2. Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol 2009;27:3742-8.
3. Attard G, Swennenhuis JF, Olmos D, et al. Characterization of ERG, AR, and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer. Cancer Res 2009;69:2912-8.
4. Ryan CJ, Shah SK, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. Clin Cancer Res 2011 June 1 (Epub ahead of print).
5. Messiou C, Cook G, Reid AH, et al. The CT flare response of metastatic bone disease in prostate cancer. Acta Radiol 2011; 52:557-61.

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

TO THE EDITOR: Conroy et al. (May 12 issue)[1] report that FOLFIRINOX (a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin) provided a statistically and clinically significant benefit over single-agent gemcitabine in patients with advanced pancreatic cancer. Although the increased toxicity associated with this combination therapy may temper enthusiasm, this is the first real advance in such therapy since the introduction of gemcitabine. It has been debated whether gemcitabine-based combination therapies provide any additional benefit, and meta-analyses have reached conflicting conclusions.[2-4] A sensitivity analysis of data pooled from seven randomized trials involving 2422 patients in which single-agent gemcitabine was compared with gemcitabine in combination with cisplatin, oxaliplatin, or capecitabine indicates that the use of gemcitabine-based doublets had a clinically negligible, although statistically significant, absolute survival benefit (Table 1). However, power calculations reliably (80% power, two-tailed alpha of 0.05) rule out the possibility that gemcitabine-based doublets could

Table 1. Results of Meta-Analysis of Trials Evaluating Overall Survival in Patients Receiving Gemcitabine-Based Combination Therapy, as Compared with Single-Agent Gemcitabine.*

Drug Combined with Gemcitabine	Randomized Clinical Trials†	No. of Trials	No. of Patients	Hazard Ratio (95% CI)	P Value		Absolute Difference at 1 Yr (%)	No. Needed to Treat‡
					Between-Group Comparison	Heterogeneity		
Cisplatin	Colucci et al. (2002) Heinemann et al. Colucci et al. (2010)	3	702	0.94 (0.76–1.17)	0.61	0.19	NA	NA
Oxaliplatin	Louvet et al. Poplin et al.	2	868	0.86 (0.74–0.99)	0.04	0.65	2.6	38–39
Capecitabine	Cunningham et al. Herrmann et al.	2	852	0.86 (0.75–0.99)	0.04	0.94	3.0	33–34
Total		7	2422	0.87 (0.80–0.96)	0.005	0.53	2.3	43–44

* NA denotes not applicable.
† Included in the meta-analysis were the following studies: Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. Cancer 2002;94:902-10; Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006;24:3946-52; Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. J Clin Oncol 2010;28:1645-51; Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005;23:3509-16; Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:3778-85. [Erratum, J Clin Oncol 2009;27:5859.]; Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009;27:5513-8; Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007;25:2212-17.
‡ The number needed to treat refers to the number of patients who would need to be treated with the combination therapy for one patient to benefit in terms of outcome.

improve 1-year survival by more than 5%. In that respect, the results of the FOLFIRINOX study strongly suggest that moving away from using gemcitabine alone versus using gemcitabine-based combinations is actually a wiser, more creative, and more effective strategy to improve outcomes in patients with advanced pancreatic cancer. In addition, trials of such combination chemotherapy regimens could foster the development of molecularly targeted agents in this disease.[5]

Vanja Vaccaro, M.D.
Isabella Sperduti, Ph.D.
Michele Milella, M.D.

Regina Elena National Cancer Institute
Rome, Italy
vanja.vaccaro@hotmail.it

No potential conflict of interest relevant to this letter was reported.

1. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
2. Bria E, Milella M, Gelibter A, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. Cancer 2007;110:525-33.
3. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 2008;8:82.
4. Heinemann V, Labianca R, Hinke A, Louvet C. Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study. Ann Oncol 2007;18:1652-9.
5. Vaccaro V, Melisi D, Bria E, et al. Emerging pathways and future targets for the molecular therapy of pancreatic cancer. Exp Opin Target Agents (in press).

THE AUTHORS REPLY: We agree with Vaccaro et al. that numerous phase 3 trials of gemcitabine in combination with different cytotoxic or molecularly targeted agents have resulted in no substantial clinical improvement over the use of gemcitabine alone. Only the addition of erlotinib to gemcitabine resulted in a significant but very small improvement in overall survival.[1]

It is unclear whether the pooled data analysis presented here is based on the literature alone or on updated survival analyses of individual patient data, which is the preferred standard.[2] However, there is no evidence for heterogeneity in the trials comparing single-agent gemcitabine with gemcitabine-based combination chemotherapy with platinum analogues or capecitabine. Because of the short median survival in advanced pancreatic cancer, we do not think that a meta-analysis of individual patient data could substantially change the results, and we agree that gemcitabine does not have to be the backbone of future chemotherapy combinations.[3]

Thierry Conroy, M.D.

Centre Alexis Vautrin
Nancy, France
t.conroy@nancy.fnclcc.fr

Sophie Gourgou-Bourgade, M.Sc.

Centre Val d'Aurelle
Montpellier, France

Michel Ducreux, M.D., Ph.D.

Institut Gustave Roussy
Villejuif, France

Since publication of their article, the authors report no further potential conflict of interest.

1. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6.
2. Pignon JP, Hill C. Meta-analyses of randomised clinical trials in oncology. Lancet Oncol 2001;2:475-82.
3. Kim R. FOLFIRINOX: a new standard treatment for advanced pancreatic cancer? Lancet Oncol 2011;12:8-9.

Selenium and the Course of Mild Graves' Orbitopathy

TO THE EDITOR: In the European Group on Graves' Orbitopathy (EUGOGO) trial, Marcocci et al. (May 19 issue)[1] find a beneficial effect of therapy with selenium in mild Graves' orbitopathy. However, I am concerned about the possibility of selenium-induced type 2 diabetes, and this concern makes me cautious about considering this therapy. Stranges et al.[2] observed an increased risk for diabetes after long-term treatment with 200 μg of selenium per day. Moreover, the third National Health and Nutrition Examination Survey (NHANES III)[3] found a significant correlation between high selenium levels and the prevalence of type 2 diabetes. In the study by Marcocci et al., nothing is mentioned about this possible side effect of selenium. Did the authors monitor patients for the development of type 2 diabetes mellitus during treatment with selenium?

Michael Weissel, M.D.

Medical University of Vienna
Vienna, Austria
michael.weissel@meduniwien.ac.at