(PFS) or overall survival (OS), compared with standard cisplatin (CIS) plus docetaxel (DOC). Rafael Rosell, MD, USP Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain, presented data from the Multicenter, Predictive, Prospective, Phase 3, Open, Randomized Pharmacogenomic Study in Patients With Advanced Lung Carcinoma study [BREC; NCT00617656; Moran T et al. *J Clin Oncol* 2013 (suppl; abstr LBA8002)].

Previous studies have demonstrated that levels of BRCA1 and a component of the BRCA1 complex, called RAP80, can influence patient outcomes when treated with CIS plus gemcitabine (GEM), CIS plus DOC, or DOC alone [Rosell R et al. *PLoS ONE* 2009]. Overexpression of BRCA1 can confer resistance to agents such as CIS, yet high sensitivity to agents such as paclitaxel, DOC, and vinorelbine [Quinn JE et al. *Cancer Res* 2003]. The hypothesis of the BREC trial was that customizing lung cancer treatment based on BRCA1 and RAP80 levels would improve patient outcomes compared with noncustomized CIS plus DOC.

In the multicenter, prospective Phase 3 BREC trial, 382 patients with advanced lung cancer and wild-type EGFR were randomized 1:1 to receive treatment based on BRCA1 or RAP80 levels or standard treatment with CIS and DOC. Patients with low levels of RAP80 received CIS and GEM, regardless of BRCA1 levels; patients with intermediate to high levels of RAP80 and low to intermediate levels of BRCA1 received CIS and DOC; and patients with intermediate to high levels of RAP80 and high BRCA1 levels received DOC only.

The histology of the tumors was 50.9% adenocarcinoma, 35.5% squamous-cell carcinoma, 8.2% large-cell carcinoma, and 5.4% undifferentiated carcinoma. The primary endpoint of the BREC study was PFS. OS and tumor response rate, as measured by RECIST, were the secondary endpoints of the trial. The planned interim analysis occurred when disease progression occurred in 50% of the patients. The interim analysis analyzed data from 287 patients.

The primary endpoint was not reached. PFS was significantly longer in the control arm, with a PFS of 5.49 months, compared with 4.38 months in the experimental arm (p=0.07), resulting in an HR of 1.35 (95% CI, 1.02 to 1.78; p=0.03). Interestingly, the PFS was similar among the patients that received DOC plus CIS (control arm; 5.49 months), GEM plus CIS (5.43 months), and DOC plus CIS (5.49 months). However, patients that received only DOC had a median PFS of 2.50 months (p=0.003) associated with an HR of 2.65 (p=0.0001). In addition, the rate of OS was 12.66 months in the control arm, compared with 8.52 months in the experimental arm (p=0.006). Patients that received GEM plus CIS, DOC plus CIS, and DOC alone had an OS of 7.70 months (p=0.02), 11.25 months (p=0.28), and 7.24 months (p=0.001), respectively.

A multivariate analysis of the experimental arm, BRCA1, RAP80, tumor histology, smoking status, and metastatic site was performed. An increased risk of progression was associated only with extrathoracic metastases (HR, 1.78; p=0.02).

Due to the increased risk of PFS in the experimental group, the BREC trial was closed prematurely. Prof. Rosell concluded by suggesting that the negative outcome of the study may have been, in part, due to the poor predictive capacity of RAP80 for treatment customization. In addition, he pointed out that DOC plus CIS may not be an optimal choice for the control arm.

PRONOUNCE Study Results

Written by Mary Beth Nierengarten

In patients with advanced nonsquamous non-small cell lung cancer (NSCLC), first-line treatment with pemetrexed plus carboplatin (PemC) followed by maintenance Pem is not associated with superior progression-free survival without Grade 4 toxicities (G4PFS) compared with treatment with paclitaxel/carboplatin/bevacizumab (PCB) followed by maintenance bevacizumab (BEV).

Ralph Zinner, MD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented the results of the Study of Patients With Advanced Non-Small Cell Lung Cancer [PRONOUNCE; NCT0948675; Zinner R et al. *J Clin Oncol* 2013 (suppl; abstr LBA8003)], a randomized, open-label, Phase 3 study that assessed the superiority of 2-drug regimen PemC compared with 3-drug regimen PCB in patients with advanced NSCLC.

A total of 361 patients were enrolled in the study, all of who met the eligibility criteria: age ≥18 years, stage IV NSCLC, an ECOG PS of 0 to 1, chemotherapy-naïve status, and stable treated central nervous system metastases. Patients with uncontrolled effusions were excluded from the study.

Of the 361 patients, 182 were randomized to PemC and 179 to PCB. Patients in both arms received 4 cycles of induction therapy followed by maintenance therapy in the absence of progressive disease or discontinuation of therapy. The PemC group received 4 cycles of induction Pem (500 mg/m^2) and CBP (area under the curve [AUC]=6) followed by Pem maintenance therapy, and the PCB group received induction paclitaxel (200 mg/m^2), CBP (AUC=6), and BEV (15 mg/kg) followed by BEV maintenance therapy.

Baseline characteristics were similar between the two treatment groups, with a median age of 66 years, 42% female, the majority Caucasian, 47% ECOG PS 0, and 70% disease stage M1b.

The primary endpoint of the study was a composite endpoint of G4PFS. Secondary endpoints included PFS, overall survival (OS), response rates (RR), disease-control rates (DCR), and safety/tolerability.

Based on an intention-to-treat analysis, the study found no difference in G4PFS between PemC and PCB (median 3.9 vs 2.9 months; HR, 0.85; 90% CI, 0.70 to 1.04; log-rank p=0.176).

In addition, the study found no differences between PemC and PCB in PFS (median 4.4 vs 5.5 months; HR, 1.06; 95% CI, 0.84 to 1.35; log-rank p=0.610), OS (median 10.5 vs 11.7 months; HR, 1.07; 95% CI, 0.83 to 1.36; log-rank p=0.616), RR (23.6% vs 27.4%; p=0.414), or DCR (59.9% vs 57.0%; p=0.575).

Based on the actual study regimen of 171 patients treated with PemC and 166 treated with PCB, the study found that the PemC group had significantly more drug-related Grade 3/4 anemia (18.7% vs 5.4%; p<0.001) and thrombocytopenia (24.0% vs 9.6%; p<0.001). Patients treated with PCB had significantly more drug-related Grade 3/4 neutropenia than the PemC group (48.8% vs 24.6%; p<0.001) and Grade 1 and Grade 2 alopecia (16.3% vs 5.8%;p=0.003; and 12.0% vs 2.3%; p<0.001, respectively).

According to the investigators, there were no unexpected toxicities and both treatments demonstrated tolerability.

RIGHT Study Results

Written by **Maria Vinall**

Rechallenge of imatinib significantly improves progression-free survival (PFS) and disease control rate (DCR) in patients with advanced gastrointestinal stromal tumor (GIST) after the failure of at least imatinib and sunitinib, likely by continuous kinase inhibition of the bulk of disease clones which retain imatinib sensitivity. Tyrosine-kinase inhibitor (TKI)-resistant clones continue to progress, however, resulting in a relatively brief duration of benefit.

Despite having received highly effective treatments such as imatinib and sunitinib, >80% of patients with advanced GIST experience disease progression. Based on evidence of rapid GIST progression after discontinuation of all TKIs, common practice has been to resume imatinib therapy in these patients, even though the efficacy of this approach has not been proven in prospective clinical trials. Yoon-Koo Kang, MD, PhD, University of Ulsan College of Medicine, Seoul, South Korea, presented data from the Rechallenge of Imatinib in GIST Having No Effective Treatment study [RIGHT; NCT01151852; Kang YK et al. *J Clin Oncol* 2013 (suppl; abstr LBA10502)], which evaluated the efficacy of imatinib rechallenge in patients with advanced GIST following failure of all TKIs.

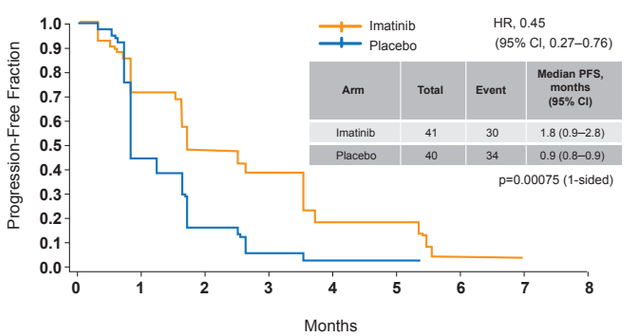
Eligible patients included adults with metastatic and/or unresectable GIST and prior benefit from first-line imatinib (defined as complete response [CR], partial response [PR], or stable disease [SD] for >6 months on imatinib 400 mg/day) and disease progression with at least both first-line imatinib and second-line sunitinib. Stratification was based on ECOG PS (0 to 1 vs 2 to 3) and use of third-line TKI. Subjects were randomized to receive oral imatinib 400 mg QD or placebo.

At the time of disease progression, subjects in the placebo group were permitted to cross over to open-label imatinib. Subjects receiving imatinib were permitted to continue or stop imatinib. The primary study endpoint was PFS determined by blinded external radiology review according to RECIST v1.0. Response was evaluated by computed tomography, every 4 weeks for the first 4 months then every 8 weeks until disease progression or death. Secondary endpoints included disease control rate (DCR: CR+PR+SD) at 12 weeks, overall survival (OS), time to progression, and safety.

Between July 2010 and January 2013, 81 patients were randomized (imatinib, n=41; placebo, n=40) at a single Korean center. More than 65% of the study participants were men; the median age was 60 years. Approximately 40% of subjects had received ≥3 prior TKIs. The small bowel was the most common disease site followed by the stomach. About 60% of patients had received imatinib as first-line therapy for >2 years.

At study end in March 2013, median PFS was significantly longer for patients randomized to imatinib (1.8 months) versus placebo (0.9 months; HR, 0.45; 95% CI, 0.27 to 0.76; p=0.00075; Figure 1). The HR was <0.6 for all of the preplanned subgroups, strongly favoring imatinib. DCR at 12 weeks was 31.7% for imatinib versus 5% for placebo (p=0.003). The median PFS for the 37 subjects in the placebo arm who crossed over to imatinib after progression was 1.7 months, indicating the limited duration of the treatment response. Median OS was 8.2 months for imatinib versus 7.5 months for placebo (HR, 0.99; p=0.4912; Figure 2). The most common Grade 3 or higher treatment-emergent AEs during the double-blind period in the imatinib arm included anemia (29%), fatigue (10%), and hyperbilirubinemia (7%).

Figure 1. Progression-Free Survival



PFS=progression-free survival.

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