Efficacy and Safety of FOLFIRINOX in Patients with Metastatic Pancreatic Cancer

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

Conroy T et al.

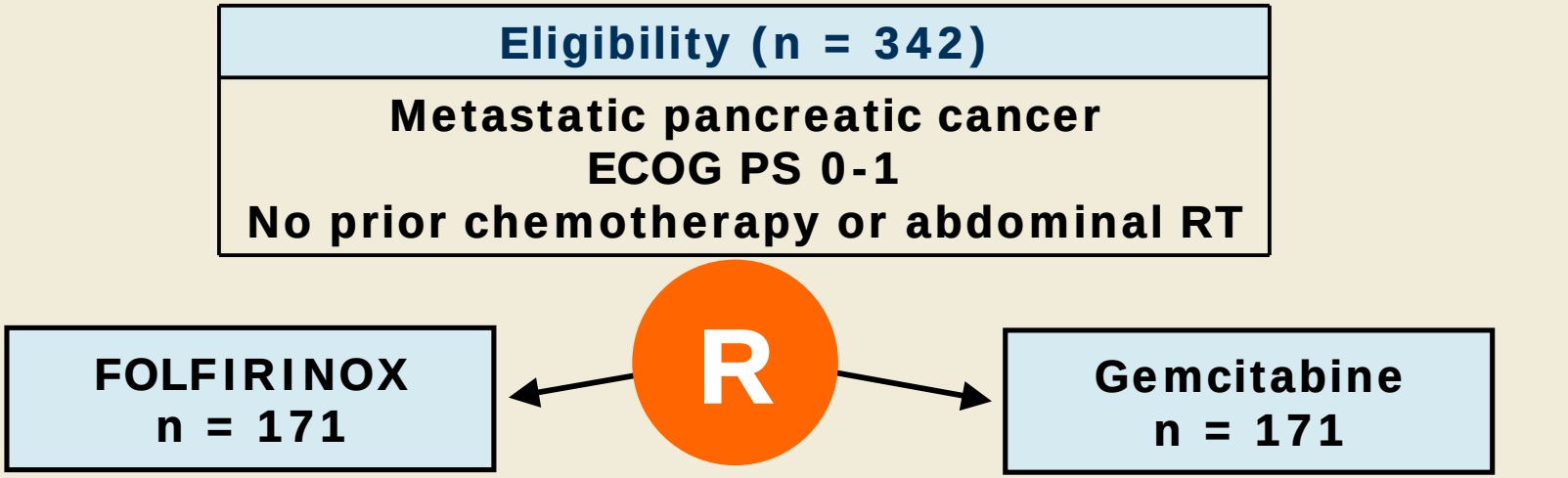
Proc ASCO 2010;Abstract 4010.

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.

Phase III PRODIGE 4/ACCORD 11 Study Design



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

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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

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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.

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.

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.

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.

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

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