Neratinib + fulvestrant for HER2-mutant, HR-positive, metastatic breast cancer: Updated results from the phase 2 SUMMIT trial


Background
- HER2 mutations define a rare subset of metastatic breast cancer (MBC) with a unique mechanism of oncogenic addiction to HER2 signaling.
- Somatic HER2 mutations occur in ~2% of MBC. 5% of estrogen receptor (ER+ MBC), and 5%–15% of endocrine-resistant tumors.
- Recent preclinical studies suggest that acquired or de novo HER2 mutations may confer resistance to endocrine therapies. In MBC, HER2 mutations have been more commonly observed in endocrine-resistant cancers.
- Neratinib is an oral, irreversibly pan-HER tyrosine kinase inhibitor that has demonstrated single-agent clinical activity in HER2-mutant MBC.
- In HER2-mutant, hormone receptor-positive (HR+ER+) cell lines and patient-derived xenograft (PDX) models, neratinib + fulvestrant (N+F) appears synergistic vs single-agent neratinib, possibly due to more complete inhibition of its directional signaling between HER2 and ER.
- To date, we present updated results from the N+F treated, HER2-mutant, HR+ breast cohort from the SUMMIT trial.

Figure 1. SUMMIT study design (Amendment 4)

Table 1. Baseline demographics: HR+ breast cohort

Table 2. Disease characteristics

Table 3. Prior therapies

Table 4. Efficacy summary

Table 5. Incidence of treatment-emergent adverse events (≥15%)

Table 6. Characteristics of darwin

Conclusions
- HER2 mutations represent a clinically actionable, oncogenic driver in MBC.
- Neratinib combined with fulvestrant may demonstrate encouraging clinical activity in HER2-mutant, HR+ MBC patients:
  - ORR 30%, median DOR 22.2 months, median PFS 5.4 months.
- For patients who were unmasked to fulvestrant- and CDK4/6-inhibitor-prepared patients:
  - Patients with prior CDK4/6-inhibitor exposure had a longer median duration on study treatment (6.6 months) than their prior CDK4/6-inhibitor therapy (3.5 months).
- No new safety signals were identified in patients treated with neratinib + fulvestrant.
- The rate of diarrhea, the most common AE, was similar to that observed with single-agent neratinib, was not dose-limiting, and was manageable by standard prophylaxis.
- The SUMMIT study has been amended to evaluate combining neratinib with trastuzumab + fulvestrant in HER2-mutated breast cancer patients.

References

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