Updates in PDAC

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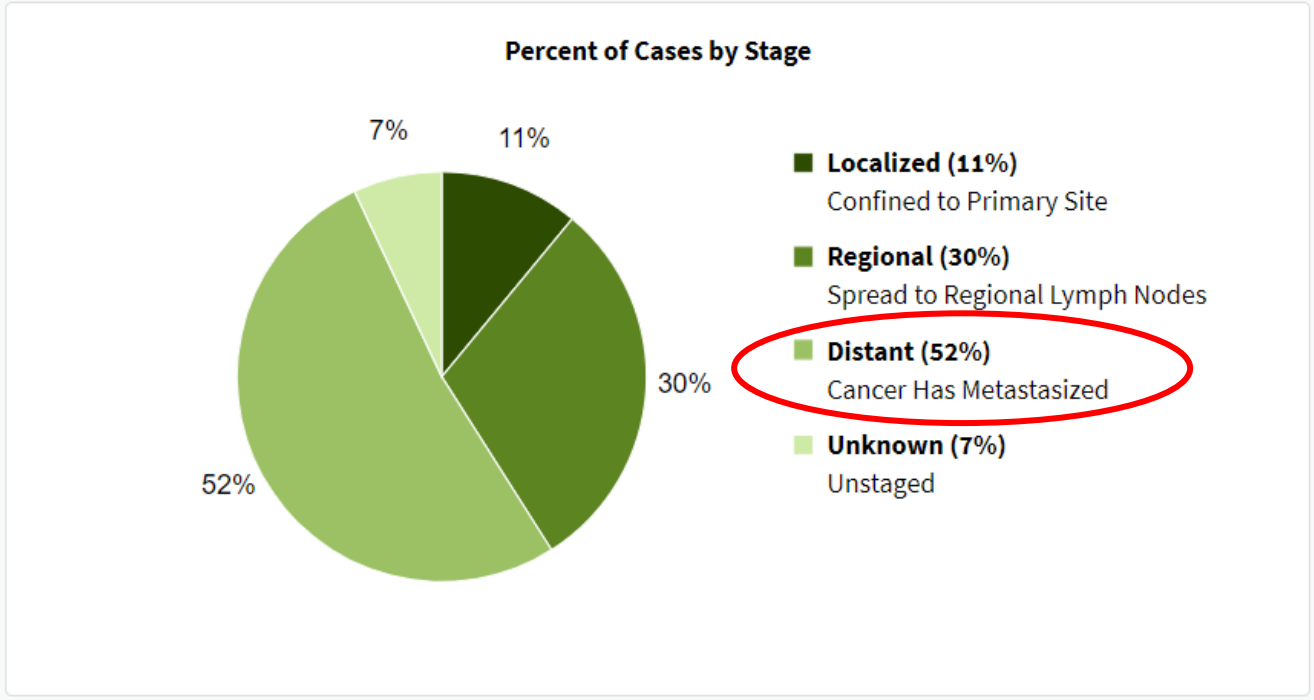
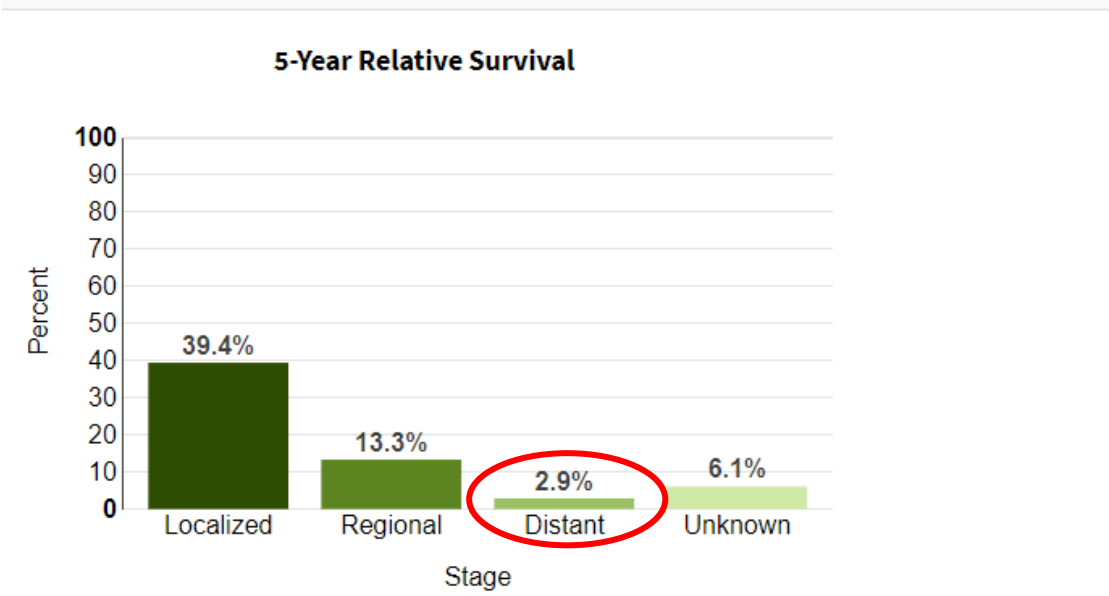
Agenda

- The current state of pancreatic cancer treatment
- Benchmarks for PDAC
- Immunotherapy in pancreatic cancer
- Summary

SEER 18 2010–2016, All Races, Both Sexes by SEER Summary Stage 2000

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Pancreatic Cancer





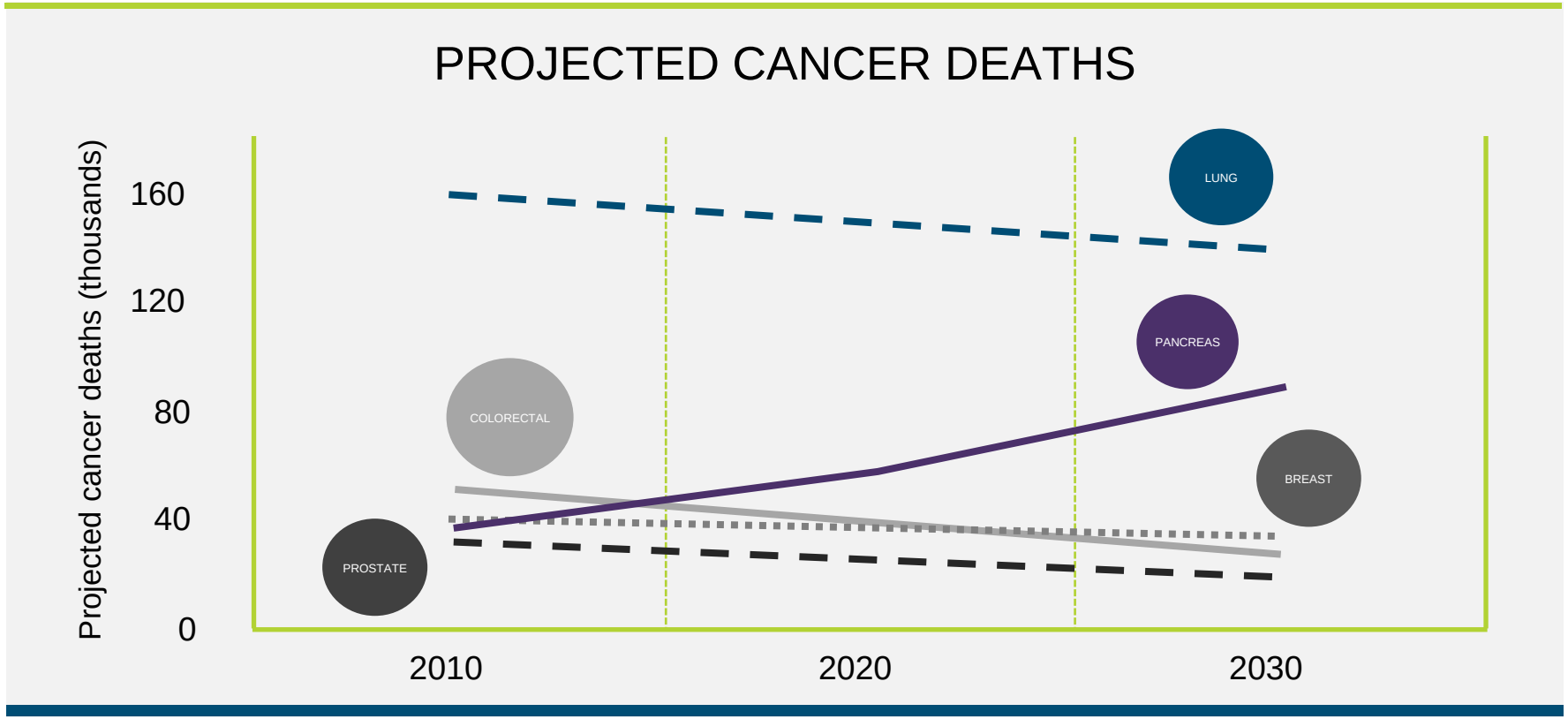
The majority of PDAC patients are diagnosed with metastatic disease

https://seer.cancer.gov/statfacts/html/pancreas.html

The current state of pancreatic cancer treatment

Within this decade, pancreatic cancer will become the 2nd leading cause of cancer death in the United States

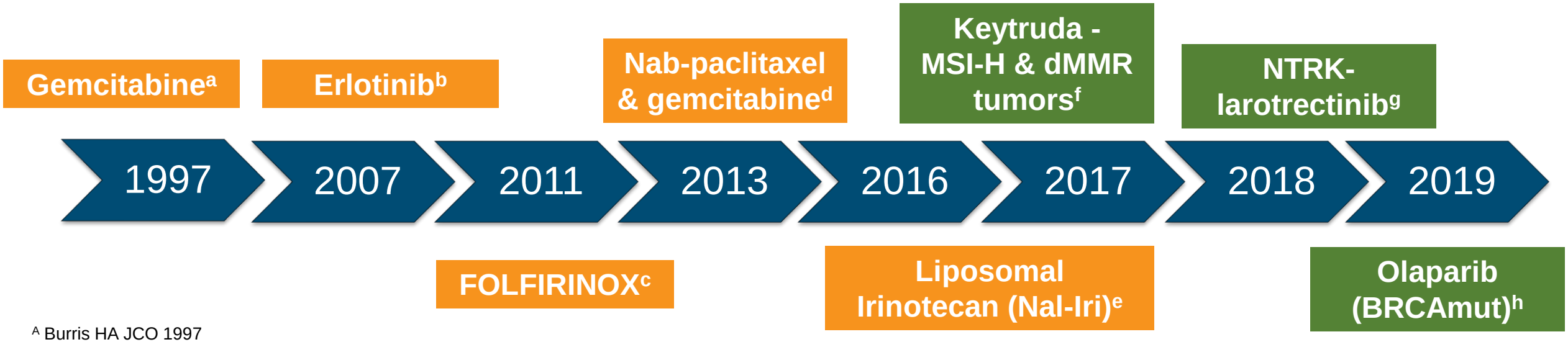
- Pancreatic cancer is the only one of the top 5 cancer killers for which deaths are **projected to increase**



Multiple Drugs and Targets Have Failed in Clinical Trials PDAC: Dec 2015 – Dec 2020

Drug	Target/Mechanism	Phase	Number of Patients
Evofosfamide	Alkylator (Hypoxia)	III	694
Ruxolitinib	JAK1/2	III	Early termination
Necuparanib	Heparan mimetic	I/II	128
Masitinib	TKI (Kit, Lyn, Fyn)	III	353
Vandetanib	TKI (VEGFR2, RET, EGFR)	II	142
Algenpantucel-L	Vaccine	III	722
CRS-207 + GVAX	Vaccine	IIb	240
Tarextumab	Notch2/3	II	177
Demcizumab	DLL4	II	204
^{90}Y-Clivatuzumab Tetraxetan	MUC1	III	334
Apatorsen	HSP27	II	132
Z-360	CCK2	II	167
Simtuzumab	LOX-2	II	240 (159)
MM-141	IGF-1R/ErbB-3	II	88
Ibrutinib	BTK	III	424
Napabucasin	STAT3	III	>1,100
Pegilodecakin (AM0010)	pegylated IL-10	III	567
PEGPH20	Hyaluron	III	500
Cabiralizumab	CSFR-1	IIb	160

Therapeutics in advanced PDAC Over 2 Decades



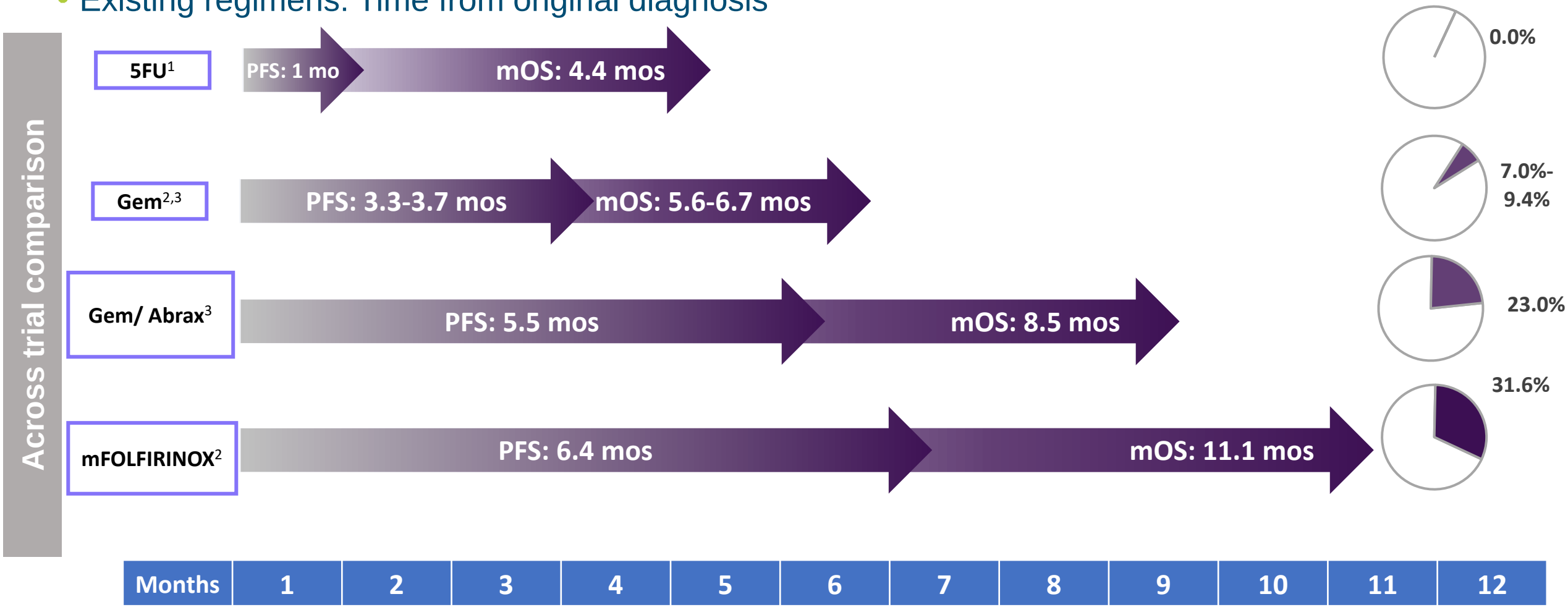
[A] Burris HA JCO 1997
[b] Moore M, JCO 2007
[C] Conroy T NEJM 2011
[D] Von Hoff DD NEJM 2013
[E] Wang-Gillam A Lancet 2016
[f] Le et al Science; 2017
[G] Drilon et al NEJM 2018
[h] Golan et al. NEJM 2019

Orange: chemotherapy and biological
Green: biomarker driven targeted therapy

Benchmark for Pancreatic Cancer

There is a significant unmet need to prolong disease control and survival as part of first-line treatment for patients with pancreatic cancer

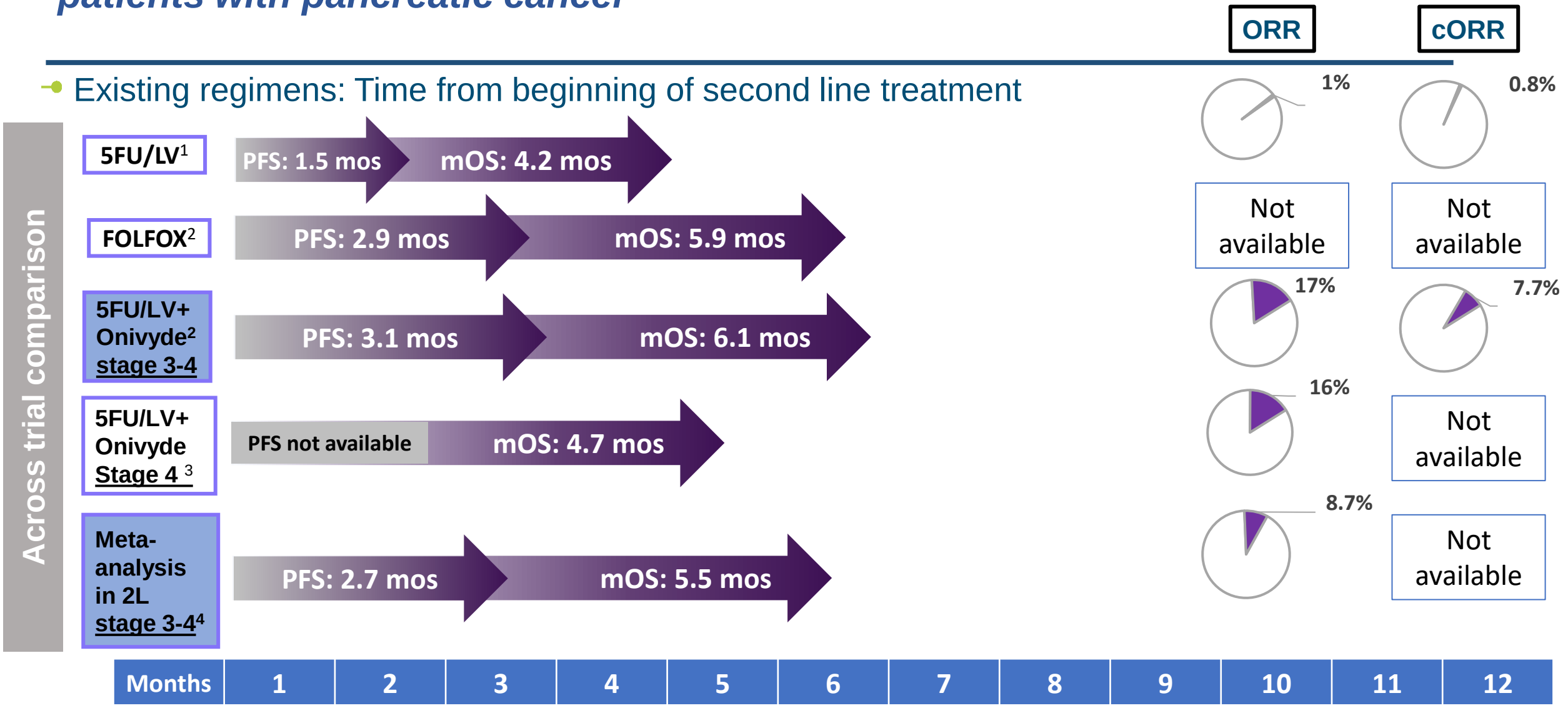
- Existing regimens: Time from original diagnosis



- mPFS values in graphic; mPFS varies between studies due to study design, inclusion/exclusion criteria and patient demographics. 5-FU=5-flurouracil.
- 1. Burris HA et al. J Clin Oncol. 1997; 2. Conroy T et al, NEJM 2011; 3. Von Hoff et al. NEJM 2013

There is also an unmet need to prolong survival in second line treatment for patients with pancreatic cancer

- Existing regimens: Time from beginning of second line treatment



- mPFS values in graphic; mPFS varies between studies due to study design, inclusion/exclusion criteria and patient demographics. 5-FU=5-flurouracil.
- 1. Wang Gillam et al EJC 2016; 2. Oettle et al, JCO 2014; 3. Macarulla Mercade et al, Pancreas 2020; 4. Petrelli et al EJC 2017 (Iri-based)

Summary Pancreatic Cancer Benchmark for 2L PDAC Diagnosed at Metastatic Stage

Endpoint	NAPOLI-1 stage IV at diagnosis subgroup (n=61)	Meta-analysis IRI based 2L (7 studies n=396) Includes all stages at diagnosis
mOS (mos)	4.7	5.5
mPFS (mos)	3.1 (stage III-IV n=117)	2.7
ORR (%)	16%	8.7%
cORR (%)	7.7% (stage III-IV n=117)	NA
DCR (%)	52% (stage III-IV n=117)	29.4%

Immunotherapy in pancreatic cancer

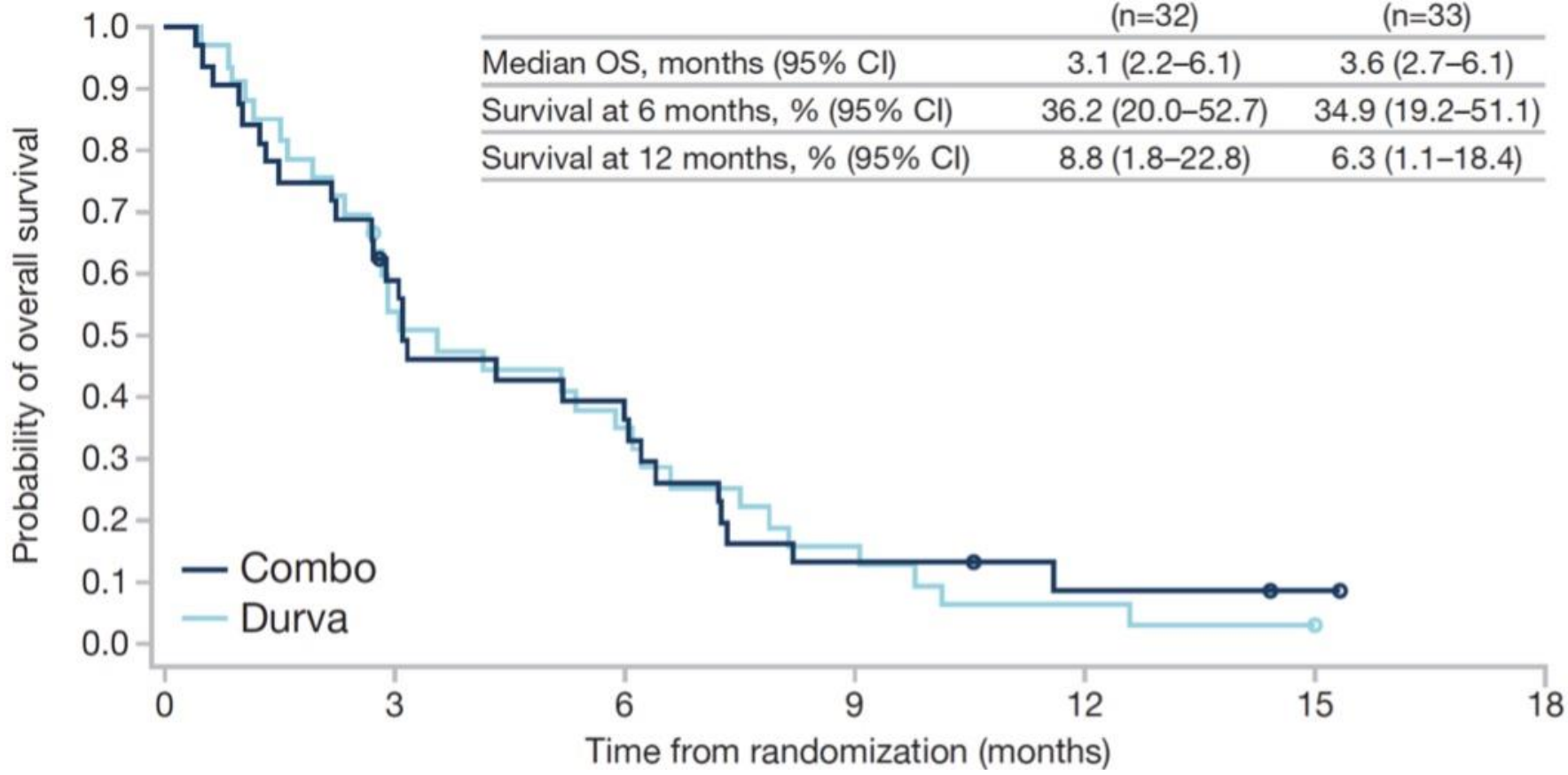
Immunotherapy for Pancreatic Cancer

- Pancreatic cancer has been regarded as non-immunogenic
  - immunosuppressive cells and cytokines
  - low tumor mutational burden
  - paucity of T cells in tumor (number and function)?? Controversial since recent studies demonstrate that the majority of primary tumors are infiltrated with T-cells
  - efficacy of checkpoint inhibitors in PDAC was found to be absent
  - multiple immune inhibitory mechanisms in the tumor microenvironment
  - Single-agent therapeutic approaches focusing on overcoming T-cell immunologic endpoints with immune checkpoint inhibitors or vaccines are not encouraging

Royal RE, et al. *J Immunother.* 2010;33(8):828-833. Topalian SL, et al. *N Engl J Med.* 2012;366(26):2443-2454. Morrison AH et al Trends Cancer. 2018;4(6):418-28. Poschke I et al Oncoimmunology. 2016;5(12):e1240859.

PDL-1 inhibitor (durvalumab) with or without CTLA4 inhibitor (tremelimumab) in 2nd line : did not work!

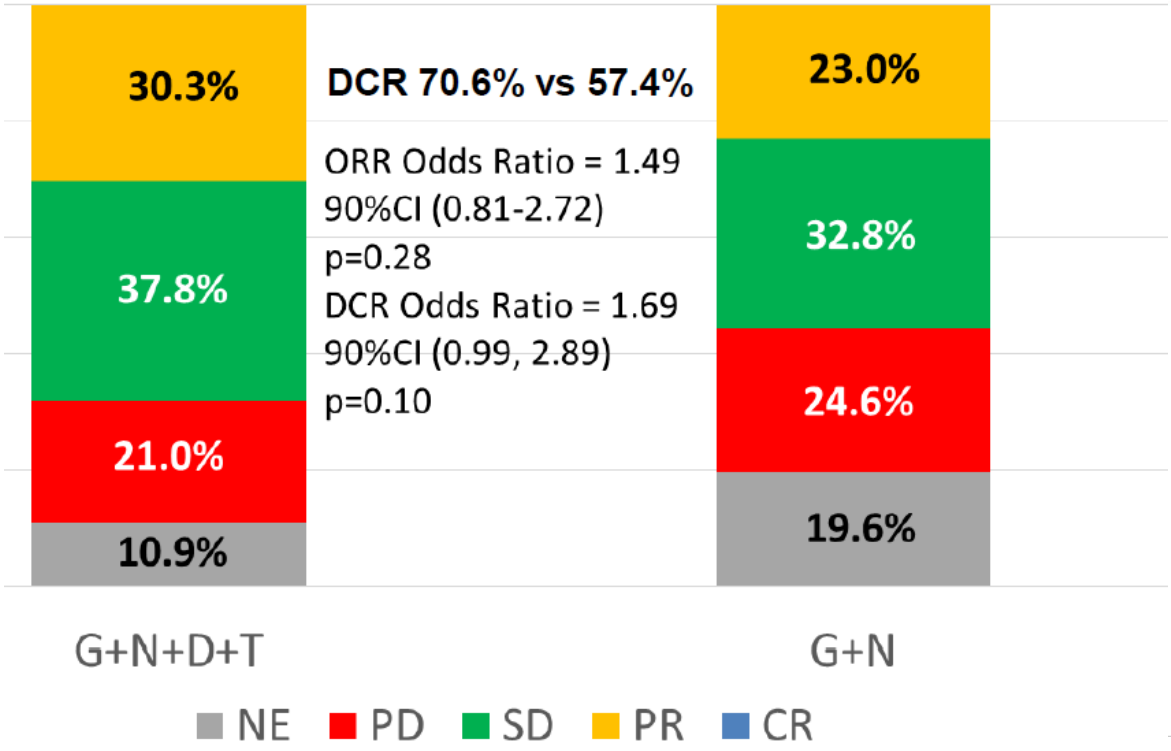
	D + T (n=32)	D (n=33)
Median OS, months (95% CI)	3.1 (2.2–6.1)	3.6 (2.7–6.1)
Survival at 6 months, % (95% CI)	36.2 (20.0–52.7)	34.9 (19.2–51.1)
Survival at 12 months, % (95% CI)	8.8 (1.8–22.8)	6.3 (1.1–18.4)



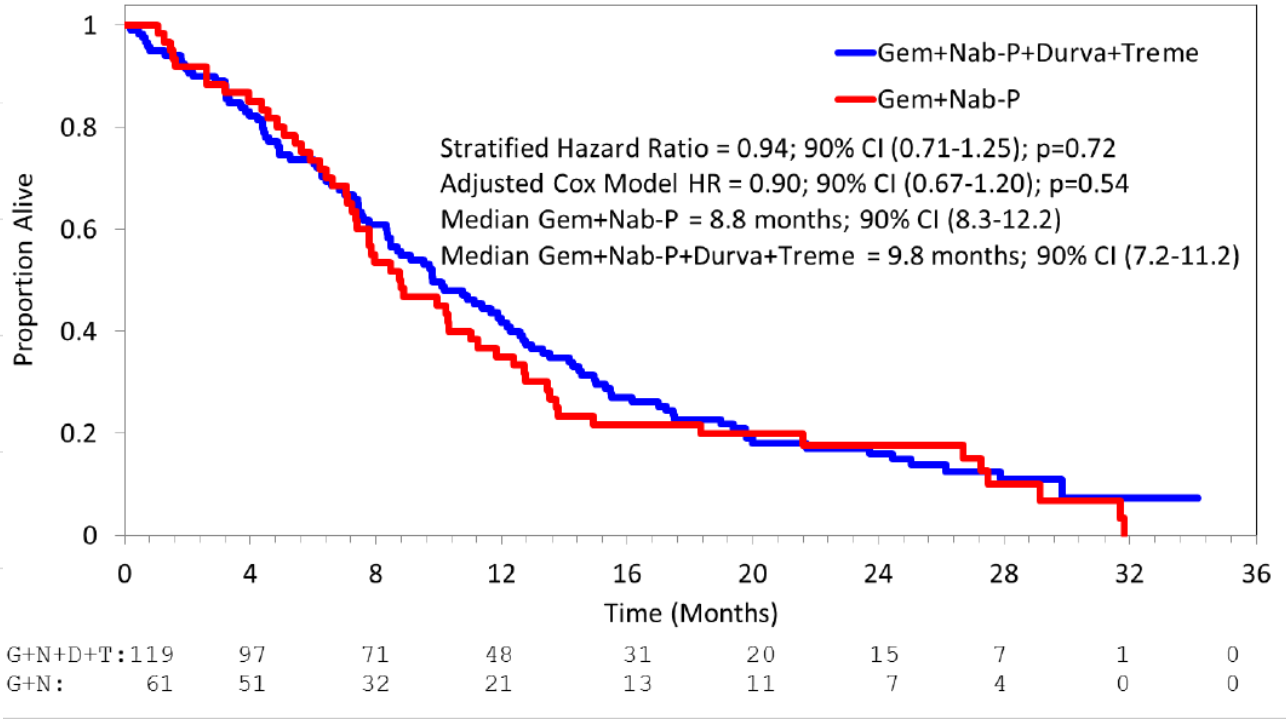
O'Reilly et al, ASCO GI, 2018

Combination of Checkpoint inhibitor and chemotherapy did not improve the chemotherapy efficacy in first line

Results: Objective Response Rate



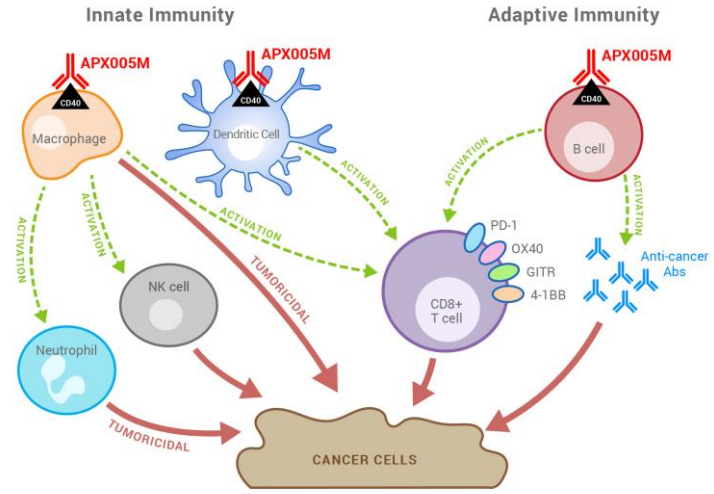
Results: Overall Survival

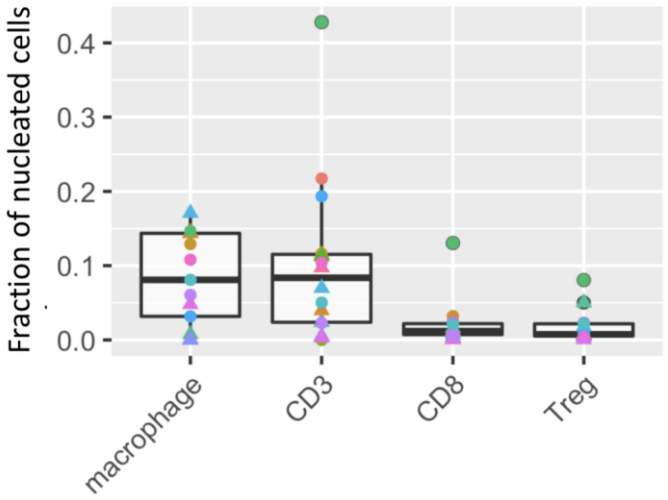


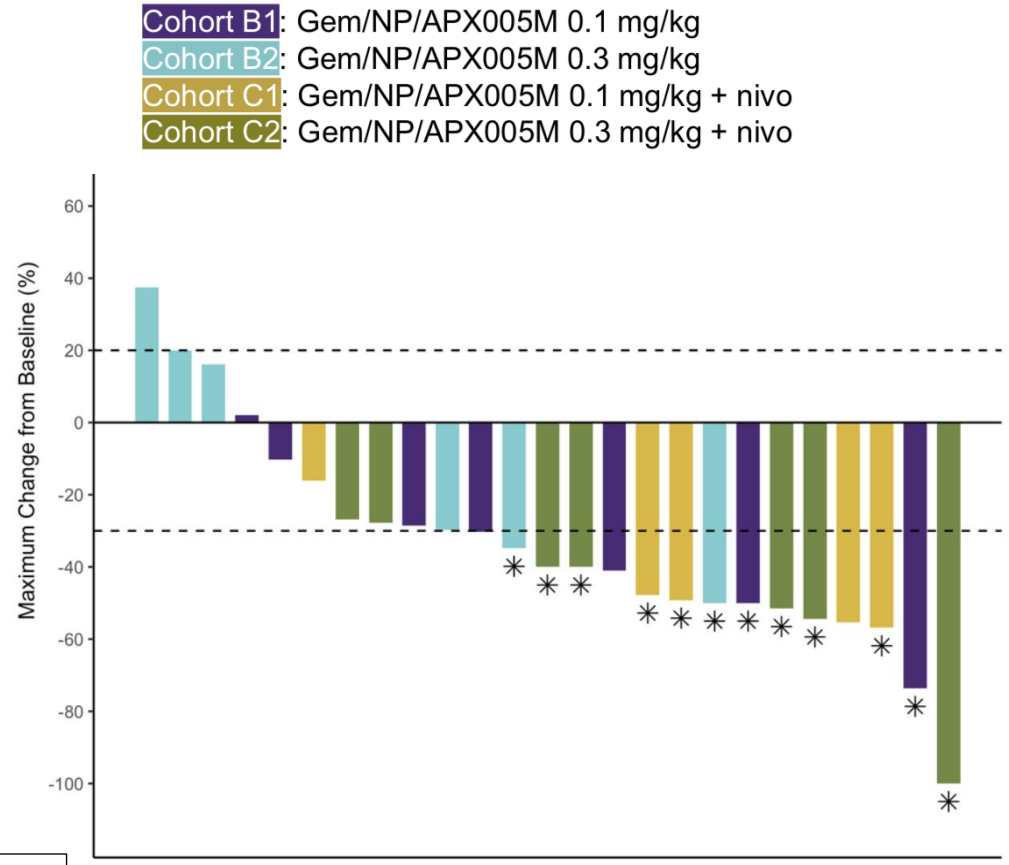
Renouf et al, ESMO 2020

Triple combination approaches are promising in PDAC

APX005M (CD40 agonist) mAb together with gemcitabine/nabpaclitaxel +/- nivolumab as 1st Line treatment







Overall response rate 54%
In all four combo 67%

O'Hara, et al, Parker Institute, AACR 2019

Summary

- Cytotoxic therapy is the mainstay of systemic therapy resulting in modest benefit in pancreatic cancer
- Single molecule/pathway targeting is unlikely to result in significant clinical benefit
- Single-agent therapeutic approaches focusing on overcoming T-cell immunologic endpoints with immune checkpoint inhibitors or vaccines are not encouraging
- Immuno combinatorial therapy is the likelier strategy to succeed
- Strong scientific rationale for which combinations is needed
- Pancreatic cancer is a tough disease and incremental improvements are clinically meaningful