The results of the PHARE trial were inconclusive for the noninferiority hypothesis. Nevertheless, a trend favoring the standard 12 months of treatment in DFS and OS was observed.

Breast Cancer: Updated Overall Survival Results from EMILIA

Written by Phil Vinall

Trastuzumab emtansine (T-DM1) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate, composed of trastuzumab, a stable thioether linker, and the potent cytotoxic, microtubule inhibitor DM1. It retains the HER2-directed antitumor properties of trastuzumab and allows for the intracellular delivery of T-DM1 [LoRusso PM et al. *Clin Cancer Re*s 2011]. Preclinical studies have shown T-DM1 to be up to 500 times more potent than taxane. Sunil Verma, MD, Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada, reported updated study results of a trial showing that progression-free survival (PFS) and overall survival (OS) significantly improved in patients with breast cancer treated with T-DM1 compared with capecitabine (CAP) plus lapatinib (LAP). The study was published to coincide with the presentation [Verma S et al. *N Engl J Med* 2012].

An Open-Label Study of Trastuzumab Emtansine versus Capecitabine+Lapatinib in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer [EMILIA; NCT00829166] was a randomized Phase 3 trial evaluating T-DM1 compared with CAP plus LAP. Patients with HER2-positive locally advanced or metastatic breast cancer, previously treated with taxane and trastuzumab were randomized to intravenous T-DM1 (3.6 mg/kg every 3 weeks; n=495) or oral CAP (1000 mg/m^2 BID on Days 1 to 14 every 3 weeks plus oral LAP 1250 mg QD on Days 1 to 21; n=496). The primary study end points were PFS, OS, and safety.

Subjects were a median age of 53 years, mostly White, and had an Eastern Cooperative Oncology Group Performance Status score of 0 (61% to 64%) or 1 (36% to 39%). Up to 80% of patients had measurable disease; up to 68% had visceral disease, and up to 33% had at least 3 sites of metastatic disease. About 55% of patients were estrogen and/or progesterone (ER/PR)-positive.

The final PFS and first interim OS analyses were presented at the 2012 annual American Society of Clinical Oncology meeting [Blackwell KL et al. ASCO 2012. Abstract LBA1]. The first interim OS analysis (median OS: CAP plus LAP, 23.3 months; T-DM1 not reached; HR, 0.621; 95% CI, 0.48 to 0.81; p=0.0005) did not cross the efficacy stopping

boundary (p=0.0003 or HR=0.617). Dr. Verma presented results of a second interim analysis conducted after 52% of the total targeted number of OS events had been reached. In this analysis, OS significantly favored T-DM1 (30.9 vs 25.1 months; p=0.0006); median follow-up was 19.1 months for T-DM1 and 18.6 months for CAP plus LAP. The OS benefit was observed in most subgroups, including line of metastatic therapy (1st, 2nd, 3rd, or later), ER/PR status, and age, although the subgroup of patients aged >75 years was too small to confirm benefit. The secondary endpoints of objective response rate and duration of response also favored T-DM1.

Approximately 53% of CAP patients and 27% of LAP patients required a dose reduction compared with 16% of T-DM1 patients. T-DM1 was well tolerated and associated with fewer grade ≥3 adverse events (40.8% vs 57.0%), except for thrombocytopenia (12.9 % vs 0.2%), increased serum aminotransferase levels, and anemia. Adverse events leading to treatment discontinuation were higher for CAP plus LAP (10.7%) patients relative to T-DM1 (5.9%) patients. The rates of cardiac dysfunction adverse events were low and similar in both arms.

The study researchers concluded that T-DM1 should offer an important therapeutic option in the treatment of HER2-positive metastatic breast cancer patients. Final OS analysis (descriptive only) is expected in 2014.

Phase 3 Study of Crizotinib Versus Pemetrexed or Docetaxel Chemotherapy in Patients with Advanced ALK-Positive NSCLC

Written by Toni Rizzo

Although single-agent second-line chemotherapy has limited efficacy in unselected non-small cell lung cancer (NSCLC), its effect in advanced anaplastic Kinase positive (ALK+) NSCLC is uncertain. Crizotinib has marked clinical activity in ALK+ NSCLC [Camidge DR et al. *Lancet Onco*l 2012; Kim DW et al. ASCO 2012. Abstract 7533]. The PROFILE 1007 [NCT00932893] trial, presented by Alice Tsang Shaw, MD, PhD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, compared the efficacy and safety of crizotinib with standard chemotherapy as second-line therapy in patients with advanced ALK+ NSCLC.

A total of 347 patients with previously treated stage IIIB/IV ALK+ NSCLC were randomized to crizotinib (250 mg BID, orally, 21-day cycle; n=173) versus pemetrexed

(500 mg/m^2 IV) or docetaxel (75 mg/m^2 IV) on Day 1 of a 21-day cycle (n=174). The primary endpoint was progression-free survival (PFS). The secondary endpoints included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes. Median follow-up was 12.2 months for the crizotinib group and 12.1 months for the chemotherapy group. Baseline characteristics for the 2 treatment arms were similar.

Median PFS in the crizotinib group was 7.7 versus 3.0 months in the chemotherapy group (HR, 0.49; 95% CI, 0.37 to 0.64; p<0.0001). When stratified according to chemotherapy, median PFS was 4.2 months in the pemetrexed group (n=99; HR, 0.59; 95% CI, 0.43 to 0.80; p=0.0004) and 2.6 months in the docetaxel group (n=72; HR, 0.30; 95% CI, 0.21 to 0.43; p<0.0001).

ORR was 65.3% with crizotinib versus 19.5% with chemotherapy (pemetrexed, 29.3%; docetaxel, 6.9%; ORR ratio, 3.4; 95% CI, 2.5 to 4.7; p<0.0001). Interim analysis showed a median OS of 20.3 months with crizotinib (n=173) versus 22.8 months with chemotherapy (n=174 [111 patients who had disease progression were allowed to crossover to crizotinib]; HR, 1.02; 95% CI, 0.68 to 1.54; p=0.5394; HR adjusted for crossover, 0.83; 95% CI, 0.36 to 1.35).

Any-cause grade 3/4 adverse events (AEs) occurring in ≥3% of patients with crizotinib versus chemotherapy were elevated transaminases (16% vs 2%), pulmonary embolism (5% vs 2%), dyspnea (4% vs 3%), pneumonia (4% vs 2%), hypokalemia (4% vs 0%), electrocardiogram QTc prolongation (4% vs 0%), neutropenia (13% vs 19%), febrile neutropenia (1% vs 9%), anemia (2% vs 5%), decreased white blood cells (1% vs 5%), and fatigue (2% vs 4%). A total of 25 (15%) deaths occurred with crizotinib versus 7 (4%) with chemotherapy. There were 11 (6%) study treatment-related permanent discontinuations with crizotinib versus 17 (10%) with chemotherapy.

Patients reported greater improvement from baseline in lung cancer symptoms with crizotinib versus chemotherapy (p<0.0001). Patient-reported global quality of life (European Organization for Research and Treatment quality of life questionnaires QLQ-C30 and QLQ-LC13) was significantly better with crizotinib versus chemotherapy (estimated difference, 9.84; 95% CI, 5.39 to 14.28; p<0.0001).

PROFILE 1007 showed that crizotinib significantly prolonged PFS and improved ORR compared with single-agent chemotherapy in patients with advanced previously treated ALK+ NSCLC. No statistically significant difference in OS was observed, but the interim analysis was immature and may have been affected by crossover to crizotinib from the chemotherapy groups.

Crizotinib has a distinct AE profile compared with chemotherapy, but AEs generally were tolerable and manageable. Compared with single-agent chemotherapy, crizotinib was associated with significantly greater improvement from baseline in lung cancer symptoms and quality of life. According to Dr. Shaw, these results establish crizotinib as the standard of care for patients with advanced previously treated ALK+ NSCLC.

CORRECT Trial of Regorafenib in Metastatic Colorectal Cancer: Overall Survival Update

Written by Phil Vinall

There is a significant unmet clinical need for treatment options for metastatic colorectal cancer (mCRC). Regorafenib (BAY 73-4506) is an oral multikinase inhibitor that targets multiple tumor pathways [Wilhelm SM et al. *Int J Cancer* 2011; Mross K et al. *Clin Cancer Res* 2012; Strumberg D et al. *Expert Opin Investig Drugs* 2012]. Eric Van Cutsem, MD, University Hospitals Gasthuisberg/Leuven, Leuven, Belgium, presented updated overall survival (OS) data from the Patients with Metastatic Colorectal Cancer Treated with Regorafenib or Placebo After Failure of Standard Therapy [CORRECT; NCT01103323] trial. The study demonstrated increased survival benefits following regorafenib treatment in patients with previously treated mCRC.

CORRECT was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial conducted from May 2010 through March 2011 in 114 centers in 16 countries. Patients with mCRC treated with available standard therapies (chemotherapy and monoclonal antibodies) and progressing during or ≤3 months after last standard therapy were randomized to regorafenib (160 mg PO QD, 3 weeks on, 1 week off; no crossover at progression permitted) plus best supportive care (n=505) or placebo (QD, 3 weeks on, 1 week off) plus best supportive care (n=255), with treatment continued until disease progression, unacceptable toxicity, or patient or investigator stopped the treatment. The primary endpoint was OS. Secondary endpoints included disease control rate and safety. This trial met its primary endpoint at a preplanned interim analysis, the results of which have been presented previously [Van Cutsem E et al. *J Clin Oncol* 2012]. Updated OS data are reported here.

Subjects were mostly white (>77%) with a median age of 61 years (range 22 to 85). For regorafenib and placebo, they had an Eastern Cooperative Oncology Group Performance Status of 0 (52.5% vs 57.3%, respectively)