INTERVIEW

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Tracks 1-15

Select Excerpts from the Interview

Track 2

DR LOVE: To date, we only have indirect comparisons of the efficacy of FOLFIRINOX and gemcitabine/*nab* paclitaxel in advanced pancreatic cancer. What is your perspective on these regimens?

DR O'REILLY: Compared to single-agent gemcitabine, both regimens have shown improved tumor response, disease control and overall survival. The numerical outcomes

in terms of median survivals favor FOLFIRINOX, but one has to consider that these studies were conducted in somewhat different patient populations.

FOLFIRINOX was studied in patients with an ECOG performance status of 0 to 1 and an upper age limit of 75. Gemcitabine/paclitaxel was studied in a broader community-/academic-based setting, including patients with a lower performance status and without an upper age limit.

The US Oncology Network reported some interesting data from a retrospective analysis of patients in their database suggesting that in equivalent populations, FOLFIRINOX fared favorably compared to gemcitabine and *nab* paclitaxel, but this is not a direct head-to-head comparison in a randomized study (Cartwright 2014). I believe the choice of chemotherapy largely depends on what toxicities are acceptable to patients.

Track 4

DR LOVE: Would you discuss the results of the Phase III NAPOLI-1 trial evaluating nanoliposomal irinotecan, or MM-398, for patients with metastatic pancreatic cancer (Von Hoff 2014; [3.1, 3.2])?

DR O'REILLY: The NAPOLI-1 trial evaluated nanoliposomal irinotecan with or without infusional 5-FU and leucovorin (5-FU/LV) versus 5-FU/LV. This was a pragmatic study in terms of its design. The eligibility criteria were interesting. Patients had to have received at least one prior gemcitabine-based regimen, and that could have been first-line treatment for metastatic disease, a neoadjuvant regimen or a front-line treatment in the locally advanced disease setting.

The bottom line was that a survival benefit was seen with the addition of MM-398 to 5-FU/LV compared to the control arm of 5-FU/LV. We're still awaiting the detailed breakdown of those who benefited to see if any subgroups of patients within the broad inclusion criteria benefited more than others. The toxicity profile appeared fairly similar to what one might see with irinotecan in its parent form. We're hopeful that this may offer an additional option in the previously treated disease setting. However, it is unlikely to replace currently available therapies.

3.1

NAPOLI-1: Efficacy Results of a Phase III Trial of MM-398, with or without 5-Fluorouracil (5-FU) and Racemic Leucovorin (LV) versus 5-FU/LV in Metastatic Pancreatic Cancer After Gemcitabine-Based Therapy

Outcome	MM-398 + 5-FU/LV (n = 1,117)	5-FU/LV (n = 149)	MM-398 (n = 151)
Median overall survival	6.1 mo	4.2 mo	4.9 mo
Hazard ratio (*p*-value) vs 5-FU/LV	0.67 (0.012)	Reference	0.99 (0.9416)
Median progression-free survival	3.1 mo	1.5 mo	2.7 mo
Hazard ratio (*p*-value) vs 5-FU/LV	0.56 (0.0001)	Reference	0.81 (0.1001)
Objective response rate (*p*-value) vs 5-FU/LV	16% (<0.001)	1% Reference	6% (0.019)

Von Hoff D et al. *Proc ESMO WCGC* 2014;**Abstract O-0003**.

3.2

NAPOLI-1 Trial: Select Adverse Events of Grade 3 or Higher

Grade ≥3 adverse events	MM-398 + 5-FU/LV (n = 117)	5-FU/LV (n = 134)	MM-398 (n = 147)
Decreased neutrophil count	20%	2%	16%
Fatigue	14%	4%	6%
Diarrhea	13%	5%	21%
Vomiting	11%	3%	14%
Nausea	8%	3%	5%

Von Hoff D et al. *Proc ESMO WCGC* 2014;**Abstract O-0003**.

Tracks 6-7

DR LOVE: What are your thoughts on the results of the Phase II SWOG-S0809 trial of adjuvant capecitabine/gemcitabine followed by concurrent capecitabine and radiation therapy for extrahepatic cholangiocarcinoma and gallbladder carcinoma?

DR O'REILLY: This nonrandomized adjuvant trial that was presented at ASCO 2014 was for patients with either a margin-positive or a node-positive extrahepatic cholangiocarcinoma or gallbladder carcinoma (Ben-Josef 2014; [3.3]). The median overall survival was 34 months. This is a study that will likely provide the reference arm for a future randomized Phase III trial in North America, but we need prospective data to better guide treatment decision-making in these scenarios.

DR LOVE: In what situations outside of a trial setting will you use adjuvant systemic therapy and/or radiation therapy?

DR O'REILLY: It depends on whether the patient has intrahepatic or extrahepatic biliary cancer. The intrahepatic biliary cancers are different. In general, factors such as node-positive or margin-positive disease, many satellite tumors or significant vascular and/

3.3

SWOG-S0809: Efficacy and Safety Results from the Phase II Trial of Adjuvant Capecitabine and Gemcitabine Followed by Concurrent Capecitabine and Radiation Therapy in Extrahepatic Cholangiocarcinoma (EHCC) and Gallbladder Carcinoma (GBCA)

Outcome	All patients (n = 79)	R0 cohort (n = 54)	R1 cohort (n = 25)	EHCC (n = 49)	GBCA (n = 30)
Median OS	34 months	33 months	36 months	NR	NR
Two-year OS	64%	67%	57%	68%	57%
Two-year DFS	51%	54%	45%	54%	47%
Two-year LR	12%	9%	16%	11%	13%

R0 and R1 = margin of resection; OS = overall survival; NR = not reported; DFS = disease-free survival; LR = local relapse

In 79 evaluable patients (54 R0, 25 R1), Grade 3/4 adverse events (AEs) were observed in 52% and 11% of patients. The most common Grade 3/4 AEs included neutropenia (44%), hand-foot syndrome (13%), diarrhea (8%), lymphopenia (8%) and leukopenia (6%).

Ben-Josef E et al. *Proc ASCO* 2014;**Abstract 4030**.

or perineural invasion sway me in favor of considering adjuvant treatment, the mainstay being systemic therapy.

A big question is whether to include radiation therapy. For intrahepatic cholangiocarcinoma, margins are usually not the issue, and I am less convinced that radiation therapy has a role. For extrahepatic cholangiocarcinoma, however, margins are usually challenging and often may be technically negative, close and/or positive, and I believe a role exists for adjuvant radiation therapy in that setting.

For gallbladder cancer, I keep an open mind. The patterns of failure are different and are typically more metastatic and more peritoneal for gallbladder cancer. And in the absence of positive margins, it has been our practice not to routinely consider the inclusion of radiation therapy for those patients outside of a study setting.

We have adopted the SWOG-S0809 regimen of 4 cycles of gemcitabine administered on day 1 and day 8 and capecitabine on days 1 through 14 every 3 weeks followed by capecitabine-based radiation therapy. We more selectively incorporate, outside of a trial setting, the use of 5-FU-based chemoradiation therapy, depending on whether it's gallbladder versus extrahepatic or intrahepatic cholangiocarcinoma.

Tracks 12-14

DR LOVE: Let's talk about pancreatic neuroendocrine tumors (NET). How do you sequence everolimus and sunitinib for advanced disease and what are the side effects?

DR O'REILLY: Sequencing of these agents depends on physician and patient biases and preferences. Everolimus has an established oncologic value in terms of disease stabilization. Even though the overall response rate to everolimus is low, it is my preferred choice compared to sunitinib. I believe that the toxicity profile is better, but I know one can't say that from the Phase III data. It's generally well tolerated but is associated with hyperglycemia. The more problematic toxicities are mucositis, fatigue and pneumonitis (Yao 2011).

I believe that fatigue is worse with sunitinib, and this may be my subjective opinion, but mucositis and myelosuppression are more complicated. That's not based on hard data. Both everolimus and sunitinib are acceptable choices for treating pancreatic NET. It is unclear if an optimal sequence exists and whether the sequence matters.

DR LOVE: What's your clinical experience with temozolomide and capecitabine?

DR O'REILLY: It is an active, generally well-tolerated regimen. We currently have data from a single-institution, multicenter Phase II study (Fine 2014) but no prospective randomized Phase III study data. Our approach is to administer capecitabine for 14 days and temozolomide with prophylactic antiemetics on days 10 through 14. For some patients receiving this regimen, fatigue, myelosuppression and hand-foot symptoms are problematic. ■

SELECT PUBLICATIONS

Cartwright TH et al. **Use of first-line chemotherapy for advanced pancreatic cancer: FOLFIRINOX versus gemcitabine-based therapy.** *Proc ASCO* 2014;**Abstract 4132**.

Fine RL et al. **Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors.** Gastrointestinal Cancers Symposium 2014;**Abstract 179**.

Yao JC et al. **Everolimus for advanced pancreatic neuroendocrine tumors.** *N Engl J Med* 2011;364(6):514-23.