Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Emerging Data in the Management of Noncolorectal GI Cancers — Johanna C Bendell, MD

Select Publications

Bang YJ et al. **Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012.** *Proc ASCO* 2015;**Abstract 4001**.

Chen LT et al. **Expanded analyses of napoli-1: Phase 3 study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy.** Gastrointestinal Cancers Symposium 2015;**Abstract 234**.

Hurwitz H et al. **JANUS 1: A phase 3, placebo-controlled study of ruxolitinib plus capecitabine in patients with advanced or metastatic pancreatic cancer (mPC) after failure or intolerance of first-line chemotherapy.** *Proc ASCO* 2015;**Abstract TPS4147**.

Hurwitz HI et al. **Randomized, double-blind, Phase II study of ruxolitinib or placebo in combination with capecitabine in patients with metastatic pancreatic cancer for whom therapy with gemcitabine has failed.** *J Clin Oncol* 2015;33(34):4039-47.

Katz MHG et al. **Preoperative modified FOLFIRINOX (mFOLFIRINOX) followed by chemoradiation (CRT) for borderline resectable (BLR) pancreatic cancer (PDAC): Initial results from Alliance Trial A021101.** *Proc ASCO* 2015;**Abstract 4008**.

O'Reilly EM et al. **JANUS 2: A phase III study of survival, tumor response, and symptom response with ruxolitinib plus capecitabine or placebo plus capecitabine in patients with advanced or metastatic pancreatic cancer (mPC) who failed or were intolerant to first-line chemotherapy.** *Proc ASCO* 2015;**Abstract TPS4146**.

Shah MA et al. **The BRIGHTER trial: A phase III randomized double-blind study of BBI608 + weekly paclitaxel versus placebo (PBO) + weekly paclitaxel in patients (pts) with pretreated advanced gastric and gastro-esophageal junction (GEJ) adenocarcinoma.** *Proc ASCO* 2015;**Abstract TPS4139**.

Emerging Data in the Management of Non-Colorectal GI Cancers

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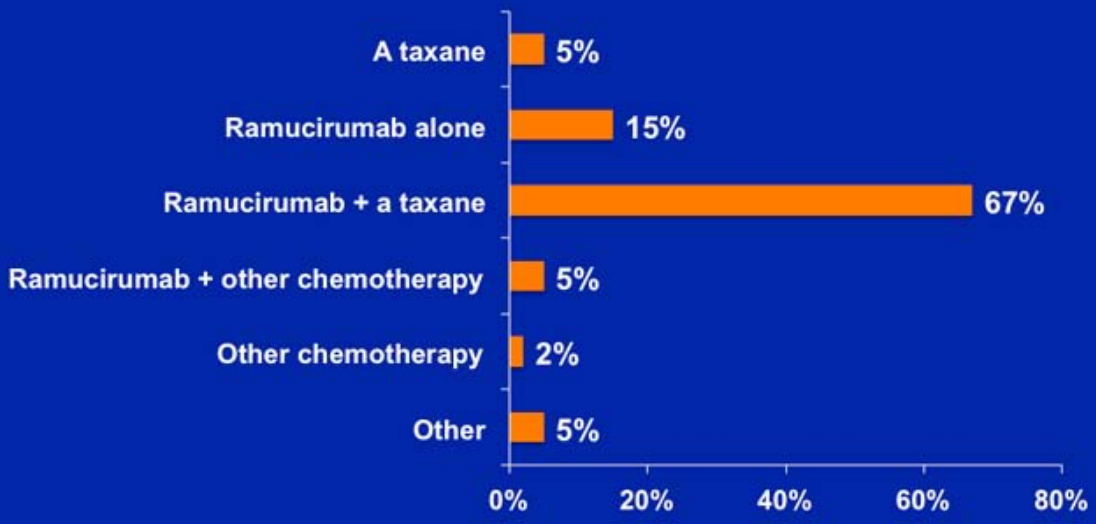
Disclosures

No financial interests or affiliations to disclose.

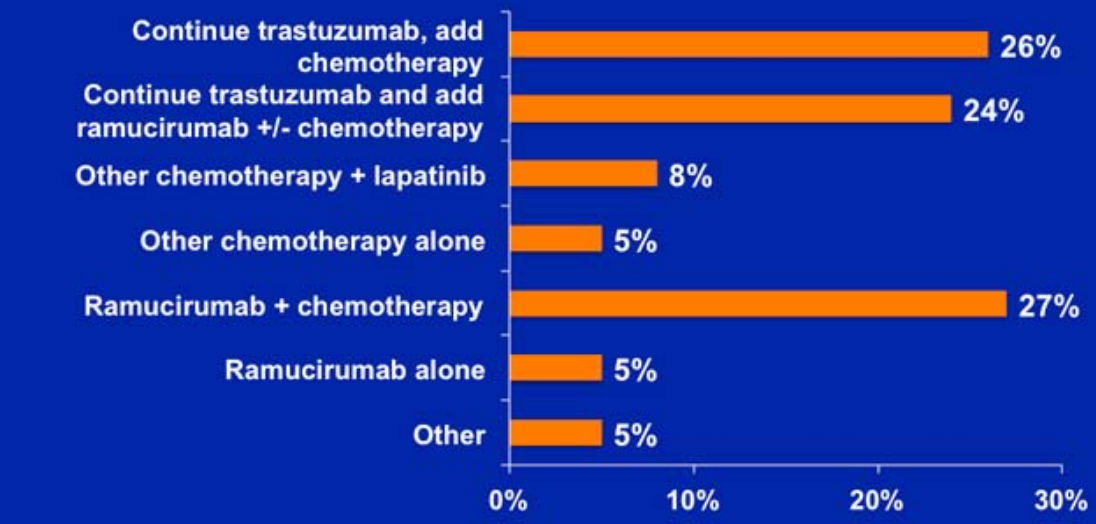
AUDIENCE POLL

A 60-year-old patient with metastatic HER2-negative gastric cancer receives FOLFOX with initial stable disease but experiences disease progression after 8 months. Which systemic treatment would you prefer to use?



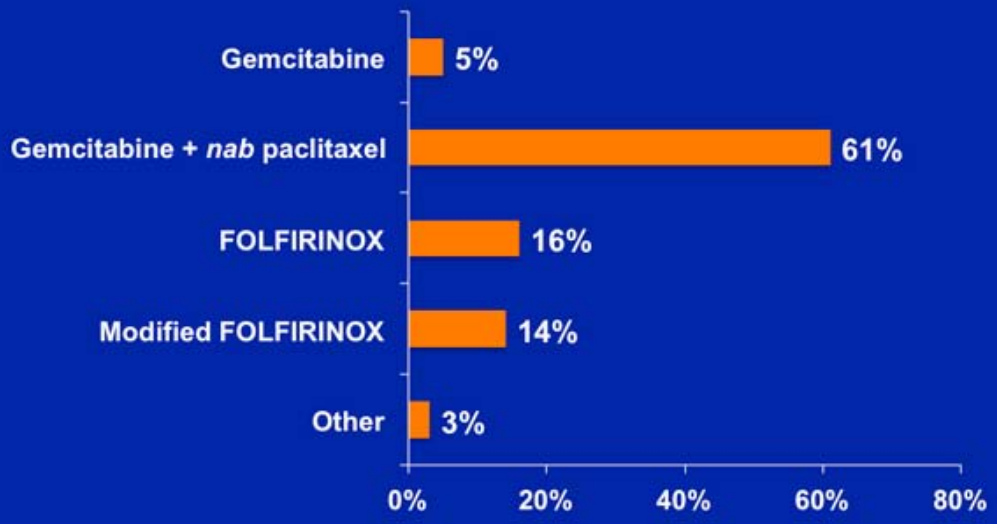
AUDIENCE POLL

A 60-year-old patient with metastatic HER2-positive gastric cancer receives FOLFOX/trastuzumab for 5 months with a partial response. After 1 year he experiences objective disease progression while receiving maintenance trastuzumab. What would you most likely recommend?



AUDIENCE POLL

Which first-line systemic therapy would you generally recommend for an otherwise healthy 70-year-old patient with metastatic pancreatic cancer?



Relationship Between PD-L1 Expression and Clinical Outcomes in Patients with Advanced Gastric Cancer Treated with the Anti-PD-1 Monoclonal Antibody Pembrolizumab (MK-3475) in KEYNOTE-012

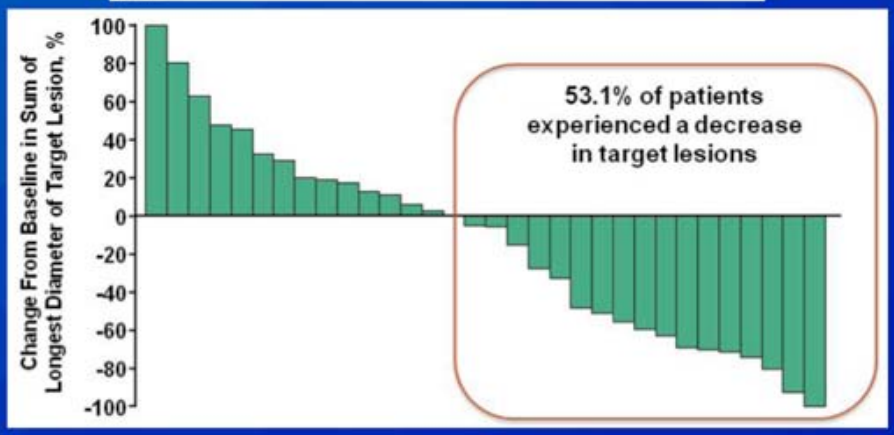
Bang YJ et al.

Proc ASCO 2015;Abstract 4001.

Best Response and Maximum Percentage Change from Baseline in Tumor Size

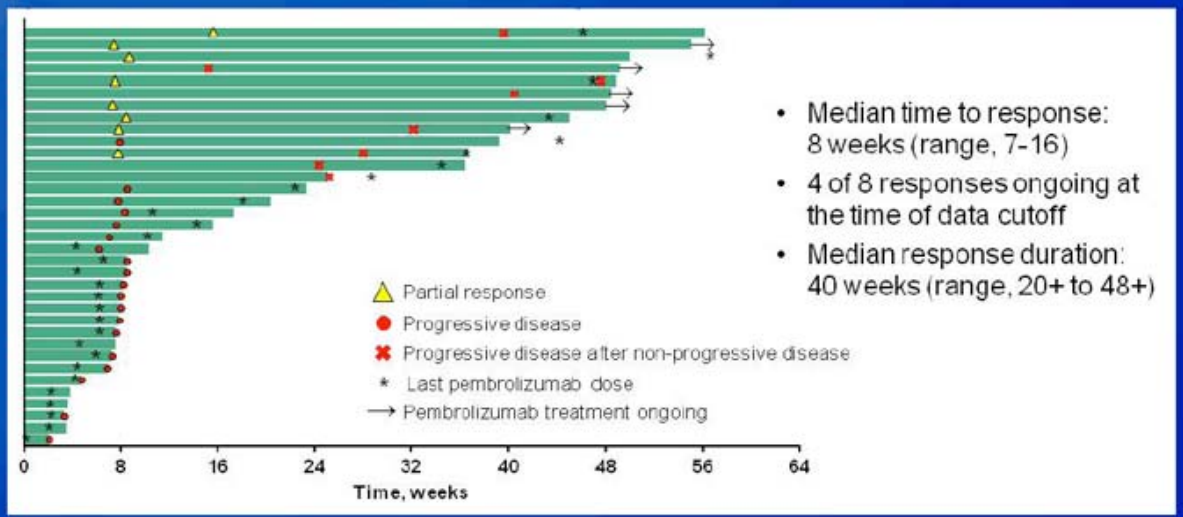
	Central Review N = 36[a]	Investigator Review N = 39
ORR,[b] % (95% CI)	22.2 (10.1-39.2)	33.3 (19.1-50.2)
Best overall response, n (%)		
Complete response[b]	0	0
Partial response[b]	8 (22.2)	13 (33.3)
Stable disease	5 (13.9)	3 (7.7)
Progressive disease	19 (52.8)	23 (59.0)
No assessment[c]	1 (2.8)	0
Not determined[d]	3 (8.3)	0

[a]Patients with measurable disease per RECIST v1.1 by central review at baseline. [b]All responses were confirmed. [c]Patient with centrally evaluable disease at baseline who discontinued therapy due to clinical progression before the first scan. [d]Patients with centrally evaluable disease at baseline for whom best overall response could not be determined.



Bang YJ et al. *Proc ASCO* 2015;Abstract 4001.

Treatment Exposure and Response Duration



Bang YJ et al. *Proc ASCO* 2015;Abstract 4001.

Association Between Efficacy and PD-L1 Expression

- Preliminary evidence of a relationship between PD-L1 expression and efficacy in this preselected population
- Data suggest a relatively low cutoff is sufficient to detect most responders
- Data support further study of pembrolizumab for advanced gastric cancer
  - KEYNOTE-059: A Phase II study of pembrolizumab monotherapy or in combination with chemotherapy
  - KEYNOTE-061: A Phase III study of pembrolizumab vs paclitaxel as second-line therapy

Bang YJ et al. *Proc ASCO* 2015;Abstract 4001.

Conclusions

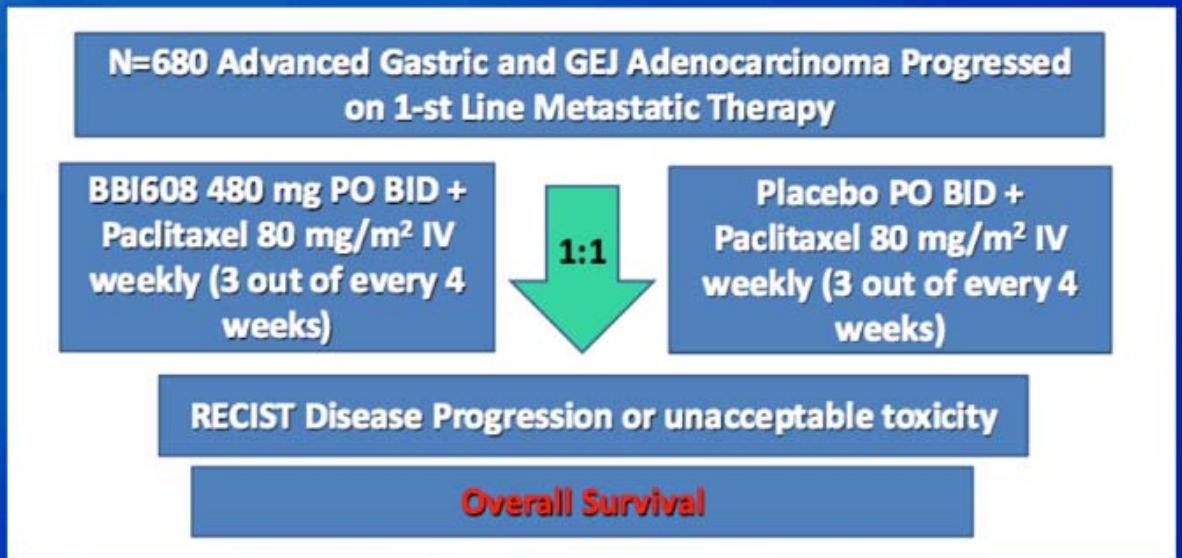
Critical finding(s): Patients with heavily pretreated advanced gastric cancer who were defined as PD-L1+ (40% of those tested) show an impressive 22% response rate. Preliminary PFS was 1.9 months and overall survival was 11.4 months. Even more compelling was the median response duration of 40 weeks. There does seem to be a relationship between the amount of PD-L1 positivity and survival outcomes.

Clinical implication(s): These data show that the use of immunotherapy for gastric cancer patients shows incredible promise for those who respond. It is important to try to enroll patients with gastric cancer onto immunotherapy trials so that we can further understand this potential benefit.

Conclusions

Research relevance: Multiple studies are ongoing with immunotherapy for gastric cancer patients. These include KEYNOTE-059 (nonrandomized Phase II evaluating pembrolizumab in PD-L1+ or PD-L1- refractory patients, PD-L1+ first-line patients and in combination with first-line cisplatin/5-FU), KEYNOTE-061 (randomized Phase III evaluating pembrolizumab versus paclitaxel second line), nivolumab plus ipilimumab, pembrolizumab plus ramucirumab, bevacizumab plus atezolizumab, tremelimumab plus MEDI4736, avelumab.

BRIGHTER: A Phase III Study of BBI608 + Weekly Paclitaxel as Second-Line Treatment for Gastric and Gastroesophageal Junction (GEJ) Cancer



Shah MA et al. *Proc ASCO* 2015;Abstract TPS4139.

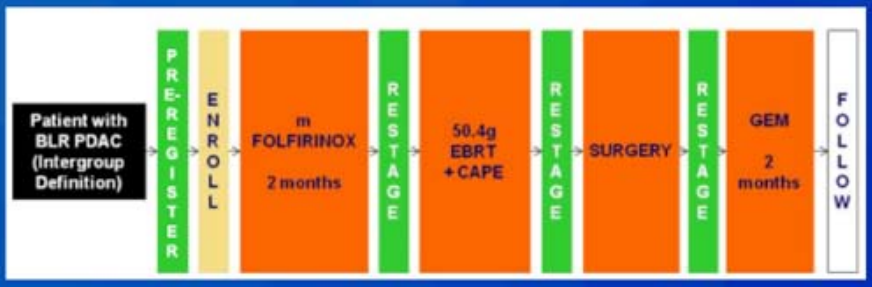
PANCREATIC CANCER

Preoperative Modified FOLFIRINOX (mFOLFIRINOX) Followed by Chemoradiation (CRT) for Borderline Resectable (BLR) Pancreatic Cancer (PDAC): Initial Results from Alliance Trial A021101

Katz MHG et al.

Proc ASCO 2015;Abstract 4008.

Study Design, Safety and Surgical Outcomes



Overall Preoperative Treatment-Related Toxicity

- 64% of patients experienced ≥ 1 Grade 3 AE
  - 50% experienced ≥1 mFOLFIRINOX-related Grade 3 AE
  - 36% experienced ≥1 CXRT-related Grade 3 AE

Pancreatectomy (N=15)	N	%*
Portal V resection	12	80
Hepatic A resection	4	27

* Among 15 patients who underwent pancreatectomy

Pathologic variable	N	%*	%**
R0	14	64	93
N0	10	46	67
< 5% residual cells	7	32	47
pCR	2	9.1	13

* Among patients who initiated mFOLFIRINOX (n = 22)
** Among patients who underwent pancreatectomy (n = 15)

Katz MHG et al. *Proc ASCO* 2015;Abstract 4008.

Conclusions

Critical finding(s): Use of FOLFIRINOX, which has one of the highest reported response rates in a large randomized trial for metastatic pancreatic cancer, in combination with chemoradiation therapy for borderline resectable pancreatic cancer patients showed a good response rate (27%, including 2 CRs [9%]). Ninety-five percent of patients were able to complete all preoperative therapy, and 68% went to surgical resection with 64% overall undergoing R0/1 resection.

Clinical implication(s): With the only potential for long-term survival for patients with pancreatic cancer being surgical resection, increasing the number of patients who potentially can undergo resection is key. We now have

Conclusions

chemotherapy regimens with improved response rates compared to historical rates, and combining these regimens with chemoradiation therapy in the preoperative/ borderline setting makes sense. This study shows this can be done, but we do not have data yet to tell us that survival outcomes will be better.

Research relevance: There are multiple ongoing studies looking at the preoperative setting for borderline resectable and resectable pancreatic cancer. There will also be a follow-up Intergroup study for this trial. Most of these studies are looking at augmenting chemotherapy (using FOLFIRINOX, gemcitabine/*nab* paclitaxel or other versions of these chemotherapies), evaluating other

Conclusions

radiation modalities (proton beam, SBRT/IMRT) and adding novel therapeutics (CCR2, immunotherapies, et cetera).

Most notable studies:

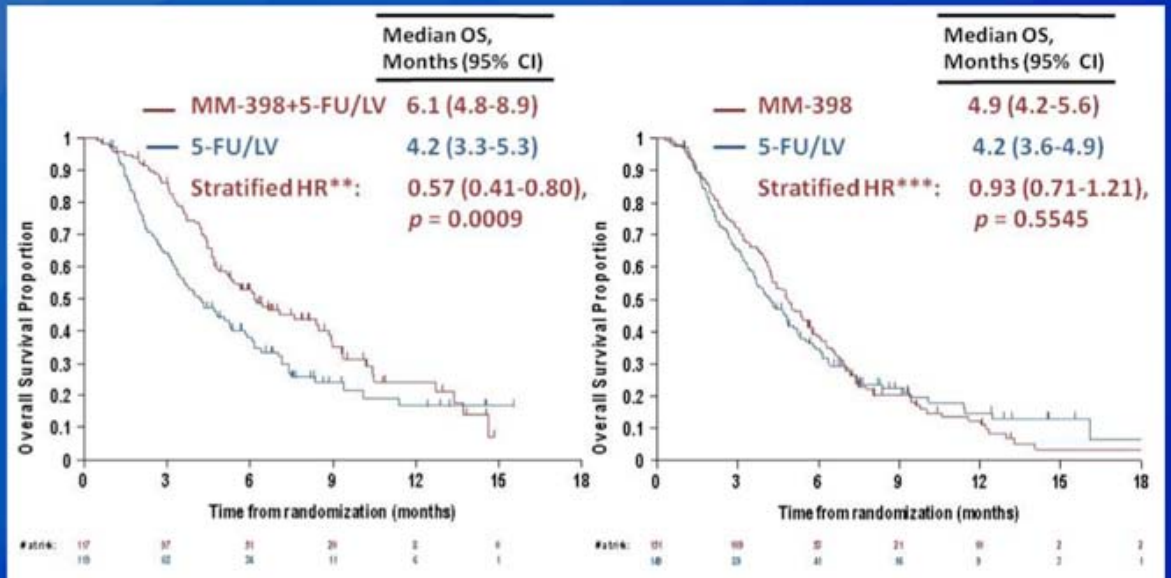
- Randomized Phase III IMPRESS (resectable) and PILLAR (BR/LA) – irradiated pancreatic cancer vaccine
- Randomized Phase II/III Danish study of resectable patients treated with surgery and adjuvant gemcitabine versus FOLFIRINOX pre- and postop

Expanded Analyses of NAPOLI-1: Phase 3 Study of MM-398 (nal-IRI), with or without 5-Fluorouracil and Leucovorin, versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer (mPAC) Previously Treated with Gemcitabine-Based Therapy

Chen LT et al.

GI Cancers Symposium 2015;Abstract 234.

Overall Survival: Intent-to-Treat



* Protocol-defined primary analysis data cut (14Feb2014, after 305 events). Survival follow-up is ongoing and the final results will be reported once all patients are off treatment and at least 90% events have taken place. Primary analysis for the study was by un-stratified log-rank test.

** Un-stratified HR: 0.67 (0.49-0.92), $p = 0.0122$

*** Un-stratified HR: 0.99 (0.77-1.28), $p = 0.9416$

Chen LT et al. GI Cancers Symposium 2015;Abstract 234.

Conclusions

Critical finding(s): This study showed that MM-398, a nanoparticle irinotecan, improves survival when used in combination with 5-FU/LV versus 5-FU/LV alone as postgemcitabine therapy for metastatic pancreatic cancer patients (HR 0.57, 6.1 versus 4.2 months). OS improvement was consistent across prognostic subgroups. MM-398 is potentially a new agent for the treatment of metastatic pancreatic cancer.

Clinical implication(s): We will hopefully soon have MM-398 available as a treatment option for our patients. Since this study was performed we also have FOLFIRINOX and gemcitabine/*nab* paclitaxel as treatment options for our patients. It remains to be seen how

Conclusions

MM-398 will fit into the sequence of treatment. Most likely it will be in the second line after progression on gemcitabine/*nab* paclitaxel, but it was not directly tested in this setting.

Research relevance: The next study about to open will look at MM-398 in the first-line setting. This will be a randomized Phase II study of gemcitabine/*nab* paclitaxel versus 5-FU/LV/MM-398 versus 5-FU/LV/MM-398/ oxaliplatin.

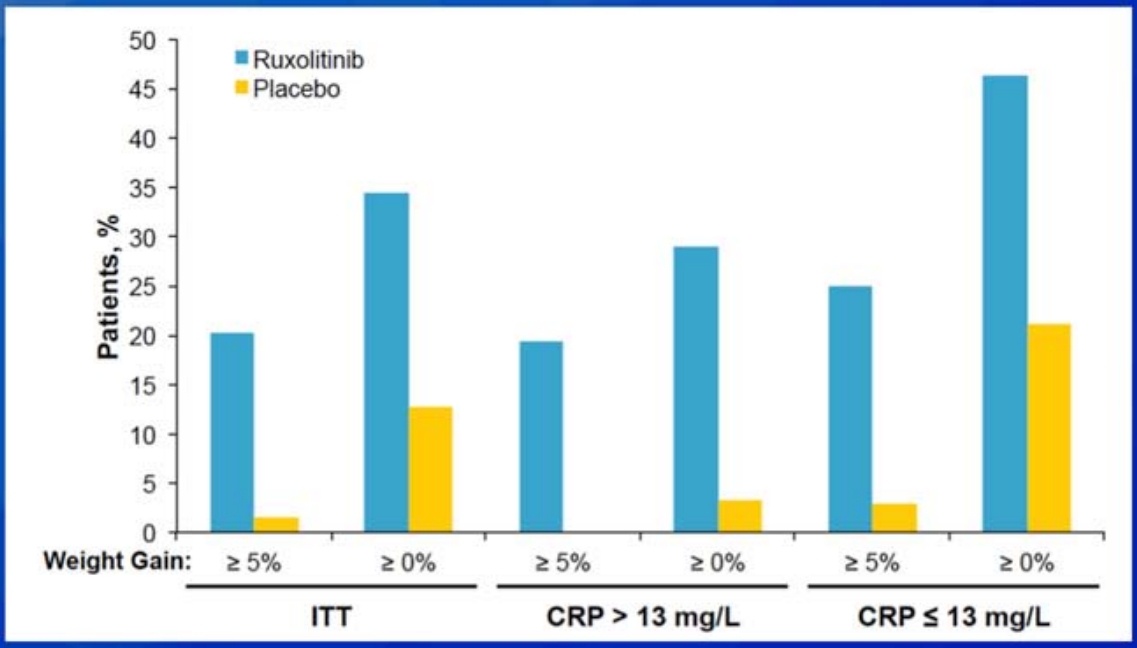
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed

Herbert I. Hurwitz, Nikhil Uppal, Stephanie A. Wagner, Johanna C. Bendell, J. Thaddeus Beck, Seaborn M. Wade III, John J. Nemunaitis, Philip J. Stella, J. Marc Pipas, Zev A. Wainberg, Robert Manges, William M. Garrett, Deborah S. Hunter, Jason Clark, Lance Leopold, Victor Sandor, and Richard S. Levy

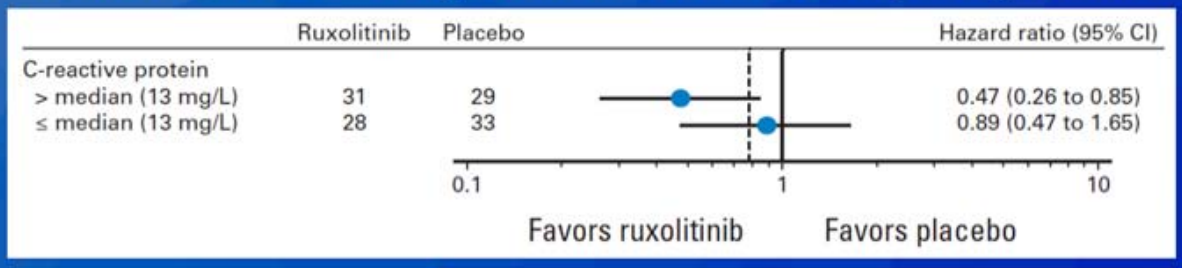
Epub ahead of print Sept 8, 2015

Proportion of Patients with ≥0% or ≥5% Weight Gain

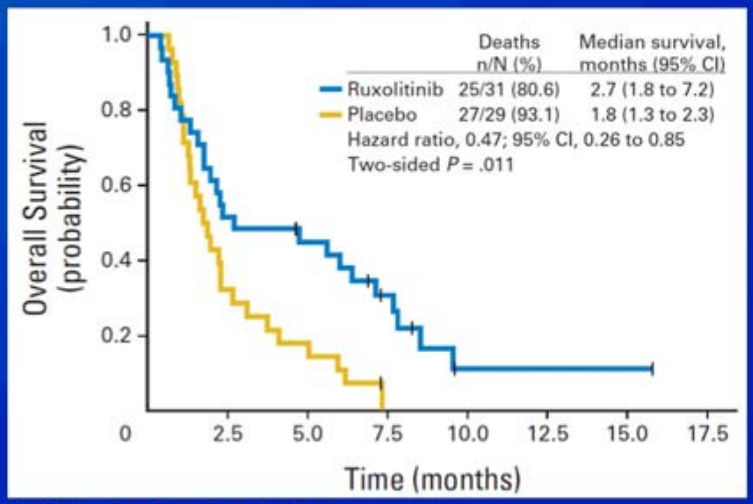


Hurwitz HI et al. *J Clin Oncol* 2015;[Epub ahead of print].

Forest Plot of OS by C-Reactive Protein (CRP) Level



OS, CRP >13 mg/L



Hurwitz HI et al. *J Clin Oncol* 2015;[Epub ahead of print].

Conclusions

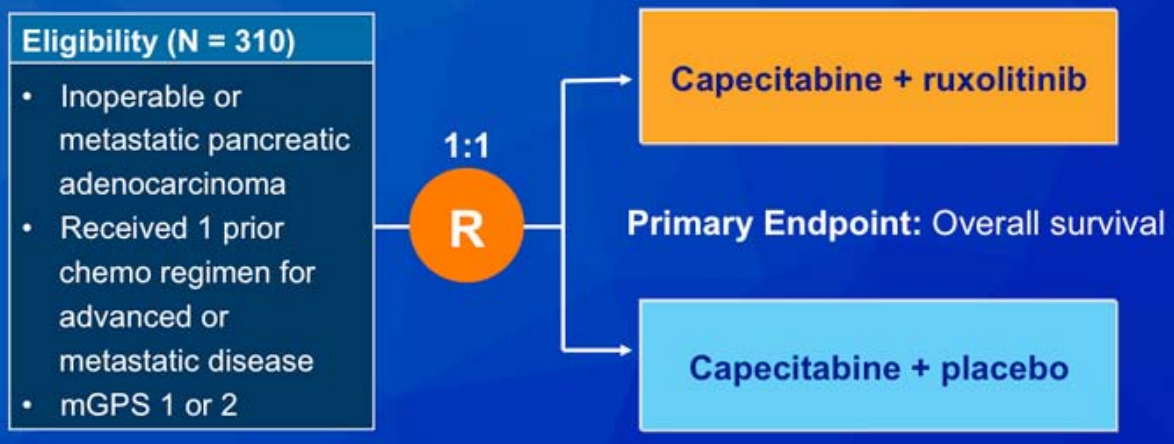
Critical finding(s): Ruxolitinib plus capecitabine versus capecitabine alone as second-line treatment for metastatic pancreatic cancer showed a trend toward improvement in PFS (HR 0.75 [0.52-1.10]) and OS (HR 0.79 [0.53-1.18]). Ruxolitinib as a JAK/STAT inhibitor may decrease inflammation associated with pancreatic cancer. For patients with high inflammatory state as defined by mGPS 1 or 2 (high CRP and low albumin), OS HR was much better (0.60 [0.35-1.03]).

Clinical implication(s): We are seeing that a high inflammatory state is associated with a poor prognosis for patients with pancreatic cancer. There is interest in drug development looking at addressing this inflammatory state.

Conclusions

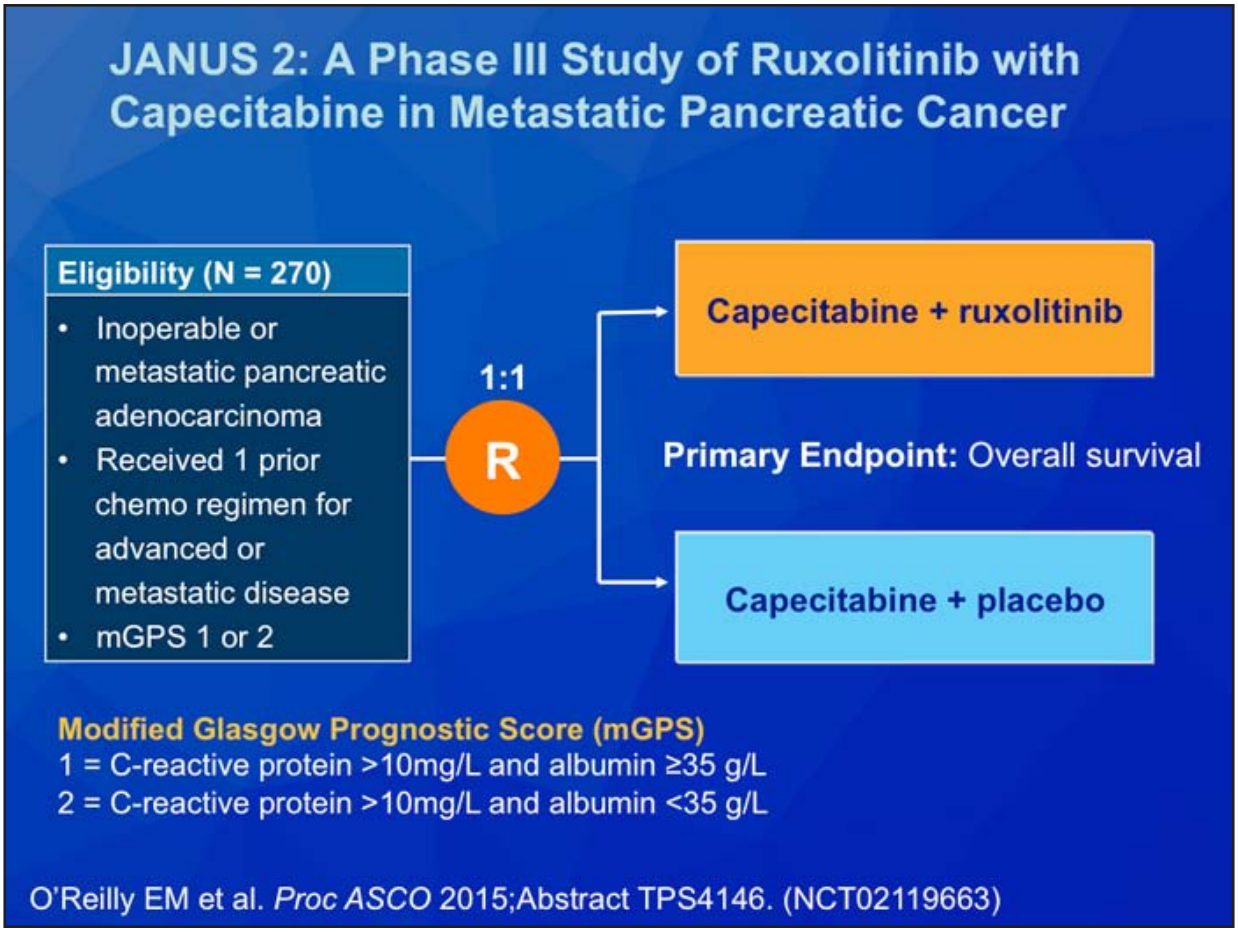
Research relevance: There are 2 ongoing randomized Phase III studies of capecitabine +/- ruxolitinib for patients with mGPS 1 or 2 (JANUS 1 and 2) to define the benefit seen with the addition of ruxolitinib to capecitabine in the second-line setting.

JANUS 1: A Phase III Study of Ruxolitinib with Capecitabine in Advanced or Metastatic Pancreatic Cancer



Modified Glasgow Prognostic Score (mGPS)
1 = C-reactive protein >10mg/L and albumin ≥35 g/L
2 = C-reactive protein >10mg/L and albumin <35 g/L

Hurwitz H et al. *Proc ASCO* 2015;Abstract TPS4147. (NCT02117479)


JANUS 2: A Phase III Study of Ruxolitinib with Capecitabine in Metastatic Pancreatic Cancer
Eligibility (N = 270)
• Inoperable or metastatic pancreatic adenocarcinoma
• Received 1 prior chemo regimen for advanced or metastatic disease
• mGPS 1 or 2
1:1
R
Capecitabine + ruxolitinib
Primary Endpoint: Overall survival
Capecitabine + placebo
Modified Glasgow Prognostic Score (mGPS)
1 = C-reactive protein >10mg/L and albumin ≥35 g/L
2 = C-reactive protein >10mg/L and albumin <35 g/L
O'Reilly EM et al. Proc ASCO 2015;Abstract TPS4146. (NCT02119663)