OPTiM Study Results

Written by Maria Vinall

Results from the Efficacy and Safety Study of OncoVEX Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Compared to GM-CSF in Melanoma [OPTiM; NCT00769704; Andtbacka RHI et al. *J Clin Oncol* 2013 (suppl; abstr LBA9008)] reported by Robert H. I. Andtbacka, MD, University of Utah, Salt Lake City, Utah, USA, showed that a genetically modified version of herpes simplex virus type 1 (talimogene laherparepvec [T-VEC]), is safe and improves durable response rate (DRR) in patients with unresectable stage IIIB-IV melanoma.

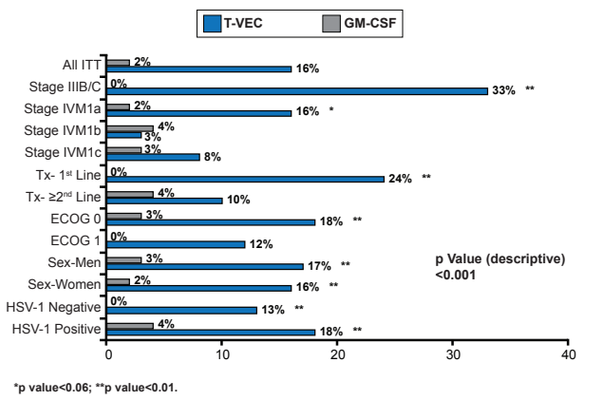
T-VEC is an oncolytic immunotherapy derived from herpes simplex virus type-1 designed to selectively replicate within tumors and to produce GM-CSF to enhance systemic antitumor immune responses. OPTiM is a randomized, Phase 3 trial of T-VEC or GM-CSF in patients with unresected melanoma with regional or distant metastases.

OPTiM enrolled adult patients with injectable unresectable stage IIIB/C or IV melanoma. Subjects were randomized to receive intralesional T-VEC (initially ≤4 mL x 106 plaque forming units [pfu]/mL then after 3 weeks, ≤4 mLx108 pfu/mL Q2W) or subcutaneous GM-CSF (125 µg/m^2 for 14 days of every 28-day cycle). T-VEC injection volume was based on lesion size. Patients remained on treatment beyond progression unless clinically significant after 24 weeks. The primary study endpoint was DRR, defined as objective complete response (CR) or partial response (PR) lasting for at least 6 months and beginning within 12 months of treatment. Secondary endpoints included overall survival (OS), objective overall response rate (ORR), time-to-treatment failure (TTF) and safety. Responses were per modified World Health Organization criteria by blinded central review.

The intention-to-treat population (57% men; 51% <65 years) comprised 295 subjects randomized to T-VEC and 141 randomized to GM-CSF. About two thirds of the study participants were stage IV (IVM1a 27%, IVM1b 21%, IVM1c 22%) the remainder were stage IIIB/C. T-VEC patients were treated for a median of 23 weeks (range, 0.1 to 78.9) versus 10 weeks (range, 0.6 to 72) for patients receiving GM-CSF.

The DRR for T-VEC was 16.3% versus 2.1% with GM-CSF (unadjusted OR, 8.9; 95% CI, 2.7 to 29.2; p<0.0001). The ORR with T-VEC was 26.4% (95% CI, 21.4 to 31.5) with 10.8% CR and 15.6% PR compared with an ORR of 5.7% (95% CI, 1.9 to 9.5) with 0.7% CR and 5.0% PR for GM-CSF. T-VEC was associated with an improvement in DRR in all of the major planned subset analyses, particularly in patients with nonvisceral disease and among patients for whom T-VEC was used as first-line therapy (Figure 1).

Figure 1. Durable Response Rate by Key Covariates



GM-CSF=granulocyte-macrophage colony-stimulating factor; HSV=herpes simplex virus; ITT=intention to treat; T-VEC=talimogene laherparepvec.

Median TTF was 8.2 months for patients treated with T-VEC versus 2.9 months for GM-CSF-treated patients (HR, 0.42; 95% CI, 0.32 to 0.54; p<0.0001). There was a trend to improved OS with T-VEC.

Eleven patients in the T-VEC arm (3.8%) discontinued the study due to an adverse event (AE) compared with 3 patients (2.4%) in the GM-CSF arm. AEs occurring in >20% of patients with T-VEC were fatigue, chills, pyrexia, nausea, flu-like symptoms, injection-site pain and vomiting. The only Grade 3/4 AE occurring in >2% of patients was cellulitis (2.1%). There were 10 fatalities in the T-VEC arm, but none were treatment related.

T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a Phase 3 trial and represents a novel potential treatment option for melanoma with regional or distant metastases.

FOLFIRI Plus Cetuximab Prolongs Overall mCRC Survival

Written by Maria Vinall

In a head-to-head comparison, cetuximab (CET; an epidermal growth factor receptor inhibitor) combined with first-line leucovorin/5-fluorouracil/irinotecan (FOLFIRI) chemotherapy improved overall survival (OS)

relative to bevacizumab (BEV; an angiogenesis inhibitor) plus FOLFIRI in patients with KRAS wild-type metastatic colorectal cancer (mCRC). Sebastian Stintzing, MD, Ludwig-Maximilian-University of Munich, Munich, Germany, presented the results of the 5-FU, Folinic Acid and Irinotecan (FOLFIRI) Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First-Line Treatment Colorectal Cancer (CRC) study, [FIRE-3; NCT00433927; Heinemann V et al. *J Clin Oncol* 2013 (suppl; abstr LBA3506)].

FIRE-3 was a randomized, Phase 3, multicenter trial conducted at 150 centers in Germany and Austria to compare the efficacy of FOLFIRI Q2W (Tournigand regimen) plus CET (400 mg/m^2 Day 1, followed by 250 mg/m^2 weekly; n=297) or the FOLFIRI regimen plus BEV (5 mg/kg Q2W; n=295). Participants were adults (aged ≥18 years) with histologically confirmed diagnosis of mCRC KRAS wild type and ECOG-PS 0 to 2. Prior adjuvant chemotherapy was permitted if completed >6 months before study start.

The primary study endpoint was overall response rate (ORR) measured by modified RECIST v1.0. Secondary endpoints included progression-free survival (PFS), OS, time to failure of strategy, tumor volume changes, and safety and tolerability.

In total, 752 patients were enrolled in the study, of which 592 were KRAS wild type and formed the intention-to-treat (ITT) population. For the response analysis, a second population was predefined to include patients who received ≥3 cycles of chemotherapy and one computed tomography (CT) scan after baseline (n=526). Study participants were 66% men, median age 64 years; 98% were ECOG PS 0 to 1. There was no significant difference in tumor subtype characteristics, the number of metastatic sites or prior types of treatment between the two groups; ~31% of patients in both groups had liver metastasis only. Treatment duration was similar, but patients in the BEV arm received a median of two more cycles than those in the CET arm (p=0.014).

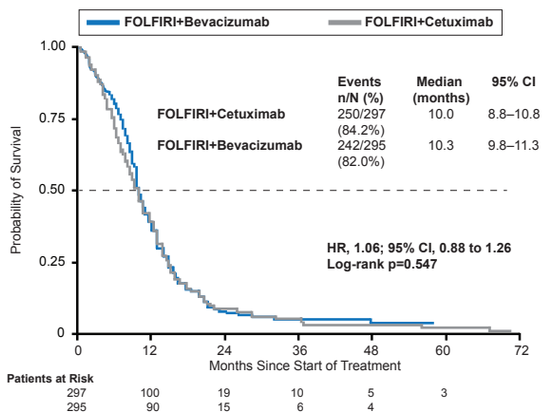
Within the ITT population, there was no significant difference in ORR (CET 62% vs BEV 58%; OR, 1.18; 95% CI, 0.85 to 1.64; p=0.183). The primary endpoint of the study has therefore not been met. However, in the 526 patients assessable for response, the ORR for CET was significantly higher than with BEV (72.2% vs 63.1%; OR, 1.52; 95% CI, 1.05 to 2.19; p=0.017).

In the ITT population, more patients receiving CET had a complete response, while more patients receiving BEV had stable disease. Median PFS did not differ between the CET (10.0 months) and BEV (10.3 months) treatment groups (HR, 1.06; 95% CI, 0.88 to 1.26; p=0.547; Figure 1).

However, OS was significantly prolonged in the CET arm (28.7 months) compared with the BEV arm (25.0 months; HR, 0.77; 95% CI, 0.62 to 0.96; p=0.017; Figure 2).

An exploratory subgroup analysis (age, gender, number of metastatic sites, liver limited disease, and leukocyte counts) favored FOLFIRI plus CET for OS. There were no significant differences in hematological toxicities between treatment arms. Nonhematologic toxicities were comparable for ≥Grade 3, but for any grade toxicity, hand-foot syndrome was more common in the CET arm while nausea and vomiting were more frequent with BEV. Sixty-day mortality was low in both arms (1.01% for CET vs 2.71% for BEV).

Figure 1. Progression-Free Survival



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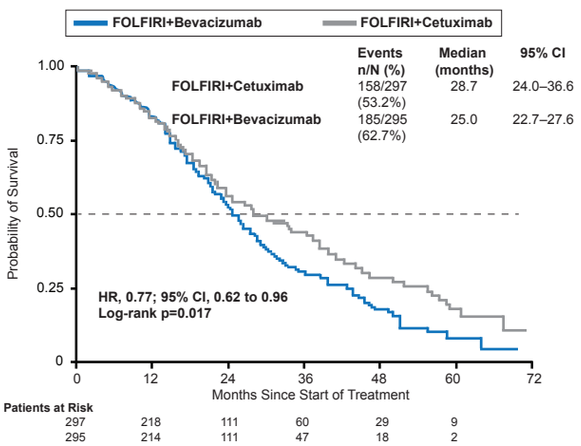
In explaining the possible reason for the differences in OS, Prof. Stintzing pointed to the CRYSTAL trial, which showed that tumor size reduction is more predictive of OS than PFS [Mansmann UR et al. *J Clin Oncol* 2013 (suppl; abstr 3630)]. There is currently an ongoing independent review of the FIRE-3 CT scans to assess tumor volume changes.

Figure 2. Overall Survival



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