Presidential session V

Thursday 24 September 2009, 12.30–14.30

J Clin Oncol 27:18s, 2009 (suppl; abstr 3)

G2 ASCO ABSTRACT

Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): results of a randomized phase II trial

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Background: TNBC is an aggressive breast cancer subtype that shares molecular and pathologic features with BRCA1-related breast cancers. BRCA-deficient cells are sensitive to inhibition of PARP1, a critical enzyme of cell proliferation and DNA repair, and thus represent a rational target of PARP inhibitor-based cancer therapy. The objectives of this study were to evaluate BSI-201, a potent PARP1 inhibitor, in combination with gemcitabine/carboplatin (G/C) in subjects with metastatic TNBC.
Methods: Eligible subjects had measurable disease and had $\leqslant$2 prior cytotoxic regimens for ER-, PR-, and HER2-negative metastatic breast cancer. Patients were randomized (1:1) to G/C alone or G/C + BSI-201. Gemcitabine (1000 mg/m^2) and carboplatin (AUC = 2) were given on days 1 and 8, and BSI-201 (5.6 mg/kg; iv; biweekly) on days 1, 4, 8, and 11 every 21 days. Endpoints were clinical benefit rate (CBR = CR + PR + SD $\geqslant$6 months), progression-free survival (PFS) and overall survival (OS).
Results: Analyses of the first 86 of a planned 120 patients showed that BSI-201 + G/C had improved CBR, median PFS, and median OS, compared with G/C alone. The frequency and nature of adverse events (AEs) did not differ between arms.
Conclusions: This preliminary analysis demonstrates that BSI-201 + G/C significantly improves CBR, PFS, and OS, compared with G/C alone. BSI-201 + G/C was well tolerated, with BSI-201 adding no significant toxicity to G/C. Updated CBR, PFS, and OS for all 120 patients and exploratory correlative analyses of PARP expression and clinical response will be presented.

J Clin Oncol Vol 27, No 15S (May 20 Supplement), 2009: CRA5507

G3 ASCO ABSTRACT

A phase III study comparing concurrent gemcitabine (Gem) plus cisplatin (Cis) and radiation followed by adjuvant Gem plus Cis versus concurrent Cis and radiation in patients with stage IIB to IVA carcinoma of the cervix

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Background: Cervical cancer is the second-most common cancer among women worldwide, in both incidence and mortality. Current standard therapy for locally advanced disease consists of concurrent Cis and external-beam radiation (XRT). This multicenter, open-label, randomized, phase III trial aimed to improve outcomes, capitalizing on the synergistic activity of Gem, Cis, XRT, and the potential value of adjuvant therapy.
Methods: Eligible patients (pts) with bulky stage IIB to IVA, 18–70 years of age, chemotherapy- and radiotherapy-naive, with a Karnofsky Performance Status score $\geqslant$70, were randomized to Arm A: Cis 40 mg/m2 followed by Gem 125 mg/m2 weekly $\times$6 doses with concurrent XRT (50.4 Gy: in 28 fractions: 1.8 Gy/day, 5 days/week), followed by brachytherapy (brachy) (30–35 Gy) and then 2 adjuvant 21-day cycles of Gem (1,000 mg/m2 on Days 1 and 8) plus Cis (50 mg/m2 on Day 1); or Arm B: Cis 40 mg/m2 weekly $\times$6 doses with concurrent XRT followed by brachy, given as in Arm A. Primary endpoint was progression-free survival (PFS) at 3 years, compared between arms using Kaplan–Meier methods and a Z-statistic.
Results: 515 pts were enrolled between 5/02 and 3/04 (259 pts Arm A, 256 pts Arm B). Median age was 46 years; stage IIB/IIIB/IVA in 61/37/2% of pts. Compliance in the concurrent and brachy phase was >90% for both arms; adjuvant cycles were completed by >75% of pts in Arm A. PFS at 3 years was 74% in Arm A compared to 65% in Arm B, resulting in a statistically significant improvement (p = 0.029). Overall survival (log-rank p = 0.0224) and time to progressive disease (log-rank p = 0.0008) were also significantly improved. Significantly more pts in Arm A experienced grade 3/4 toxicities (86.5%), compared to pts in Arm B (46.3%; Fisher's p < 0.001). In Arm A, 2 pts died due to causes probably related to treatment compared to 0 pts in Arm B.
Conclusions: This novel regimen of concurrent Gem plus Cis and XRT followed by brachy and adjuvant Gem plus Cis significantly improved outcomes in pts with locally advanced carcinoma of the cervix, at the expense of increased but acceptable toxicity, compared to the current standard of care.

7BA BEST ABSTRACT

Trastuzumab added to standard chemotherapy (CT) as first-line treatment in human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC): efficacy and safety results from the Phase III ToGA trial

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Background: Mortality due to GC remains unacceptably high and there is an urgent need for new treatments that are effective and less toxic than current therapies. Trastuzumab (Herceptin®; H), which has shown survival benefits in patients with HER2-positive breast cancer, was investigated for efficacy and safety in combination with CT for advanced HER2-positive GC in a randomised, prospective, Phase III trial: ToGA (BO18255; F Hoffmann-La Roche).
Materials and Methods: Patients with locally advanced, recurrent or metastatic HER2-positive gastro-oesophageal cancer or GC were randomised to receive either H+CT (cisplatin + either 5-fluorouracil or capecitabine) q3w for 6 cycles or CT alone. H therapy was continued until disease progression. The primary end point was overall survival (OS); secondary end points included progression-free survival (PFS), time to progression (TTP), overall response rate (ORR), duration of response (DoR), clinical benefit rate (CBR) and safety. Data release is based on the recommendation of the Independent Data Monitoring Committee following an interim analysis at which 75% of events (deaths) had occurred (median follow-up 17.1 months).
Results: Baseline characteristics were comparable across arms (CT, n = 290; H+CT, n = 294). Median OS was significantly improved in the H+CT arm compared with CT alone, as were all other efficacy parameters. Summaries of multiple and univariate Cox regression for OS will be presented.

	H+CT (n = 294)	CT (n = 290)	p value	Hazard ratio	95% CI
Median OS, months	13.8	11.1	0.0046	0.74	0.60, 0.91
Median PFS, months	6.7	5.5	0.0002	0.71	0.59, 0.85
Median TTP, months	7.1	5.6	0.0003	0.70	0.58, 0.85
ORR, %	47.3	34.5	0.0017		
Median DoR, months	6.9	4.8	0.0001	0.54	0.40, 0.73
CBR, %	78.9	69.3	0.0081		

Safety profiles in both arms were good: 201 (68%) and 198 (68%) patients in the H+CT and CT arms, respectively, experienced grade 3/4 adverse events. An increased frequency of diarrhoea was observed in the H+CT arm versus CT (37% vs 28%, respectively), though this was lower than expected. No difference in symptomatic congestive heart failure was observed between arms. Asymptomatic decreases in left ventricular ejection fraction were reported in 4.6% and 1.1% of patients in the H+CT and CT arms, respectively.
Conclusions: ToGA results show a significant and clinically meaningful improvement in OS and all secondary efficacy parameters. Addition of H to CT is a novel, effective and well-tolerated treatment that sets a new standard in patients with HER2-positive GC.