Abstract: P459

Title: DISEASE MONITORING OF *NPM1*-MUTANT (MUT) ACUTE MYELOID LEUKEMIA (AML) USING MEASURABLE RESIDUAL DISEASE (MRD) ASSESSMENTS DURING ORAL AZACITIDINE (ORAL-AZA) TREATMENT (TX): A QUAZAR AML-001 SUBANALYSIS

Abstract Type: Poster Presentation

Session Title: Acute myeloid leukemia - Biology & Translational Research

Background:

NPM1 is mutated in 20–30% of patients (pts) with AML at diagnosis (Dx), with greater frequency among pts with normal karyotype. As *NPM1* mutations are generally stable at relapse and AML-specific, dynamic PCR-based measurement of residual disease provides a reliable and quantifiable marker of prognosis. In QUAZAR (NCT01757535), Oral-AZA significantly prolonged survival vs placebo (PBO) in pts with AML in remission after intensive chemotherapy (IC), including pts who were MRD+ by multiparameter flow cytometry (MFC). The impact of Oral-AZA on *NPM1*mut MRD via PCR-based methods and concordance with MFC in *NPM1*mut AML is not known.

Aims:

To examine changes in *NPM1*mut MRD status by PCR vs MFC during Oral-AZA Tx, and associations between molecular *NPM1*mut MRD and clinical outcome.

Methods:

Quantitation of *NPM1*mut variants by PCR (types A/B/D by QuantStudio 6 or 7500 Fast qRT-PCR; types G/I by QX200 ddPCR; sensitivity range: 0.001–0.023%) in QUAZAR was performed on bone marrow (BM) mononuclear cell RNA collected at screening post IC (81/472 pts), during Tx (end of cycle [C] 6/C12; 14 days [d] Tx per 28d cycle) and morphologic relapse (≥5% BM blasts) from pts with investigator-reported *NPM1*mut AML at Dx. *NPM1* transcript copy number was normalized to *ABL* (%). MFC MRD was analyzed centrally using 22 cell surface markers (MRD+: ≥0.1% blasts). A multivariable Cox regression model evaluated associations of specific covariates (*NPM1*mut status, cytogenetic risk, MFC MRD) with RFS.

Results:

In pts with *NPM1*mut AML reported at Dx pre IC and in remission per protocol requirements post IC (n=81; CR: 87.7%, CRi: 12.3%; ≥1 consolidation cycles: 86.4%, median 2 cycles), *NPM1*mut+ MRD (PCR) was present in 38.3% (31/81; type A, 90.3% [28/31]). MRD+ by MFC was reported in 37.0% (30/81) of pts. At the end of C6, MRD was present in 39.1% (25/64) by PCR and 27.4% (17/62) by MFC.

Median *NPM1:ABL* % among pts with *NPM1*mut MRD by PCR at screening was 0.064 vs 164.5 at relapse (Mann-Whitney test $P<0.0001$). At relapse, *NPM1*mut+ was observed in 80% (35/44) by PCR.

At all cycles, *NPM1* PCR and MFC MRD were generally concordant (Spearman r=0.5, $P<0.0001$); *NPM1*mut+/MFC MRD+ 25.4% (61/240) and *NPM1*mut–/MFC MRD– 44.2% (106/240). In outlier analyses, 17.5% of cases were *NPM1*mut+ by PCR (42/240) and MRD– by MFC (*NPM1:ABL* % 0.24 vs 44.3 for *NPM1*mut+/MRD+, n=61), whereas 12.9% (31/240) were *NPM1*mut–/MFC MRD+. Post IC, both MRD+ and – segments (n=15/80 vs 34/80) aligned with inferior or favorable RFS, respectively. Discordant MRD +/– and –/+ segments (n=16/80 vs 15/80) were not clearly associated with RFS. With Oral-AZA, 57% (8/14) of *NPM1*mut+ pts converted to *NPM1*mut– status or achieved log reduction in *NPM1* (at C6/C12) vs 30% (3/10) with PBO.

Of 44 paired *NPM1*mut– samples available at screening and relapse, 20.5% (9/44) remained *NPM1*mut– at relapse by PCR (no difference between Tx arms) and were characterized by other mutations detected by NGS including

EZH2 (3 cases) and *TET2*, *TP53* and *PHF6* (2 cases).

After adjusting for prognostic variables post IC, Oral-AZA remained independently associated with favorable RFS, while *NPM1*mut+ status by PCR post IC was associated with inferior RFS (**Table**).

Summary/Conclusion:

For pts with *NPM1*mut AML at Dx, *NPM1* PCR was positive in 38.3% at screening. *NPM1*mut was not detected in 20.5% of cases at morphologic relapse. For pts with *NPM1*mut AML at Dx, PCR is informative and concordant with MFC MRD. *NPM1* monitoring has prognostic value in AML and, importantly, achievement of *NPM1* negativity post IC is associated with better clinical outcomes with Oral-AZA.

Table. Multivariable analysis of *NPM1*+ pts

	RFS HR (95% CI), n=81	*P* value
Oral-AZA vs PBO*	0.5 (0.3, 0.9)	0.0259
PCR *NPM1*+†	2.1 (1.2, 3.8)	0.0099
Poor cytogenetic risk‡	3.7 (1.1, 12.7)	0.0402
MFC MRD+§	1.4 (0.8, 2.5)	0.2654

Hazard ratios (HR) were calculated using a Cox proportional hazards regression model. *P* values were calculated using a log-rank test. *n=45 vs n=36; †n=31; ‡n=4; §n=30

Keywords: Acute myeloid leukemia, Clinical trial, Maintenance