

400 mg or 800 mg daily:

Months on Therapy	Percent with CCyR (No. evaluable)			P value
	Nilotinib	Imatinib 400 mg	Imatinib 800 mg	
3mo	95 (22)	37 (49)	62 (202)	< 0.0001
6mo	100 (13)	54 (48)	82 (199)	< 0.0001
12mo	100 (11)	65 (48)	86 (197)	0.0007

The median QPCR with nilotinib at 3, 6, and 12 months were, respectively, 0.52% (range, 0.0-29.5%), 0.03% (range, 0.0-9.13%), and 0.09% (range, 0.0-16.21%). At 3 mo follow-up, major molecular response (MMR; BCR-ABL/ABL ratio  $\leq$ 0.05%) was observed in 3/22 patients (14%), 7/13 (54%) at 6 mo, and 5/11 (45%) at 12 mo. 12-mo rates of

MMR for the historical imatinib groups treated at 400 mg and 800 mg were 24% and 47%, respectively ( $p=0.02$ ). None of the molecular responses has been lost while on therapy. Grade 3-4 neutropenia was observed in 2 (7%) pts, and thrombocytopenia in 1 (3%). Other grade 3-4 adverse events included elevation of lipase ( $n=3$ , 9%), or bilirubin

( $n=2$ ; 6%), and amylase elevation, back pain, and infection (1 each). Twelve pts had transient treatment interruptions (median 11 days), most frequently due to pain ( $n=3$ ; musculoskeletal 2, abdominal 1), lipase elevation ( $n=2$ ). Seven patients had their dose reduced to 400 mg daily, 2 to 200 mg twice daily, and 1 to 200 mg daily due to extramedullary toxicity. Three patients decided to change therapy after 4, 6 and 8 months; 2 switched to imatinib and 1 received SCT.

### Conclusion

Nilotinib 400 mg orally twice daily suggest significant efficacy manifested by complete cytogenetic responses in nearly all patients as early as 3 months after the start of therapy with a favorable toxicity profile. \*

## [817] AZACITIDINE (AZA) TREATMENT PROLONGS OVERALL SURVIVAL (OS) IN HIGHER-RISK MDS PATIENTS COMPARED WITH CONVENTIONAL CARE REGIMENS (CCR): RESULTS OF THE AZA-001 PHASE III STUDY.

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### Background

A previous CALGB trial (JCO 2002;20:2429) showed a positive OS trend with AZA vs best supportive care (BSC) in MDS. The objective of this Phase III, international, multicenter, randomized, prospective trial was to demonstrate the superiority of AZA + BSC for prolonging OS vs CCR + BSC. Design: Higher-risk MDS patients (pts), FAB-defined as RAEB, RAEB-T, or CMML (10-29% marrow blasts) with an IPSS of Int-2 or High by central pathology/cytogenetic review, were enrolled. Before randomization, investigators preselected pts to 1 of 3 CCR: BSC only (transfusions, antibiotics, and G-CSF for neutropenic infection); low-dose ara-C (LDAC, 20 mg/m<sup>2</sup>/d x 14d, q 28d); or standard

chemotherapy (Std CT: conventional induction/consolidation). Pts were stratified by FAB/IPSS and randomized to AZA (75 mg/m<sup>2</sup>/d x 7d, q 28d) or CCR. This trial did not allow erythropoietin. All analyses used the ITT population.

### Results

In all, 358 pts (70% male), were randomized at 79 sites to AZA (N=179) or CCR (N=179): BSC only (N=105, 59%), LDAC (N=49, 27%), or Std CT (N=25, 14%). Median age was 69 yrs (38-88) and per treatment (TX): AZA (69 yrs); BSC only (70 yrs); LDAC (71 yrs); and Std CT (65 yrs). The AZA and CCR groups were comparable for baseline (BL) parameters. At BL, 95% of pts were higher risk: RAEB

(58%), RAEB-T/WHO AML (34%), CMML (3%), and other (5%). By IPSS, 87% were higher risk: Int-2 (40%), High (47%), and 13% indeterminate/other. AZA was administered for a median of 9 cycles; LDAC for 4 cycles. Median followup for the OS analysis was 21.1 months (mo). AZA demonstrated statistically superior OS vs CCR (stratified log-rank  $p=0.0001$ ). AZA showed a median Kaplan-Meier (KM) OS time of 24.4 mo vs 15 mo with CCR (Figure). The hazard ratio (HR, Cox Model) was 0.58 (95% CI: 0.43, 0.77) for a 74% OS improvement. At 2 yrs, there was a 2-fold OS advantage: AZA (51%) vs CCR (26%), 95% CI: 13, 36%,  $p<0.0001$ . Differences in OS KM medians (HR; log-

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