5 Minute JournalClub

Key ASCO Presentations
Issue 8, 2010

Efficacy and Safety of FOLFIRINOX in Patients with Metastatic Pancreatic Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Employ an understanding of the Phase III efficacy and safety of FOLFIRINOX to identify patients with metastatic pancreatic cancer who may be benefit from intensive systemic treatment.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: Amgen Inc, Genentech BioOncology, Genomic Health Inc, Myriad Genetics Inc, Oncothyreon, Poniard Pharmaceuticals, Sanofi-Aventis; Consulting Agreements: Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Myriad Genetics Inc, Oncothyreon, Poniard Pharmaceuticals, Sanofi-Aventis.

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This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

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To go directly to the slides and commentary, **click here**.

Medical oncology has always challenged both patient and physician to make brutally difficult decisions concerning treatments that often provide modest benefits at the expense of significant toxicity. Nowhere has this paradigm been more evident than at the recent GI session in Chicago where French investigators **reported** that in advanced pancreatic cancer FOLFIRINOX (with full-dose oxaliplatin and irinotecan) not only improved progression-free survival and response rate but also overall survival (from 6.8 to 11.1 months). Within a couple of weeks of the presentation, I had chatted with Rich Goldberg, Axel Grothey and Malcolm Moore about this controversial data set. The bottom line? In spite of increased myelosuppression, particularly neutropenia, and other predictable problems with the combination, all three investigators are now considering FOLFIRINOX for younger, healthier patients.

Another provocative **data set** out of ASCO was a Spanish trial demonstrating that in patients receiving XELOX/bevacizumab as first-line therapy for metastatic colon cancer, maintenance therapy with bev alone may be as effective as maintenance with XELOX/bev. Axel, who was still a bit cranky after watching Spain run circles around his German team in the World Cup, believes this study has an inferior design to the ongoing German trial comparing capecitabine/bev to bev as maintenance that also includes a control arm of no maintenance.

The latest in a series of innovative pilot studies from Memorial examining local therapy in colon and rectal cancer also generated some buzz in Chicago. Deborah Schrag **reported** on 30 patients with T2-3 primary rectal cancer, many with nodal mets, who received pre-op FOLFOX/bev *without* radiation therapy. The resectability rate in this experience was similar to those that have been seen with neoadjuvant chemo/radiation therapy. Although this strategy is far from ready for prime time, Axel told me about a patient he had recently treated with this approach because prior radiation therapy for cervical cancer precluded further RT. Perhaps not surprisingly, she responded to FOLFOX and then underwent successful surgery.

Several other notable ASCO papers focused on EGFR antibody treatment for colorectal cancer, specifically cetuximab. K-ras status (wild type) was once again determined to have predictive value in the metastatic setting while B-raf was not, and data from an **NCCTG trial** evaluating mFOLFOX6 alone or with cetuximab in the adjuvant setting

disappointingly demonstrated no additional benefit with the combination, regardless of K-ras status.

The concluding sound bite from this, our final ASCO highlights issue, is another chemo/bev study that resulted in a response and a progression-free survival advantage but no survival benefit. "**AVAGAST**" focused on gastric cancer, and because survival was the primary endpoint, the study was considered negative. At the prostate cancer session, similar results and conclusions were reported for docetaxel/bevacizumab, and the recent ODAC opinion on chemo/bev in breast cancer suggests that the acceptability bar is being raised, even for an agent whose most significant toxicity is often financial.

Enjoy the rest of your summer. We will be back right around Labor Day with our next installment of Consensus or Controversy — this time in non-small cell lung cancer.

Neil Love, MD
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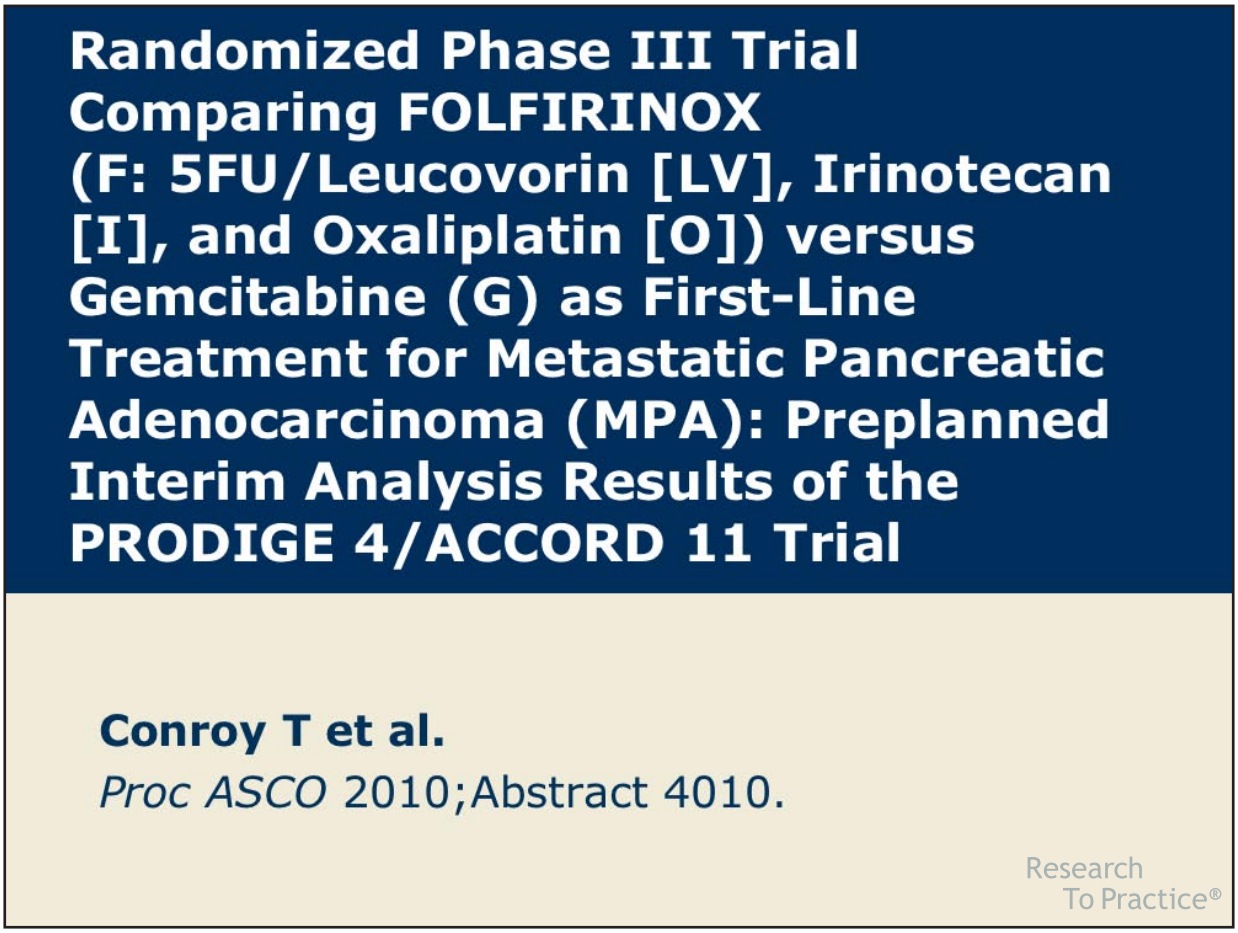
Efficacy and Safety of FOLFIRINOX in Patients with Metastatic Pancreatic Cancer

Presentation discussed in this issue

Conroy T et al. **Randomized phase III trial comparing FOLFIRINOX (F: 5FU/ leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial.** *Proc ASCO* 2010;**Abstract 4010**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Richard M Goldberg, MD (6/23/10) and Malcolm J Moore, MD (6/21/10)



Introduction

- Metastatic pancreatic cancer (mPC) is an incurable disease with few good treatment options.
- Single-agent gemcitabine (Gem) is standard treatment with median survival rates of approximately 6-7 months.
- FOLFIRINOX is a promising regimen in patients with advanced PC and a good performance status (PS):
  - Median survival = 10.2 months (*J Clin Oncol* 2005;23:1228)
- Phase II ACCORD 11 study compared FOLFIRINOX to Gem in patients with mPC:
  - Response rate = 31.8% vs 11.4% (*Proc ASCO* 2007;Abstract 4516)
- **Current study objective:**
  - Compare the efficacy and safety of FOLFIRINOX versus Gem in patients with mPC.

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

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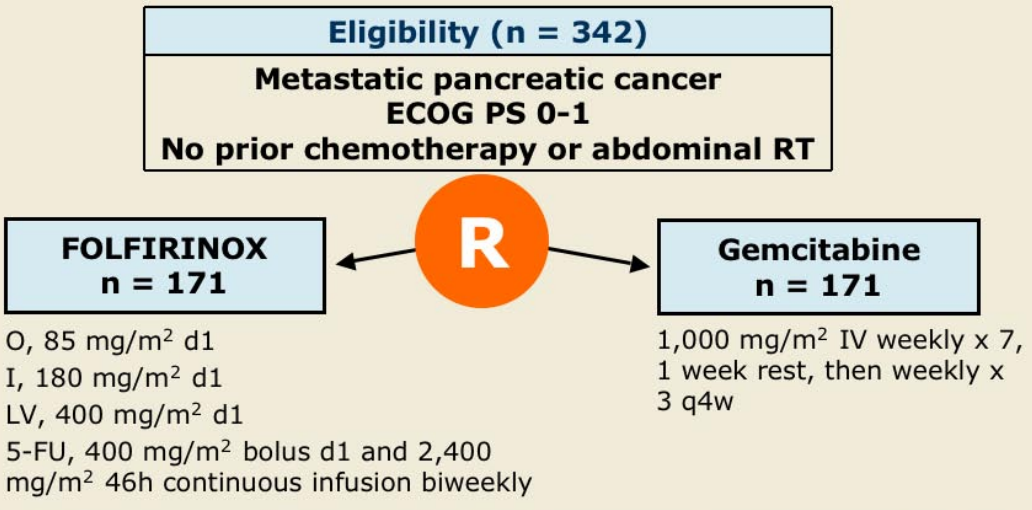
Phase III PRODIGE 4/ACCORD 11 Study Design



6 months of chemotherapy recommended and CT scans performed every 2 months for both arms

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

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Survival

	FOLFIRINOX n = 171	Gem n = 171	Hazard ratio	*p*-value
Median PFS	6.4 months	3.3 months	0.47	<0.0001
Median OS	11.1 months	6.8 months	0.57	<0.0001
1-year survival rate	48.4%	20.6%	—	—
18-month survival rate	18.6%	6%	—	—

PFS = progression-free survival; OS = overall survival

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

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Objective Response Rate

	FOLFIRINOX n = 171	Gem n = 171	*p*-value
Complete response (CR)	0.6%	0%	—
Partial response (PR)	31%	9.4%	0.0001
Stable disease (SD)	38.6%	41.5%	—
Disease control (CR + PR + SD)	70.2%	50.9%	0.0003
Progression	15.2%	34.5%	—
Not assessed	14.6%	14.6%	—
Median duration of response	5.9 months	4 months	NS

NS, not significant

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

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Grade 3/4 Adverse Events: Hematologic

Adverse Event	FOLFIRINOX n = 167	Gem n = 169	*p*-value
Neutropenia	45.7%	18.7%	0.0001
Febrile neutropenia	5.4%	0.6%	0.009
Anemia	7.8%	5.4%	NS
Thrombocytopenia	9.1%	2.4%	0.008

42.5% of patients in the FOLFIRINOX arm received G-CSF versus 5.3% in the gemcitabine arm.
One toxic death occurred in each arm.

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

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Select Grade 3/4 Adverse Events: Non-Hematologic

	FOLFIRINOX n = 167	Gem n = 169	*p*-value
Infection w/o neutropenia	1.2%	1.8%	NS
Peripheral neuropathy	9%	0%	0.0001
Vomiting	14.5%	4.7%	0.002
Fatigue	23.2%	14.2%	0.036
Diarrhea	12.7%	1.2%	0.0001
Alopecia (Grade 2)	11.4%	0.6%	0.0001
Alanine aminotransferase elevation	7.3%	18.6%	0.0022

Conroy T et al. *Proc ASCO* 2010;Abstract 4010.

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Conclusions

- FOLFIRINOX improves OS and PFS in comparison to Gem for patients with mPC and good PS.
  - Median PFS: 6.4 vs 3.3 months (HR 0.47, $p < 0.0001$)
    - Risk of disease progression reduced by 53%
  - Median OS: 11.1 vs 6.8 months (HR 0.57, $p < 0.0001$)
- FOLFIRINOX is more toxic but has a manageable toxicity profile.
  - Grade 3/4 febrile neutropenia: 5.4% vs 0.6% ($p = 0.009$)
- FOLFIRINOX may be a potential new standard of care for patients with mPC and good PS.
- Plans to evaluate FOLFIRINOX in the adjuvant setting are underway.

Conroy T et al. *Proc ASCO* 2010;Abstract 4010; Tempero M. ASCO 2010. Discussant.

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Investigator comment on the results of PRODIGE 4/ACCORD 11: FOLFIRINOX versus gemcitabine as first-line treatment of metastatic pancreatic cancer

This was arguably the most surprising study to be presented in the GI noncolorectal session. The study compared FOLFIRINOX, which is an intensive treatment that uses the full doses of 85 mg/m^2 of oxaliplatin and 180 mg/m^2 of irinotecan and standard doses of 5-FU, to gemcitabine.

The toxicity was obviously greater with the three-drug regimen, and the most noticeable issue was a five percent febrile neutropenia rate compared to a 0.6 percent rate with gemcitabine. There was also more vomiting, fatigue and diarrhea with the three-drug regimen.

However, the results make it worth considering the three-drug regimen for patients who are robust enough to tolerate it. There was a 32 percent response rate compared to 9.4 percent in the gemcitabine arm. There was a significant progression-free survival difference — 6.4 months versus 3.3 months with gemcitabine. The most startling result was an 11.1 versus a 6.8-month median survival advantage with the three-drug regimen. This is the first positive Phase III study that we've had in pancreatic cancer in a long time, and I've already incorporated the results into my practice.

Interview with Richard M Goldberg, MD, June 23, 2010

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Investigator comment on the results of PRODIGE 4/ACCORD 11: FOLFIRINOX versus gemcitabine as first-line treatment of metastatic pancreatic cancer

From a clinical practice point of view, the French study was significant, demonstrating the value of an intensive chemotherapy regimen in advanced pancreatic cancer. This is almost a paradigm shift in this disease for which we've always thought of using relatively nonaggressive chemotherapy.

The Europeans did a small, Phase II study some years ago in pancreatic cancer and demonstrated some interesting activity with this three-drug regimen. Based on that they finally launched this Phase III study.

Considering how many negative studies we've had in pancreatic cancer, they dramatically showed a greater than four-month improvement in median survival with this three-drug regimen. So the median survival on gemcitabine was 6.8 months, which is fairly typical for this disease and the median survival for FOLFIRINOX was 11.1 months. That is a substantial improvement and certainly beyond what has been seen with any other regimen in pancreatic cancer.

Interview with Malcolm J Moore, MD, June 21, 2010

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