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A SPECIAL MEETING REVIEW EDITION

Highlights in Pancreatic Cancer From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

A Review of Selected Presentations From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium • January 18-20, 2018 • San Francisco, California

Special Reporting on:

- Dose Modifications of Liposomal Irinotecan + 5-Fluorouracil/Leucovorin in NAPOLI-1: Impact on Efficacy
- A Phase IB/II Randomized Study of mFOLFIRINOX + Pegylated Recombinant Human Hyaluronidase Versus mFFOX Alone in Patients With Good Performance Status Metastatic Pancreatic Adenocarcinoma: SWOG S1313 (NCT #01959139)
- Subgroup Analysis by Baseline Pain and Weight Among Patients in the NAPOLI-1 Trial
- Phase II LAPACT Trial of Nab-Paclitaxel Plus Gemcitabine for Patients With Locally Advanced Pancreatic Cancer
- Subgroup Analysis by Measurable Metastatic Lesion Number and Selected Lesion Locations at Baseline in NAPOLI-1: A Phase III Study of Liposomal Irinotecan ±5-Fluorouracil/Leucovorin in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine-Based Therapy
- Mapping the Immune Landscape in Pancreatic Cancer
- Nomogram for Predicting Overall Survival in Patients Treated With Liposomal Irinotecan ± 5-Fluorouracil/Leucovorin in Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine-Based Therapy in NAPOLI-1
- Genomics-Driven Precision Medicine for Advanced Pancreatic Ductal Carcinoma: Early Results From the COMPASS Trial (NCT02750657)

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, GI Program, Mayo Clinic Cancer Center
Senior Associate Consultant, Mayo Clinic
Phoenix, Arizona

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Educational Objectives

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- Describe how data from recent clinical trials in pancreatic cancer may impact clinical care
- Stratify patients according to risk factors
- Describe insights from the latest genomic studies in pancreatic cancer
- Discuss novel treatment approaches in pancreatic cancer

Faculty

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, GI Program, Mayo Clinic Cancer Center
Senior Associate Consultant, Mayo Clinic
Phoenix, Arizona

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Dose Modifications of Liposomal Irinotecan + 5-Fluorouracil/ Leucovorin in NAPOLI-1: Impact on Efficacy

In the phase 3 NAPOLI-1 trial (Nanoliposomal Irinotecan), the addition of nanoliposomal irinotecan to 5-fluorouracil (5-FU) and leucovorin improved overall survival as compared with 5-FU/leucovorin alone among patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy.[1] The median overall survival was 6.1 months with nanoliposomal irinotecan, 5-FU, and leucovorin vs 4.2 months with 5-FU and leucovorin (HR, 0.67; 95% CI, 0.49-0.92; *P*=.012). The protocol for the NAPOLI-1 study permitted up to 2 dose reductions for nanoliposomal irinotecan and 5-FU, as well as a dose delay of up to 3 weeks, in cases of toxicity-related adverse events.[1] Dr Andrea Wang-Gillam and colleagues presented data from an exploratory analysis of NAPOLI-1, which sought to determine whether overall survival was impacted by dose reductions or dose delays used to manage an adverse event within the first 6 weeks of the study. A dose reduction was defined as any decrease in the scheduled dose from the initial administered dose. A dose delay was defined as a dose that was given more than 3 days after the scheduled date.[2]

In NAPOLI-1, patients were randomly assigned to a 6-week treatment regimen consisting of nanoliposomal irinotecan alone (120 mg/m^2 every 3 weeks); 5-FU (2000 mg/m^2 weekly for 4 weeks) and leucovorin (200 mg/m^2 weekly for 4 weeks); or nanoliposomal irinotecan (80 mg/m^2 every 2 weeks) plus 5-FU (2400 mg/m^2 weekly every 2 weeks) and leucovorin (400 mg/m^2 every 2 weeks).[1]

More patients in the nanoliposomal irinotecan plus 5-FU and leucovorin combination arm experienced adverse events that required dose delays and/or dose reductions vs the 5-FU and leucovorin-alone arm (62% vs 33%).[1] In the exploratory post hoc analysis, a dose modification during the first 6 weeks of treatment was required for 53 patients (45%) treated with nanoliposomal irinotecan plus 5-FU and leucovorin. Of these, 49 patients required a dose delay and 34 patients required a dose reduction. Four patients who received a dose reduction did not require a dose delay.[2]

The most common grade 3/4 adverse events reported in patients who required a dose delay in the first 6 weeks of treatment with nanoliposomal irinotecan plus 5-FU and leucovorin were white blood cell decrease (n=11), neutrophil count decrease (n=9), neutropenia (n=8), diarrhea (n=6), and platelet count decrease (n=5). Among patients who required a dose reduction, the most common grade 3/4 adverse events were neutrophil count decrease (n=7), neutropenia (n=5), and white blood cell decrease (n=5).[2]

An analysis of overall survival compared outcomes with and without the addition of nanoliposomal irinotecan. Overall survival was prolonged in the nanoliposomal irinotecan plus 5-FU and leucovorin arm, regardless of the type of dose modification. Among patients who required a dose delay, the median overall survival was 8.44 months in the nanoliposomal irinotecan plus 5-FU and leucovorin arm vs 4.17 months in the 5-FU and leucovorin arm (hazard ratio [HR], 0.66; 95% CI, 0.46-0.95; Figure 1). Among patients with a dose reduction, the median overall survival was 9.36 months with nanoliposomal irinotecan vs 4.17 months without (HR, 0.58; 95% CI, 0.38-0.88; Figure 2).[2]

Within the cohort of patients treated with nanoliposomal irinotecan

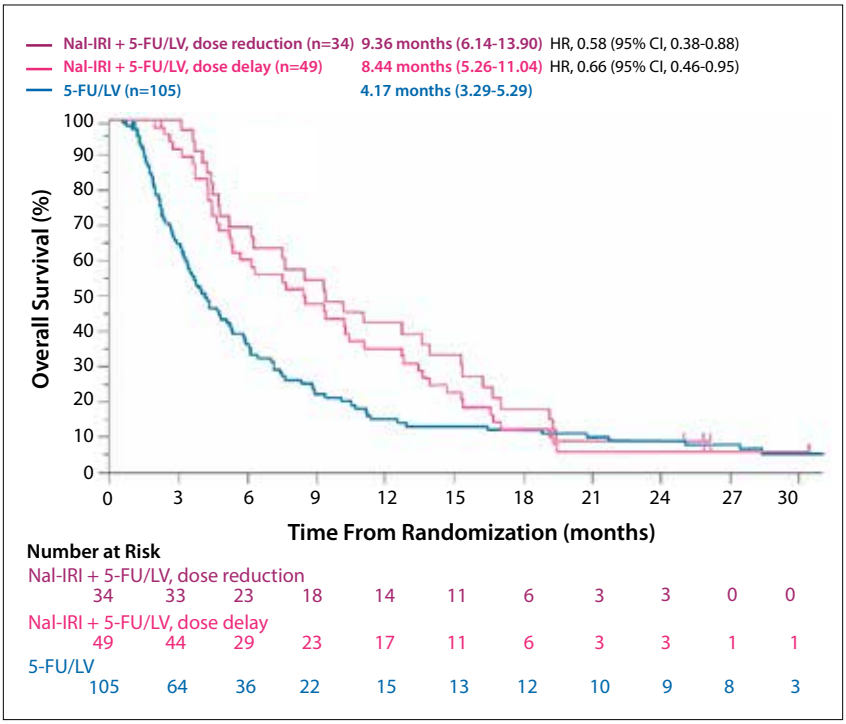

Figure 1. Overall survival among patients from the NAPOLI-1 trial in whom the dose of nanoliposomal irinotecan was reduced or delayed. 5-FU/LV, 5-fluorouracil/leucovorin; HR, hazard ratio; nal-IRI, nanoliposomal irinotecan; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. ASCO GI abstract 388. *J Clin Oncol.* 2018;36(suppl 4S).[2]

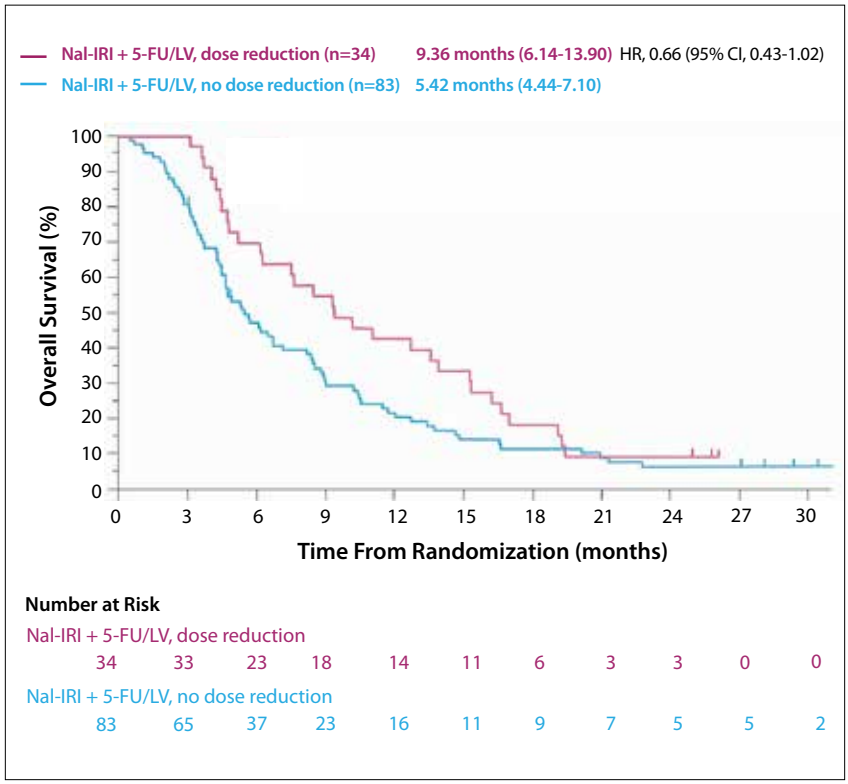

Figure 2. Overall survival among patients from the NAPOLI-1 trial in whom the dose of nanoliposomal irinotecan was or was not reduced. 5-FU/LV, 5-fluorouracil/leucovorin; HR, hazard ratio; nal-IRI, nanoliposomal irinotecan; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. ASCO GI abstract 388. *J Clin Oncol.* 2018;36(suppl 4S).[2]

plus 5-FU and leucovorin, the median overall survival was 9.4 months in the 34 patients who had a dose reduction vs 5.4 months in the 83 patients who did not (HR, 0.66; 95% CI, 0.43-1.02). This difference did not reach statistical significance. A similar, non-significant trend was seen with dose delays. The median overall survival was 8.4 months among the 49 patients who had a dose delay vs 5.6 months in the 68 patients who did not (HR, 0.84; 95% CI, 0.57-1.23).[2] This exploratory analysis suggested that an appropriate dose modification of nanoliposomal irinotecan, consisting of a dose reduction or a dose delay during the first 6 weeks of treatment, can be made without adversely affecting a patient's survival.[2]

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A Phase IB/II Randomized Study of mFOLFIRINOX + Pegylated Recombinant Human Hyaluronidase Versus mFFOX Alone in Patients With Good Performance Status Metastatic Pancreatic Adenocarcinoma: SWOG S1313 (NCT #01959139)

Hyaluronan is overexpressed in more than 80% of pancreatic cancers, and accumulating hyaluronan is associated with the development of high interstitial fluid pressure and drug resistance. Expression of hyaluronan is linked to disease progression and poor prognosis. Pegylated recombinant human hyaluronidase (PEGPH20) has demonstrated activity in a mouse pancreatic cancer model, by decreasing stromal expression of hyaluronan, normalizing the interstitial fluid pressure, and re-expanding the microvasculature.[1] When combined with gemcitabine, PEGPH20 depleted the tumor microenvironment and improved survival.[2]

At the 2018 American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) symposium, Dr Ramesh Ramanathan presented results from the SWOG S1313 study, which evaluated the activity of PEGPH20 in combination with a modified regimen of oxaliplatin, irinotecan, leucovorin, and 5-FU (mFOLFIRINOX) among patients with metastatic pancreatic cancer.[3] Importantly, this study did not select patients according to hyaluronan expression.

Patients ages 75 years and younger were eligible for enrollment into SWOG S1313 if they had metastatic and measurable disease and had not received prior treatment for their metastatic disease. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function. The study criteria excluded patients previously treated with warfarin, those with

ABSTRACT SUMMARY Nano-Liposomal Irinotecan and 5-FU/LV for the Treatment of Advanced PDAC

A retrospective chart review explored the postapproval safety, tolerability, and effectiveness of nanoliposomal irinotecan added to 5-FU and leucovorin since the approval of this therapy by the US Food and Drug Administration in October 2015 (Abstract 471). The chart review included all patients at Memorial Sloan Kettering Cancer Center who initiated therapy with nanoliposomal irinotecan plus 5-FU and leucovorin between October 2015 and June 2017. A total of 56 patients were identified. For patients who received this regimen in the first-line setting (n=4), the median PFS was 10.8 months. Median PFS was 4.3 months, 2.4 months, and 2.5 months for patients treated in the second-line, third-line, or beyond third-line settings, respectively. This trend was statistically significant (*P*=.0031). A similar statistically significant trend (*P*=.0002) was demonstrated for median overall survival, which was not reached for patients treated in the first-line setting, 8.4 months in the second-line setting, 3.9 months in the third-line setting, and 4.5 months for those treated beyond the third-line setting. Statistically significant trends in median PFS and median overall survival were also apparent when patients were stratified according to prior treatment with irinotecan. The following all-grade adverse events were reported: anemia (89%), fatigue (80%), diarrhea (63%), nausea (59%), anorexia (57%), vomiting (32%), and neutropenia (29%). Fatigue and anemia were more common in the real-world patient population compared with the NAPOLI-1 study. The authors observed that these safety and efficacy data reinforce the results of NAPOLI-1. They noted that responses to nanoliposomal irinotecan plus 5-FU and leucovorin were better among patients without disease progression during prior treatment with irinotecan-based therapy. Median overall survival was encouraging with sequential therapy consisting of nab-paclitaxel plus gemcitabine followed by nanoliposomal irinotecan added to 5-FU and leucovorin. The authors concluded that these findings underscore the utility of nanoliposomal irinotecan added to 5-FU and leucovorin for patients with advanced pancreatic adenocarcinoma.

a previous cerebrovascular accident or a transient ischemic attack, and those with preexisting carotid artery disease requiring intervention.[3]

The SWOG S1313 study was initiated in January 2014 and terminated in March 2017 at the interim futility analysis. A phase 1b dose-finding cohort of mFOLFIRINOX plus PEGPH20 was followed by a phase 2 portion, in which patients were randomly assigned to treatment with mFOLFIRINOX plus PEGPH20 (n=55) or mFOLFIRINOX alone (n=56). The study was amended to include use of prophylactic low-molecular weight heparin in the combination arm, based on an increase in thromboembolic events. The primary study endpoint was overall survival, with a null median overall survival of 10 months and an alternative of 15 months. Planned correlative studies included analysis of pretreatment biopsy samples for hyaluronan expression, as well as measurement of serum levels of hyaluronic acid at baseline and throughout the course of treatment.[3]

The phase 1b dose-escalation portion of the study established a dose of 3 µg/kg of PEGPH20 on day 1 of 2-week cycles for further

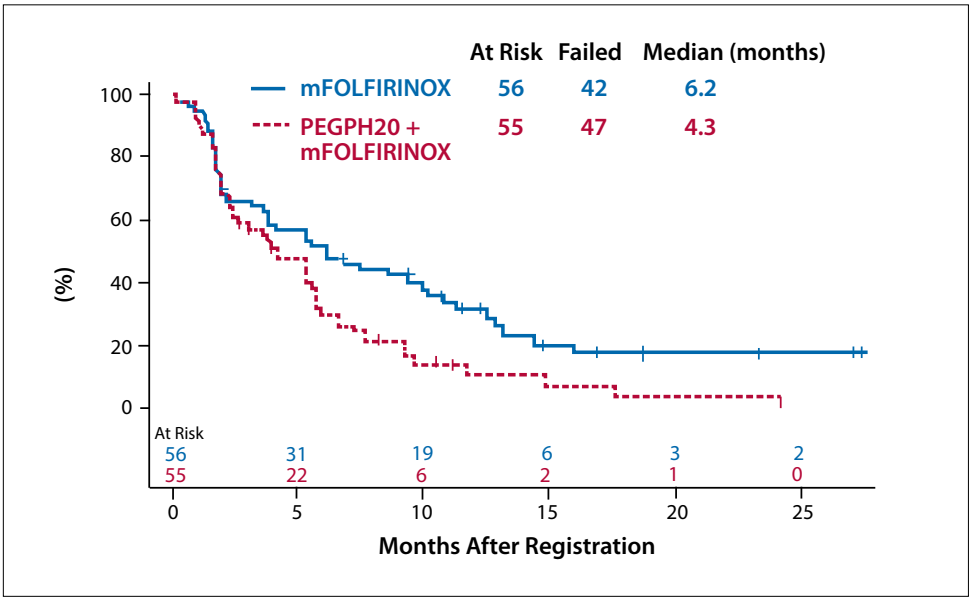

Figure 3. Progression-free survival among patients treated with mFOLFIRINOX with or without the addition of PEGPH20. mFOLFIRINOX, modified oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil; PEGPH20, pegylated recombinant human hyaluronidase. Adapted from Ramanathan RK et al. ASCO GI abstract 208. *J Clin Oncol.* 2018;36(suppl 4S).[3]

ABSTRACT SUMMARY Deposition Characteristics and Resulting DNA Damage Patterns of Liposomal Irinotecan in Pancreatic Cancer Xenografts

An analysis evaluated the pharmacokinetic and extended pharmacodynamic effects of nanoliposomal irinotecan compared with conventional nonliposomal irinotecan in pancreatic tumor models (Abstract 335). Three different tumors (AsPC-1, BxPC-3, and CFPAC-1) were grown as xenografts in mice. The animals were dosed every 7 days with either 25 mg/kg to 50 mg/kg nonliposomal irinotecan or 5 mg/kg to 10 mg/kg of nanoliposomal irinotecan. A more sustained circulation and delivery of irinotecan was observed with nanoliposomal irinotecan vs nonliposomal irinotecan. At the same irinotecan dose levels, nanoliposomal irinotecan was associated with prolonged circulation and tumor exposure of both irinotecan and its metabolite, SN-38. At a 5-fold lower dose, nanoliposomal irinotecan resulted in a similar degree of DNA damage vs nonliposomal irinotecan. DNA damage occurring in tumors treated with nanoliposomal irinotecan (10 mg/kg) peaked at 72 hours, vs 6 hours in tumors treated with nonliposomal irinotecan (50 mg/kg). Tumor volume growth was reduced to a greater degree with 10 mg/kg of nanoliposomal irinotecan vs 50 mg/kg of nonliposomal irinotecan. Studies with fluorescently labeled nanoliposomal irinotecan showed a deposition pattern in tumors around functional vessels, with peak liposomal accumulation between 6 and 24 hours. Liposomes are predominantly taken up by macrophages, followed by tumor and stromal cells. Extensive DNA damage was observed at 24 to 72 hours after nanoliposomal irinotecan treatment. DNA damage after nanoliposomal irinotecan treatment was primarily confined to tumor cells. The authors concluded that treatment with nanoliposomal irinotecan improves tumoral deposition of its irinotecan "payload" in pancreatic tumor xenograft models. Liposomal deposition is primarily restricted to the perivascular area, and occurs mainly in stromal macrophages. The DNA damage inflicted by nanoliposomal irinotecan, however, is primarily confined to tumor cells outside of the liposomal deposition area.

phase 2 study. mFOLFIRINOX was fixed at 85 mg/m^2 of oxaliplatin, 180 mg/m^2 of irinotecan, 400 mg/m^2 of leucovorin, and 2400 mg/m^2 of 5-FU administered intravenously throughout 46 hours.[3]

At baseline, the median patient age was 63.9 years in the combination arm and 60.5 years in the mFOLFIRINOX arm. The combination arm included fewer men (44% vs 55%). In both arms, most patients had an ECOG performance status of 0 (58% vs 55%).[3]

During the phase 2 portion of the trial, the rate of grade 3 to 5 adverse events was increased in the mFOLFIRINOX plus PEGPH20 arm vs the mFOLFIRINOX-alone arm (HR, 2.7). Grade 3/4 events reported at a higher frequency in the combination arm vs the mFOLFIRINOX-alone arm included nausea (25% vs 15%), diarrhea (24% vs 19%), vomiting (22% vs 13%), and fatigue (20% vs 11%). In the combination arm, the rate of all-grade thromboembolic events decreased from 18% to 9% with the introduction of prophylactic low-molecular-weight heparin.[3]

An interim futility analysis, triggered when 35 deaths occurred in 113 patients, demonstrated that the addition of PEGPH20 to mFOLFIRINOX did not show benefit over mFOLFIRINOX alone. The study therefore met the criteria to halt enrollment. The median overall survival was 7.7 months with PEGPH20 plus mFOLFIRINOX vs 14.4 months with mFOLFIRINOX alone (HR, 0.50; 95% CI, 0.31-0.81; *P*<.01). The median progression-free survival (PFS) showed a similar lack of benefit, at 4.3 months with PEGPH20 plus mFOLFIRINOX vs 6.2 months with mFOLFIRINOX alone (HR, 0.61; 95% CI, 0.40-0.93; *P*=.02; Figure 3). There was no benefit in the response rate, which was 33% (95% CI, 21%-47%) in the combination arm vs 45% (95% CI, 31%-59%) in the monotherapy arm.[3]

The authors concluded that the addition of PEGPH20 to mFOLFIRINOX not only increased toxicity, but also appeared to be detrimental to patient survival and response outcomes. The authors speculated that this detrimental effect might have been caused by lower exposure to mFOLFIRINOX treatment in the combination arm vs the mFOLFIRINOX-alone arm (median of 4 cycles vs 8 cycles, respectively), which in turn was attributed to higher toxicity in the combination arm. The results obtained in the SWOG S1313 trial are contradictory to the more favorable results reported in the HALO 202 phase 3 study with the combination of PEGPH20 plus gemcitabine/nab-paclitaxel.[4] More study is needed.

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Subgroup Analysis by Baseline Pain and Weight Among Patients in the NAPOLI-1 Trial

Dr Teresa Macarulla Mercadé and colleagues presented the results from subgroup analyses of the NAPOLI-1 trial.[1] Outcome was evaluated according to patients' baseline pain intensity and analgesic use[2] and baseline weight-associated parameters.[3] These analyses were post hoc, and therefore the reported *P* values are descriptive.

Baseline pain intensity and analgesic use were calculated based on the average value throughout the 7-day period before the first dose of the study drug. Pain was evaluated daily, and pain intensity during the previous 24 hours was recorded on a visual analog scale. Patients recorded analgesic consumption in a daily diary. Analgesic consumption was also tracked based on prescriptions and reported in the patient medical records. Patients' analgesic needs were evaluated and converted to morphine equivalents (mg/day) for standardization.[2]

Numerical differences emerged in the patient demographics and baseline characteristics among the baseline pain intensity and analgesic use subgroups. For example, sex and ethnicity varied across baseline pain intensity and analgesic use subgroups compared with the corresponding overall intent-to-treat populations. There was variability in the Karnofsky performance scale distribution across the subgroups for baseline pain intensity and use of analgesics compared with the corresponding overall intent-to-treat populations, which was expected. Among 417 patients in the intent-to-treat population, 295 had data for baseline pain intensity and 299 had data for baseline analgesic use. The median baseline pain intensity was 25.0 on the visual analogue scale, and median baseline analgesic use was 8.1 mg/day.[2]

There was an increase in the mortality risk for patients with more baseline pain or analgesic use (Table 1). Median overall survival was also lower in these patients (Table 2).[2]

The safety profiles for nanoliposomal irinotecan plus 5-FU and leucovorin within the baseline pain intensity and analgesic use subgroups were consistent with the overall NAPOLI-1 population. There were no clinically important differences between the subgroups with high vs low baseline pain intensity and analgesic use, except for a higher incidence of abdominal pain in the subgroups of patients with lower baseline pain intensity and analgesic use. Drug discontinuations owing to treatment-emergent adverse events were increased among patients with higher rates of pain and analgesic use.[2]

The data from this post hoc analysis support the use of nanoliposomal irinotecan plus 5-FU and leucovorin in patients previously treated with gemcitabine-based therapy regardless of baseline pain intensity or analgesic use. The authors concluded that higher baseline pain intensity and analgesic use might be useful prognostic parameters for patients with metastatic pancreatic cancer who have received previous treatment with gemcitabine-based therapy.[2]

The weight-based analysis by Dr Mercadé and colleagues focused on the effect of baseline body surface area, body mass index (BMI), and weight on outcome.[3] Baseline weight parameters were available for all patients in the intent-to-treat population (N=417). At baseline, the median body surface area was 1.71 m^2, the median BMI was 22.9 kg/m^2, and the median baseline weight was 63.6 kg.[3]

Table 1. Mortality Risk According to Baseline Pain and Analgesic Use in the NAPOLI-1 Trial

Comparison	Hazard Ratio	95% CI	*P* Value
BPI >0 vs BPI=0	2.01	1.38-2.95	.0002
BPI >25 vs BPI ≤25	1.95	1.49-2.53	<.00000x
BAU >0 vs BAU=0	1.85	1.42-2.43	<.00000x
BAU >8.1 vs BAU ≤8.1	1.67	1.28-2.17	.0001

BAU, baseline analgesic use; BPI, baseline pain index; NAPOLI-1, Nanoliposomal Irinotecan.

Data from Mercadé TM et al. ASCO GI abstract 379. *J Clin Oncol.* 2018;36(suppl 4S).[2]

Table 2. Median Overall Survival According to Baseline Pain and Analgesic Use in the NAPOLI-1 Trial

Comparison	Median Overall Survival (months)
BPI >0 vs BPI=0	4.7 vs 8.9
BPI >25 vs BPI ≤25	4.0 vs 6.3
BAU >0 vs BAU=0	4.3 vs 7.1
BAU >8.1 vs BAU ≤8.1	4.4 vs 6.4

BAU, baseline analgesic use; BPI, baseline pain index; NAPOLI-1, Nanoliposomal Irinotecan.

Data from Mercadé TM et al. ASCO GI abstract 379. *J Clin Oncol.* 2018;36(suppl 4S).[2]

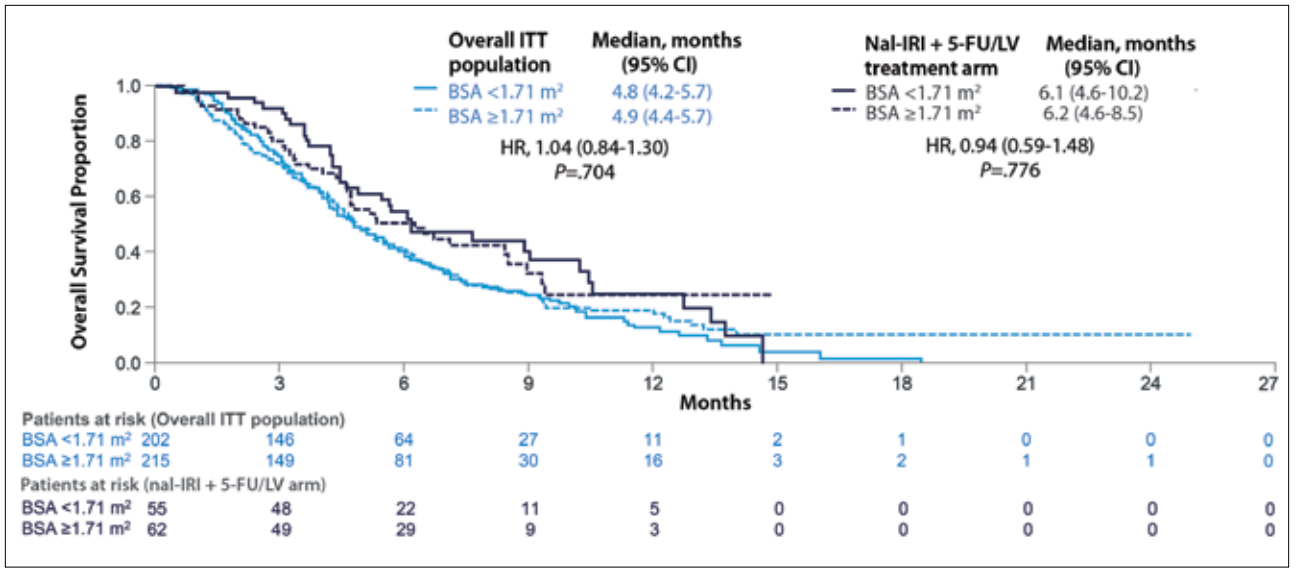

Figure 4. A subanalysis of the NAPOLI-1 trial showed that the mortality risk did not significantly differ according to the patient's baseline weight. BSA, body surface area; HR, hazard ratio; ITT, intent to treat; nal-IRI, nanoliposomal irinotecan; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Mercadé TM et al. ASCO GI abstract 410. *J Clin Oncol.* 2018;36(suppl 4S).[3]

ABSTRACT SUMMARY A Randomized Phase 2 Study of Durvalumab Monotherapy and in Combination With Tremelimumab in Patients With Metastatic Pancreatic Ductal Adenocarcinoma: ALPS Study

The randomized phase 2 ALPS trial (Phase II Study of MEDI4736 Monotherapy or in Combinations With Tremelimumab in Metastatic Pancreatic Ductal Carcinoma) assessed the efficacy and safety of durvalumab, either alone or in combination with tremelimumab, for the treatment of patients with metastatic pancreatic ductal adenocarcinoma (Abstract 217). The ALPS study was divided into 2 parts. In part A, patients were randomly assigned to treatment with durvalumab (1.5 g every 4 weeks) plus 4 doses of tremelimumab (75 mg every 4 weeks) in combination (n=32) or durvalumab (1.5 g every 4 weeks) alone (n=33). Treatment was continued for up to 12 months or until disease progression or unacceptable toxicity. At randomization, patients were stratified by their best response to prior first-line chemotherapy and prior first-line chemotherapy regimen (5-FU–based or gemcitabine-based). Expansion to part B, in which patients were to enroll in a nonrandomized or randomized controlled trial according to the magnitude of the efficacy signal observed in part A, did not occur because the threshold for efficacy was not met. A total of 65 patients were randomly assigned to treatment. There was 1 response (a partial response) among patients treated with durvalumab plus tremelimumab. The rate of responses plus stable disease was 9.4% in the durvalumab plus tremelimumab arm and 6.1% in the durvalumab-alone arm. The median PFS was 1.5 months in both arms, and the 6-month PFS rate was 9.4% with durvalumab plus tremelimumab and 3.6% with durvalumab. The median overall survival was also similar between the arms (3.1 months vs 3.6 months, respectively). The most frequently reported grade 3 or higher treatment-related adverse events included diarrhea (9.4%) and fatigue (6.3%) in the combination arm, and ascites (3.1%), hepatitis (3.1%), and increased lipase (3.1%) in the durvalumab monotherapy arm.

The mortality risk did not significantly differ among patients with baseline weight characteristics that were less than vs greater than or equal to the median values (Figure 4). The authors of this post hoc subgroup analysis concluded that the 3 baseline patient weight parameters considered—body surface area, BMI, and baseline weight—did not provide prognostic evidence for patient mortality or disease progression in this group of patients. Patients in both high and low baseline weight parameter subgroups showed a general improvement in overall survival when treated with nanoliposomal irinotecan plus 5-FU and leucovorin compared with 5-FU and leucovorin alone.[3]

Drug-related adverse events of grade 3 or higher occurred at a higher rate in lower-weight parameter subgroups (with the exception of BMI), and were more frequent in patients treated with nanoliposomal irinotecan plus 5-FU and leucovorin. Dose discontinuations occurred in similar numbers of patients in all baseline weight subgroups.[3] The data from this post hoc analysis support the use of nanoliposomal irinotecan plus 5-FU

and leucovorin in patients previously treated with gemcitabine-based therapy regardless of their baseline weight parameter values.[2]

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Phase II LAPACT Trial of Nab-Paclitaxel Plus Gemcitabine for Patients With Locally Advanced Pancreatic Cancer

Nab-paclitaxel combined with gemcitabine showed efficacy as a treatment for patients with metastatic pancreatic cancer in an exploratory analysis of the phase 3 MPACT trial (Metastatic Pancreatic Adenocarcinoma Clinical Trial).[1] This combination was associated with an approximate 3-fold greater median percentage reduction in the primary pancreatic tumor burden vs gemcitabine alone. Notably, this combination has a category 2A recommendation in guidelines from the National Comprehensive Cancer Network for treatment of patients with locally advanced pancreatic cancer and good performance status, based on extrapolation of data from the MPACT study.[2]

At the 2018 ASCO GI meeting, Dr Pascal Hammel and colleagues presented results of the LAPACT trial (Phase 2 Nab-Paclitaxel [Abraxane] Plus Gemcitabine in Subjects With Locally Advanced Pancreatic Cancer), which prospectively evaluated this treatment combination as induction therapy in patients with newly diagnosed, locally advanced pancreatic cancer.[3] Patients with treatment-naive, locally advanced pancreatic cancer were treated with up to 6 cycles of induction therapy with nab-paclitaxel (125 mg/m^2 weekly for 3 of 4 weeks) plus gemcitabine (1000 mg/m^2 for 3 of 4 weeks). Surgical intervention was allowed prior to the completion of the 6 treatment cycles, if the disease was deemed operable by the treating medical team. After completion of induction, patients without disease progression or unacceptable toxicity proceeded to treatment according to the investigator's choice: either continued nab-paclitaxel plus gemcitabine, chemoradiation (concurrent capecitabine or gemcitabine plus radiation according to the institutional practice), or surgical resection. The primary study endpoint was the time to treatment failure. Secondary endpoints included the disease control rate, overall response rate, PFS, overall survival, safety, and quality of life. Additionally, a post hoc evaluation of the resection rate and quality was planned.[3]

The intent-to-treat population consisted of 107 patients, of whom 106 received induction therapy and 61 completed treatment. Among these 61 patients, 45 went on to receive the investigator's choice of therapy, with 12 patients continuing nab-paclitaxel plus gemcitabine, 17 patients receiving chemoradiation, and 16 patients undergoing surgical resection. In the intent-to-treat population, the median age was 65.0 years (range, 42-85 years), and 59% were female. Patients had an ECOG performance status of 0 (46.7%) or 1 (53.3%). The median sum of the longest diameter of pancreatic tumor target lesions was 44.0 mm (range, 17-130 mm).[3]

The median time to treatment failure was 8.8 months (90% CI, 6.67-9.82; Figure 5). This duration exceeded the protocol-specified median time to treatment failure target of 6.6 months. Median PFS was 10.8 months (90% CI, 9.26-11.63). The estimated 12-month overall survival rate was 72% (90% CI, 64.5-78.9). In the intent-to-treat population, the overall response rate was 32.7%; all of the responses were partial. Most patients showed some measurable decrease in the sizes of their lesions. The disease control rate, defined as stable disease for 24 or more weeks, was 65.4%. Among the 16 patients (15%) who were able to undergo surgery after induction therapy, the resection margin status was R0 in 7 and R1 in 9.[3]

The median number of induction cycles was 5 (range, 1-6). Approximately half of patients required at least 1 dose delay of each drug, and approximately two-thirds of patients required at least 1 dose reduction of each drug.[3]

Among the 106 patients who received induction therapy, the most common all-grade nonhematologic treatment-emergent adverse events were fatigue (50.0%), diarrhea (46.2%), and asthenia (34.9%). Additional all-grade adverse events of special interest included peripheral sensory neuropathy, occurring in 23.6%, and peripheral neuropathy, occurring in 22.6%. The most frequent all-grade hematologic

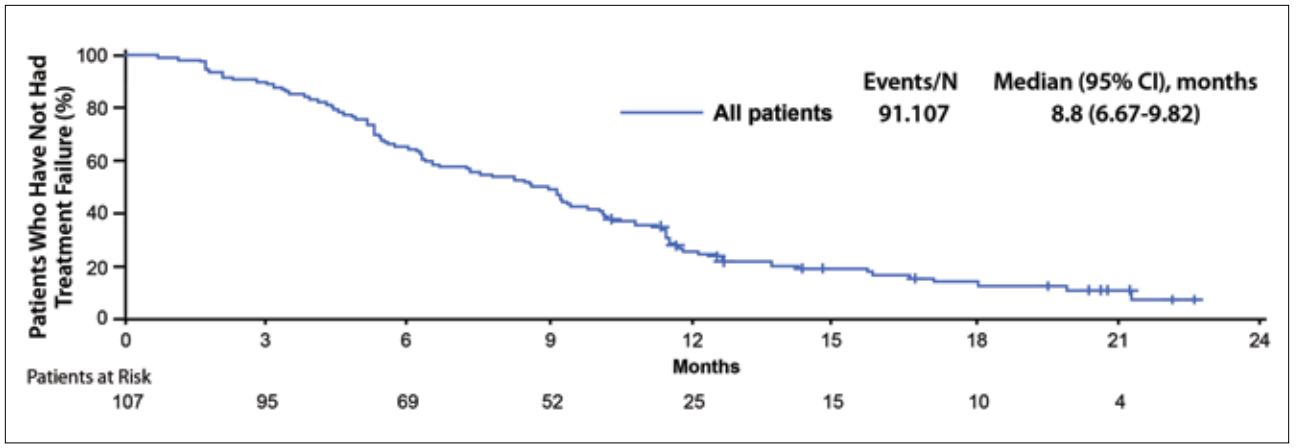

Figure 5. The median time to treatment failure in the phase 2 LAPACT trial of nab-paclitaxel plus gemcitabine for patients with locally advanced pancreatic cancer. LAPACT, Phase 2 Nab-Paclitaxel [Abraxane] Plus Gemcitabine in Subjects With Locally Advanced Pancreatic Cancer. Adapted from Hammel P et al. ASCO GI abstract 204. *J Clin Oncol*. 2018;36(suppl 4S).[3]

treatment-emergent adverse events included neutropenia (58.5%), anemia (47.2%), and thrombocytopenia (41.5%). The grade 3/4 hematologic adverse events included neutropenia (41.5%), anemia (11.3%), and thrombocytopenia (7.5%). During induction therapy, patients' overall quality of life was maintained throughout the 6 cycles of treatment.[3]

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Subgroup Analysis by Measurable Metastatic Lesion Number and Selected Lesion Locations at Baseline in NAPOLI-1: A Phase III Study of Liposomal Irinotecan ±5-Fluorouracil/Leucovorin in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine-Based Therapy

Dr Jens Siveke and colleagues presented results of a post hoc subgroup analysis of the NAPOLI-1 study, focusing on the baseline number of measurable metastatic lesions and lesion locations.[1,2] The reported *P* values are descriptive.

The study analyzed investigator-assessed baseline measurement of the number of metastatic lesions (either 1, 2, 3, or >3), and primary and metastatic lesion locations (in either the pancreas, liver, distant/regional lymph nodes, lung, peritoneum, or other areas) among patients with measurable or nonmeasurable disease (per version 1.1 of the Response Assessment in Solid Tumors criteria). Patients with more than 1 lesion location were counted once for each location. Additionally, lesion locations were categorized into different subgroups: patients with metastatic lesions in a specific location only (location only), patients with metastatic lesions other than that location only (no location only), patients with lesions in that and other locations (any location) and patients without lesions in that location (no location).[2]

At baseline, 354 of the 417 patients in the intent-to-treat population had measurable metastatic lesions, and 1080 lesion locations were recorded. There were differences in the patient demographics and baseline characteristics between the metastatic lesion and lesion location baseline subgroups, which was likely further influenced by the variable patient numbers. Sex, ethnicity, and Karnofsky performance scale score distribution all differed numerically across baseline metastatic lesion and lesion location subgroups compared with the corresponding overall intent-to-treat populations.[2]

In the overall intent-to-treat

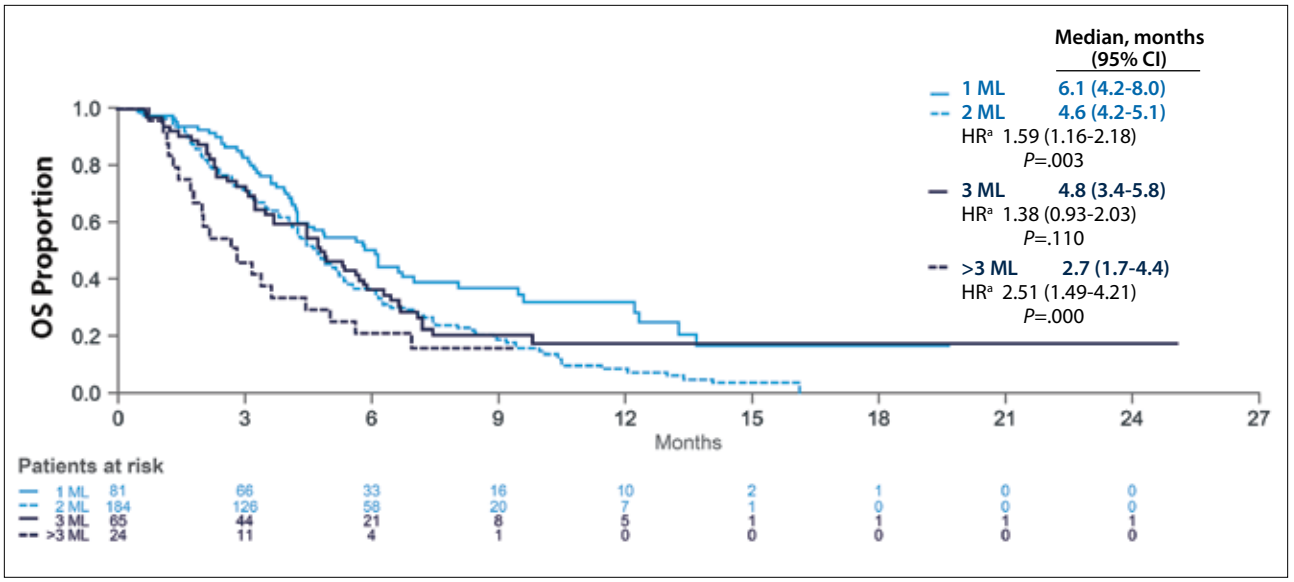

Figure 6. Overall survival in the NAPOLI-1 trial according to the number of selected measurable metastatic lesions at baseline in the intent-to-treat population. [a]The reference group for comparisons consisted of patients with 1 metastatic lesion. HR, hazard ratio; ML, metastatic lesion; OS, overall survival; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Siveke JT et al. ASCO GI abstract 460. *J Clin Oncol*. 2018;36(suppl 4S).[2]

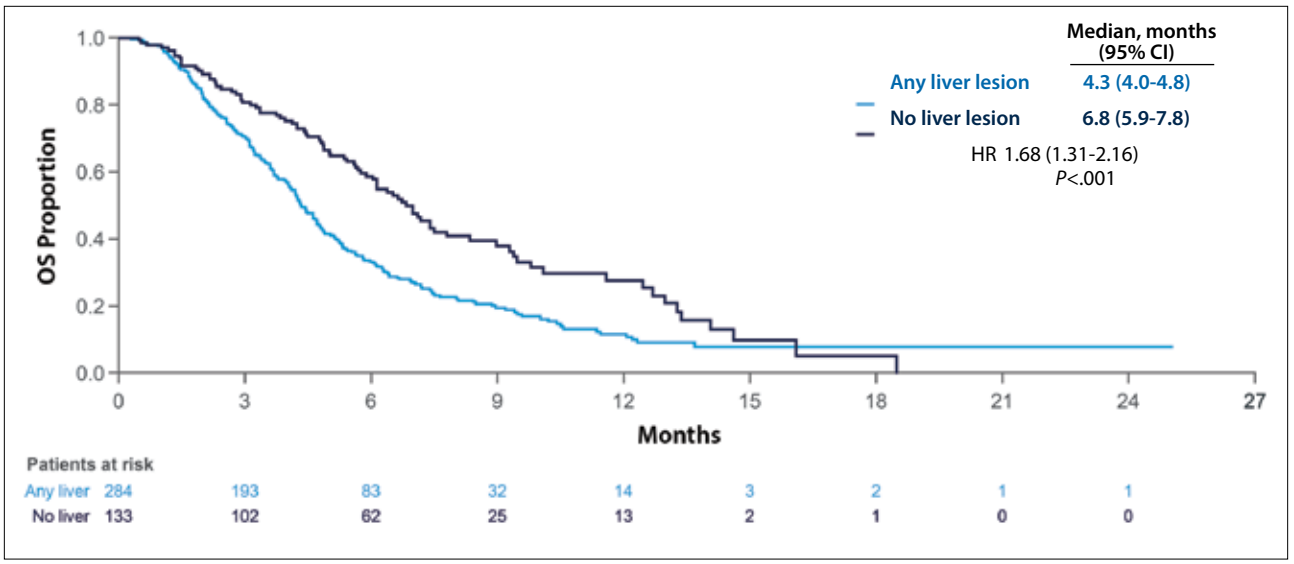

Figure 7. Overall survival in the NAPOLI-1 trial in patients who did or did not have liver lesions at baseline. HR, hazard ratio; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Siveke JT et al. ASCO GI abstract 460. *J Clin Oncol*. 2018;36(suppl 4S).[2]

population, patients with 1 selected metastatic lesion at baseline had a lower risk of mortality (Figure 6). The median overall survival was 6.1 months (95% CI, 4.2-8.0) for those with 1 lesion vs 4.6 months (95% CI, 4.2-5.1) for those with 2 lesions (HR, 1.59; *P*=.003). Patients with a liver lesion at baseline had a significantly increased risk of mortality vs patients without a liver lesion at baseline. The median overall survival was 4.3 months vs 6.8 months, respectively (HR, 1.68; 95% CI, 1.31-2.16; *P*<.001; Figure 7). The location of the lesion did not impact median overall survival in patients with lesions in the lung or peritoneum. Additionally, the lung only (n=9) and peritoneal only (n=18) groups contained too few patients to present as separate subgroups.[2]

The study authors concluded that this post hoc analysis suggested that the presence of lesions in the liver and, to some degree, the number of measurable metastatic lesions at baseline could potentially be used as prognostic indicators for mortality. A benefit to treatment with nanoliposomal

irinotecan plus 5-FU and leucovorin vs 5-FU and leucovorin alone was observed in most baseline metastatic lesions and lesion location subgroups. However, the differences did not reach statistical significance in all groups, possibly owing to the low patient numbers in many of the subgroups. The data from this post host subgroup analysis support the use of nanoliposomal irinotecan plus 5-FU and leucovorin regardless of the number of measurable metastatic lesions or lesion locations at baseline.

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Mapping the Immune Landscape in Pancreatic Cancer

The keynote lecture at the 2018 ASCO GI symposium was delivered by Dr Steven Leach, who focused on the changing treatment landscape in pancreatic cancer with emerging immunotherapies.[1] One of the first points Dr Leach made was that optimal use of immunotherapy in pancreatic cancer will require an individualized approach to ensure optimal biomarker-driven selection. He noted that this requirement is not unique to immunotherapy, but that patients treated with molecular therapy and even chemotherapy would benefit from individualized selection. The approach in pancreatic cancer has been to identify subsets of patients predicted to maximally benefit from a given therapy, converting a one-size-fits-all approach to a strategy individualized according to a patient's biomarkers. As one example, Dr Leach described the use of a *BRCA* mutation to identify patients who may be particularly sensitive to platinum-based chemotherapy, especially when combined with inhibitors of poly (ADP-ribose) polymerase (PARP).[2] The targeting of metastatic pancreatic cancers with evidence of *BRCA* mutations was successful in a phase 1 clinical study, which reported substantial activity with the addition of the PARP inhibitor veliparib to gemcitabine and cisplatin chemotherapy.[3] Based on promising results seen with targeting pancreatic cancers with *BRCA* mutations, current research is focused on identifying those pancreatic adenocarcinomas with a *BRCA*-ness phenotype, resulting in impaired DNA repair.

Expanding upon the idea of identifying particular molecular aberrations, Dr Leach discussed some of the barriers to identifying novel molecular targets in pancreatic cancer. Chief among these is the lack of a substantial tumor biopsy specimen with which to perform whole genome sequencing. Generally, pancreatic cancers are biopsied using fine needle aspiration, which typically does not provide a sufficient sample for detailed molecular analysis (particularly when it is considered that pancreatic tumors exhibit low cellularity). As research studies begin to focus on developing a molecular signature for pancreatic cancer, it is becoming increasingly important to design clinical trials that adequately target identified mutations. This approach is more difficult in pancreatic cancer than in other solid tumors, such as breast cancer and lung cancer, which often segregate into a few dominant molecular subtypes. In contrast, pancreatic tumors tend to exhibit a "smear" of mutations and aberrations

ABSTRACT SUMMARY Phase II Study of Olaparib for *BRCA*ness Phenotype in Pancreatic Cancer

In pancreatic cancer, *BRCA*ness is identified by family history, loss of ATM protein expression, and the homologous recombination deficiency signature. The efficacy of PARP inhibition in patients with a *BRCA*ness phenotype is unknown. A phase 2 study evaluated the PARP inhibitor olaparib as a treatment in this patient population (Abstract 297). All patients were treated with olaparib monotherapy. At the time of the report, a total of 33 patients had initiated treatment (21 at the Sheba Medical Center in Israel and 12 at the MD Anderson Cancer Center in the United States). Among these patients, 12 showed genomic aberrations associated with DNA damage repair, 14 patients had a family history of the *BRCA* mutation, and 5 patients exhibited *ATM* loss. Genetic aberrations associated with DNA damage repair included those affecting the genes *ATM* (n=6), *PALB2* (n=1), *BRCA* somatic (n=2), *FANCB* (n=1), *PTEN* (n=1), and *CCNE1* (n=1). Among the 32 patients treated, 2 had a partial response and 11 had stable disease (5 of whom maintained stable disease for more than 16 weeks). The median PFS was 14 weeks in the Israeli group and 24.7 weeks in the US group. The median duration of treatment was 16 weeks vs 20 weeks, respectively. The most frequent adverse events reported with olaparib were anemia, fatigue, and nausea.

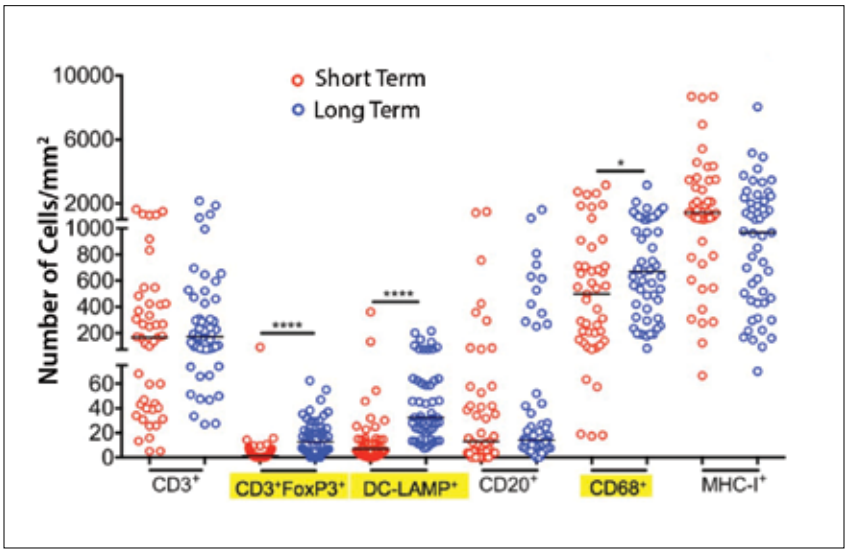

Figure 8. Intratumoral immunity in short-term and long-term survivors of pancreatic adenocarcinoma. Adapted from Balachandran VP et al. *Nature*. 2017;551(7681):512-516.[6]

across a wide variety of genes and pathways, with many showing a typical frequency of just a few percentage points. This challenge was recently exemplified by the finding that fewer than 2% of patients who had their pancreatic tumors molecularly profiled were able to enter a clinical trial targeting their identified mutation, even at a large institution like Memorial Sloan Kettering Cancer Center, which has a robust clinical trials portfolio.[4]

Dr Leach discussed immunotherapies and their potential impact in pancreatic adenocarcinoma. He noted that immunotherapies have revolutionized the treatment of patients with multiple solid tumor types. Much of this advancement has been driven by the identification and targeting of immune checkpoints. Microsatellite instability (MSI) status has emerged as a major biomarker predicting response to immune checkpoint therapy, but many patients with microsatellite-stable disease will also respond to immunotherapy. Dr Leach made the comparison to identifying tumors with a *BRCA*ness phenotype, stating it was now necessary to define the full spectrum of "MSIness" in order to predict response to immune checkpoint inhibitors.

There has simultaneously been a great deal of interest in identifying which characteristics of pancreatic cancer define its characteristic resistance to immunotherapy. Pancreatic adenocarcinoma has classically been considered a nonimmunogenic tumor, with a low burden of somatic mutations.[5] Recent sequencing efforts, including one pursued at Memorial Sloan Kettering Cancer Center involving laser capture microdissected material, have suggested that pancreatic cancer may have a rate of 2 mutations per megabase and therefore generate a regular, frequent immune response. Because there appears to be several mutations present creating an environment of regular neoantigen formation, these tumors should be well-targeted by immune checkpoint inhibitors. Alternative explanations are therefore needed to explain why pancreatic cancer may be largely resistant to checkpoint inhibitors. To address this question, Dr Vinod Balachandran and colleagues evaluated a cohort of pancreatic adenocarcinoma survivors with a particularly long survival time.[6] The median survival of these patient was 6 years, and several patients had survived for more than 10 years. The study demonstrated that long-term survivors display enhanced intratumor immunity with a 12-fold increase in cytolytic CD8+ T cells, an immunogenic environment, and a polyclonal tumor-specific T-cell repertoire (Figure 8). Whole-genome sequencing had identified putative neoantigens in pancreatic adenocarcinoma, and a combination of neoantigen burden and activated T cells seemed to define patients with the longest survival times. The quality (but not the quantity) of the neoepitopes within these neoantigens also contributed to their prognostic significance. Tumor neoepitopes with known homology to epitopes from microbial pathogens are associated with an increased immune response and long-term survival.

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Nomogram for Predicting Overall Survival in Patients Treated With Liposomal Irinotecan ± 5-Fluorouracil/Leucovorin in Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine-Based Therapy in NAPOLI-1

In a post hoc exploratory analysis of the NAPOLI-1 study, Dr Andrea Wang-Gillam and colleagues evaluated baseline patient characteristics and other variables in an effort to develop a nomogram to predict overall survival in patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.[1,2] Because the analysis was based on data from the NAPOLI-1 study, the nomogram was developed to predict 6-month and 12-month overall survival after treatment with nanoliposomal irinotecan plus 5-FU and leucovorin.[2]

Both univariate and multivariate analyses were performed to identify factors within the NAPOLI-1 clinical study that were significantly predictive of overall survival. The univariate analysis identified 21 independent factors that contributed to overall survival. Clinically relevant variables found to be significantly (or nearly significantly) associated with overall survival were used in the multivariate analysis. They included a baseline Karnofsky performance scale score of 90 or higher, baseline albumin of 4 g/dL or higher, a neutrophil-to-lymphocyte ratio greater than 5, the presence of liver metastases, a baseline CA19-9 level at or greater than the median (1542 U/mL), stage IV disease at diagnosis, treatment with nanoliposomal irinotecan plus 5-FU and leucovorin, and a BMI greater than 25 kg/m^2. After the multivariate analysis, a multivariate Cox regression analysis was repeated using various stratification criteria to ensure clinical relevance.[2]

In the resulting nomogram, Karnofsky performance scale status contributed the largest number of points to the predicted overall survival, followed by the presence of liver metastasis and the randomized treatment arm. Each clinical factor is assigned a numerical value point by drawing a line upward from the observed value through to the points line. After this is performed for each of the clinical factors, the total sum of points is tabulated and plotted on the total points line. The corresponding predictions for 6-month and 12-month survival probability can then be determined by drawing a vertical line straight down. Larger values of total points on the nomogram correspond to a greater 6- and 12-month survival probability.[2]

When this nomogram was applied to the nanoliposomal irinotecan plus 5-FU and leucovorin arm of NAPOLI-1, it was able to discern lower (n=131), intermediate (n=137), and higher (n=131) risk groups corresponding to median overall survival values of 8.5 months, 5.3 months, and 2.9 months, respectively (Figure 9). The investigators concluded that this nomogram may have utility for distinguishing among patient risk groups to aid in clinical decision making. The study authors acknowledged that this exploratory analysis was limited, in that the nomogram was not validated against an external patient population.[2]

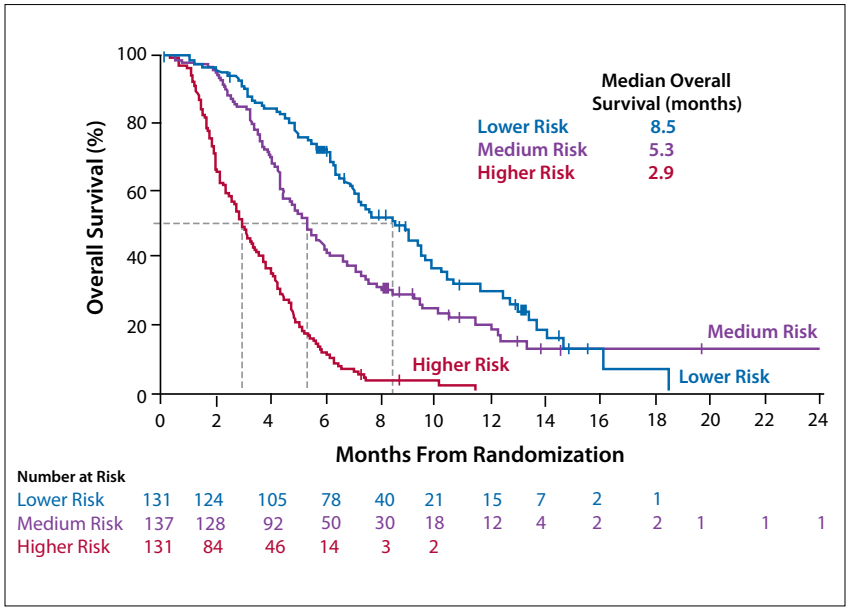

Figure 9. Overall survival according to risk groups identified by a nomogram drawn from data in the NAPOLI-1 trial. NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. ASCO GI abstract 459. *J Clin Oncol.* 2018;36(suppl 4S).[2]

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Genomics-Driven Precision Medicine for Advanced Pancreatic Ductal Carcinoma: Early Results From the COMPASS Trial (NCT02750657)

The ongoing COMPASS trial (Study of Changes and Characteristics of Genes in Patients With Pancreatic Cancer for Better Treatment Selection) was designed to obtain a biopsy of a primary tumor from patients with locally advanced or metastatic pancreatic cancer at baseline, and to then perform genomic analysis prior to starting the first-line chemotherapy.[1,2] After biopsy, tumor specimens underwent whole-genome sequencing and whole transcriptome sequencing. Patients were then treated with standard first-line chemotherapy consisting of either mFOLFIRINOX or nab-paclitaxel as palliative treatment, or combination treatment with mFOLFIRINOX or nab-paclitaxel, with or without other investigational agents, within a clinical trial as first-line palliative treatment. After progression, patients received second-line therapy. The primary study endpoint was to determine the feasibility of reporting results from whole-genome sequencing prior to the first disease assessment at the first 8-week computed tomography scan. A secondary endpoint was the discovery of patient subsets with predictive mutational and transcriptional signatures to guide therapy.

At the time of the report, 71 patients were enrolled, of whom 63 safely underwent a baseline biopsy. Whole-genome sequencing was successful in 62 of the 63 biopsies (98%). The median time to reporting the whole-genome sequencing results was 35 days (range, 19-52 days). Therefore, the primary study endpoint was met. The main genomic drivers in advanced pancreatic cancer were similar to those already identified for earlier-stage disease, and included *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*. Germline *BRCA* mutations were identified in 2 patients; one had somatic loss of heterozygosity and the other did not. Three patients had unstable genomic subtypes, as indicated by the presence of more than 200 structural variants. Among these 3 patients, 2 had a duplication signature without any pathogenic germline mutations, and the third had a *BRAF* mutation and numerous translocations. Potentially actionable somatic alterations were identified in 16 patients (25%), and included *ARID1A* mutation (n=5), *PIK3CA* mutation (n=4), *PTEN* mutation (n=3), *CDK4/6* amplification (n=3), and *BRAF* mutation (n=1).[1]

RNA sequencing for whole transcriptome sequencing demonstrated that 24% of the tumor specimens had basal-like RNA signatures, whereas the remaining 76% had a classical signature. Subsequent RNA in situ hybridization showed that *GATA6* expression was higher among patients with a classical signature vs a basal-like signature, which is consistent with prior reports.[1]

There were statistically significant differences in tumor response by RNA subtype among the 50 evaluable patients. More patients with the classical signature achieved tumor responses and partial responses compared with the basal-like signature (34% vs 8%; *P*=.0002). The mean percent change was increased in the basal-like signature (+17%) and decreased in the classical signature (–19.5%; *P*=.004). Among the 3 patients with unstable genomes, 2 achieved a partial response, and the third patient had tumor shrinkage of 20%. These tumor responses translated into survival differences. Both median PFS and median overall survival were prolonged in patients with a classical RNA signature. The median PFS was 6.4 months in patients with a classical signature vs 2.3 months in patients with a basal-like signature (HR, 0.28; 95% CI, 0.14-0.57; *P*<.001). Similarly, the median overall survival was 10.4 months vs 6.3 months, respectively (HR, 0.33; 95% CI, 0.15-0.7; *P*=.004).[1]

The authors concluded that obtaining a prospective genomic profile in advanced pancreatic cancer is safe and feasible, with a clinically meaningful turnaround time. Genomic characteristics may help to identify patients who might respond better to chemotherapy. Further study is needed to validate the prognostic and predictive value of these genomic biomarkers and to develop better patient selection treatment strategies.[1]

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Highlights in Pancreatic Cancer From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium: Commentary

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, GI Program, Mayo Clinic Cancer Center
Senior Associate Consultant, Mayo Clinic
Phoenix, Arizona

Many presentations focusing on pancreatic cancer at the 2018 American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) symposium helped further our knowledge of this deadly disease. Data from clinical trials, such as subanalyses from the NAPOLI-1 study (Nanoliposomal Irinotecan), focused on refining our understanding of which groups of patients are more likely to benefit from second-line therapy with nanoliposomal irinotecan. Further data from clinical trials provided insight into the potential successes and failures of pegylated hyaluronidase (PEGPH20), durvalumab, and olaparib.

Nanoliposomal Irinotecan

Dr Andrea Wang-Gillam and colleagues evaluated data from the NAPOLI-1 trial to see whether dose modifications of nanoliposomal irinotecan, in combination with 5-fluorouracil (5-FU), impacted efficacy.[1] The randomized phase 3 NAPOLI-1 trial enrolled patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy. The study showed that the addition of nanoliposomal irinotecan to 5-FU increased survival to 6.1 months, vs 4.2 months with 5-FU alone (hazard ratio, 0.67; P=.012).[2] The study was positive for its primary endpoint of overall survival, as well as for the secondary endpoints, such as progression-free survival and response rate. The study by Dr Wang-Gillam was an exploratory analysis to evaluate whether dose reductions or delays secondary to adverse events impacted overall survival.[1] As expected, patients treated with nanoliposomal irinotecan, 5-FU, and leucovorin experienced more adverse events that required dose reductions or delays, at 62% vs 33%. Interestingly, among patients treated with nanoliposomal irinotecan, 5-FU, and leucovorin, the median overall survival was numerically, but not significantly, higher in patients who had a dose reduction or a dose delay. This analysis therefore shows that in patients treated with nanoliposomal irinotecan, 5-FU, and leucovorin, dose modifications related to toxicities do not significantly impact overall survival. Even when the dose of nanoliposomal irinotecan was reduced, survival remained better than with 5-FU and leucovorin alone.

This study is important because in clinical practice, there is always the concern that a reduced dose will decrease benefit. This analysis of NAPOLI-1 suggested that patients treated with nanoliposomal irinotecan, 5-FU, and leucovorin do equally well, and perhaps slightly better, than patients treated with 5-FU and leucovorin, regardless of dose delays and dose reductions. These data emphasize the importance of modifying the dose of nanoliposomal irinotecan when needed for adverse events, since this strategy does not adversely impact outcomes.

Another analysis of the NAPOLI-1 trial by Dr Wang-Gillam looked at whether a nomogram could be established to help predict survival in patients treated with nanoliposomal irinotecan.[3] The study included both univariate and multivariate analysis to identify factors that might predict for overall survival. The model was created using several factors that were assigned points equal to the weight sum of relative significance of each valuable. A C-index was then evaluated by internal bootstrap validation. There were data from 417 patients for the univariate analysis and 399 patients for the multivariate analysis (in 18 patients, baseline data were missing). Positive predictors of overall survival included treatment with nanoliposomal irinotecan, 5-FU, and leucovorin; Karnofsky performance status of 90 or higher; a neutrophil-to-lymphocyte ratio of more than 5; and an albumin level of 4 g/dL or higher. Negative predictors of survival included the presence of liver metastases, CA-99 levels higher than the median of the study (1542 U/mL), and stage 4 at diagnosis. This analysis matched findings from all other studies in pancreatic cancer

This nomogram may help to stratify patients and inform decisions. In clinical practice, however, the factors used to select treatment are performance status, comorbidities, and patient/physician preferences. The nomogram helps us understand that there are different risk groups. Future studies should aim to identify the molecular and genetic differences that may lead to the various risk profiles. Currently, there are rough clinical characteristics that may or may not provide a clear picture to the best approach in managing this challenging disease.

Modified FOLFIRINOX Plus Pegylated Hyaluronidase

Dr Ramesh Ramanathan presented results from a phase 1b/2 randomized study of PEGPH20 plus modified FOLFIRINOX in patients with

metastatic pancreatic cancer and a good performance status.[4] PEGPH20 degrades hyaluronan, a major component of the stroma. Preclinical models suggest that the degradation of hyaluronan will increase delivery of chemotherapy and potentially prolong survival.[5] Many ongoing and recently published studies include patients selected for tumor hyaluronan.[6] The study by Dr Ramanathan did not select for these patients, although it did collect for tissue and will include a retrospective analysis to determine whether hyaluronan expression had any impact. The trial started as a phase 1b run-in study, and then randomly assigned patients to FOLFIRINOX plus PEGPH20 vs FOLFIRINOX alone. The planned analysis included 138 patients. The study was closed when a preplanned interim analysis showed futility with the addition of PEGPH20 to FOLFIRINOX. As expected, PEGPH20 increased the risk of clotting. Ultimately, all patients in the PEGPH20 arm were treated with low-molecular-weight heparin after an amendment was put in place.

Surprisingly, the survival differential favored the control arm, FOLFIRINOX. The median survival was 14.4 months with FOLFIRINOX alone and only 7.7 months with PEGPH20 plus FOLFIRINOX. Progression-free survival was also lower among patients treated with PEGPH20. These outcomes contrast with more favorable results that were reported for the combination of gemcitabine and nab-paclitaxel with PEGPH20.[6] Previous studies that have included stromal modifiers, such as the hedgehog inhibitors, added to chemotherapy have also yielded results that were either nonsuperior or even inferior to chemotherapy alone.[7] The cumulative data raise the question of whether stroma is a friend or a foe. Some data suggest that, in pancreatic cancer, the stroma may protect against the development of early metastases. At the same time, the stroma also exerts some negative immunosuppressive elements. The question remains about how to optimally target the stroma without negatively impacting outcome. The negative results from the PEGPH20 study, with a nearly 50% detrimental effect on survival, are very concerning.[4] An ongoing study with gemcitabine nab-paclitaxel with or without PEGPH20 is selecting patients for high hyaluronan stains, and results should hopefully provide more insight.[8]

Durvalumab

Dr Eileen O'Reilly presented results of a study evaluating the combination of durvalumab, a programmed death ligand 1 inhibitor, and tremelimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint inhibitor, in patients with pancreatic ductal adenocarcinoma.[9] These agents are active across multiple tumor types.[10,11] Individually, they have not had much activity in pancreatic cancer. It was thought that the combination might synergistically increase the level of blockade and improve outcome in patients with previously treated metastatic pancreatic cancer. This study randomly assigned 65 patients to durvalumab alone or durvalumab plus tremelimumab. (One patient in the durvalumab-alone arm died before treatment began.) Among the 64 patients who received treatment, all experienced at least 1 adverse event thought to be treatment-related. None of the toxicities were fatal. The safety profiles were typical for these agents. Among the patients treated with durvalumab plus tremelimumab, 1 patient had a confirmed partial response, which lasted more than 12 months. The disease control rate was 9.4% in the combination arm. With durvalumab alone, there were 2 patients with unconfirmed partial responses, and the disease control rate was a meager 6.1%. In both arms, the median progression-free survival was 1.5 months. The median overall survival was 3.1 months with the combination vs 3.6 months with the monotherapy. These results were disappointing, and this regimen had no meaningful activity in the second-line setting for unselected patients with metastatic pancreatic cancer. Immune-based strategies continue to be very disappointing in pancreatic cancer, and further developments in this field remain challenging.

Olaparib

Dr Talia Golan presented results from a study evaluating olaparib in patients with pancreatic cancer who have the *BRCA*ness phenotype.[12] Among patients with pancreatic ductal adenocarcinoma, those with DNA damage repair from *BRCA1/2* have a somewhat more favorable prognosis and tend to be sensitive to platinum analogs and poly(ADP-ribose) polymerase (PARP) inhibitors. Olaparib and rucaparib each have single-agent activity in patients with pancreatic cancer with these alterations.[13,14] Veliparib, on the other hand, seems to be relatively inactive, including in highly selected patient populations. The study by Dr Golan enrolled patients with DNA damage repair deficiency without *BRCA* mutations (*BRCA*-ness). Approximately 10% to 15% of patients with pancreatic cancer are expected to fit this phenotype, and studies in ovarian cancer have shown benefit from PARP inhibitors in this group.[15]

The presentation by Dr Golan provided results of two parallel, ongoing phase 2 studies, one in Israel and the other in the United States.[12] *BRCA*-ness was defined as a negative germline *BRCA1/2* mutation, but a personal or family history of a *BRCA*-related cancer, loss of ATM, and genetic aberrations associated with homologous recombination deficiency. DNA damage repair genomic analyses identified *ATM*, *PALB2*, *BRCA* somatic, *FANCB*, *PTEN*, and *CCNE1*.

The study in Israel enrolled 21 patients, and the one in the United States included 11 patients. The Israeli study had only 5 patients with stable disease lasting for more than 4 months.

In the US trial, which primarily enrolled platinum-sensitive patients, 2 patients had a partial response, and 6 had stable disease. The progression-free survival was 14 weeks in the Israeli study and 25 weeks in the US study.

This small study shows encouraging initial anti-tumor activities in platinum-sensitive germline, *BRCA*-negative patients with pancreatic ductal adenocarcinoma.[12] The study is interesting, as it shows a potential benefit from PARP inhibitors in this *BRCA*ness phenotype that includes up to 20% of all patients with pancreatic cancer.

Predictive Mutational Transcriptional Features

The ongoing, prospective COMPASS trial (Study of Changes and Characteristics of Genes in Patients With Pancreatic Cancer for Better Treatment Selection), from the Princess Margaret Cancer Centre in Toronto, is evaluating the predictive mutational transcriptional features in advanced pancreatic cancer.[16] The goal is to improve patient stratification and treatment selection. The trial prospectively recruited patients with advanced pancreatic cancer before they started treatment. Patients underwent whole genome sequencing and RNA sequencing. Fresh tumor tissue was acquired from the patients. The tissue underwent laser capture microdissection and high genomic analysis. The primary endpoint of the study was feasibility—whether it was possible to report results from whole genome sequencing before the first disease assessment. This study, performed between 2016 and 2017, provided data for 63 patients. The genomic analyses were successful in more than 95% of the patients. The genomic results were available 35 days after biopsy, which was considered acceptable in Canada and met the primary feasibility endpoint. An unstable genomic subtype was identified in 3 patients, all of whom responded well to modified FOLFIRINOX. For these 3 patients, the predictive value of the genomic test led them to FOLFIRINOX, and all had a good response. Among 2 patients who had the same germline *BRCA2* mutations, one responded to chemotherapy with loss of heterozygosity, which is a genomic hallmark of double-stranded break repair deficiency. A basal-like RNA expression signature was identified in 25% of the tumors. These patients were resistant to chemotherapy, and those that exhibited the classical RNA type had tumor shrinkage. This finding is interesting. In the clinic, we do not usually distinguish between basal-like RNA and classical RNA because these tests are not routine.

The COMPASS study provided several important insights. Close examination of the RNA sequencing reveals that 24% of patients had a basal-like RNA expression signature. These patients do not appear to respond to chemotherapy as well. The remaining 76% of patients, who have the classical RNA subtype, tend to respond better to chemotherapy. It is often thought to be difficult to find any actionable mutagenic alterations in pancreatic cancer. The COMPASS trial, however, showed that 30% of patients had potentially actionable genetic alterations. This finding is important because pancreatic cancer has been largely omitted from research in genomics and immunotherapy. This study continues to highlight the importance of precision medicine in cancer.

Disclosure

Dr Bekaii-Saab has no real or apparent conflicts of interest to report.

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Highlights in Pancreatic Cancer From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

CME Post-Test: *Circle the correct answer for each question below.*

1. In a subanalysis of the NAPOLI-1 trial that evaluated patients who required a dose delay, what was the median overall survival among patients treated with nanoliposomal irinotecan plus 5-FU and leucovorin?

   a. 5.15 months
   b. 6.49 months
   c. 7.81 months
   d. 8.44 months

2. In the SWOG S1313 study, what was the median overall survival with PEGPH20 plus mFOLFIRINOX?

   a. 6.5 months
   b. 7.7 months
   c. 8.1 months
   d. 9.4 months

3. In the ALPS trial, what was the rate of responses plus stable disease in patients treated with durvalumab plus tremelimumab?

   a. 6.3%
   b. 7.6%
   c. 8.1%
   d. 9.4%

4. Which of the following is the active metabolite of irinotecan?

   a. Immunoglobulin G
   b. Monomethyl auristatin E
   c. Succinate
   d. SN-38

5. In a subanalysis of the NAPOLI-1 trial, the median overall survival was __ for patients with 2 metastatic lesions.

   a. 4.6 months
   b. 5.1 months
   c. 6.3 months
   d. 7.6 months

6. In the LAPACT trial of induction therapy with nab-paclitaxel plus gemcitabine, what was the estimated 12-month overall survival?

   a. 59%
   b. 64%
   c. 72%
   d. 81%

7. True or False: Most patients with pancreatic tumors who undergo molecular profiling are able to enter a clinical trial targeting their identified mutation.

   a. True
   b. False

8. In the COMPASS trial, which mutation was NOT identified as a main genomic driver in advanced pancreatic cancer?

   a. *BRAF*
   b. *CDKN2A*
   c. *KRAS*
   d. *TP53*

9. In the COMPASS trial, whole-genome sequencing was successful in ___ of biopsies.

   a. 81%
   b. 86%
   c. 95%
   d. 98%

10. Recent sequencing efforts have suggested that pancreatic cancer may have a rate of ___ mutations per megabase.

    a. 0.5
    b. 1
    c. 2
    d. 3

Evaluation Form: Highlights in Pancreatic Cancer From the 2018 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 13249**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Medical ❒ Oncology, Hematology/Oncology ❒ Oncology, Other

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week who have pancreatic cancer?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Describe how data from recent clinical trials in pancreatic cancer may impact clinical care
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
Stratify patients according to risk factors
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
Describe insights from the latest genomic studies in pancreatic cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
Discuss novel treatment approaches in pancreatic cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
The content was evidence based
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
The educational material provided useful information for my practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
The activity enhanced my current knowledge base
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree
The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented
❒ My current practice has been reinforced by the information presented
❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name*_____

Degree*_____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax_____

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Signature* _____ Date _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.50 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10