Case Discussion

74 yo woman with a history of biliary pancreatitis presented with bloating and abdominal pain

CT scan showed peritoneal carcinomatosis, large right ovarian mass, ascites and either a pancreatic pseudocyst or tail mass

Cytology from ascites favored pancreatic adenocarcinoma, confirmed by FNA, genetic testing: BRCA-negative

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CT scan showed peritoneal carcinomatosis, large right ovarian mass, ascites and either a pancreatic pseudocyst or tail mass

Cytology from ascites favored pancreatic adenocarcinoma, confirmed by FNA, genetic testing: BRCA-negative

Received 7 cycles of FOLFIRINOX with mixed response

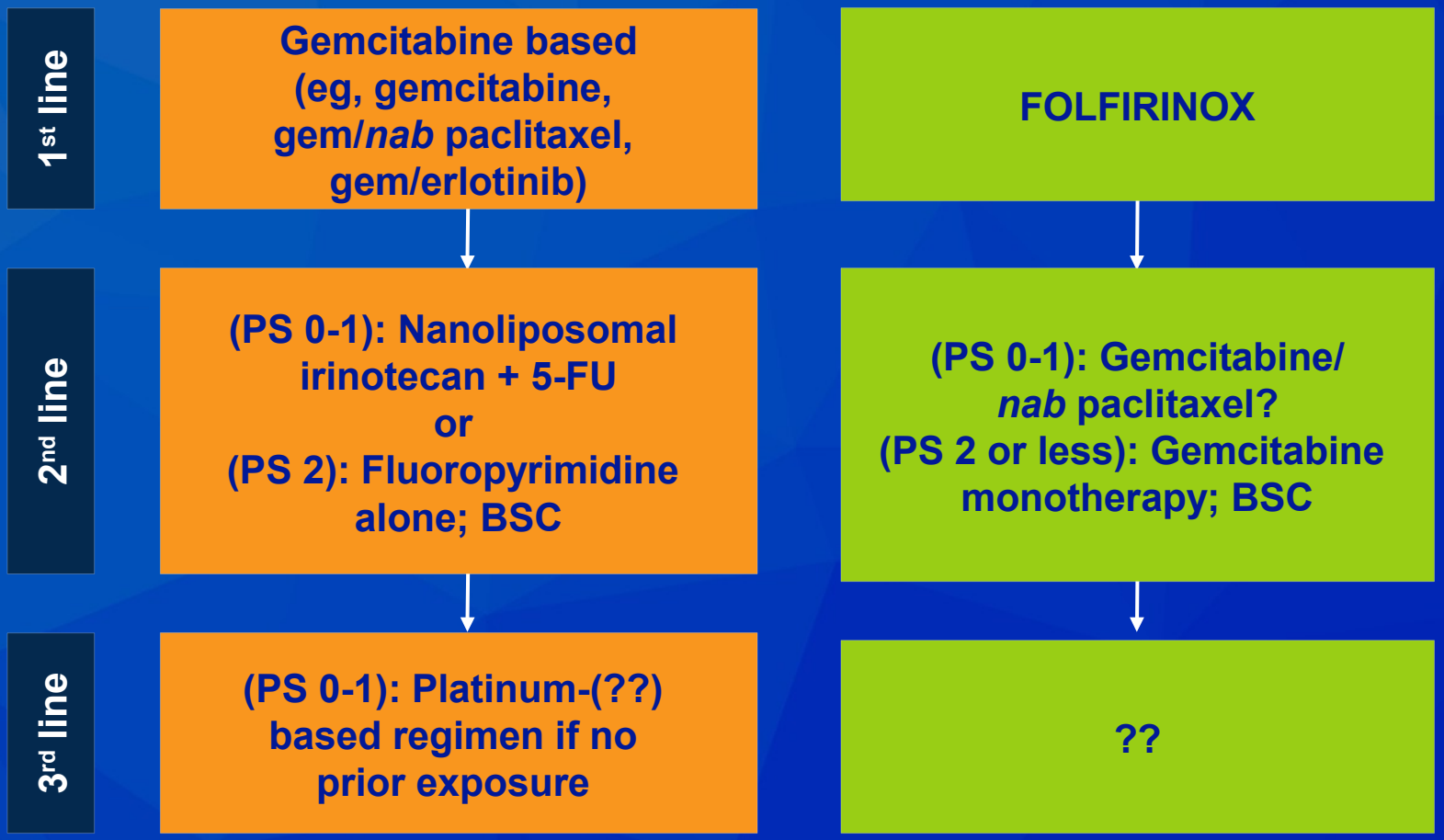
Underwent surgical debulking resection

At progression, received *nab* paclitaxel/gem with short-lived response.

At reprogression tried different therapies.

Expired shortly thereafter

Current Approach in Treatment Sequencing for Metastatic Pancreatic Cancer

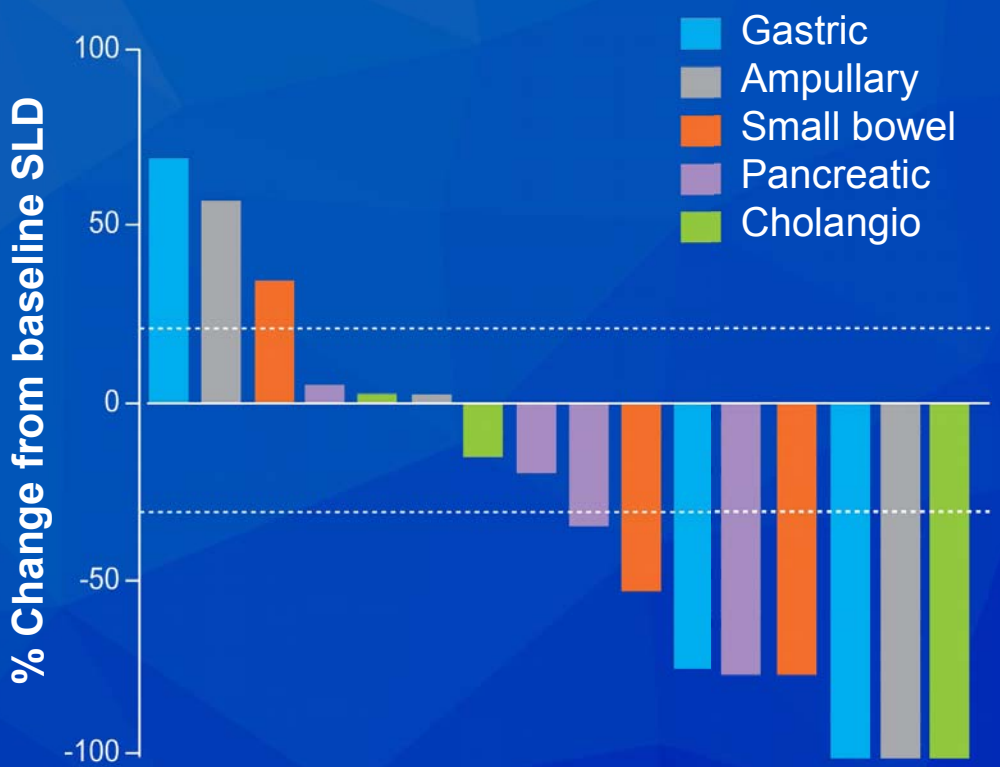


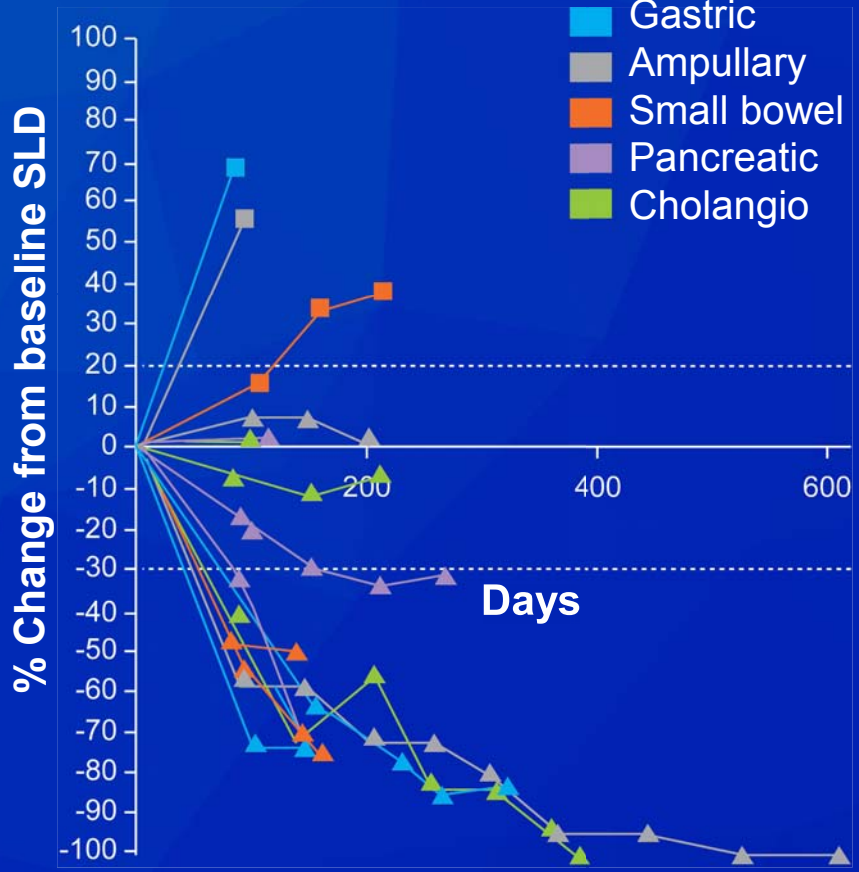
BSC = best supportive care; PS = performance status

Courtesy of Dr Tanios Bekaii-Saab.

Response to Pembrozilumab in Mismatch Repair-Deficient Non-CRC GI Cancers

- 17 patients with non-CRC GI cancers (pancreatic cancer n = 4) deficient in mismatch repair, treated with pembrozilumab





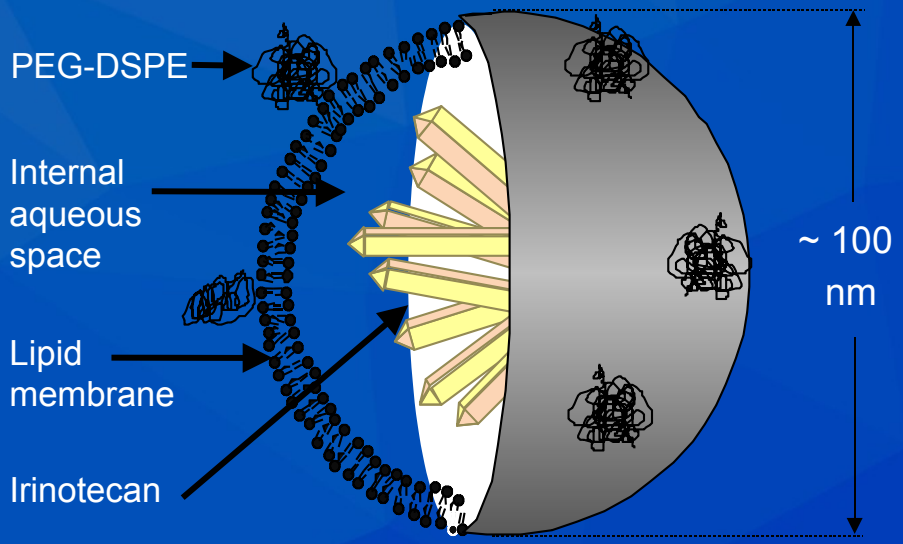
Le D et al. Gastrointestinal Cancers Symposium 2016;Abstract 195.

NAPOLI-1: Nal-IRI ± 5-FU/LV versus 5-FU/LV for mPDAC After Gemcitabine Failure

Outcome	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)	Nal-IRI (n = 151)
Median OS	6.2 months	4.2 months	4.9 months
Median PFS	3.1 months	1.5 months	2.7 months
ORR	17%	1%	6%

Wang-Gillam A et al. *Proc ASCO* 2016;Abstract 4126; *Lancet* 2016;387:545-57.

Nanoliposomal Irinotecan (Nal-IRI)



- Nal-IRI has 70x higher AUC of total irinotecan in blood *vs* conventional irinotecan (300 mg/m^2)[1]
- MM-398 achieved 5x higher levels of SN-38 (active metabolite) in tumor compared to blood at 72 hours[2]

~80,000 irinotecan molecules/liposome

[1] Roy AC et al. *Ann Oncol* 2013;24(6):1567-73. [2] Ramanathan RK et al. *Proc AACR* 2014;CT224.

NAPOLI-1: Select Adverse Events

Adverse event (Grade 3/4)	Nal-IRI + 5-FU/ LV (n = 117)	Nal-IRI (n = 151)	5-FU/LV (n = 134)
Neutropenia	28%	15%	2%
Diarrhea	13%	21%	5%
Vomiting	12%	14%	4%
Fatigue	14%	6%	4%
Nausea	8%	5%	3%

Grade ≥3 febrile neutropenia: Nal-IRI + 5-FU/LV: 2%; nal-IRI: 4%

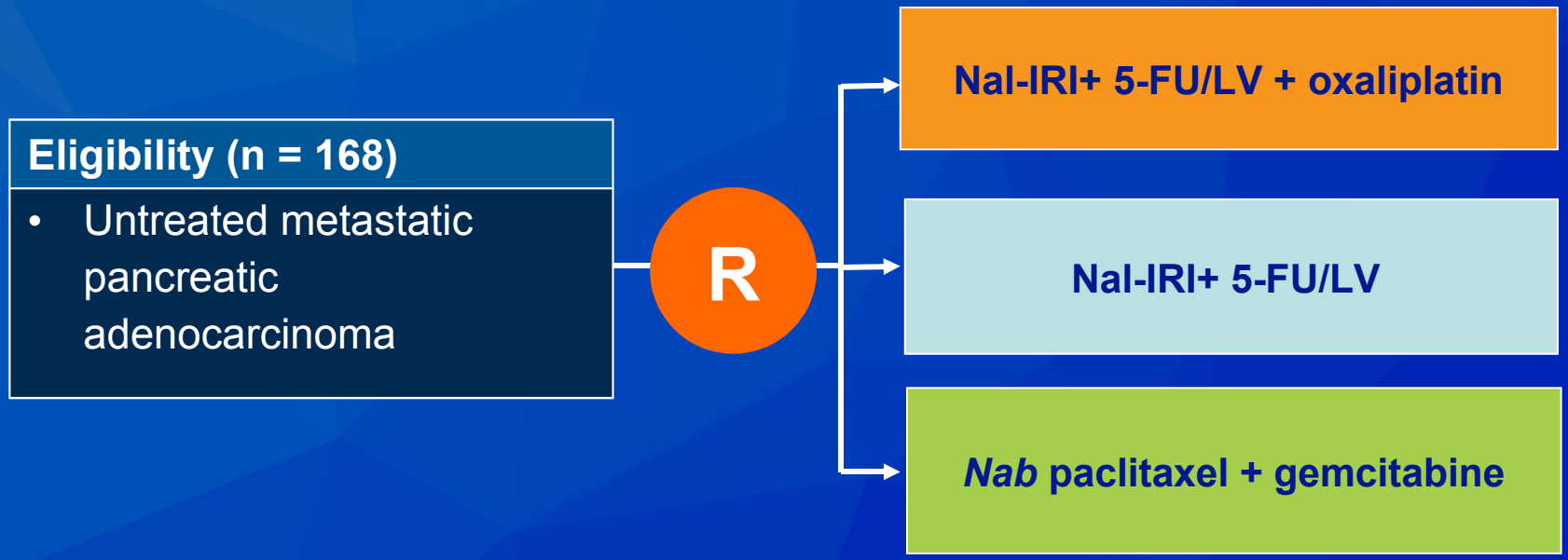
Wang-Gillam A et al. *Proc ASCO* 2016;Abstract 4126.

Serum CA 19-9 as a screening marker for patients with pancreatic cancer

“We are used to seeing pseudoprogression in other diseases, but pseudoprogression can actually happen in pancreatic cancer, much like in breast cancer. If you have someone with bone mets and you treat the bone mets, their bone mets look worse while they’re getting better. But having another test, like the CA 19-9, can help you dissect out and discriminate between real progression and pseudoprogression.”

Dr Margaret Tempero

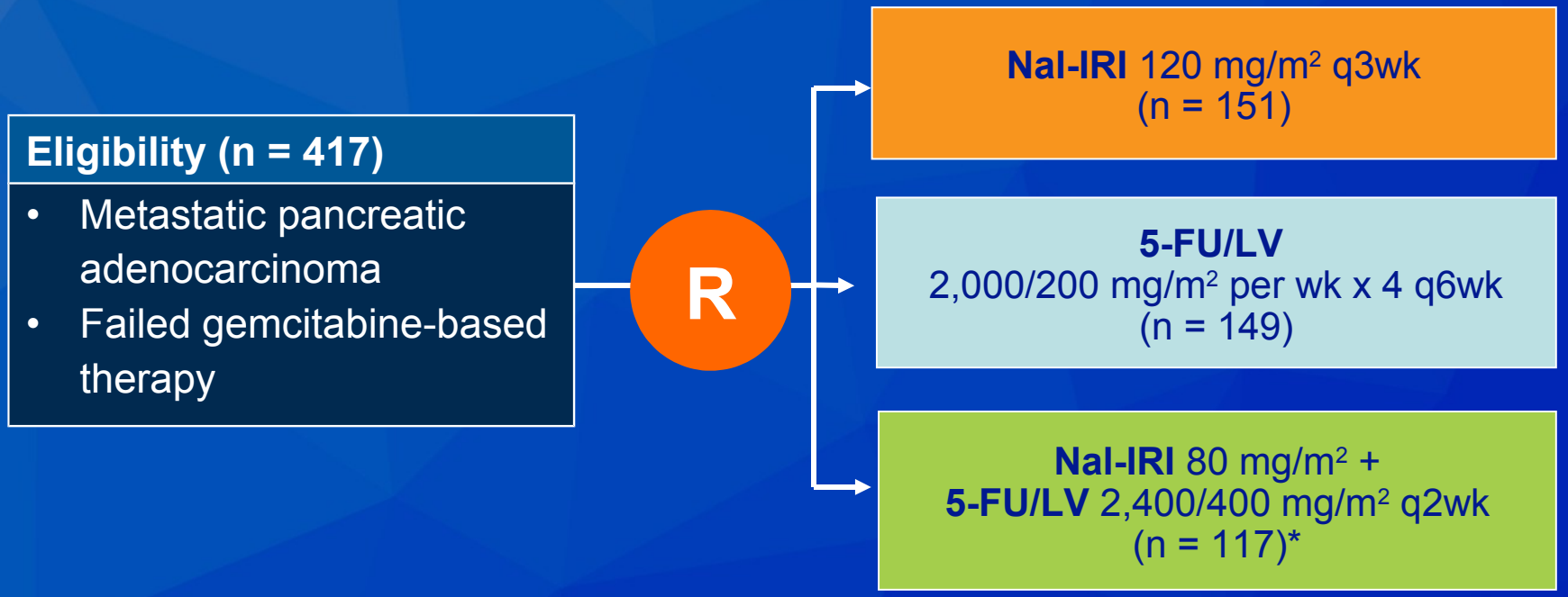
Ongoing Phase II Study of Nal-IRI-Containing Regimens for Patients with Untreated mPDAC



Primary Endpoint: Progression-free survival

www.clinicaltrials.gov. Accessed November 2016. NCT02551991

NAPOLI-1: Nal-IRI ± 5-FU/LV vs 5-FU/LV in mPDAC



* Combination arm added after safety data were available.

- 5-FU/LV arm used as control for combination arm.

Primary Endpoint: Overall survival

Wang-Gillam A et al. *Lancet* 2016;387:545-57.

Phase II Trial of Carboplatin/Paclitaxel with or without Pelareorep in the Up-Front Treatment of mPDAC

- Randomized study of patients with untreated, metastatic pancreatic adenocarcinoma
- Arm A (n = 36) carboplatin/paclitaxel with oncolytic virus pelareorep
- Arm B (n = 37) carboplatin/paclitaxel
- Median PFS: arm A: 4.9 mo; arm B: 5.2 mo (p = 0.6)

Noonan AM et al. *Mol Ther* 2016;24(6):1150-8.

Modified Irinotecan and Infusional 5-Fluorouracil (mFOLFIRI) in Patients with Refractory Advanced Pancreas Cancer

- Retrospective analysis of 40 patients with metastatic PC who had failed at least 1 prior line of therapy

Outcome	(n = 40)
Median PFS	2.6 mo
Median OS	4.75 mo

- The most common AEs included fatigue (98%), neuropathy (83%), anorexia (68%), nausea (60%) and constipation (55%).

Bupathi M et al. *Med Oncol* 2016;33(4):37.

Case Discussion

94 yo man who presented in early 2015 with abdominal pain, was diagnosed with a mass in the tail of his pancreas.

Surgical resection with positive retroperitoneal margin and 2 of 11 nodes positive.

RT administered to primary and supraclavicular nodes.

Case Discussion

94 yo man who presented in early 2015 with abdominal pain, was diagnosed with a mass in the tail of his pancreas.

Surgical resection with positive retroperitoneal margin and 2 of 11 nodes positive.

RT administered to primary and supraclavicular nodes.

Multiple new pulmonary nodules found in July 2015

Received single-agent gemcitabine but after 4 cycles progressive pulmonary nodules and increasing CA19-9.

Perspective on the rewarding experience of being an oncologist

“I think the biggest success that I feel and the biggest reward I feel is that when I’m able to give a patient a little time, quality time along with extra time to enjoy whatever they want to enjoy, even if it’s a short amount of time, a summer in Maine, seeing the birth of a grandchild, achieving a certain milestone and then realize that at the transition point where they need to be transferred from active care to palliative care and comfort care and allow that transition eventually to death to be as peaceful and dignifying as possible, then I think I’ve done my job. And it’s very gratifying from that standpoint.”

Dr Tanios Bekaii-Saab

Case Discussion

65 yo man with longstanding history of type 2 diabetes presented with abdominal discomfort in December 2015.

CT scan showed a pancreatic mass as well as carcinomatosis.

Endoscopic ultrasound and biopsy revealing adenocarcinoma of the pancreas.

Received FOLFIRINOX, which was poorly tolerated.

Association Between Diabetes and PDAC

- Most patients have diabetes or impaired glucose tolerance
- Diabetes occurs with small tumors or before tumor is radiographically detectable
- Longstanding diabetes gets worse prior to diagnosis
- Diabetes improves after resection
- Replicated in hamster model of PDAC
- Various model systems, including clinical models, support insulin resistance and beta cell dysfunction

Courtesy of Dr Margaret Tempero.

Case Discussion

65 yo man with longstanding history of type 2 diabetes presented with abdominal discomfort in December 2015.

CT scan showed a pancreatic mass as well as carcinomatosis.

Endoscopic ultrasound and biopsy revealing adenocarcinoma of the pancreas.

Received FOLFIRINOX which was poorly tolerated.

Switched to gemcitabine/*nab* paclitaxel with dramatic improvement in performance status, radiographic findings and tumor markers.

Viewpoint on the Use of FOLFIRINOX in Elderly Patients with PDAC

“We don’t have good safety data on patients who are, say, 76 or older. So typically the cutoff would be around 75. But that doesn’t mean I wouldn’t treat the patient who’s 77 with FOLFIRINOX, if they’re incredibly healthy and strong. But I’m very reluctant to go above 75. In fact, I’m very reluctant to go above 70, in many ways, with FOLFIRINOX.”

Dr Tanios Bekaii-Saab

What Might Neoadjuvant Therapy Do?

Advantages

- Provides a biologic waiting period — with early progression, patients who shouldn't be resected aren't resected
- Reduces the chance of an R1 resection — is this treatment effect or natural selection?

Disadvantages

- Use of radiation therapy may interfere with optimal therapy later
- Use of radiation therapy without sufficient systemic therapy may place the subset of patients who are destined to have metastases at a disadvantage

Courtesy of Dr Margaret Tempero.

MDACC Neoadjuvant Experience in Clearly Resectable Disease

Study	Regimen	N	Chemo RT	Laparotomy	Resected
Evans et al	Gem/RT	86	86	73	64
Varadhachary et al	Gem/cis/ RT	90	79	62	52

- 28%-43% were not resected (early progression?)
- About 12% who “looked resectable” undergoing laparotomy after preop treatment were not resectable

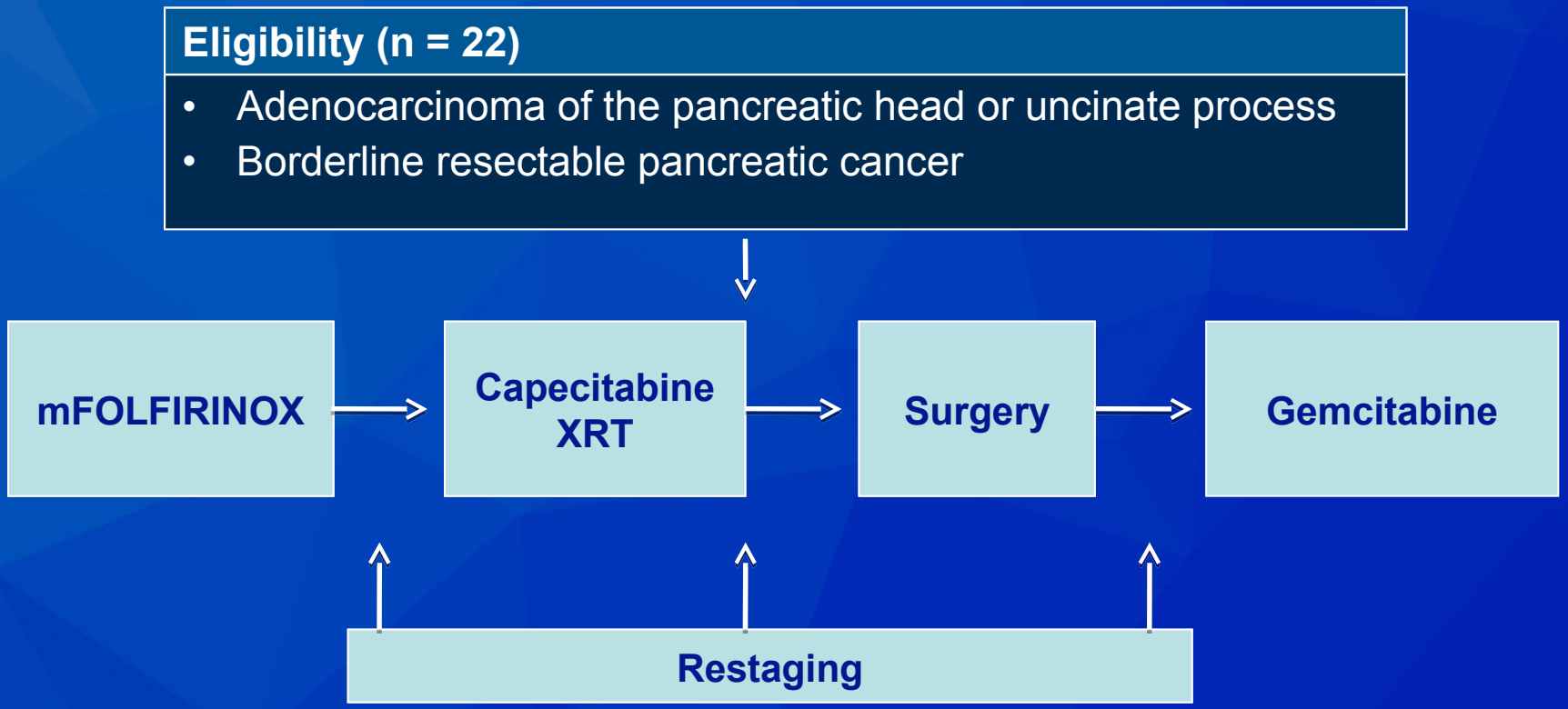
Evans DB et al. *J Clin Oncol* 2008;26(21):3496-502.
Varadhachary GR et al. *J Clin Oncol* 2008;26(21):3487-95.

Overall Survival After Neoadjuvant Therapy

Study	All patients	Resected	Not resected
Evans et al (n = 86)	22.7 mo	34.0 mo	7.0 mo
Varadhachary et al (n = 90)	17.4 mo	31.0 mo	10.5 mo
Ko et al (n = 25)	—	—	13.5 mo

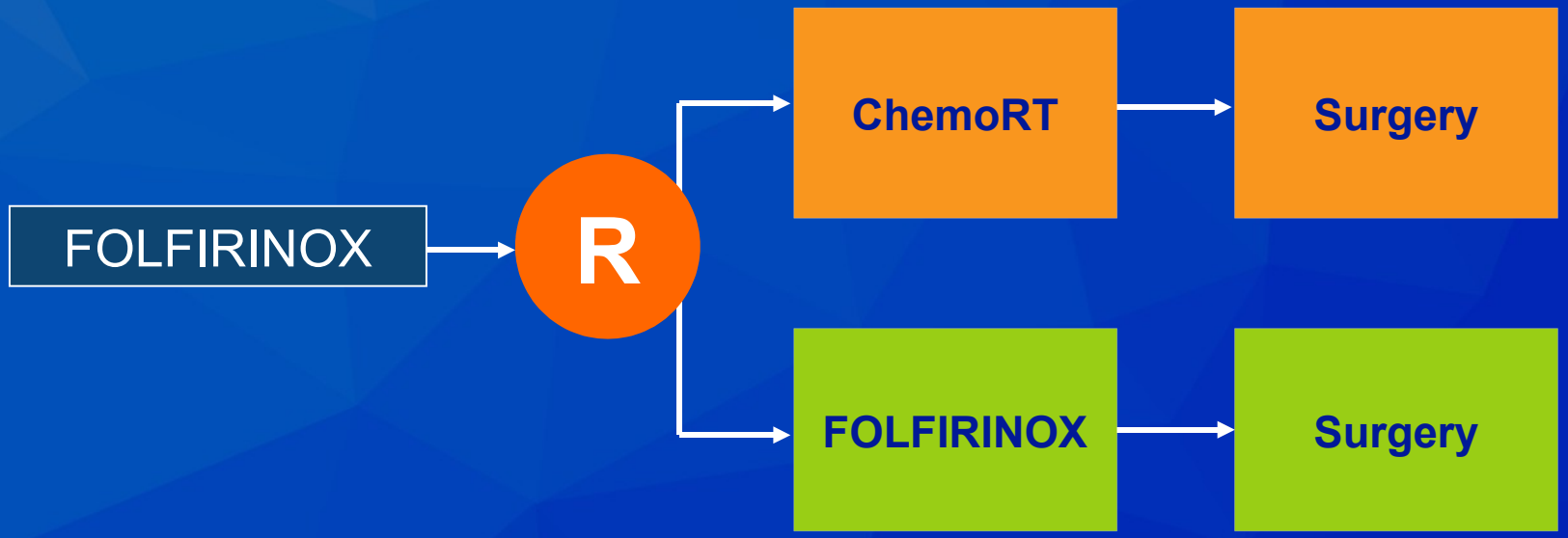
Evans DB et al. *J Clin Oncol* 2008;26(21):3496-502.
Varadhachary GR et al. *J Clin Oncol* 2008;26(21):3487-95.
Ko A et al. *Int J Radiat Oncol Biol Phys* 2007;68(3):809-16.

A021101: A Phase II Study of mFOLFIRINOX → Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer



Katz MH et al. *JAMA Surg* 2016;151(8):37:e161137; www.clinicaltrials.gov. NCT01821612

Neoadjuvant FOLFIRINOX versus Chemoradiation for Borderline Resectable Pancreatic Cancer



Courtesy of Dr Margaret Tempero.

Case Discussion

69 yo man with borderline resectable pancreatic adenocarcinoma

Treated on a clinical trial with neoadjuvant therapy using PEGPH20, gemcitabine and *nab* paclitaxel.

Achieved a very deep CA19-9 and radiographic response and was resected with vascular reconstruction.

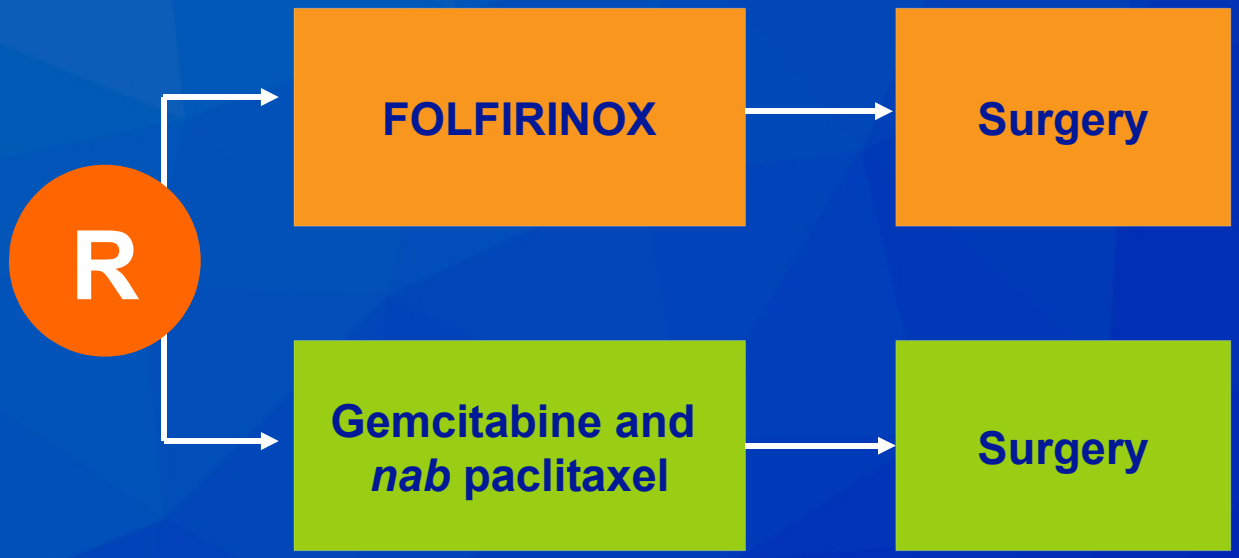
Randomized Phase II Study of PEGPH20 and *Nab*-Paclitaxel/Gemcitabine in Stage IV Previously Untreated PC

Progression-free survival	PEGPH20 + *nab* pac/gemcitabine	*Nab* pac/ gemcitabine	HR
All patients (n = 66, 52)	6.8 mo	5.3 mo	0.61
HA-low (n = 44, 31)	5.4 mo	4.8 mo	0.72
HA-high (n = 22, 21)	9.2 mo	6.0 mo	0.46

HA = hyaluronan

Bullock A et al. *Proc ASCO* 2016;Abstract 4104.

Phase II Trial of Neoadjuvant Chemotherapy for Resectable Pancreatic Cancer



Endpoints: pCR rate, R1 resection rate, DFS, OS

Courtesy of Dr Margaret Tempero.

Case Discussion

66 yo man initially diagnosed with Stage I pancreatic cancer in 2013

Treated with a Whipple and 6 months of gemcitabine

Experienced disease recurrence in liver and lungs 6 months later

Case Discussion

66 yo man initially diagnosed with Stage I pancreatic cancer in 2013

Treated with a Whipple and 6 months of gemcitabine

Experienced disease recurrence in liver and lungs 6 months later

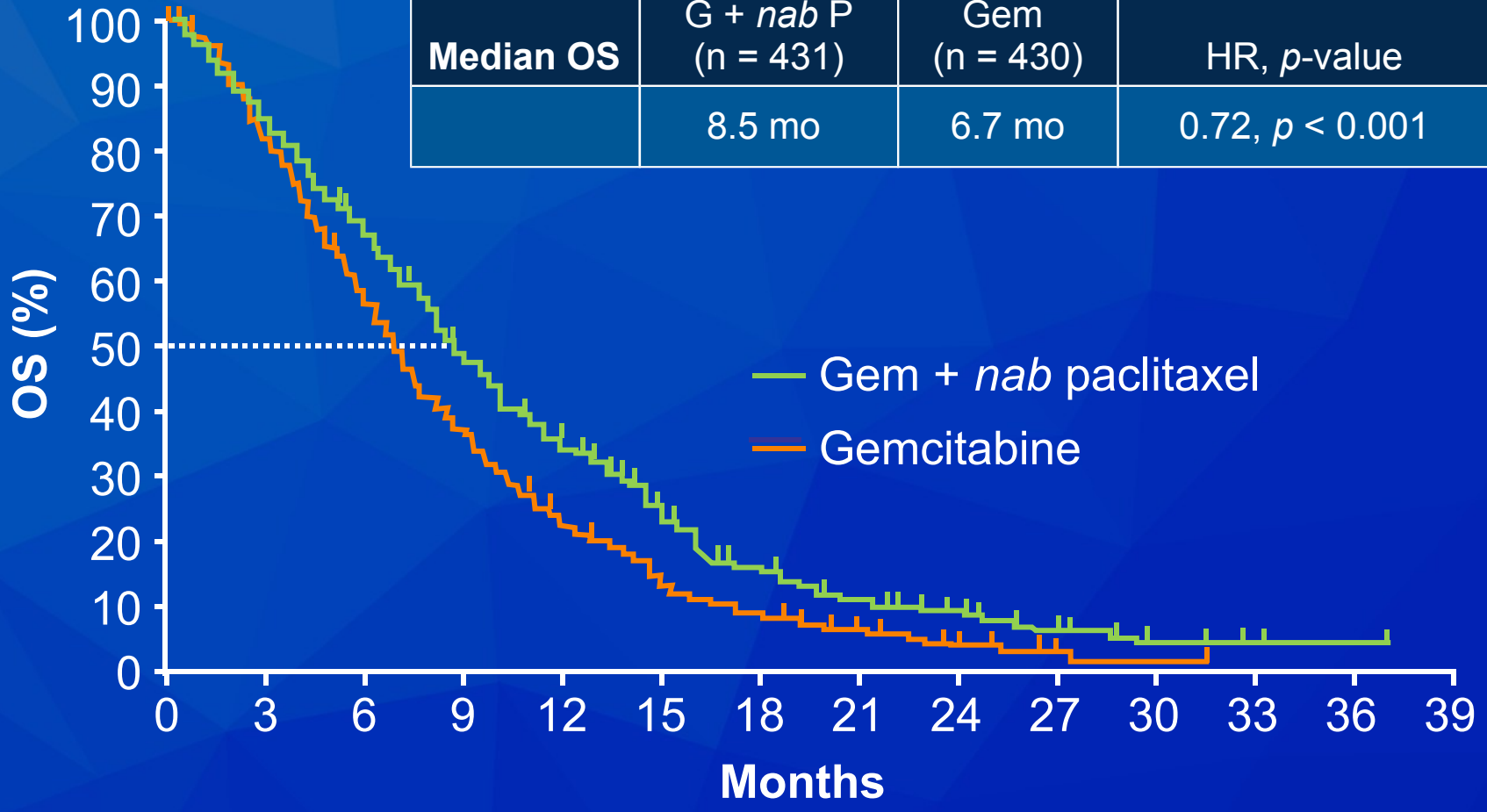
Achieved a partial response to gemcitabine and *nab* paclitaxel

Received nal-IRI and 5-FU/LV for progressive disease after about a year and a half

Disease progression after 4 months

MPACT: Gemcitabine ± *Nab* Paclitaxel in mPAC — Overall Survival

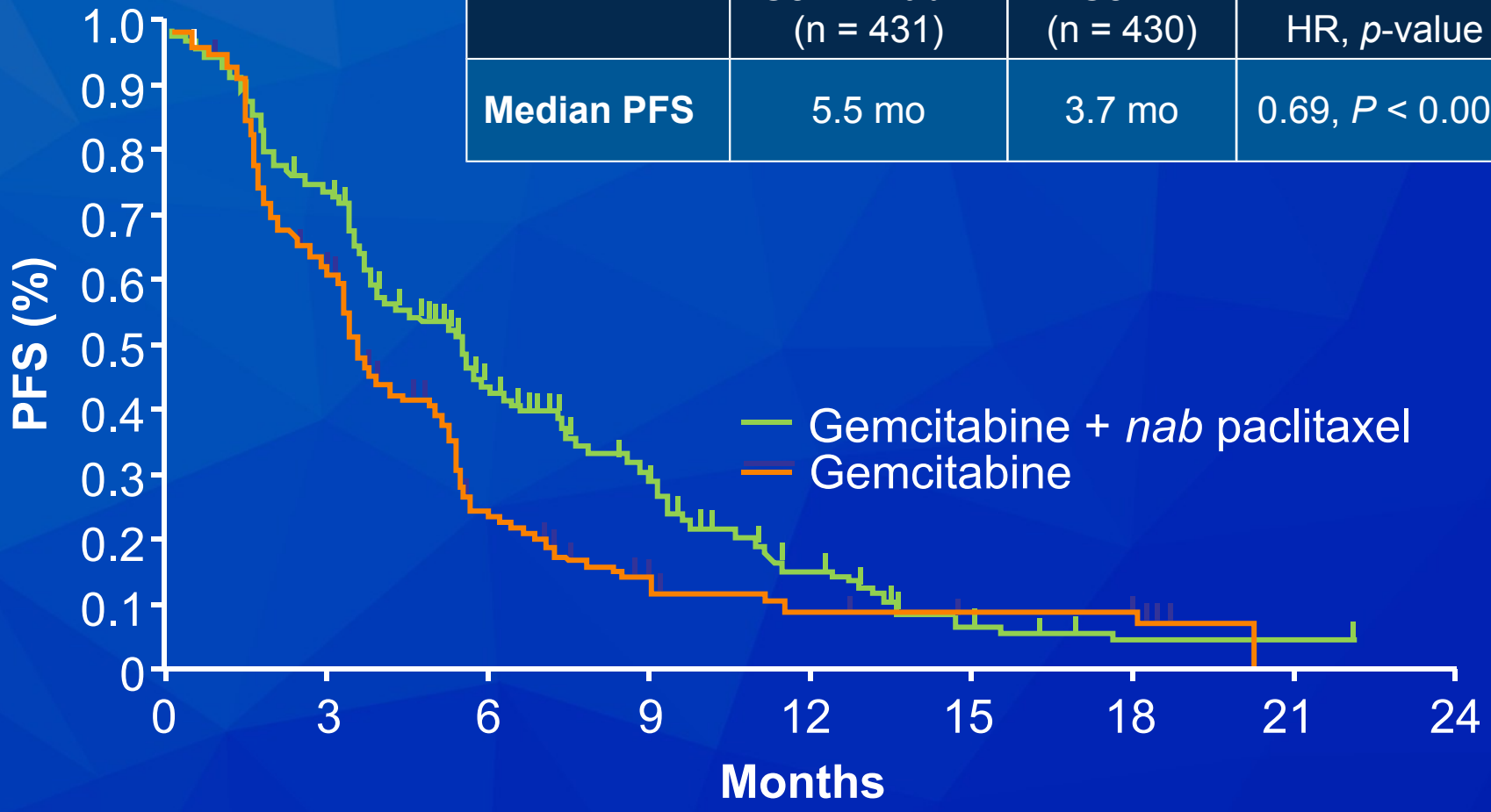
Median OS	G + *nab* P (n = 431)	Gem (n = 430)	HR, *p*-value
	8.5 mo	6.7 mo	0.72, $p < 0.001$



Von Hoff DD et al. *N Engl J Med* 2013;369:1691-703.

MPACT: Progression-Free Survival

	Gem + *nab* P (n = 431)	Gem (n = 430)	HR, *p*-value
Median PFS	5.5 mo	3.7 mo	0.69, $P < 0.001$



Von Hoff DD et al. *N Engl J Med* 2013;369:1691-703.

Overall Survival Benefit of Gemcitabine/*Nab* Paclitaxel Seen Across Most Prespecified Subgroups

Subgroup	Overall Survival: *nab* Paclitaxel-Gemcitabine (no. of events/no. of patients)	Overall Survival: Gemcitabine (no. of events/no. of patients)	Hazard Ratio for Death (95% CI)
All patients	333/431	359/430	0.72 (0.62-0.83)
Age			
<65 yr	188/254	209/242	0.65 (0.53-0.79)
≥65 yr	145/177	150/188	0.81 (0.63-1.03)
Sex			
Female	138/186	141/173	0.72 (0.57-0.93)
Male	195/245	218/257	0.72 (0.59-0.88)
Karnofsky performance-status score			
70-80	142/179	146/161	0.61 (0.48-0.78)
90-100	187/248	212/268	0.75 (0.62-0.92)
Primary tumor location			
Head	142/191	155/180	0.59 (0.46-0.75)
Other	188/237	201/246	0.80 (0.65-0.98)
Liver metastases			
Yes	290/365	309/360	0.69 (0.59-0.81)
No	43/66	50/70	0.86 (0.56-1.33)
No. of metastatic sites			
1	21/33	16/21	0.41 (0.19-0.88)
2	159/202	163/206	0.75 (0.60-0.95)
3	104/136	121/140	0.79 (0.61-1.04)
>3	49/60	59/63	0.50 (0.33-0.76)
Level of CA19-9			
Normal	47/60	43/56	1.07 (0.69-1.66)
<59× ULN	96/122	95/120	0.83 (0.61-1.12)
≥59× ULN	151/197	171/195	0.61 (0.48-0.77)
Region			
Australia	50/61	53/59	0.67 (0.44-1.01)
Eastern Europe	62/64	59/62	0.84 (0.58-1.23)
Western Europe	14/38	17/38	0.72 (0.35-1.47)
North America	207/268	230/271	0.68 (0.56-0.82)

CA19-9 = carbohydrate antigen 19-9; PS = performance status; ULN = upper limit of normal range

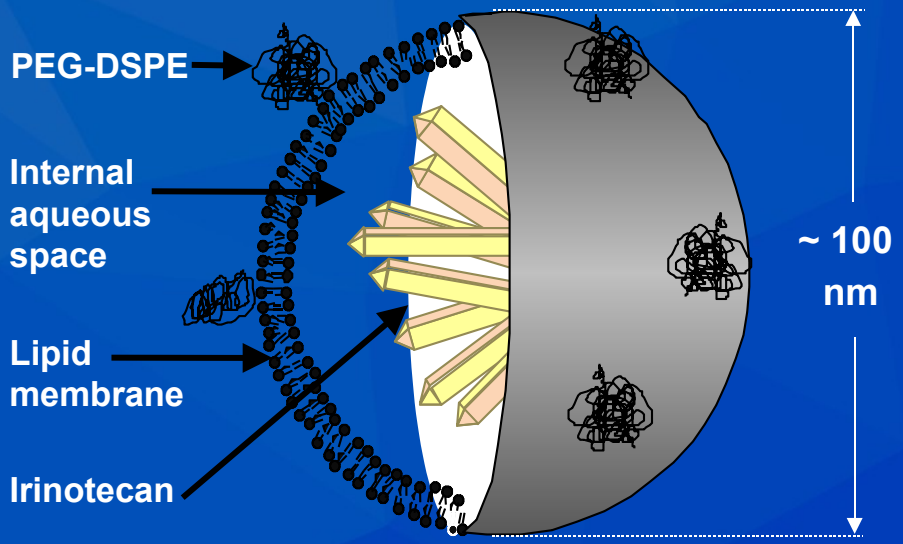
Von Hoff DD et al. *N Engl J Med* 2013;369:1691-703.

Results from 2 Phase III Trials of FOLFIRINOX or Gemcitabine/*Nab* Paclitaxel in mPC

Parameter	FOLFIRINOX[1] (n = 342)	Gemcitabine/ *nab* paclitaxel[2] (n = 861)
Study locations	France	North America, Eastern + Western Europe, Australia
Eligibility (performance status)	ECOG 0-1	KPS 70-100
Head/nonhead, %	39/61	44/56
Median OS (mo)	11.1	8.5
Median PFS (mo)	6.4	5.5
Toxicity (Grade 3/4), %	Fatigue 23.6 Neutropenia 45.7	Fatigue 17 Neutropenia 38

[1] Conroy T et al. *N Engl J Med* 2011;364(19):1817-25.
[2] Von Hoff DD et al. *N Engl J Med* 2013;369(18):1691-703.

MM-398, Nanoliposomal Irinotecan (Nal-IRI)



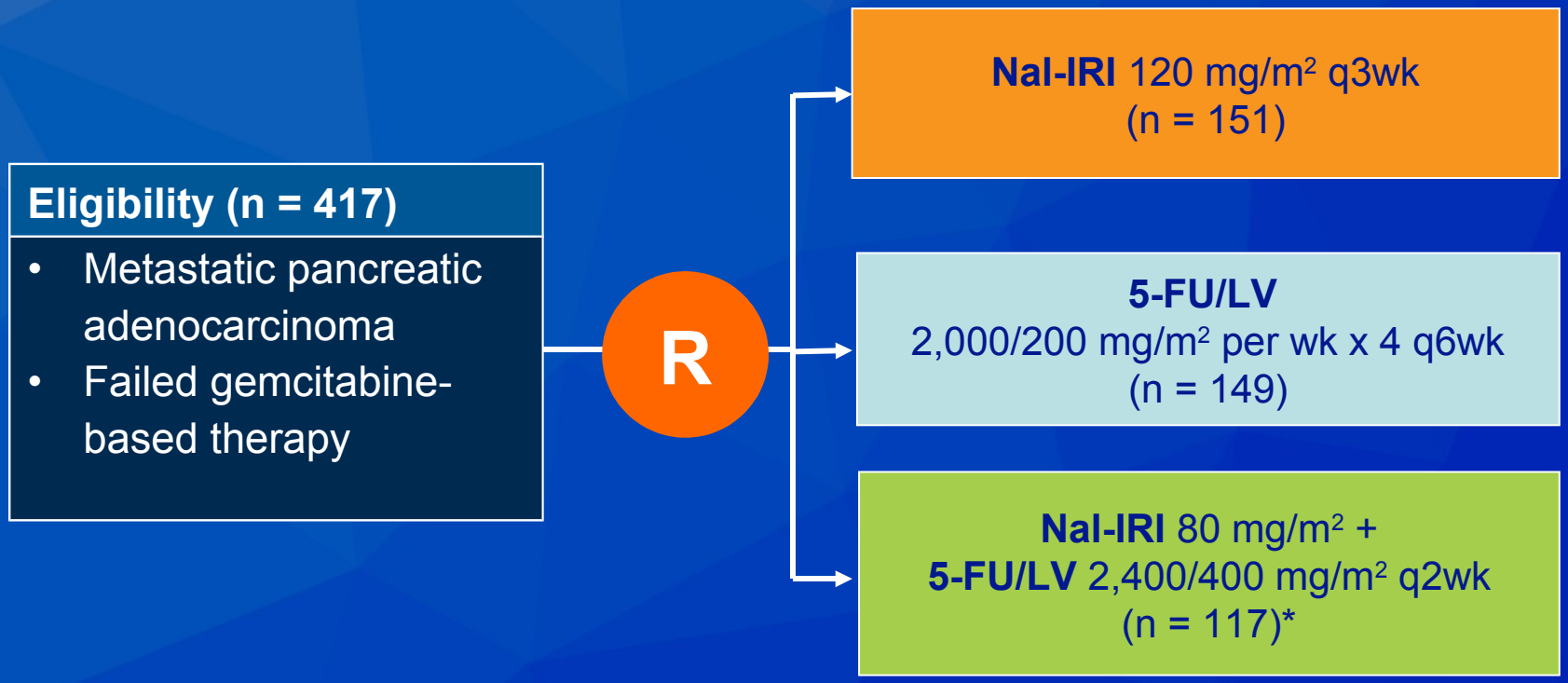
- MM-398 (120 mg/m^2) clinical PK show extended circulation
  - 70x higher AUC of total irinotecan in blood *vs* conventional irinotecan (300 mg/m^2)[1]
- MM-398 achieved 5x higher levels of SN-38 (active metabolite) in tumor compared to blood at 72 hours[2]

~80,000 irinotecan molecules/liposome

- Median OS of 5.2 months in Phase II study of gemcitabine-refractory mPC[3]

[1] Roy AC et al. *Ann Oncol* 2013;24(6):1567-73.
[2] Ramanathan RK et al. *Proc AACR* 2014;Abstract CT224.
[3] Ko AH et al. *Br J Cancer* 2013;109(4):920-5.

NAPOLI-1: Nal-IRI ± 5-FU/LV vs 5-FU/LV in mPDAC



* Combination arm added after safety data were available.

- 5-FU/LV arm used as control for combination arm.

Primary Endpoint: Overall survival

Wang-Gillam A et al. *Lancet* 2016;387:545-57.

NAPOLI-1: Efficacy and Safety Results

Outcome	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)	Nal-IRI (n = 151)
Median OS	6.2 months	4.2 months	4.9 months
Median PFS	3.1 months	1.5 months	2.7 months
ORR	17%	1%	6%
Select AE (any grade)	**n = 117**	**n = 134**	**n = 147**
Diarrhea	59%	26%	70%

Wang-Gillam A et al. *Proc ASCO* 2016;Abstract 4126; *Lancet* 2016;387:545-57.

Case Discussion

68 yo man diagnosed with pancreatic adenocarcinoma. CT showed a single 6-mm pulmonary nodule (PET-negative)

Started on neoadjuvant FOLFIRINOX x 4 doses. Less than 20% response.

A few months later the pulmonary nodule increased to 9 mm.

He completed 8 cycles of adjuvant gemcitabine but 4 months later had multiple pulmonary nodules and liver metastases.

Started on adjuvant gemcitabine and completed 8 cycles.

Restarted FOLFIRINOX without BOLUS (3 cycles)

Currently receiving gemcitabine/*nab* paclitaxel with improvement in CA19-9

Treatment Holidays

"I like treatment holidays across the board with a good discussion with the patient… There's still the question mark whether it affects outcome, overall survival, across multiple malignancies. And so especially with FOLFIRINOX, this is when patients get really, really tired after 6 months. So what I've done, actually, is a gradation. So 3, 4 months of FOLFIRINOX, whenever I use FOLFIRINOX in this setting, 2 to 4 months of FOLFIRI/5-FU and then it's almost like weaning them off and testing the biology as I shave off one drug after the other. Again, this is not a scientific way to do it. This is just a personal way."

Dr Bekaii-Saab

Management of Isolated Pulmonary Metastases

"Some patients have isolated lung metastases after resection of localized pancreatic adenocarcinoma. A growing body of evidence in this population suggests that these patients have a prolonged survival compared to patients with metastases in other locations.

Preliminary data also suggest that pulmonary metastasectomy may be advantageous in this population. More data are needed before recommendations can be made regarding the management of pulmonary metastases of pancreatic cancers."

NCCN Guidelines Version 2.2016; pancreatic adenocarcinoma

Case Discussion

A 67-year-old man with a history of abdominal discomfort.

CT scan found to have a lesion on the tail of the pancreas, with biopsy confirming adenocarcinoma.

Subsequent distal pancreatectomy and splenectomy revealed an intraductal papillary mucinous neoplasm with high-grade intraepithelial neoplasm and microscopic foci of invasive adenocarcinoma.

Pathology: T1N1 disease with 8 of 17 nodes positive.

Phase III ESPAC4 Trial: OS and PFS

Survival	Gem + capecitabine (n = 364)	Gem (n = 366)	HR	*p*-value
Median OS	28 months	25.5 months	0.82	0.032
5-year OS	28.8%	16.3%	—	—

- Schedule: Gem (1,000 mg/m^2; d1, 8, 15) x 6 and cape (1,660 mg/m^2/day, q3wk)
- The most common Grade ≥3 AEs:
  - Neutropenia = 38% (gem/cape) vs 24% (gem)
  - Hand-foot syndrome = 7% (gem/cape) vs 0% (gem)

Neoptolemos J et al. *Proc ASCO* 2016;Abstract LBA4006.

Case Discussion

A 67-year-old man with a history of abdominal discomfort.

CT scan found to have a lesion on the tail of the pancreas, with biopsy confirming adenocarcinoma.

Subsequent distal pancreatectomy and splenectomy revealed an intraductal papillary mucinous neoplasm with high-grade intraepithelial neoplasm and microscopic foci of invasive adenocarcinoma.

Pathology: T1N1 disease with 8 of 17 nodes positive.

Received gemcitabine, but initial course of treatment was complicated by difficulties of pancreatitis.

NED, merely postoperative changes over the course of the past few months.

Case Discussion

85 yo male underwent a prior Whipple procedure in 2004 for localized pancreatic cancer (T3N0).

Received adjuvant radiation therapy with capecitabine.

Tolerated treatment well received gemcitabine.

After several months of treatment developed hemolytic uremic syndrome.

Managed with plasma exchange and steroids.

Now 12 years later without evidence of recurrent cancer.

Has chronic mild renal insufficiency and thrombocytopenia.

Management of Hemolytic Uremic Syndrome (HUS)

“We treat those patients with daclizumab. And they actually reverted back and were able to continue. These were metastatic patients, and we were able to treat them. In fact, interestingly, 1 patient went back on gemcitabine after failing 3 or 4 other lines of therapy, and she was off daclizumab. I mean, after she reverted back. And she didn’t show any signs of HUS with rechallenging gemcitabine.”

Dr Bekaii-Saab

Case Discussion

70 yo male presented with abdominal pain, early satiety and weight loss and found to have a 5-cm pancreatic mass with extensive hepatic metastases.

Biopsy showed adenocarcinoma.

Reluctantly started on FOLFIRINOX.

On day 9, he had severe pins and needles in both legs and cold sensitivity in fingers. This subsequently became pain in both calves, and he was found to have bilateral DVT.

Symptoms managed with enoxaparin.

Continued FOLFIRINOX.

Case Discussion

34 yo woman diagnosed 1 year ago with metastatic pancreatic cancer involving the head and spread to the liver.

She had an extensive family history of cancer, including breast and uterine cancers.

Genetic testing reveals BRCA2 mutation.

Started modified FOLFIRINOX, and within 6 months she achieved a CR with normalization of her CA19-9.

Tolerated treatment well with only G1 neurotoxicity.

Requested to discontinue her therapy at that time and remains disease free since then.

Ongoing Phase II/III Trials for gBRCA-Mutated mPC

Trial name	Phase	N	Treatment arm
NCT02184195 (POLO)	III	145	• Olaparib • Placebo
NCT01585805	II	107	• Gem/cis/veliparib • Gem/cis • Veliparib
NCT02511223	II	24	• Olaparib

www.clinicaltrials.gov. Accessed November 2016.

Ongoing Trials of Immune Checkpoint Inhibitors in PC

Trial name	Phase	Target (N)	Treatment arm
NCT02923934	II	60	• Ipilimumab + nivolumab
NCT02451982	I/II	50	• Cyclophosphamide + GVAX + nivolumab • Cyclophosphamide + GVAX
NCT02758587 (FAK-PD1)	I/II	59	• Pembrolizumab + defactinib
NCT02309177	I	138	• Nivolumab + *nab* P + gemcitabine • Nivolumab + *nab* P

www.clinicaltrials.gov. Accessed November 2016.