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Comparison of Gilteritinib and Salvage Chemotherapy in FLT3-Mutated Acute Myeloid Leukemia on the Number Needed to Treat for Various Clinical Outcomes: A Secondary Analysis of the Admiral Trial

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Introduction/background: FMS-like receptor tyrosine kinase-3 (*FLT3*) mutations are common in acute myeloid leukemia (AML) and are associated with poor prognosis. Historically, patients with relapsed/refractory (R/R) *FLT3* mutation–positive (*FLT3*$^{mut+}$) AML experienced dismal survival outcomes. Gilteritinib, a highly potent and selective *FLT3* inhibitor, was recently approved as the first targeted therapy for patients with R/R *FLT3*$^{mut+}$ AML, and has the potential to bring significant clinical benefits to these patients. The randomized, phase 3 ADMIRAL trial (NCT02421939; Perl, et al. 2019) was the first head-to-head study that evaluated 120-mg/day gilteritinib versus salvage chemotherapy in R/R *FLT3*$^{mut+}$ AML patients. The ADMIRAL trial demonstrated that gilteritinib was superior to salvage chemotherapy based on significantly longer median overall survival (OS) and higher response rates, including complete remission/complete remission with partial hematological recovery (CR/CRh), composite CR (CRc), and hematopoietic stem cell transplantation (HSCT) rate. Based on these results, the current study estimated the number needed to treat (NNT) with gilteritinib, compared with salvage chemotherapy, in order to evaluate its clinical benefit with CR/CRh, CRc, 1-year OS, and HSCT rates.

Methods: NNT is an established and easily interpretable measure to assess the effectiveness of healthcare interventions. The clinical event estimates (ie, CR/CRh rate, CRc rate, 1-year OS, and HSCT rate) of gilteritinib and salvage chemotherapy among R/R *FLT3*$^{mut+}$ AML patients were obtained from the ADMIRAL trial. CR/CRh was defined as the combined rate of CR and CRh. CRc was defined as the combination of CR, CR with incomplete hematologic recovery, and CR with incomplete platelet recovery. OS was defined as time from randomization to death due to any cause. The NNT is calculated as the inverse of the absolute rate difference between the event rates of gilteritinib and salvage chemotherapy. Positive NNT values represent treatment benefit, with lower values indicating greater benefit of gilteritinib over salvage chemotherapy. The 95% confidence interval (CI) of the NNT was derived from the 95% CI of the event rate difference.

Results: In the ADMIRAL trial, patients assigned to gilteritinib had significantly higher CR/CRh rates (34.0% vs 15.3%) and CRc rates (54.3% vs 21.8%) than patients assigned to salvage chemotherapy. The NNT for CR/CRh and CRc was 5.35 (95% CI: 3.66, 9.98) and 3.08 (95% CI: 2.38, 4.36), suggesting that treating five and three patients with gilteritinib instead of salvage chemotherapy would result in one additional patient achieving CR/CRh and CRc, respectively. With respect to the survival outcome, patients randomized to gilteritinib had significantly prolonged OS compared to those randomized to salvage chemotherapy (median OS: 9.3 vs 5.6 months; hazard ratio: 0.64); rates of 1-year survival were 37.1% versus 16.7%, respectively. The NNT comparing gilteritinib with salvage chemotherapy was 4.90 (95% CI: 3.29, 9.64) for 1-year OS, which suggests that treating approximately five patients with gilteritinib instead of salvage chemotherapy would lead to one additional survivor at the end of the first year. Lastly, more patients underwent HSCT in the gilteritinib arm versus the salvage chemotherapy arm (25.5% vs 15.3%); the corresponding NNT was estimated at 9.82 (95% CI: 5.40, 54.59) for gilteritinib versus salvage chemotherapy.

Conclusion: The results demonstrated that treatment with gilteritinib compared with salvage chemotherapy leads to more R/R *FLT3*$^{mut+}$ AML patients achieving CR/CRh, CRc, and proceeding to HSCT, as well as more patients remaining alive at 1 year. This NNT analysis supports the superior clinical benefit of gilteritinib versus salvage chemotherapy in R/R *FLT3*$^{mut+}$ AML patients.

Disclosures:

Pandya: *Astellas Pharma, Inc.:* Current Employment. **Qi:** *BMS:* Other: Employee of Analysis Group Inc., which received consulting fees; *Astellas Pharma, Inc.:* Research Funding. **Yang:** *Analysis Group Inc.:* Current Employment; *Takeda Pharmaceutical Company Ltd:* Research Funding. **Garnham:** *Astellas Pharma, Inc.:* Current Employment. **Shah:** *Astellas:* Current Employment. **Zeidan:** *Taiho:* Consultancy, Honoraria; *Celgene / BMS:* Consultancy, Honoraria, Research Funding; *Cardinal Health:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Trovagene:* Consultancy, Honoraria, Research Funding; *Otsuka:* Consultancy, Honoraria; *CCITLA:* Other; *ADC Therapeutics:* Research Funding; *Seattle Genetics:* Consultancy, Honoraria; *Aprea:* Research Funding; *MedImmune/Astrazeneca:* Research Funding; *Astex:* Research Funding; *Daiichi Sankyo:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Acceleron:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Incyte:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria; *Agios:* Consultancy, Honoraria; *Boehringer-Ingelheim:* Consultancy, Honoraria, Research Funding; *Epizyme:* Consultancy, Honoraria; *Leukemia and Lymphoma Society:* Other; *Ionis:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria, Research Funding; *BeyondSpring:* Consultancy, Honoraria; *Cardiff Oncology:* Consultancy, Honoraria, Other.

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