INTERVIEW

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Tracks 1-8

Track 1 Efficacy, tolerability and sequencing of FOLFIRINOX and *nab* paclitaxel/gemcitabine in metastatic pancreatic cancer (mPC)

Track 2 Results of the Phase II RECAP trial of capecitabine with or without the selective oral JAK1 and JAK2 inhibitor ruxolitinib as second-line therapy for mPC

Track 3 Ongoing Phase III trials — JANUS 1 and 2 — evaluating capecitabine and ruxolitinib for patients with metastatic adenocarcinoma of the pancreas with disease progression or intolerance to first-line chemotherapy

Track 4 Discussing risk stratification and treatment options for patients with Stage II colon cancer

Track 5 Investigating potential predictors of benefit for bevacizumab in mCRC and other solid tumors

Track 6 STEAM: An ongoing Phase II trial of sequential and concurrent FOLFOXIRI/bevacizumab versus FOLFOX/bevacizumab as first-line therapy for mCRC

Track 7 Understanding and targeting resistance to anti-angiogenic therapies

Track 8 Novel approach to the management of regorafenib-associated hand-foot syndrome

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss the data set you presented at the ASCO 2014 meeting evaluating capecitabine and the oral JAK1/JAK2 inhibitor ruxolitinib in metastatic pancreatic cancer?

DR HURWITZ: This study was a randomization of 127 patients to capecitabine/placebo versus capecitabine/ruxolitinib. The main endpoint was overall survival, and in the unselected population a modest improvement in overall survival was observed. The hazard ratio was 0.79, but the key message was found in the preplanned subgroup analysis of patients with a C-reactive protein (CRP) above the median, which was 13 mg/L.

In this subgroup the hazard ratio was 0.47, and the *p*-value was highly significant at 0.01 (Hurwitz 2014; [4.1]). A similar trend was also observed in the unselected and high CRP groups related to progression-free survival.

The study also evaluated inflammation, via the so-called Modified Glasgow Prognostic Score, which is essentially 2 components: CRP, cut off at 10 mg/L rather than 13 mg/L,

4.1 **RECAP: A Phase II Study of Ruxolitinib (Rux) or Placebo (Pbo) with Capecitabine (Cape) as Second-Line Therapy for Patients with Metastatic Pancreatic Cancer**

Efficacy	Rux/cape (n = 64)	Pbo/cape (n = 63)
Overall survival (intent-to-treat population)		
Median overall survival*	136.5 days	129.5 days
3-month survival rate	64%	58%
6-month survival rate	42%	35%
12-month survival rate	22%	11%
Efficacy	**Rux/cape (n = 31)**	**Pbo/cape (n = 29)**
Overall survival (patients with CRP >13 mg/L)		
Median overall survival†	83.0 days	55.0 days
3-month survival rate	48%	29%
6-month survival rate	42%	11%
12-month survival rate	11%	0%
Select Grade 3/4 adverse events	**Rux/cape (n = 59)**	**Pbo/cape (n = 60)**
Anemia	15.3%	1.7%
Thrombocytopenia	1.7%	3.3%
Neutropenia	0%	1.7%

* Hazard ratio = 0.79; 2-sided *p*-value = 0.25
† Hazard ratio = 0.47; 2-sided *p*-value = 0.01

Hurwitz H et al. *Proc ASCO* 2014;**Abstract 4000**.

and serum albumin, classified as low or normal. The patients with high CRP and low albumin benefited from ruxolitinib most.

Interestingly, patients gained weight on the ruxolitinib arm more than patients on the placebo arm, and the weight gain had to be qualified as both sustained and not associated with fluid retention. In the intent-to-treat, high CRP and low CRP groups, the amount of weight gain was greater with ruxolitinib — the percent of patients with some degree of weight gain varied between 20% and 40% on the ruxolitinib arm across those different subgroups, compared to between 5% and approximately 10% on the capecitabine/placebo arm.

The positive results from this trial led to 2 Phase III studies, JANUS 1 and JANUS 2 (NCT02117479; NCT02119663). I suspect, considering the amount of attention now placed on immunity and inflammation being linked to biology, that we will see many other strategies to try to target this axis beyond ruxolitinib.

Track 6

DR LOVE: Would you discuss the randomized Phase II STEAM trial comparing sequential and concurrent FOLFOXIRI/bevacizumab regimens to FOLFOX/bevacizumab as first-line therapy for patients with mCRC (NCT01765582)?

DR HURWITZ: This study is the US follow-up to the European Phase III TRIBE trial, which evaluated FOLFIRI/bevacizumab versus FOLFOXIRI/bevacizumab. The data looked good, with a higher response rate and better progression-free and overall survival by front-loading the more intense chemotherapy for a limited induction period, followed by maintenance (Loupakis 2014).

The American version, the STEAM trial, uses FOLFOX/bevacizumab as the control group and FOLFOXIRI/bevacizumab, as used in TRIBE, as the experimental arm. The second experimental group, so-called modified FOLFOXIRI in combination with bevacizumab, is essentially sequential FOLFOX followed by FOLFIRI (Bendell 2014). This may be a way of mitigating some of the significant myelosuppression that's sometimes observed and the side effects that come with the whole package. The study is ongoing, and it's accruing well with no unexpected side effects, at least initially, from the dose and schedule here in the US population.

Considering the activity in the TRIBE trial and the frequent use of the cousin regimen of FOLFIRINOX in pancreatic cancer, I believe that having good data on whether the triplet is better in patients with colorectal cancer would be useful, particularly for those patients who may have so-called borderline resectable disease, in which case a little extra response may be especially useful.

Track 8

DR LOVE: What's your experience with regorafenib, and how does it figure into your practice in the management of mCRC?

DR HURWITZ: The main issue with regorafenib, at least as it appears in patients in the United States, is tolerability. The 160-mg/day dose that was used in the CORRECT study, which is also in the package insert, is challenging to tolerate for many patients. A number of strategies are being evaluated to try to avoid the toxicity problems, including starting at a lower dose such as 80 mg or 120 mg instead.

The side effects tend to include fatigue, liver function changes and hand-foot syndrome, and they can be mitigated with dose adjustments. Our group is interested in a potential treatment for the associated hand-foot syndrome. We believe that it may be related to a conserved biology of the vasculature in the palms and soles and that some of it may be mediated by nitric oxide.

Agents that could be applied topically that would modulate nitric oxide might be useful, and one of them, ironically, would be a phosphodiesterase-5 inhibitor such as sildenafil. We only have anecdotal data, but you can apply it topically. You would have to obtain either the active pharmaceutical ingredient with a compounding pharmacy or grind it up — I would discourage oral administration. The dose intensity you'd be likely to observe on the skin would probably not be adequate. I am hopeful that we can garner support for a proper randomized study to ascertain whether the anecdotes can be confirmed. ■

SELECT PUBLICATIONS

Bendell JC et al. **STEAM: A randomized, open-label, phase 2 trial of sequential and concurrent FOLFOXIRI-bevacizumab (BEV) versus FOLFOX-BEV for the first-line (1L) treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC).** *Proc ASCO* 2014;**Abstract TPS3652**.

Loupakis F et al. **Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer.** *N Engl J Med* 2014;371(17):1609-18.