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Results from Phase 1/2 Trial of Tagraxofusp in Combination with Pomalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma

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Introduction and Highlights

Tagraxofusp

- Novel targeted therapy directed to CD123
- FDA-approved for the treatment of adult and pediatric patients, 2 years and older, with blastic plasmacytoid dendritic cell neoplasm (BPDCN)
  - Breakthrough Therapy Designation (BTD) designation
- Marketing Authorization Application (MAA) for BPDCN is under review by the European Medicines Agency

CD123 target

- Expressed by multiple malignancies, including certain myeloproliferative neoplasms such as multiple myeloma (MM), chronic myelomonocytic leukemia and myelofibrosis, certain acute myeloid leukemia patient subsets, BPDCN, and others

Tagraxofusp and MM

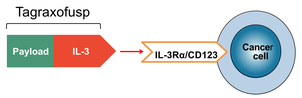
- The bone marrow microenvironment of many multiple myeloma (MM) patients contains high levels of CD123-expressing plasmacytoid dendritic cells (pDCs), which have been shown to augment MM growth and contribute to drug resistance
- Tagraxofusp was well-tolerated, with a predictable and manageable safety profile, when dosed in combination with pomalidomide (POM) + dexamethasone (DEX) in patients with relapsed or refractory (r/r) MM.
- Evidence of pDC suppression in peripheral blood and bone marrow was observed in this patient population

Background: Multiple Myeloma

- Multiple myeloma (MM) is a heterogeneous clonal B-cell malignancy characterized by the accumulation of abnormal antibody producing plasma cells in the bone marrow (BM)
- The disease is associated with a variety of clinical manifestations including lytic bone lesions, hypercalcemia, renal impairment and anemia
- MM is the second most common hematologic malignancy with an estimated 32,000 new cases and approximately 13,000 deaths per year in the US (*SEER 13, 2019*)
- Current treatment options for MM, including combinations with proteasome inhibitors (ixazomib), immunomodulatory agents (pomalidomide), monoclonal antibodies (daratumumab), and XPO1 inhibitors (selinexor) have changed the natural history of MM
- However, despite these treatment options, most patients relapse as the MM clone cannot be permanently eradicated, thus showing the necessity for new treatment modalities

Tagraxofusp, Mechanism of Action, and Rationale in MM

Tagraxofusp is a targeted therapy directed to CD123



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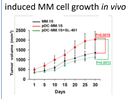
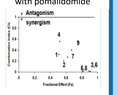
- Bone marrows of patients with MM contain high quantities of IL-3R-expressing plasmacytoid dendritic cells (pDCs)
- pDCs have been shown to augment growth of MM and contribute to drug resistance, suggesting that reducing pDCs may confer clinical benefit in MM patients (*Chauhan et al. 2009*)
- Tagraxofusp has demonstrated potent activity against MM cell lines (RPMI-8226) and primary tumor samples, which appears to be related to both direct antitumor and anti-pDC effects (*Chauhan et al. 2013*)
- Studies showed increased interleukin-3 (IL-3) levels resulting from the interaction of pDCs and MM cells, which trigger MM cell growth and pDC survival, and appear to contribute to disease aggressiveness and resistance

Tagraxofusp inhibits pDC-induced MM cell growth *in vivo*



Tagraxofusp is synergistic with pomalidomide



- Tagraxofusp has also demonstrated synergy when used in combination with traditional MM therapies, including pomalidomide (POM)
- Clinically, tagraxofusp has demonstrated high levels of anti-tumor activity in patients with an aggressive CD123+ malignancy of pDC origin, blastic plasmacytoid dendritic cell neoplasm (BPDCN)

pDCs are elevated in myeloma bone marrow

pDCs and MM cells direct contact in vivo

pDCs potentiate MM cell growth

Study Design and Inclusion Exclusion Criteria

Phase 1/2 Dose Escalation

- Trial Design (*NCT02661022*):
  - Multicenter, single arm, combination trial
- Patient Population: Relapsed or Relapsed and Refractory Multiple Myeloma Patients
  - At least 2 prior therapies including proteasome inhibitor and lenalidomide
  - Pomalidomide eligible patients
- Regimen:
  - Treated with tagraxofusp (7 or 9 ug/kg/day) in combination with pomalidomide (POM) and dexamethasone (DEX)
- Dosing Schedule:
  - Single Agent Run In – tagraxofusp: daily IV infusion for 5 days, 28-day follow up
  - Combination (Cycles 1-6): tagraxofusp: daily IV infusion for 5 days; oral POM: once daily Days 1-21 and oral DEX: once daily Days 1, 8, 15 and 22; of each 28-day cycle
  - Beyond Cycle 6 – tagraxofusp administered every other cycle (56 days); POM/DEX same as above
- Key Study Objectives:
  - To determine safety and maximum tolerated dose of Tagraxofusp in combination with POM/DEX
  - Preliminary efficacy assessment and signal detection

MM Response Criteria

- International Myeloma Working Group (IMWG) defined response criteria
- Efficacy assessments done prior to the start of each cycle

Select Inclusion Criteria

- Patient has been previously diagnosed with MM based on standard criteria and has received:
  - at least 2 prior therapies including a proteasome inhibitor (≥ 2 cycles) and lenalidomide (≥ 2 cycles), and
  - has achieved at least stable disease (SD) for ≥ 1 cycle of treatment on ≥ 1 prior treatment, and
  - has demonstrated disease progression subsequent to treatment, during or within 60 days following completion of the most recent therapy
- Patient has measurable disease defined as at least one of the following:
  - Serum monoclonal (M) protein ≥ 0.5 /dL (≥5 g/L),
  - Urine M protein ≥200 mg/24 hours, or
  - Serum free light chain (FLC) assay: involved FLC ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
- Age ≥18; ECOG PS 0-2
- Adequate baseline organ function, including: LVEF ≥ LLN, creatinine ≤2.0 mg/dL, albumin ≥3.2 g/dL, bilirubin ≤1.5 mg/dL, AST/ALT ≤2.5 times ULN, creatine phosphokinase (CPK) ≤2.5 times ULN, ANC ≥1000 cells/uL

IV=intravenous; MTD=maximum tolerated dose; ECOG= Eastern Cooperative Oncology Group; LVEF=left ventricular ejection fraction; AST/ALT=aspartate/alanine aminotransferase; ULN=upper limit of normal; ANC=absolute neutrophil count

Baseline Demographics

Age, years	n=9
Median [range]	65 [57-70]
Gender	
Male	5 (56)
Dosing	
7 mcg/kg	7
9 mcg/kg	2
Number of Prior Therapies	
Median [range]	3 [2-6]
Prior Therapies	
Dexamethasone	9 (100%)
Bortezomib	9 (100%)
Lenalidomide	9 (100%)
Cyclophosphamide	7 (77%)
Melphalan	3 (33%)

Safety and Tolerability

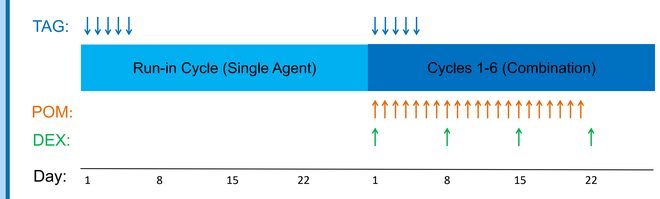
Predictable and manageable safety profile both a single agent and when combined with POM+DEX

MM, all doses, n=9

Most Common Adverse Events (≥ 35% of treatment emergent adverse effects, TEAEs)					
Preferred Term	All AEs	TEAEs n (%)			
		G1 & 2	G3	G4	G5
Hypoalbuminaemia	6 (67)	6 (67)	--	--	--
Chills	5 (56)	5 (56)	--	--	--
Fatigue	5 (56)	4 (44)	1 (11)	--	--
Insomnia	5 (56)	5 (56)	--	--	--
Nausea	5 (56)	5 (56)	--	--	--
Pyrexia	5 (56)	5 (56)	--	--	--
Dizziness	4 (44)	4 (44)	--	--	--
Headache	4 (44)	4 (44)	--	--	--
Hypophosphataemia	4 (44)	2 (22)	2 (22)	--	--
Thrombocytopenia	4 (44)	--	2 (22)	2 (22)	--
Capillary Leak Syndrome	1 (11)	1 (11)	--	--	--

There were 3 cases of neutropenia: 2 grade 3 and 1 grade 4

Dosing Schedule

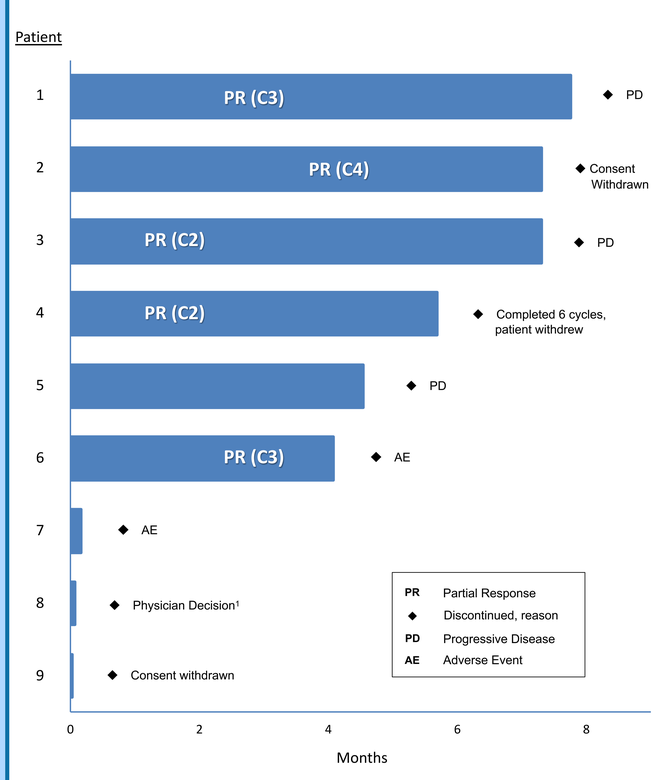


Run-in
- Tagraxofusp: IV, 7 or 9 ug/kg/day daily on Days 1-5

Cycles 1-6
- Tagraxofusp: IV, 7 or 9 ug/kg/day daily on Days 1-5
- Pomalidomide (POM): oral, 4 mg/day daily on Days 1-21
- Dexamethasone (DEX): oral, 40 mg on Days 1, 8, 15, 22
- Cycle length = 28 days

Post Cycle 6
- Tagraxofusp: IV, 7 or 9 ug/kg/day daily on Days 1-5 every other cycle
- Pomalidomide (POM): oral, 4 mg/day daily on Days 1-21
- Dexamethasone (DEX): oral, 40 mg on Days 1, 8, 15, 22
- Cycle length = 28 days

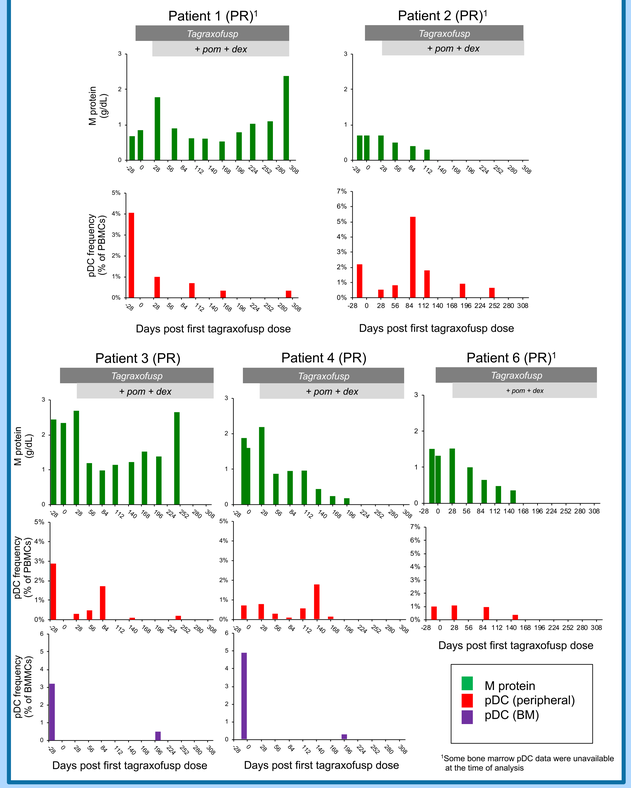
Response Evaluation and Treatment Duration



[1]Low albumin levels

Responder Analysis

- Tagraxofusp resulted in rapid and sustained decreases in both peripheral blood and bone marrow pDCs
  - Including after a single dose of tagraxofusp during the run-in phase of trial
- Suggests tagraxofusp has the potential to suppress pDCs in this heavily pretreated, poor prognosis patient population



[1]Some bone marrow pDC data were unavailable at the time of analysis

Summary of Tagraxofusp Trial Results

- In this Phase 1/2 trial, tagraxofusp was well-tolerated, with a predictable and manageable safety profile, when dosed in combination with pomalidomide (POM) and dexamethasone (DEX) in patients with heavily pretreated r/r MM
- Most common grade 3+ TEAEs were thrombocytopenia and neutropenia
- 5 patients who received tagraxofusp and POM+DEX combination had partial responses (PRs) and decreases in pDC levels while on treatment with tagraxofusp
  - These patients also experienced decreased levels of myeloma-related laboratory assessed values after 1 cycle of treatment with tagraxofusp combined with POM and DEX
- Evidence of pDC suppression in peripheral blood and BM was observed in this patient population
  - All five patients experienced decreases in pDC levels
- Given CD123 expression on pDCs in the tumor microenvironment and the potential synergy of tagraxofusp with certain MM agents, including POM, tagraxofusp may offer a novel mechanism of action in MM
- Potential avenues for further development include evaluating in other patient populations, combination with daratumumab, and/or novel agents such as XPO1 inhibitors

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Disclosures: *Wysowskyj*: Stemline - employment, equity ownership; *Chen*: Stemline - employment, equity ownership; *Brooks*: Stemline - employment, equity ownership; *Hoberman*: Stemline - employment, equity ownership; *Rupprecht*: Stemline - employment, equity ownership; *Chauhan*: Stemline- equity ownership;