SELINEXOR COMBINED WITH POMALIDOMIDE AND LOW DOSE DEXAMETHASONE (SPD) IN A RELAPSED / REFRACTORY MULTIPLE MYELOMA PATIENT POPULATION

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Abstract: PF586

Type: Poster Presentation

Presentation during EHA23: On Friday, June 15, 2018 from 17:30 - 19:00

Location: Poster area

Background

The nuclear export protein exportin 1 (XPO1) is overexpressed in a wide variety of cancers including multiple myeloma (MM). Selinexor is a first-in-class Selective Inhibitor of Nuclear Export (SINE) compound that binds and inactivates XPO1. Selinexor forces nuclear retention and reactivation of cell cycle regulators such as p53, IkB, and Rb. Pomalidomide/dexamethasone (Pd) is approved in relapsed/refractory MM (RRMM) with an overall response rate (ORR) of 30% and progression-free survival (PFS) rate of 3.6 months in patients (pts) having received a prior proteasome inhibitor (PI) and IMiD. Strategies to improve the ORR and PFS are needed. In murine MM models, the combination of selinexor with IMiDs shows synergistic anti-MM activity and good tolerability.

Aims

This Ph 1b/2 (NCT02343042), dose escalation study was designed to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for the safety, tolerability and efficacy of the combination of selinexor, pomalidomide, and low dose dex (SPd) in pts with RRMM.

Methods

Pts with RRMM who received ≥ 2 prior therapies including lenalidomide (len) and a PI were enrolled. Selinexor was evaluated in 2 different dosing schedules of once-weekly (QW, 60; 80 mg) or twice-weekly (BIW, 60; 80 mg), with pomalidomide (pom) 4 mg PO daily, and dexamethasone (dex) 20 mg BIW or 40 mg QW.

Results

As of Feb 27th 2018, 33 pts (16 male / 17 female) have been enrolled.The median age is 61 years, with a median of 4 (range, 2 – 9) prior treatment regimens. Thirty-one patients were IMiD refractory (20 len, 11 pom/len). Six dose limiting DLTs were observed: G3 fatigue (60 mg BIW, pom 4 mg), G3 febrile neutropenia (FN) (60 mg BIW, pom 3 mg), G3 FN and G4 neutropenia (ANC) (80 mg QW, pom 4), G3 thrombocytopenia (PLT) (80 mg QW, pom 3 mg) and 4 missed doses in Cycle 1 due to symptomatic hyponatremia (80 mg BIW, pom 4 mg). Enrollment on selinexor 80 mg QW, pom 3 mg is ongoing. Common treatment related Grade 1/2 adverse events (AEs) include: nausea (48%), fatigue (42%), anorexia (45%) and diarrhea (30%). Grade 3/4 AEs include: ANC (55%), PLT (30%), and anemia (27%). Twenty-seven pts were evaluable for response. Responses rates can be seen in Table 1. Median PFS is 11.6 months with a median follow up of 7.7 months.

Table 1. SPd – Response Rates in Evaluable Patients

Prior Therapy Status	N	*ORR	CBR
Pom Naïve & Len Refractory or Relapsed	19	12 (63%)	14 (74%)
Pom & Len Refractory	8	3 (38%)	5 (63%)

Overall Response Rate= VGPR + PR, Clinical Benefit Rate= VGPR + PR + MR (*Includes 1 unconfirmed PR and 1 unconfirmed MR)

Conclusion

Enrollment is ongoing to evaluating once weekly selinexor in combination with Pd. This all oral combination of

selinexor, pom and dex (SPd) has significant clinical activity with an ORR 63% in pom naive pts with heavily pretreated MM compared to previously published data of 30% ORR. No unexpected adverse events were noted. Phase 1 dose escalation of the combination of SPd is ongoing to define the RP2D. SPd appears active and supports further clinical development in RRMM.

Session topic: 14. Myeloma and other monoclonal gammopathies - Clinical

Keyword(s): Dexamethasone, Imids, Multiple Myeloma