E3A06: Randomized phase III trial of lenalidomide versus observation alone in patients with asymptomatic high-risk smoldering multiple myeloma.

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Abstract Disclosures

Background:
Smoldering multiple myeloma (SMM) is a precursor to myeloma, wherein current standard of care is observation (obs). Data from a randomized Spanish trial (Mateos et al, NEJM 2015) suggest that lenalidomide(len)/dexamethasone improves time to developing myeloma (TTP) and overall survival (OS) for patients (pts) with high risk (HR) SMM over obs. However, pts were not screened with advanced imaging techniques, used a HR definition that is not routinely available, and combination therapy limited the ability to isolate the effect of len, and thus has not become standard of care.

Methods:
E3A06 is a randomized phase III intergroup trial, testing the effect of single agent len compared with obs for pts with intermediate or high risk SMM. In an initial phase II run in all pts received len to demonstrate safety. Eligibility required ≥10% PCs and abnormal serum FLC ratio (<0.26 or >1.65). The primary endpoint was progression PFS was estimated by the Kaplan-Meier method and compared using the one-sided stratified log-rank test.

Results:

PII enrolled 44 pts and PIII randomized 182 pts to either len (n=90) or obs (n=92) [stratified on time since SMM diagnosis ≤1y vs >1y]. Baseline characteristics were similar between the arms. 80% (PII) and 51% (PIII) are off len, primarily due to adverse events (AE) or pt withdrawal. Among the len treated pts, G3/4 non-hematologic AE occurred in 28% of PIII pts with fatigue being most common (n=5). G4 hematologic AE rate was 5.7%, primarily neutropenia (n=4). 3-year cumulative incidence of invasive SPMs was 5.2% (len) and 3.5% (obs). Overall response rate was 47.7% for the phase II study, and in phase III, 48.9% for the len arm, and 0% for the obs arm. Median follow up was 71 months (PII), and 28 months (PIII). 3-year PFS was 87% for the PII cohort. One, 2 and 3-year PFS was 98%, 93%, and 91% for len, and 89%, 76%, and 66% for the obs arm (HR 0.28, p=0.0005) favoring the len arm. No difference in QOL score was noted between arms.

Conclusions:

Overall, this trial represents the largest randomized trial in SMM to date. In conjunction with the Spanish data, this trial may support a change in clinical practice. Clinical trial information: NCT01169337

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Phase 2 PFS		
1 yr	0.98	
3 yr	0.87	
5 yr	0.78	
Phase 3 PFS	Len	Obs
1 yr	0.98	0.89
2 yr	0.93	0.76
3 yr	0.91	0.66