

Contemporary Treatment Approaches for Patients with Pancreatic Cancer

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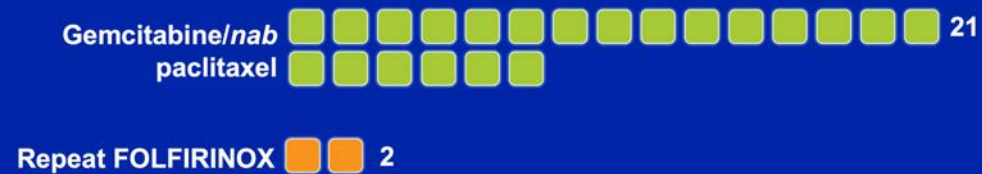
Leader, GI and Neuroendocrine Oncology

Karmanos Cancer Institute

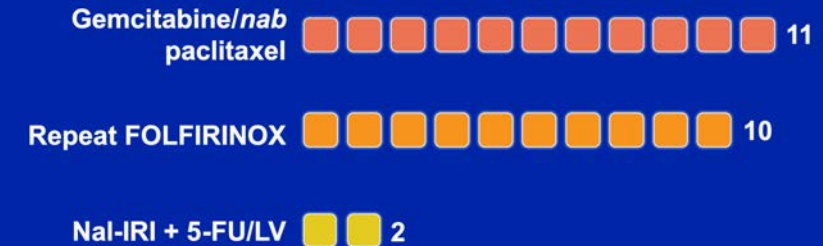
Wayne State University

Detroit, Michigan

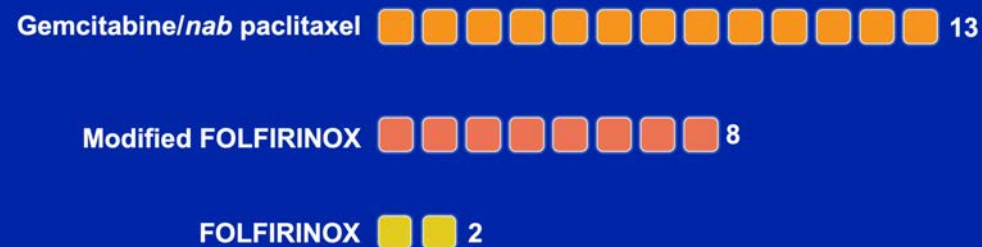
In general, what treatment would you recommend for a patient with pancreatic cancer who develops metastatic disease 5 months after neoadjuvant FOLFIRINOX followed by surgical resection?



In general, what treatment would you recommend for a patient with pancreatic cancer who develops metastatic disease 12 months after neoadjuvant FOLFIRINOX followed by surgical resection?



What is your usual first-line therapy recommendation for a 75-yo patient with newly diagnosed metastatic pancreatic cancer and a PS of 0?



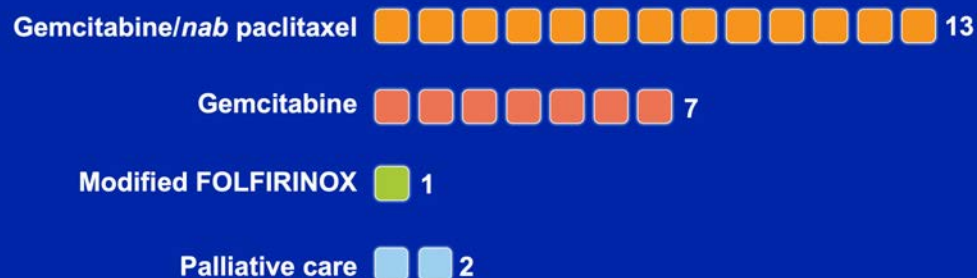
Sequencing therapy in metastatic disease

First-line treatment

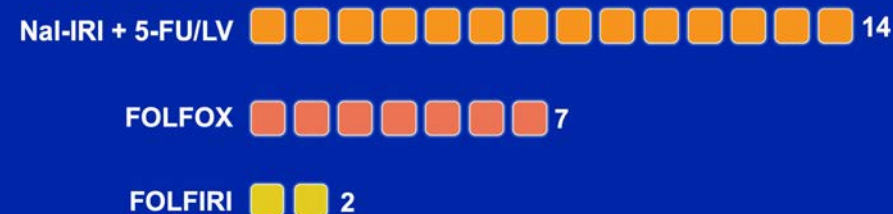
- “Younger older” patients
- Patients who have received prior neoadjuvant therapy

Later-line treatment (Nal-IRI)

What is your usual first-line therapy recommendation for a 75-yo patient with newly diagnosed metastatic pancreatic cancer who is ambulatory but unable to work (PS 2)?



A 77-yo patient who is not considered a candidate for FOLFIRINOX receives gemcitabine/*nab* paclitaxel for metastatic pancreatic cancer and experiences progression after 5 months. What second-line therapy would you recommend?



In general, which treatment would you recommend for a 65-yo patient (PS 0) who receives first-line FOLFIRINOX followed by second-line gemcitabine/*nab* paclitaxel for metastatic pancreatic cancer and experiences disease progression?



OFF (oxaliplatin/5-FU/LV) (1), 5-FU (1)

Sequencing therapy in metastatic disease

First-line treatment

- “Younger older” patients
- Patients who have received prior neoadjuvant therapy

Later-line treatment (Nal-IRI)

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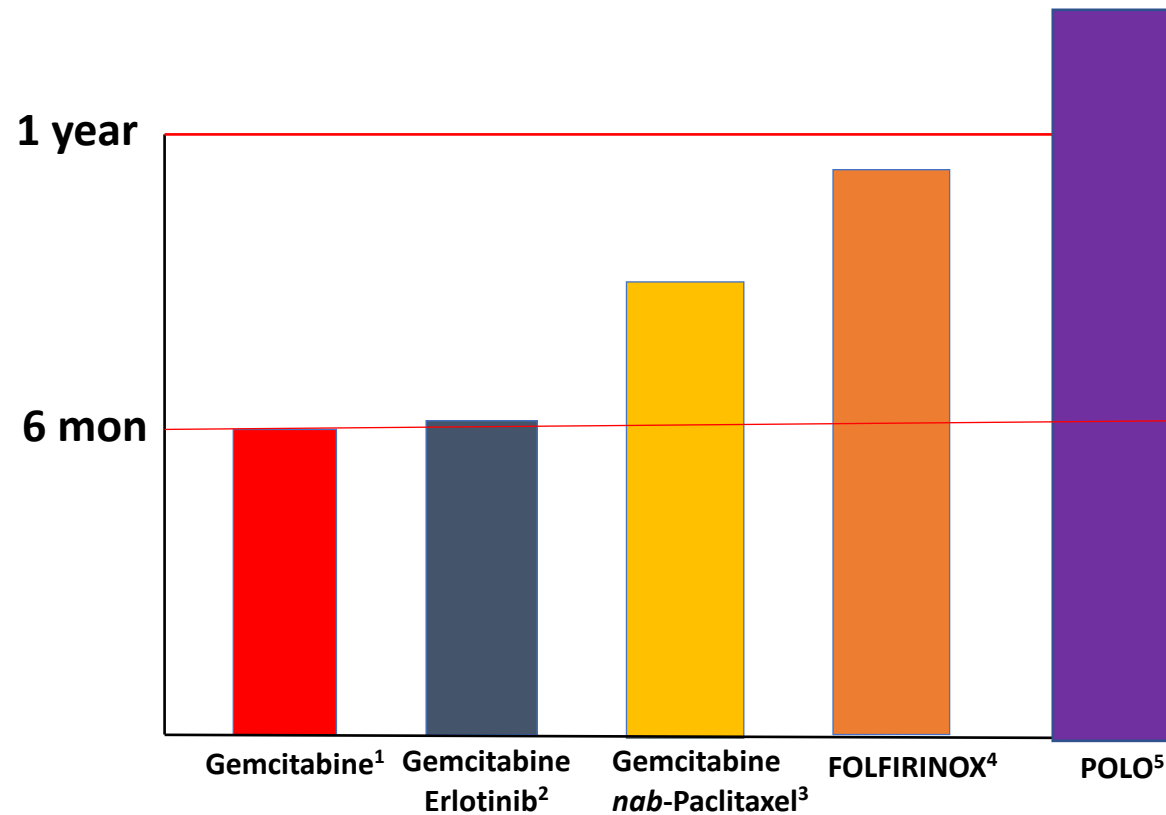
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Disclosures

Advisory Committee	ASLAN Pharmaceuticals, BioLineRx, Caris Life Sciences, Celgene Corporation, Eisai Inc, Erytech Pharma, Halozyme Inc, Ipsen Biopharmaceuticals Inc, Merck, TriSalus Life Sciences
Consulting Agreements	AbbVie Inc, Merck, Rafael Pharmaceuticals Inc, TriSalus Life Sciences
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene, BioLineRx, Boston Biomedical Inc, Bristol-Myers Squibb Company, Caris Life Sciences, Celgene Corporation, Halozyme Inc, Incyte Corporation, Lilly, Novartis, Novocure, QED Therapeutics, Rafael Pharmaceuticals Inc, Roche Laboratories Inc, Taiho Oncology Inc
Data and Safety Monitoring Board/Committee	ASLAN Pharmaceuticals, Blueprint Medicines, Erytech Pharma, Lexicon Pharmaceuticals Inc
Speakers Bureau	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Ipsen Biopharmaceuticals Inc, Merck

Incremental improvement in systemic therapies that are largely based on cytotoxic drugs



1. Burris HA 3rd, et al. *J Clin Oncol*. 1997;15(6):2403-2413.¹ 2. Moore MJ, et al. *J Clin Oncol*. 2007;25(15):1960-1966. 3. Von Hoff DD, et al. *N Engl J Med*. 2013;369(18):1691-1703. 4. Conroy T, et al. *N Engl J Med*. 2011;364(19):1817-1825; 5. Golan et al, *NEJM*, 2019.

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update *Initial Assessment*

- The goals of care
 - Include discussion of an advance directive
- Patient preferences
- Support systems should be discussed with every patient with metastatic pancreatic cancer and his or her caregivers

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update *Treatment recommendations*

- ECOG PS 0-1
- Favorable comorbidity profile
- Patient preference
- Support system for aggressive medical therapy



FOLFIRINOX

- ECOG PS of 2,
or
- A comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy



Gem

- ECOG PS 0-1
- Favorable comorbidity profile
- Patient preference
- Support system for *a relatively* aggressive medical therapy



**Gem
Nab-
paclitaxel**

- ECOG PS ≥ 3
or
- with poorly controlled comorbid conditions despite ongoing active medical care



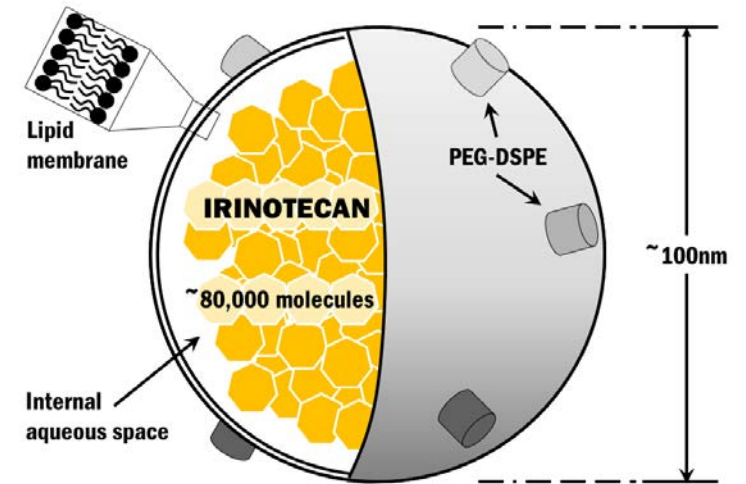
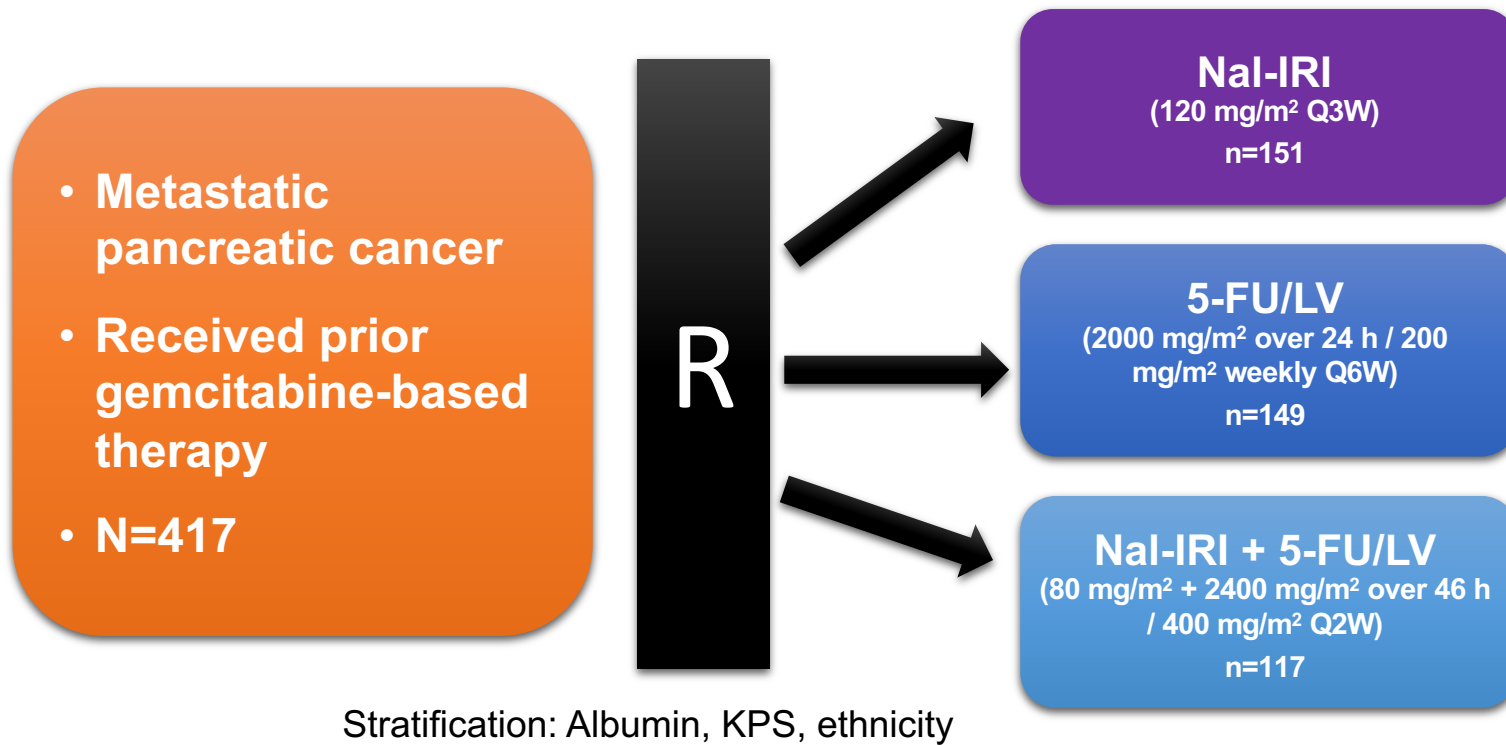
**Supportive
care**

Second-Line Oxaliplatin-Based Regimens: Conflicting Results From Phase III Trials

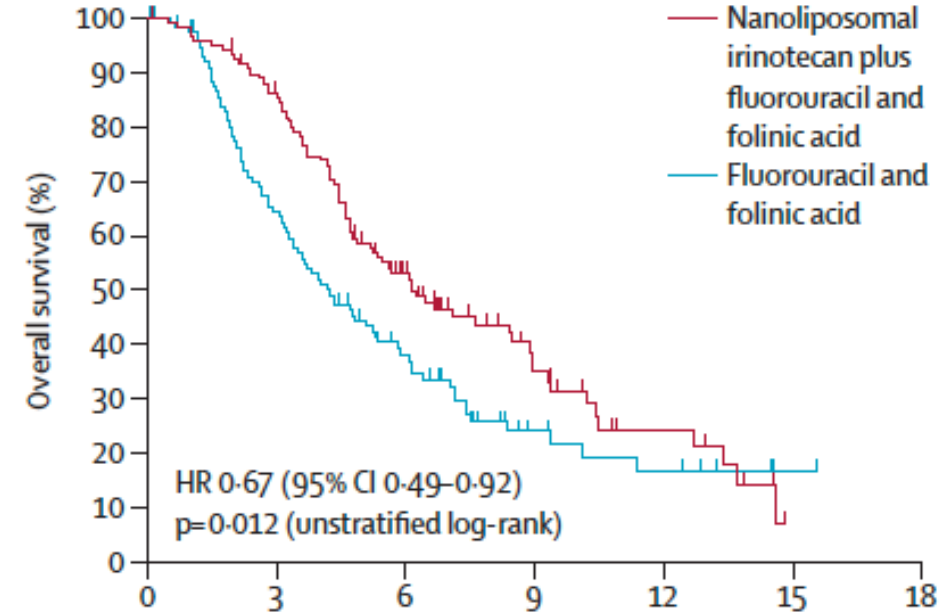
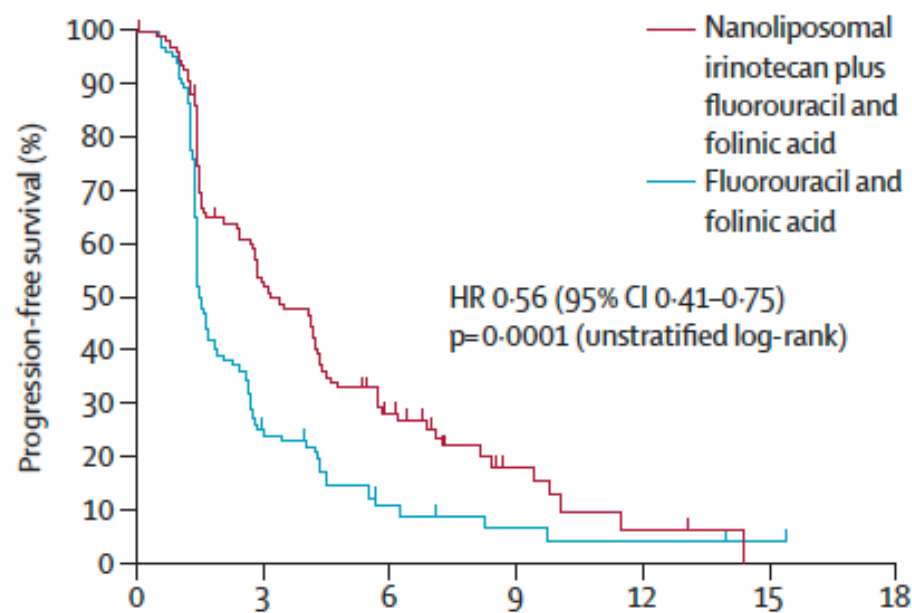
Patients (N = 268)	CONKO-003		PANCREOX	
	PD on Gem Therapy (n = 160)		Previous Gem Therapy (n = 108)	
Treatment	OFF (n = 76)	5-FU/LV (n = 84)	mFOLFOX6 (n = 54)	5-FU/LV (n = 54)
OS, median	5.9 months HR 0.66 (95% CI, 0.48–0.91) P = .01	3.3 months	6.1 months HR 1.78 (95% CI, 1.08–2.93) P = .02	9.9 months
PFS, median	2.9 months HR 0.68 (95% CI, 0.50–0.94) P = .02	2.0 months	3.1 months HR 1.00 (95% CI, 0.66–1.53) P = .99	2.9 months

Phase 3 trial of Nano-liposomal irinotecan + 5-FU/LV as 2nd-line therapy for metastatic pancreatic cancer (NAPOLI-1)

Primary endpoint: OS
Secondary endpoints: PFS, ORR, CA19-9 response, safety



NAPOLI-1: Study outcome



Grade 3 or 4 Toxicity	Nano-liri-5FU/LCV	5FU/LCV
Diarrhea	13 %	4%
Vomiting	11%	3%
Appetite	4%	2%
Fatigue	14%	4%
Neutropenia	27%	1%

NAPOX: moving Nal-Iri to the front line

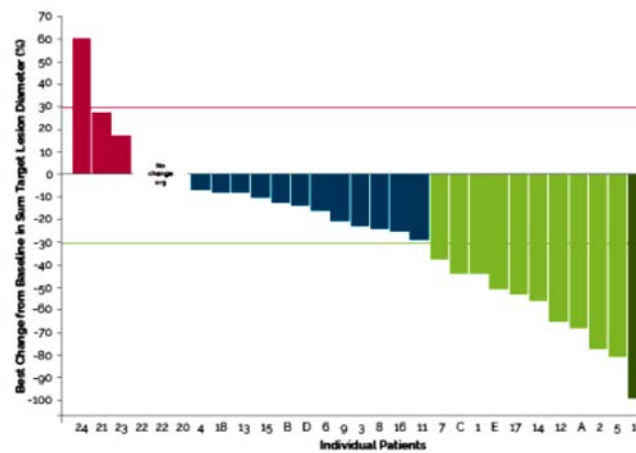
Nal-Iri/5FU/LV/Oxaliplatin

Cohort A
70/2400/400/60

Cohort B
50/2400/400/60

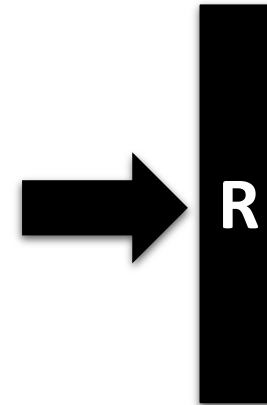
Cohort C
50/2400/400/85

Cohort D
55/2400/400/70



No grade 3 or higher
fatigue or neuropathy

Phase III



Nal-Iri 50 mg/m²
5FU 2,400 mg/m²
Oxaliplatin 60 mg/m²
Q 2 weeks

N = 750, Overall Survival

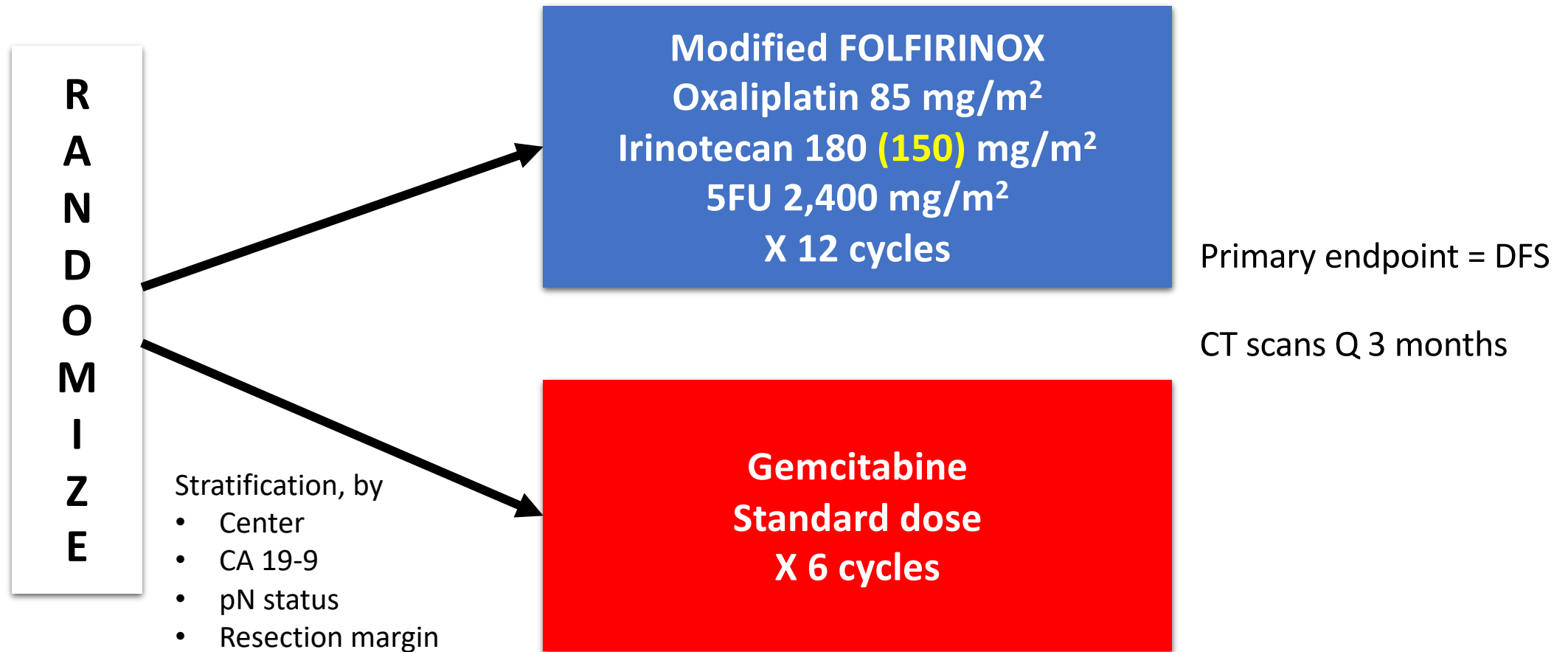
Gemcitabine/
Nab-paclitaxel
standard

NCT04083235

**Dose
exploration
&
expansion**

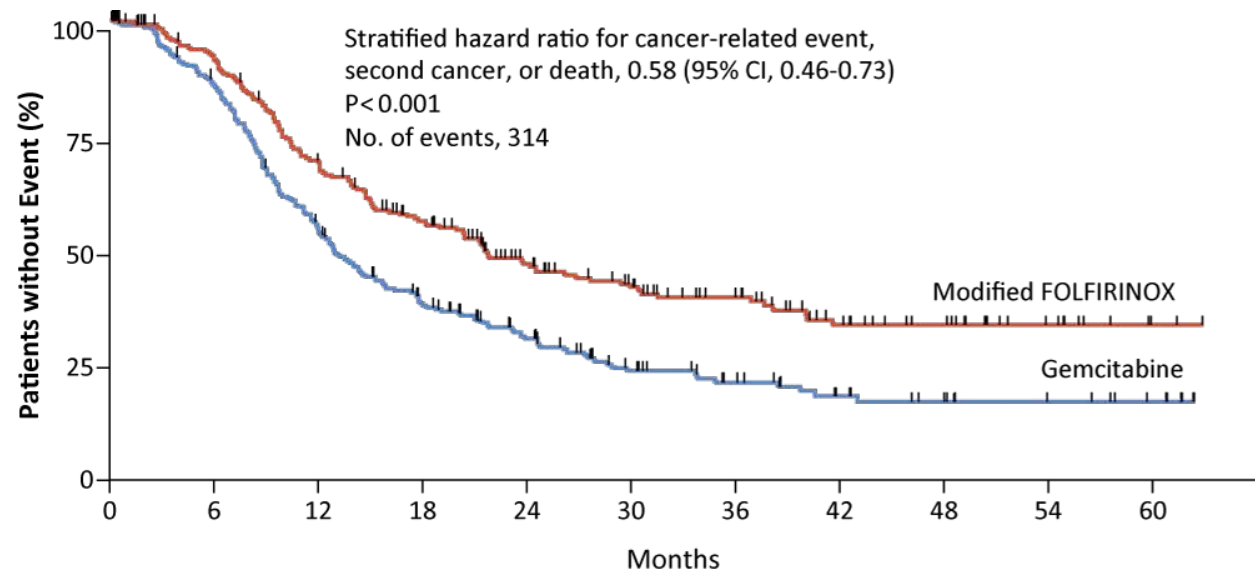
PRODIGE 24/CCTG PA.6:

Phase III adjuvant trial in *resected* pancreatic cancer

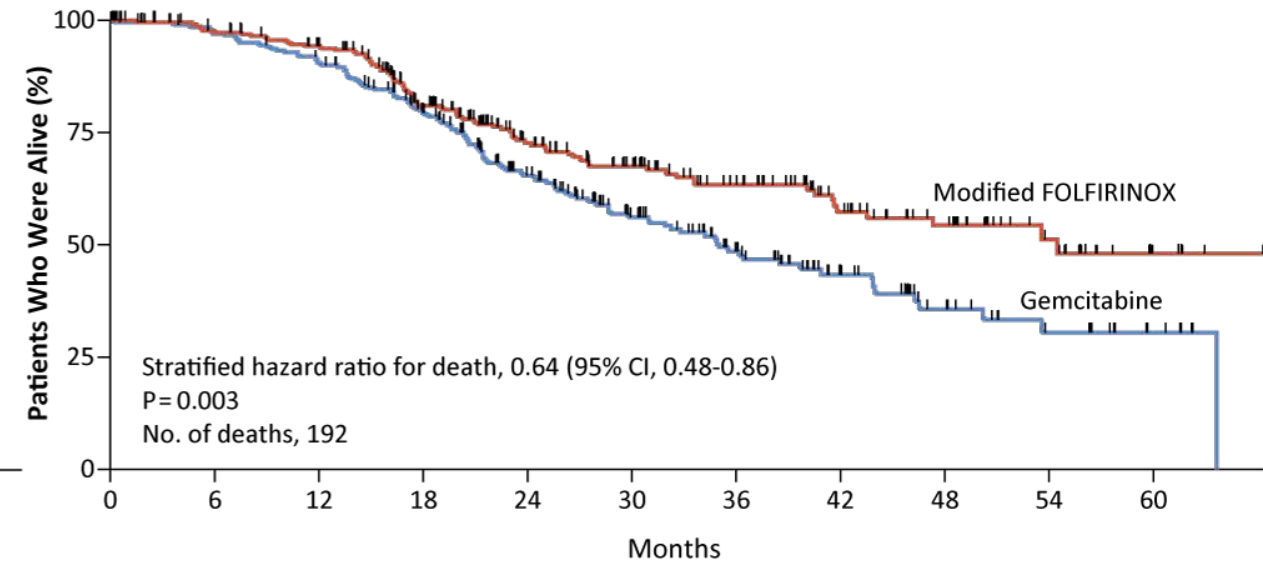


Disease-free survival and overall survival were significantly improved with modified FOLFIRINOX

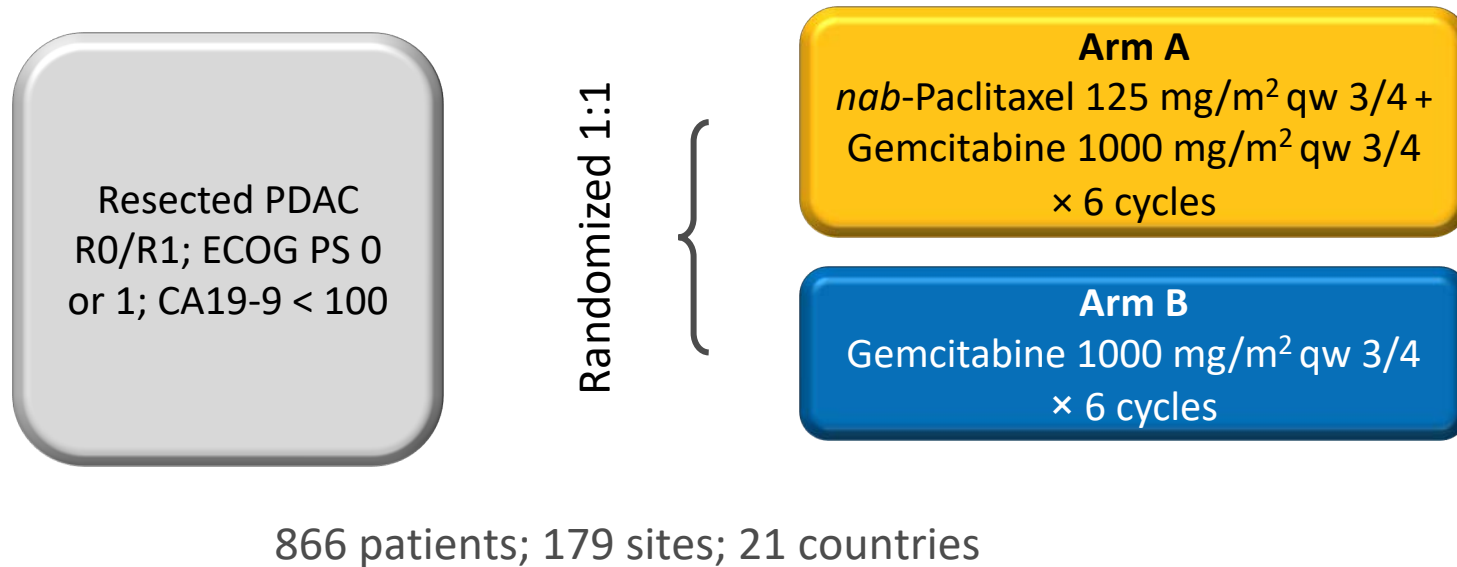
Disease-free Survival



Overall Survival

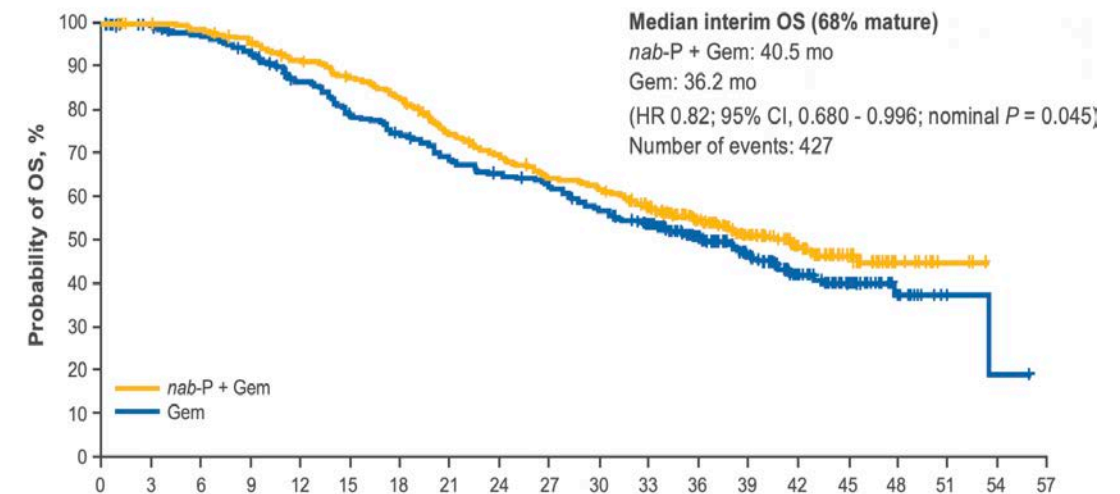
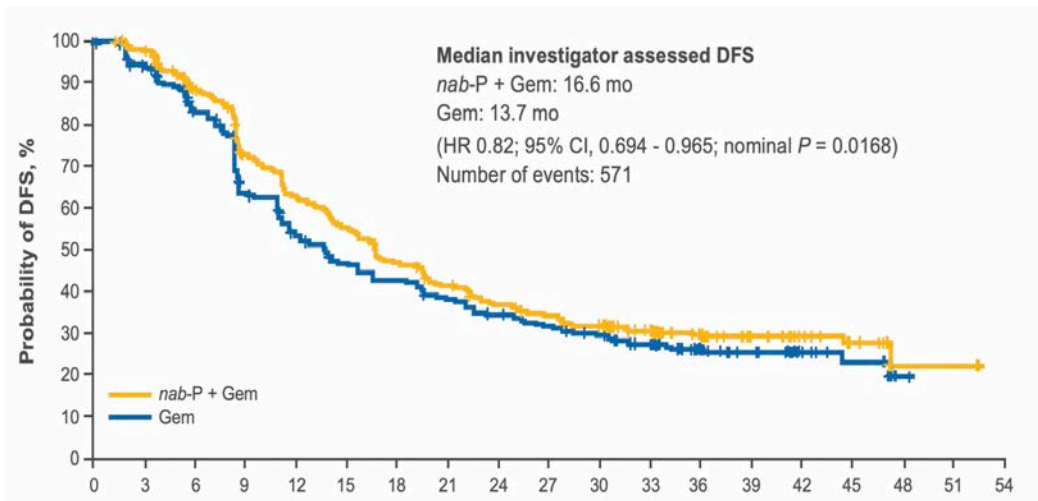
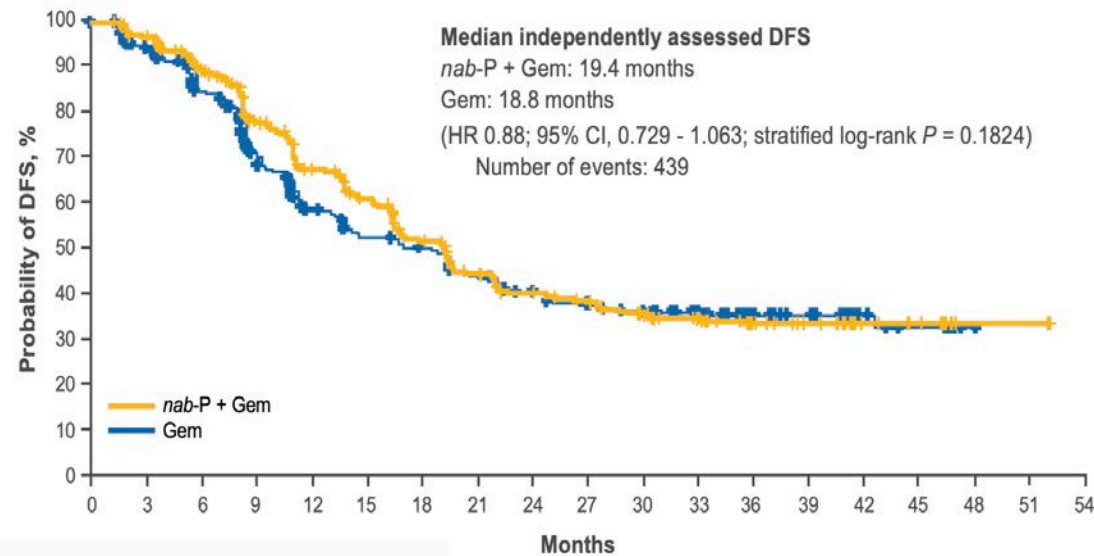


APACT: Phase III, Open-Label, Randomized Trial of Adjuvant *nab*-Paclitaxel plus Gemcitabine vs Gemcitabine for Resected Pancreatic Adenocarcinoma

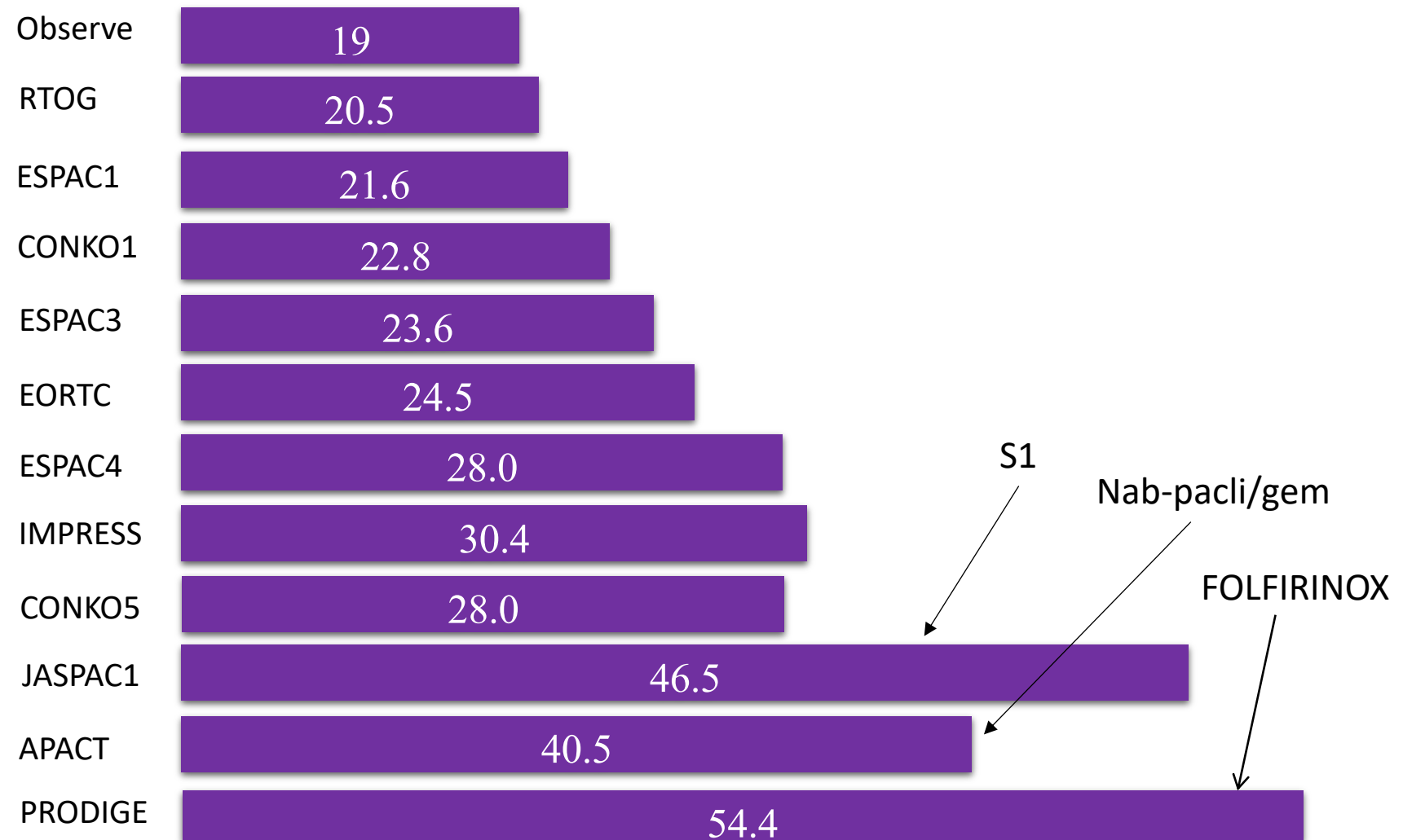


- Patients were randomized no later than 12 weeks post surgery
- Stratification factors: R0 vs R1; LN+ vs LN-; North America, Europe and Australia vs Asia Pacific

APACT did not meet the primary endpoint but demonstrated significant improvement in OS



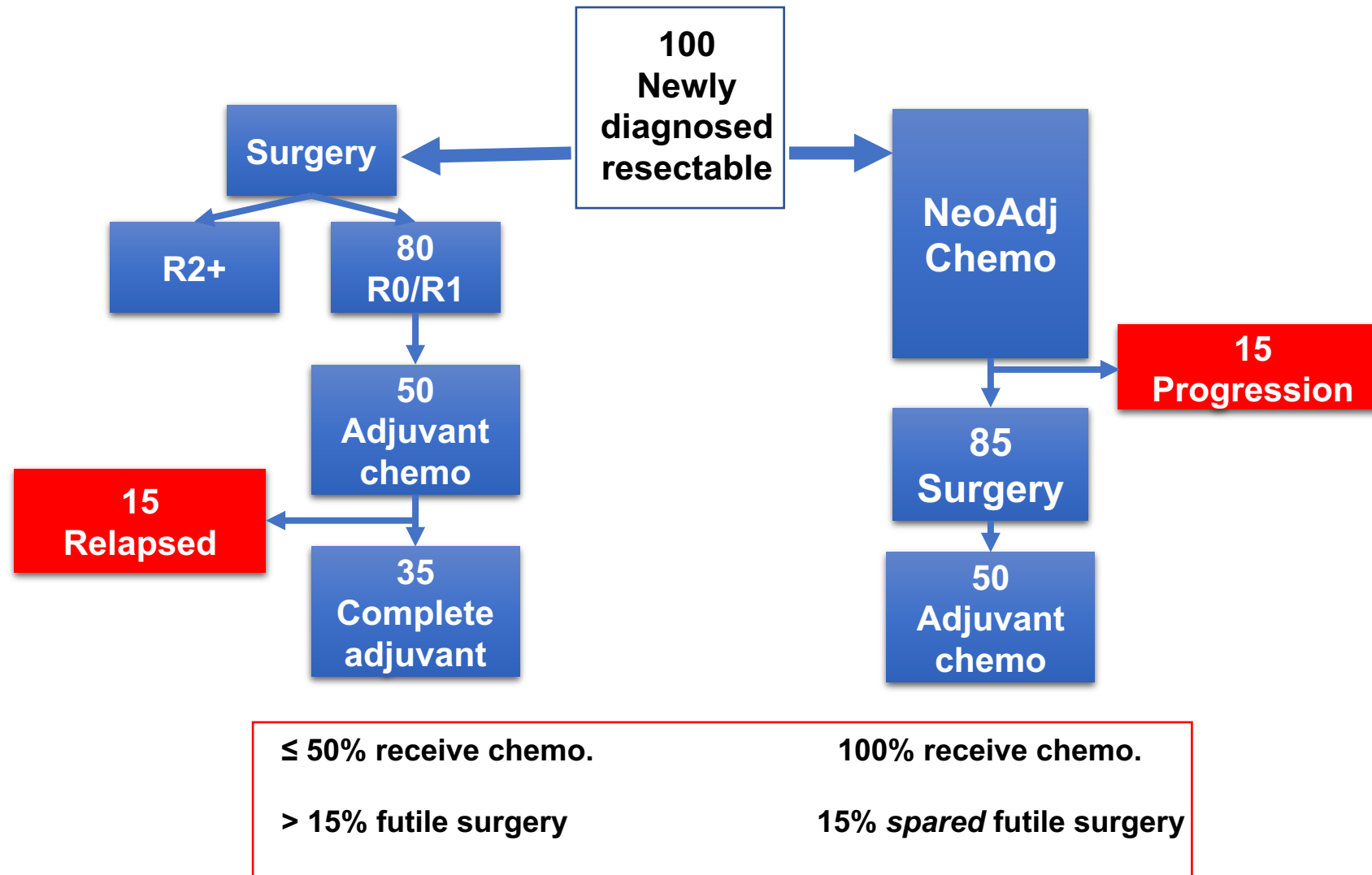
Evolution of adjuvant therapies in pancreatic cancer: median overall survival times in months



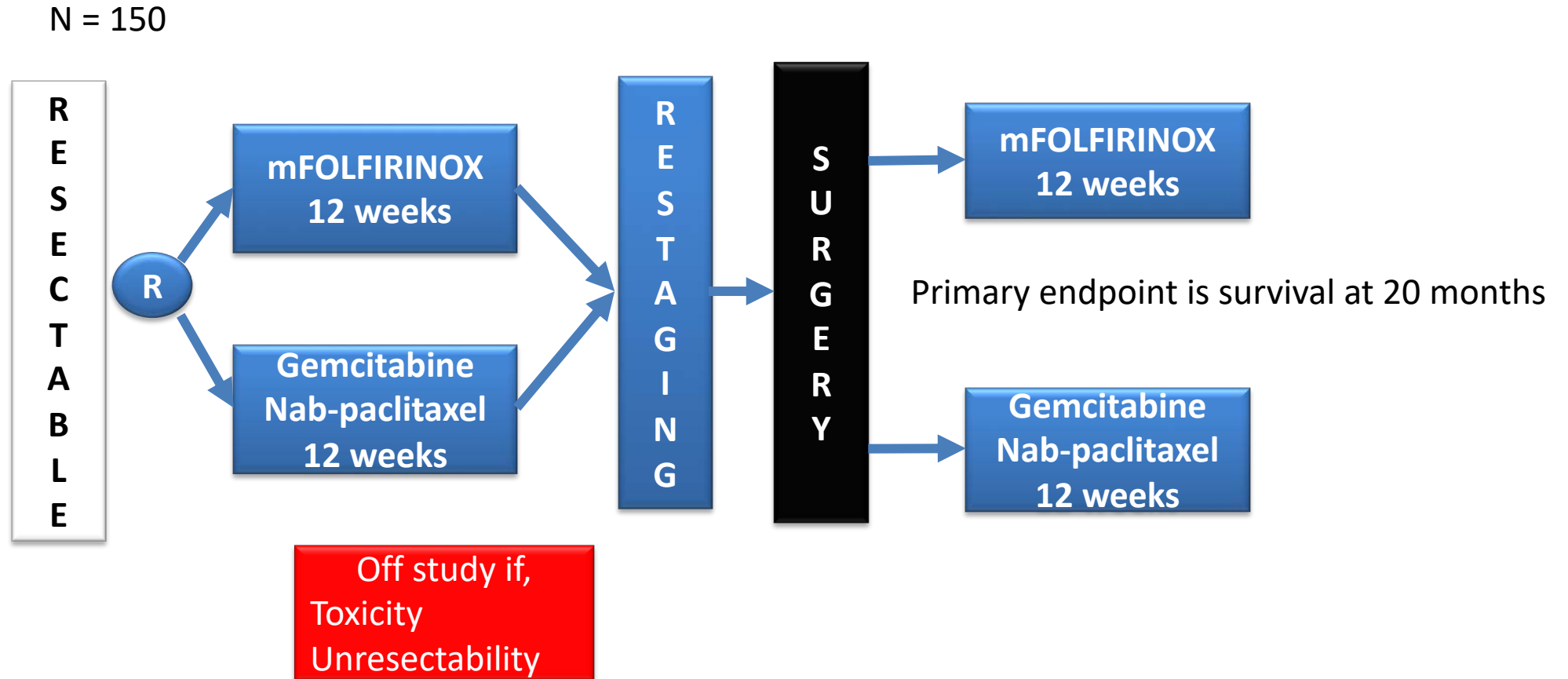
It Is a Challenge to Give Enough Combination Chemo After Surgery!

	PRODIGE ^[a]		ESPAC-4 ^[b]	
	FOLFIRINOX	Gemcitabine	Gemcitabine/ Capecitabine	Gemcitabine
Completed all cycles	66.4	79.0	54	65
Relative dose intensity of > 0.70	48.7%	91.4%	-	-

More Patients Will Receive Effective Systemic Therapy With the Neoadjuvant Approach



S-1505: picking a winner neoadjuvant regimen for resectable disease



Role of Multimodality Therapy:

The Literature Helps, But Also Confusing!

Study	Patients [n]	Regimen	Resection rate [%]	R0 rate [% of resected]	Median OS [months]
<i>Neoadjuvant trials of upfront chemoradiotherapy</i>					
Hoffman et al. (1998)	62	FU + Mitomycin + 50.4 Gy	45.3	70.8	16
Mornex et al. (2006)	41	PF + 50 Gy	63.4	80.7	12
Turrini et al. (2009)	102	PF + 45 Gy	60.8	91.8	23
Evans et al. (2008)	86	Gem + 30 Gy	64.4	86.4	34
Pisters et al. (2002)	37	PXL + 30 Gy (IORT)	54.1	70	19
Golcher et al. (2015)	29	PG + 55.8 Gy	65.5	89.5	25
Pisters et al. (1998)	35	FU + 30 Gy (IORT)	57	51	37
Sho et al. (2013)	61	Gem + 50.4-54Gy	97	92	NR
Van Buren et al. (2013)	59	Gem + Bev + 30 Gy	73	88	17
<i>Neoadjuvant trials of chemotherapy alone</i>					
Palmer et al. (2007)	50	Gem vs. PG	37.5 (Gem) 69.2 (PG)	75	28
Heinrich et al. (2008)	28	PG	89.3	80	27
O'Reilly et al. (2014)	38	GemOx	71	74	27
Tajima et al. (2012)	34	Gem + S1	100	85	56% at 24
<i>Neoadjuvant trials of chemotherapy followed by chemoradiation therapy</i>					
Varadhachary et al. (2008)	90	PG - > 30 Gy + Gem	57.8	96.2	31
Talamonti et al. (2006)	20	Gem - > 36Gy	85	80	26 (resected)
Faris et al. (2013)	22	FOLFIRINOX +/- CRT	55	42	NR

Conclusions

- FOLFIRINOX and gemcitabine/nab-paclitaxel are appropriate regimens for first line therapy with comparable efficacy
- Careful patient assessment and discussion is very important
- Nal-Iri/5FU/LCV improves survival in patients after gemcitabine based therapy
 - Current development of Nal-Iri in frontline therapy
- mFOLFIRINOX is preferred adjuvant treatment, other options include gemcitabine/capecitabine, gemcitabine/nab-paclitaxel, or gemcitabine
- Neoadjuvant therapy is preferred in patients with potentially resectable pancreatic cancer