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Two Phase I studies of PTI-188, a radiolabeled murine anti-melanin antibody, in patients with metastatic melanoma (MM)

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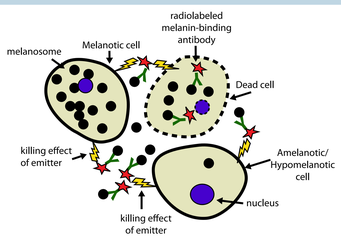
INTRODUCTION

- Melanomas are rapidly growing tumors with abundant cell turnover, ischemic necrosis and disintegration that give rise to the release of melanin pigment into the extracellular milieu. The extracellular melanin pigment can thus be targeted by melanin-binding antibodies radiolabeled with high energy beta particle emitting radionuclides that are capable of destroying the surrounding tumor tissue. Intracellular pigment that resides in intact cells is not targeted by the melanin-specific antibodies.
- PTI-188 is an anti-melanin murine immunoglobulin M monoclonal antibody radiolabeled with the high energy beta-emitter 188-Rhenium.
- In preclinical xenograft models, PTI-188 has demonstrated inhibition of tumor growth and prolonged survival with no cross-reactivity with viable (intact), melanin containing cells.
- In these two Phase I studies (Ia and Ib), a total of 20 patients with advanced metastatic melanoma (Stage IIIC and IV) were enrolled, 13 in study Phase Ia and 7 in study Phase Ib.

Figure 1. Schematic of PTI-188 "Cross-Fire" Effect When Targeting Extracellular Melanin



OBJECTIVES

- Assess the safety and tolerability of PTI-188 in patients with metastatic melanoma
- Determine the pharmacokinetic profile, biodistribution and dosimetry of PTI-188
- Evaluate the preliminary efficacy of a single intravenous dose of PTI-188 (RECIST)
- Determine the human anti-murine antibody response (HAMA) associated with a single PTI-188 administration

Phase Ia-specific objectives

- Assess the need to predose with unlabeled antibody; and, if needed,
- Identify the appropriate dose of unlabeled PTI-188 to administer prior to the administration of radiolabeled PTI-188 to achieve optimal tumor targeting

Phase Ib-specific objectives

- Determine the maximum tolerated dose (MTD) of PTI-188
- Identify dose-limiting toxicities (DLT) associated with PTI-188 administration

METHODS

Study Design

PHASE IA

- Phase I, non-randomized, open-label, single-dose, 6 week, cohort dose-escalation study
- Incremental increases in the amount of unlabeled antibody administered by cohort (3pts/cohort) at 0, 10, 20 & 50 mg prior to the administration of a fixed radiolabeled dose of PTI-188 at approximately 10 mCi / 10 mg

PHASE IB

- Phase I, non-randomized, open-label, single-dose, "3 + 3" dose-escalation study, following patients until disease progression
- Cohort 1 dose (activity/antibody) ranged from 20 – 30 mCi / 12 - 17 mg and Cohort 2 from 40 – 60 mCi / 44 - 48 mg

Key Eligibility Criteria for Patients

- Histologically or clinically confirmed Stage IIIC (unresectable) or Stage IV MM who progressed after chemotherapy, immunotherapy, radiotherapy or surgery
- Negative HAMA at screening
- At least 4 weeks since prior chemotherapy or radiation therapy and at least 1 week since IL-2 therapy with resolution of all associated adverse events from the previous therapeutic agents
- Adequate organ and marrow function defined by screening laboratory tests
- Confirmed absence of brain metastases by MRI or CT

Assessments

- Tumor response was assessed via Computed Tomography (CT) scan utilizing the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 at 2 and 6 weeks post-infusion and every 8 weeks thereafter in the Phase Ib study.
- Tumor targeting was observed by whole body planar scintigraphy and Single Photon Emission Tomography/Computed Tomography (SPECT/CT) immediately after infusion up to 72 hours.
- Dosimetry was assessed by whole body planar scintigraphy and exposure for critical organs calculated by OLINDA/EXM.
- 18F-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) imaging was performed prior to infusion and approximately 4 weeks post-infusion.
- Blood samples were collected for safety laboratory tests, pharmacokinetic analysis, radioactivity determination and HAMA.

RESULTS

- Thirteen patients were enrolled into the four cohorts of the Phase Ia study.
- Seven patients were enrolled into the initial two cohorts of the Phase Ib study. The MTD was not reached.

Table 1. Demographics and Baseline Characteristics

	Phase Ia (N=13)	Phase Ib (N=7)
Age, mean, years (min, max)	64.2 (45, 83)	64.7 (54, 80)
Sex		
Male	10 (76.9%)	5 (71.4%)
Female	3 (23.1%)	2 (28.6%)
Race		
Caucasian	13 (100%)	7 (100%)
Stage		
Stage IIIC (unresectable)	0 (0.0%)	1 (14.3%)
Stage IV	13 (100%)	6 (85.7%)
Prior Therapies		
Chemotherapy	11 (84.6%)	3 (42.9%)
Immunotherapy	9 (69.2%)	6 (85.7%)
Radiotherapy	3 (23.1%)	4 (57.1%)
Surgery	13 (100%)	7 (100%)

Table 2. Summary of Patient Status

Patient Disposition			
	Phase Ia (N=13)	**Phase Ib (N=7)**	
Completed 6 Weeks of Study	12 (92.3%)	3 (42.9%)	
Reason for Withdrawal	**Prior to 6 Weeks**	**Prior to 6 Weeks**	**Post 6 Weeks**
Progressive Disease	0 (0.0%)	3 (42.9%)	0 (0.0%)
Adverse Events	1 (7.7%)	1 (14.3%)	0 (0.0%)
Discontinuation of Study by Sponsor	0 (0.0%)	0 (0.0%)	2 (28.6%)
Patient Request	0 (0.0%)	0 (0.0%)	1 (14.3%)
Treatment Status			
Cohort (Patients)	**PTI-188 Dose Level / Unlabeled Antibody**		**Weeks of Follow-up[a]**
Phase Ia Cohort 1 (n=3)	9-11 mCi / 10 mg / 0 mg		1 - 6
Phase Ia Cohort 2 (n=4)	8-11 mCi / 10 mg / 10 mg		5 - 8
Phase Ia Cohort 3 (n=3)	5-9 mCi / 10 mg / 20 mg		6 - 9
Phase Ia Cohort 4 (n=3)	6-8 mCi / 10 mg / 50 mg		6 - 7
Cohort (Patients)	**PTI-188 Dose Level**		**Weeks of Follow-up[a]**
Phase Ib Cohort 1 (n=4)	20-30 mCi / 11-18 mg		2 - 45
Phase Ib Cohort 2 (n=3)	41-57 mCi / 44-48 mg		8 - 29

[a] Weeks of follow-up was calculated from the single dose of PTI-188 to the last patient visit to the clinic

Safety

- No DLTs were found to be associated with the administration of single doses of PTI-188 with up to 57 mCi of radioactivity.
- Three patients in the Phase Ia study and two patients in the Phase Ib study experienced SAEs (one death occurred during each study), all considered by the investigators to be unrelated to study drug.
- There were no adverse events in the Phase Ia study that occurred in more than one patient.
- In the Phase Ib study, fatigue occurred in two patients and pyrexia occurred in four patients.

Table 3. Summary of Adverse Events

Number of Patients (%)	Phase Ia	Phase Ib
Any AE	7 (53.8%)	6 (85.7%)
Any Grade 3 AE	3 (23.1%)	1 (14.3%)
Any Grade 4 AE	0 (0.0%)	0 (0.0%)
Any SAE	3 (23.1%)	2 (28.6%)
Any DLT	0 (0.0%)	0 (0.0%)
AEs Leading to Treatment Discontinuation	0 (0.0%)	0 (0.0%)
AEs Leading to Death*	1 (0.1%)	1 (14.3%)

* Not related to study drug

Biodistribution and Dosimetry

- The kidney and bone marrow had the highest radiation absorbed doses. These two organs are potential dose limiting organs. However, these doses were several times below the maximum tolerated levels for the respective organs.

Table 4. Radiation Absorbed Doses to Organs From PTI-188 (mGy/MBq)

Cohort	Liver	Spleen	Kidneys	Bone Marrow	Urine Bladder Wall	Whole Body
Phase Ia Cohort 1	0.88 ± 0.13	0.86 ± 0.09	1.35 ± 0.05	0.09 ± 0.01	0.88 ± 0.23	0.16 ± 0.01
Phase Ia Cohort 2	0.89 ± 0.20	0.67 ± 0.05	1.11 ± 0.22	0.11 ± 0.02	1.01 ± 0.12	0.15 ± 0.03
Phase Ia Cohort 3	0.90 ± 0.08	0.73 ± 0.14	1.59 ± 0.01	0.11 ± 0.0	0.86 ± 0.14	0.13 ± 0.02
Phase Ia Cohort 4	1.04 ± 0.30	0.67 ± 0.30	1.29 ± 0.12	0.14 ± 0.03	1.02 ± 0.08	0.16 ± 0.04
Phase Ib Cohort 1	0.92 ± 0.20	0.93 ± 0.32	1.99 ± 0.17	0.11 ± 0.01	0.61 ± --*	0.14 ± 0.01
Phase Ib Cohort 2	0.77 ± 0.25	1.02 ± 0.35	1.75 ± 0.25	0.10 ± 0.01	0.95 ± 0.47	0.15 ± 0.03

- A calculated estimation of 100 mCi of PTI-188 would deliver a dose to critical organs which would be approximately 5 times below the maximum tolerated dose causing 5% complications in 5 years.

Table 5. Radiation Absorbed Doses of PTI-188 and Normal Organ Tolerance (cGy)

	Liver	Kidneys	Bone Marrow	Urine Bladder Wall
PTI-188 40 - 60 mCi	130	305	17	158
PTI-188 Estimated 100 mCi	344	650	42	350
Normal Organ Tolerance	3000	2300	200	6500

Pharmacokinetics

- T_{max} values occurred at the end of the infusion time for most patients.
- The effective and biological half-lives of PTI-188 in the whole body were similar across the different dosing cohorts.

Table 6. Effective and Biological Half-Lives of PTI-188

Cohort	T_{eff}, hours, mean	T_{eff}, hours, range	T_{bio}, hours, mean	T_{bio}, hours, range
Phase Ia Cohort 1	12.2	10.6 - 13.4	46.7	28.2 - 63.3
Phase Ia Cohort 2	12.1	11.8 - 12.4	42.5	38.6 - 45.8
Phase Ia Cohort 3	12.5	11.7 - 14.1	52.8	37.5 - 82.6
Phase Ia Cohort 4	12.3	11.8 - 12.8	45.4	38.6 - 51.8
Phase Ib Cohort 1	12.8	11.9 - 13.8	53.0	39.7 - 72.0
Phase Ib Cohort 2	12.0	11.3- 12.6	41.7	33.5 - 48.6

Immunogenicity

- There appears to be no correlation between PTI-188 dosage strengths and the prevalence of a HAMA response.

Imaging

- Tomographic imaging revealed PTI-188 uptake in melanoma tumor deposits, mostly in the soft tissues.
- FDG-PET and SPECT/CT revealed biological activity in tumors.

Figure 2. ^{18}FDG PET/CT Image of a Patient with Massive Lung and Pleural Involvement

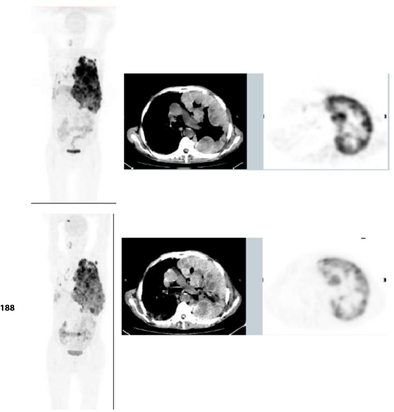


Figure 2 is an ^{18}FDG PET/CT image of a patient with massive lung and pleural involvement 10 days before administration of PTI-188 and 7 days after PTI-188 administration suggesting on-going tumoricidal activity.

Figure 3. ^{18}FDG PET/CT Image of a Patient with a Stable Tumor at 24 Weeks Post-Treatment

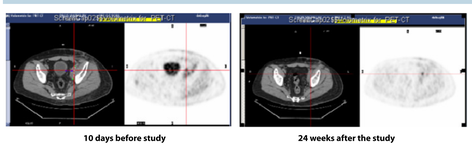


Figure 3 is an ^{18}FDG PET/CT image of a patient who received 30 mCi/16 mg PTI-188 and whose tumor was stable at 24 weeks post-treatment.

Clinical Activity

PHASE IA (13 PATIENTS)

- The tumor response in target lesions at week 6 was considered stable disease (SD) by RECIST in 9 patients.
- 3 patients met the criteria for stable disease (SD) when evaluating the overall response at week 6.
- One patient in Cohort 2 demonstrated a partial response (PR) in target lesions at week 6 with a 50.34% reduction.

PHASE IB (7 PATIENTS)

- 3 patients had stable disease (SD) by RECIST when evaluating the overall response through week 14. One of these patients had an overall response of stable disease (SD) through follow-up week 22.
- 1 patient in Cohort 1 had a partial response (PR) in target lesions (36.2% reduction) at, and stable disease (SD) up to week 34.

Table 7. Clinical Activity per RECIST Criteria v1.0

Clinical Activity	Phase Ia	Phase Ib	Phase Ib	Phase Ib	Phase Ib	Phase Ib
Follow-up Week	**6**	**6**	**14**	**22**	**26**	**34**
Overall Response	n=13	n=5	n=3	n=1	n=1	n=1
Stable Disease	3 (23.1%)	3 (60.0%)	3 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Progressive Disease	8 (61.5%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Not Evaluated	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Target Lesion Response						
Partial Response	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Stable Disease	9 (69.2%)	4 (80.0%)	3 (100.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)
Progressive Disease	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Evaluated	1 (7.7%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Target Lesion Response						
All Absent	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any Present	1 (7.7%)	2 (40.0%)	2 (66.7%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Any Progression	5 (38.5%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Evaluated	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NA	4 (30.8%)	1 (20.0%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	1 (33.33%)
Appearance of New Lesions						
No New Lesions Since Baseline	8 (61.5%)	3 (60.0%)	3 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Appearance of ≥ 1 New Lesion	5 (38.5%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)

Survival

- Overall survival, which was not a planned endpoint in either trial, was calculated as the time from study drug administration until death.
- A preliminary post hoc pooled analysis (Aug 2010) of overall survival was conducted by the primary investigative site, Hadassah Medical Center (Jerusalem). It included 17 patients from the Phase Ia and Phase Ib studies combined. Median duration of overall survival was estimated to be 20 months with 7 pts censored (5 prior to the median).
- As of May 2011, 10 out of 17 (59%) patients have an overall survival greater than 12 months, 3 patients (18%) greater than 24 months with one patient continuing to be followed at month 42. The 4 patients still being followed are currently at 22, 23, 25 and 42 weeks post PTI-188 administration.
- A more recent (May 2011) post hoc pooled analysis of overall survival among patients by Hadassah Medical Center (Jerusalem) (11 pts from Phase Ia and 6 pts from Phase Ib) established a median duration of overall survival estimated at 13 months with 4 patients censored.

SUMMARY

- Although no therapeutic benefit was expected in a single dose Phase I study, 6 patients met the RECIST criteria for stable disease at 6 weeks, 2 patients had durable disease stabilization for 14 weeks and one for 22 weeks.
- The median overall survival as of May 2011 is 13 months with 4 patients continuing in follow-up at months 22, 23, 25 and 42.
- Administration of single doses of up to 57 mCi of PTI-188 were safe and well-tolerated with no dose-limiting toxicities observed.
- The MTD has not yet been established for PTI-188, but dosimetric data suggests that significantly higher doses can be safely administered.
- No trends were noted in the types of AEs reported at any dose level and no clinically meaningful effects were noted for vital signs, laboratory safety tests, physical examination or ECGs during either study.
- Although the current studies are small and follow up continues, the results of the current studies suggest study treatment was well tolerated, higher doses can be safely administered, PTI-188 has potential to improve overall survival and further investigations are warranted.

References

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