosertib in combination with imatinib (400 mg QD)
- No cardiac toxicity was observed during the study
- Treatment-related adverse events (TRAE) were myalgia (57.1%), diarrhea (57.1%), fatigue (42.8%), and stomatitis (28.5%) with mostly grade 1 (data cut off Feb 28, 2020)

Event, n (%)	Cohort -1 (n=4)		Cohort 1 (n=3)		Overall (n=7)
	Grade 1	Grade 2	Grade 1	Grade 2	
Myalgia	1 (25%)	1 (25%)	2 (66.7%)		4 (57.1%)
Diarrhea	2 (50%)		2 (66.7%)		4 (57.1%)
Fatigue	2 (50%)		1 (33.3%)		3 (42.8%)
Stomatitis	2 (50%)				2 (28.5%)
Creatinine elevation	1 (25%)		1 (33.3%)		2 (28.5%)
Anemia	2 (50%)				2 (28.5%)
Edema	1 (25%)		1 (33.3%)		2 (28.5%)
Nausea			2 (66.7%)		2 (28.5%)
Rash	1 (25%)				1 (14.3%)
Headache	1 (25%)				1 (14.3%)
General weakness	1 (25%)				1 (14.3%)

Pharmacokinetics of Vactosertib

- The pharmacokinetics of vactosertib were examined during vactosertib monotherapy (Day 5) and after vactosertib in combination with imatinib (Day 12)



		$AUC_{0\text{-}inf}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)
100 mg BID	Day 5	3002 ± 1304	672 ± 181	1.5 [1.5-1.5]	2.5 ± 1.1
	Day 12	5031 ± 1971	1129 ± 618	1.5 [0.5-3.0]	2.8 ± 0.6
200 mg BID	Day 5	6361 ± 4024	1973 ± 1011	1.5 [1.5-3.0]	2.2 ± 0.2
	Day 12	9194 ± 2615	2397 ± 571	1.5 [0.5-1.5]	2.5 ± 0.8

SUMMARY & CONCLUSION

- The combination of vactosertib plus imatinib was well tolerated and showed promising antitumor activity
- Recommended phase 2 dose of vactosertib was defined as 200 mg BID in combination with 400 mg QD of imatinib
- The ongoing phase 2 study is further evaluating efficacy and safety of vactosertib in combination with imatinib for desmoid tumor

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References

[1]Hugo et al., Cell. 2016;165(1):35-44.

Vactosertib was provided by MedPacto, Inc.