Breast Cancer − Advanced Disease

Sunday 25 September 2011, 09:00−11:35

17LBA LATE BREAKING ABSTRACT

A Double-blind, Randomized Phase IIb Study Evaluating the Efficacy and Safety of Sorafenib (SOR) Compared to Placebo (PL) When Administered in Combination with Docetaxel And/or Letrozole in Patients with Metastatic Breast Cancer (MBC): FM-B07-01 Trial

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Background: SOR is a multi-kinase inhibitor with antiangiogenic and antiproliferative activity approved for use in renal and hepatocellular cancer. We have conducted a double-blind randomized trial of SOR vs PL in combination with docetaxel and/or letrozole as first-line therapy to investigate the potential benefit of SOR as addition to standard therapeutic approach in patients with HER-2 negative MBC.
Methods: Randomization was stratified by hormonal receptors (HR) status and visceral vs non-visceral disease. Patients with negative HR were to receive docetaxel (75 mg/m^2 IV every 3 wks) for a maximum of 6 cycles; patients with positive HR and visceral disease were to receive docetaxel (same as above) followed by letrozole (2.5 mg orally continuously) and patients with positive HR and non-visceral disease were to receive letrozole (same as above). Patients were randomized to receive PL or SOR (400 mg orally BID continuously). The primary study endpoint was PFS. Disease assessments occurred every 9 wks. A sample size of 220 pts was planned to detect the targeted HR of 0.65 (90% power and 1 sided $\alpha = 0.14$). The study registration number is ISRCTN72153214.
Results: A total of 218 patients were enrolled, 107 to PL and 111 to SOR. Visceral presentation accounted for 75% of the patients and HR negative tumors were 22%. Duration of treatment in weeks was 43 and 26, respectively. By investigator assessment, the median PFS of PL was 8.4 mos and of SOR 8.4 mos, HR 1.22 (95% CI: 0.909, 1.616). Best overall response was 43% and 42%, respectively. Overall, 67% of the patients were alive at the time of analysis. There were no treatment-related deaths in the SOR arm and 1 treatment-related death in the PL arm was attributed to docetaxel. Treatment-related toxicities of Gr 3 or 4 (PL vs SOR) included hand-foot skin reaction (HFSR) (0 vs 13%), rash (2% vs 13%), neutropenia (6% vs 14%), febrile neutropenia (0 vs 6%), asthenia (5% vs 0). Regardless of severity, adverse events led to treatment discontinuation in 11% vs 22% of the patients.
Conclusions: In this randomized double-blind phase II trial, the addition of SOR to the best standard treatment in patients with MBC did not contribute to a statistically significant improvement in therapeutic efficacy. Despite the high frequency of treatment discontinuations due to adverse events, the SOR regimen exhibited a clinically manageable toxicity profile and no new or unexpected side effects were observed with this combination.
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Central Nervous System

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18LBA LATE BREAKING ABSTRACT

Clinical, Molecular, and Molecular-Clinical Profile (MCP) Exploratory Subset Analysis of RTOG 0525: a Phase III Trial Comparing Standard (std) Adjuvant Temozolomide (TMZ) with a Dose-dense (dd) Schedule for Glioblastoma (GBM)

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Background: The RTOG 0525 trial (ASCO 2011) did not show an advantage from dd TMZ over std TMZ. We conducted exploratory, hypothesis-generating subset analyses to detect possible benefit from dd TMZ, including extensive molecular profiling.
Methods: Patients were randomized to std (150–200 mg/m^2 $\times$ 5 d) or dd TMZ (75–100 mg/m^2 $\times$ 21 d) q 4 wks for 6−12 cycles. Eligibility included age >18, KPS $\geqslant$60, and >1 cm^2 tissue for prospective MGMT analysis for stratification. Post-hoc subset analyses were performed for all randomized patients ("intent-to-treat", ITT), and for all patients starting protocol therapy (SPT) by RPA class (III, IV, V), KPS (90–100, <90), Age ($\geqslant$50, <50), resection (partial, total), gender (female, male), neurologic dysfunction (nd = none, minor, moderate), molecular (4) subgroups, and a combination of both (MCP).
Results: Overall, no significant difference was seen for median OS (16.6 vs. 14.9 mo, measured from randomization, not registration), or PFS (5.5 vs. 6.7 mo, $p = 0.06$). MGMT methylation was linked to improved OS (21.2 vs. 14 mo, $p < 0.0001$), and PFS (8.7 vs. 5.7 mo, $p < 0.0001$). For the ITT ($n = 833$), there was no OS benefit from dd TMZ in any subset. Two subsets showed a PFS benefit for dd TMZ: RPA class III (6.2 vs.12.6 months, HR 0.69, $p = 0.03$) and nf = minor (5.4 vs. 7.1 mo, HR 0.77, $p = 0.01$). For RPA III, dd dramatically delayed progression, but post-progression dd patients died more quickly than std. A similar pattern for nf = minor was observed. For the SPT group ($n = 714$) there was neither PFS nor OS benefit for dd TMZ, overall. For RPA class III and nf = minor, there was a PFS benefit for dd TMZ (HR 0.73, $p = 0.08$; HR 0.77, $p = 0.02$). For nf = moderate subset, both ITT and SPT, the std arm showed superior OS (14.4 vs. 10.9 mo) compared to dd, without improved PFS (HR 1.46, $p = 0.03$; and HR 1.74, $p = 0.01$. In terms of methylation status within this subset, there were more methylated patients in the std arm of the ITT subset ($n = 159$; 32% vs. 24%). For the SPT subset ($n = 124$), methylation status was similar between arms.
Four molecular groups (MP1−4) were identified by combining distinct prognostic biomarkers (a mRNA-based predictor, a multigene methylator predictor, an expanded MGMT promoter methylation predictor, and IDH1 mutation status). Developed first on an independent training set of 220 cases, validation on RTOG 0525 cases ($n = 715$) confirmed significant survival differences (MS = NR, 22, 17, 12 months and 2-year OS = 72%, 48%, 32%, 21%, for MP1−4); and when combined with RPA class, yielded more robust survival stratification (median OS = NR, 23, 15, 11 months and 2-year OS = 72%, 47%, 25%, 17%, for MCP1−4). However, even within these subgroups, no statistically significant survival advantage from dd TMZ was identified.
Conclusions: This study did not demonstrate improved OS for dd TMZ for any subgroup, but on post-hoc exploratory analysis, PFS was significantly increased for 2 highly functional subgroups. These data generate the testable hypothesis that intensive treatment may selectively improve disease control in some subsets, but the lack of a survival advantage still limits the value of this observation. Interpretation of this should be considered carefully due to small sample size, the process of multiple observations, and other confounders.