AMLGlobalPortal

FLT3, General AML

# ASCO 2019 | Effect of gilteritinib on survival in patients with FLT3-mutated relapsed/refractory (R/R) AML with a common AML co-mutations or a high FLT3-ITD allelic ratio

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On Saturday, June 1 2019, during the American Society for Clinical Oncology (ASCO) annual meeting in Chicago, US, Mark J. Levis, from Johns Hopkins University School of Medicine, Baltimore, US, discussed the effect of gilteritinib on the survival in patients with FLT3-mutated ($FLT3^{mut+}$) relapsed/refractory (R/R) AML who have common AML co-mutations or a high FLT3-ITD allelic ratio.

FLT3 mutations occur in approximately 30 % of patients with AML and are often associated with poor survival. Gilteritinib was recently approved by the FDA for the treatment of patients with R/R AML based on interim data from the randomized phase III ADMIRAL study (NCT02421939) which showed that the oral FLT3 inhibitor, gilteritinib provides superior response and overall survival (OS) compared with salvage chemotherapy (SC) in patients (pts) with $FLT3^{mut+}$ R/R AML.

### Patient characteristics

| **Characteristics** | **Gilteritinib ( n = 247)** | **Salvage chemotherapy ( n = 124)** | **Total ( N = 371)** |
|---|---|---|---|
| Median age, years (range) | 62 (20-84) | 61.5 (19-85) | 62 (19-85) |
| Female, n (%) | 131 (53) | 70 (56) | 201 (54) |
| **Cytogenetic risk, n (%)** | | | |
| Favorable | 4 (2) | 1 (1) | 5 (1) |
| Intermediate | 182 (74) | 89 (72) | 271 (73) |
| Unfavorable | 26 (11) | 11 (9) | 37 (10) |

| | | | |
|---|---|---|---|
| Other | 35 (14) | 23 (19) | 58 (16) |
| Centrally-confirmed FLT3 mutation status, n (%) | | | |
| FLT3-ITD alone | 215 (87) | 113 (91) | 328 (88) |
| FLT3-TKD alone | 21 (9) | 10 (8) | 31 (8) |
| FLT-ITD and FLT3-TKD | 7 (3) | 0 | 7 (2) |

**Table 1**

## Methods – Analysis of co-mutations

- Blood or bone marrow-derived from DNA samples from 361 *FLT3*$^{mut+}$ was derived from patients
- 37 recurrently mutated genes in AML were analyzed using next-generation sequencing (NGS). The cutoff point for co-mutation positivity (co-mut$^{+}$) was ≥0.027
- Analysis of 361 *FLT3*$^{mut+}$patients identified four major co-mutation cohorts, each with ≥10% of patients:

  -NPM1 : 47.9% (n = 173/361)

  -DNMT3A: 31% (n = 115/361)

  -DNMT3A/NPM1: 23.8% (n = 86/361)

  -WT1: 18.0% ( n= 65/361)

- The median *FLT3*-ITD AR value of 0.77 was used to define high (≥0.77) *vs* low (<0.77) *FLT3*-ITD AR

## Key findings:

| |
|---|
| **Treatment outcomes according to FLT3-ITD allelic ratio** |
| **High allelic ratio** |

| | Gilteritinib | Salvage chemotherapy | | *P* - value |
|---|---|---|---|---|
| **Median OS, months** | 7.1 | 4.3 | HR=0.492 (95% CI: 0.339, 0.714) | 0.0001 |
| **CR/CRh, n (%)** | 30 (27.5) | 6 (10.0) | Risk difference 17.5% (95% CI: 4.9, 30.1) | 0.010 |
| **Low allelic ratio** | | | | |
| **Median OS, months** | 10.6 | 6.9 | HR = 0.795 (95% CI: 0526, 1.200) | 0.2719 |
| **CR/CRh, n (%)** | 45 (39.8) | 10 (18.9) | Risk difference: 21.0% (95% CI: 5.7, 36.2) | 0.0081 |

**Table 2**

- Gilteritinib significantly improved OS in patients with R/R *FLT3*$^{mut+}$AML compared to salvage chemotherapy: Gilteritinib median OS 9.3 months (gilteritinib) vs 5.6 months (salvage chemotherapy); HR 0.637; P = 0.0007
- when comparing OS between high and low FLT3-ITD allelic ration an advantage was only seen in the patient group with a high FLT3-ITD allelic ratio when compared with salvage chemotherapy.
- In both arms of the study, OS was longer in the low *FLT3*-ITD AR cohort than the high *FLT3*-ITD AR (gilteritinib: HR=1.341, *P*=0.0712; SC: HR=2.01, *P* =0.0021)

| **Patients** | **CR/CRh (%)** | | | **Median OS** | | |
|---|---|---|---|---|---|---|
| | Gilteritinib | SC | Gilteritinib | SC | HR | *P* - Value |
| ITT population (n=371) | 34.0 | 15.3 | 9.3 | 5.6 | 0.637 | 0.0007 |

| | Co-mut+ cohorts | | | | | |
|---|---|---|---|---|---|---|
| NPM1 (n=173) | 32.2 | 12.1 | 8.3 | 5.1 | 0.419 | <0.0001 |
| DNMT3A(n=115) | 37.3 | 12.5 | 9.1 | 5.5 | 0.504 | 0.0031 |
| DNMT3A/NPM1(n=86) | 40.0 | 9.7 | 10.8 | 5.0 | 0.252 | <0.0001 |
| WT1 (n=65) | 35.6 | 5.0 | 9.1 | 3.4 | 0.309 | 0.0001 |

**Table 3**

- The gilteritinib arm had superior response rates all four major co-mutation cohorts (table 3)
- After adjustment for therapy duration, grade ≥3 or serious adverse events were less frequent in the gilteritinib *vs* salvage arm

## Conclusions

Dr. Levis concluded that the clinical benefit of gilteritinib was maintained regardless of the presence of NPM1, DNMT3A, and WT1 co-mutations. Relative to the other co-mutated cohorts, patients with both NPM1 AND DNMT3A co-mutations had the greatest survival benefit with gilteritinib.

In patients with a high FLT3-ITD allelic ratio, OS was significantly longer in patients treated with gilteritinib compared with those treated with salvage chemotherapy. In the gilteritinib arm, the low FLT3-ITD allelic ration cohort had a survival advantage when compared with the high FLT3-ITD allelic cohort

These findings of the ADMIRAL trial further support the use of gilteritinib in the R/R AML treatment paradigm irrespective of co-mutation status and FLT3-ITD allelic ratio.

**References**

1. Levis. J. M. Effect of gilteritinib on survival in patients with FLT3-mutated relapsed/refractory (R/R) AML with a common AML co-mutations or a high FLT3-ITD allelic ratio. 2019 American Society of Oncology (ASCO) Annual Meeting, Chicago, US.