Pancreatic Cancer UK

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Improving Access to Chemotherapy, 17th September 2020, 9 – 11am

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The Latest in Chemotherapy

Prof Juan W Valle, Professor / Honorary Consultant in Medical Oncology, University of Manchester /The Christie

Virtual Annual Summit 2020: Improving Access to Chemotherapy

Pancreatic Cancer UK

The latest in chemotherapy

Juan W Valle

Professor and Honorary Consultant in Medical Oncology
University of Manchester / The Christie
Manchester UK

17 Sep 2020

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Disclosures

Travel Grant	Celgene; NuCana; Pfizer
Speakers' Bureau	Imaging Equipment Ltd; Ipsen; Novartis; Nucana
Consulting or Advisory Role	Agios; AstraZeneca; Debiopharm; Delcath Systems; GenoScience Pharma; Imaging Equipment Ltd; Incyte; Ipsen; Keocyt; Merck; Mundipharma EDO; Novartis; Nucana; PCI Biotech; Pieris Pharmaceuticals; Pfizer; QED; Servier; Wren Laboratories

Adjuvant | why adjuvant treatment?

- Surgery remains the cornerstone of curative therapy
- Relapse rates are high (90% without additional therapy)
- Systemic chemotherapy aims at
  - eradicating micro-metastatic disease
  - reducing chance of disease recurrence
  - improving overall survival
- Current standards are for a 6-month course of treatment

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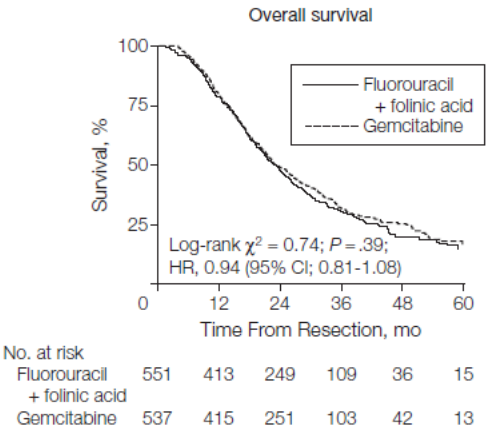
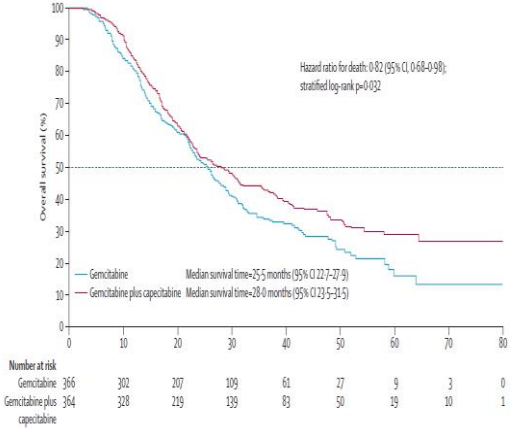
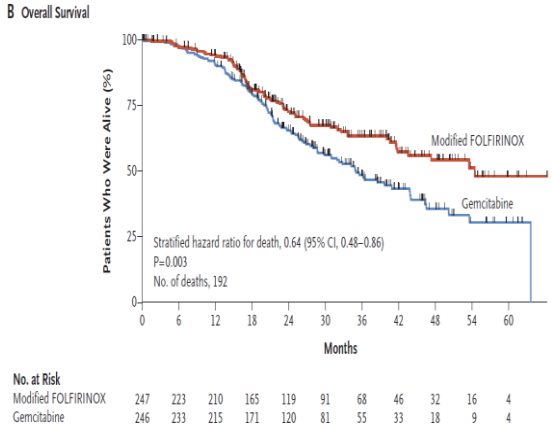
Adjuvant | 1,2 or 3 drugs?







ESPAC-3

Gemcitabine ***or*** 5FU: same results but gemcitabine less toxic

Neoptolemos et al JAMA 2010

ESPAC-4

Gemcitabine ***and*** 5FU: improved 5-year survival, more side-effects

Neoptolemos et al Lancet Oncol 2017

PRODIGE-24

FOLFIRINOX improved survival compared with gemcitabine…more toxic

Conroy et al NEJM 2018

Adjuvant chemotherapy | the reality

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Adjuvant chemotherapy | the reality

Study	Planned (N)	Started N (%)	Did not start N (%)
ESPAC-3 (chemo)	1088	964 (88.6%)	124 (11.4%)
ESPAC-4 (all)	732	707 (96.6%)	25 (3.4%)
PRODIGE-24 (FOLFIRINOX)	247	238 (96.4%)	9 (3.6%)

Patient decision
Unknown reason
Patient ill health
Disease progression
Died
Ineligible

Neoptolemos et al JAMA 2010

Neoptolemos et al Lancet Oncol 2017

Conroy et al NEJM 2018

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Adjuvant chemotherapy | the reality

Study	Planned (N)	Started N (%)	Did not start N (%)	Completed N (%)
ESPAC-3 (chemo)	1088	964 (88.6%)	124 (11.4%)	624 (64.7%)
ESPAC-4 (all)	732	707 (96.6%)	25 (3.4%)	434 (61.4%
PRODIGE-24 (FOLFIRINOX)	247	238 (96.4%)	9 (3.6%)	158 (66.4%)

Neoptolemos et al JAMA 2010

Neoptolemos et al Lancet Oncol 2017

Conroy et al NEJM 2018

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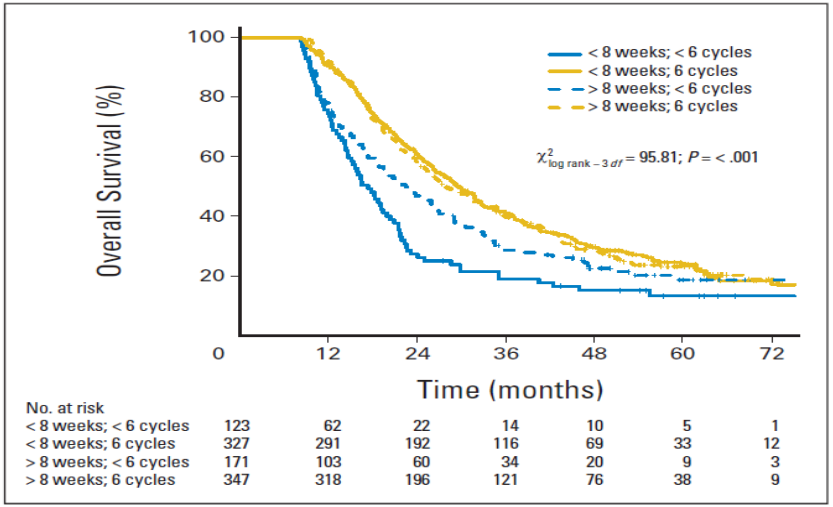
Adjuvant chemotherapy | the reality

Surgery → Recovery → Time-frame → Plan for chemo → Start chemo → Complete chemo

- No benefit from starting in less than 8 weeks post-op – safe to wait until 8-12 weeks
- Allow patients a chance to recover from surgery
- It is more important to finish the chemo (6 months) than starting early after surgery
- Role of pre-habilitation?



Valle et al; J Clin Oncol 2014 32:504-512.

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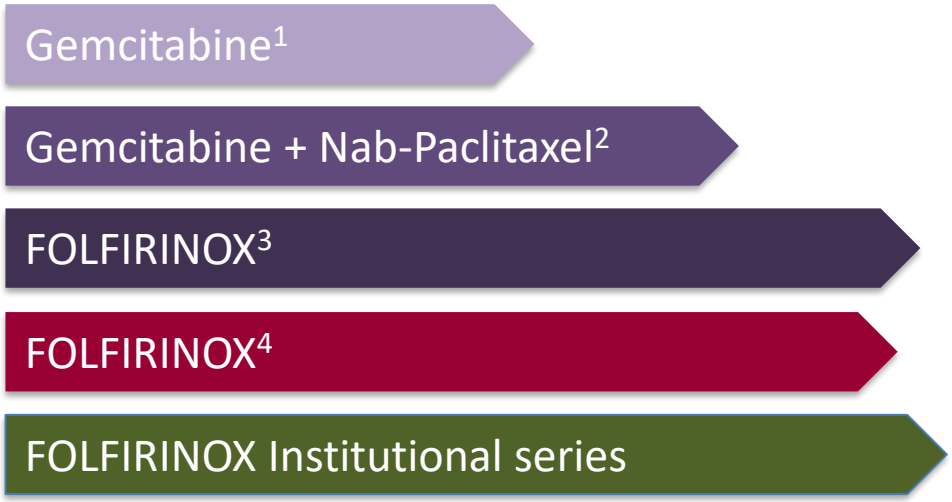
Advanced disease | modest efficacy



1 year	RR
6 months	<10%
8.7 months	23%
11.1 months	32%
10.8 months	
10-14 months	

Treatment with FOLFIRINOX is applicable in ~25% patients[5]

[1] Burris et al, J Clin Oncol 1997, [2]Von Hoff et al N Engl J Med 2013, updated Goldstein D et al GI Cancers Symposium, abstract 178, [3]Conroy et al N Engl J Med 2011, [4]Singhal ESMO abstract 617PD; [5] Gill et al. ASCO 2012 abstr. e14588

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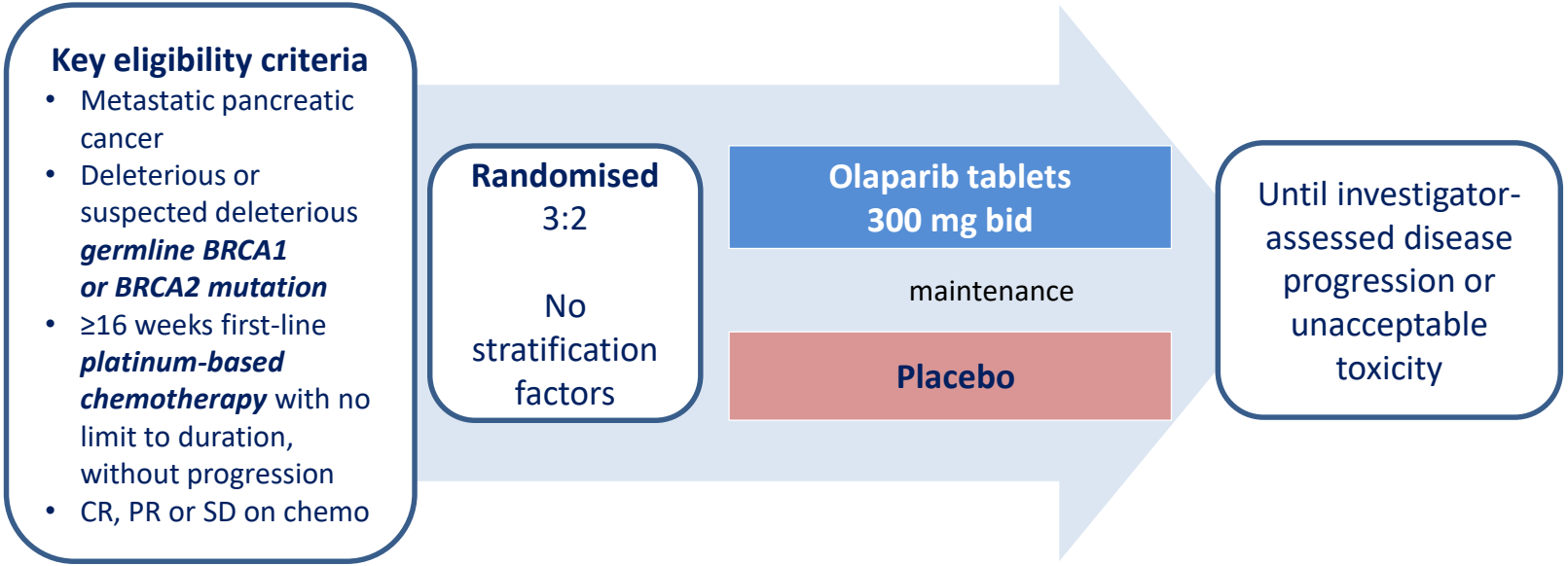
Recent notable results | negative

Study	n	Setting	Control arm	Experimental arm	Result
APACT[1]	866	Adjuvant	Gem	Gem/nab-P	Median DFS: 19.4 mo (G/nab-P) vs 18.8 mo (G) (HR 0.88; p=0.1824)
RESOLVE[2]	424	Metastatic	Gem/nab-P	Gem/nab-P + **ibrutinib**	Median OS 10.8 mo (no ibrutinib) vs. 9.7 mo (with ibrutinib)(HR 1.2; p=0.32)
HALO-301[3]	492	Metastatic	Gem/nab-P	Gem/nab-P + **PEGPH20**	Median OS 11.5 mo (no PEGPH20) vs. 11.2 mo (with PEGPH20)(HR 1.0; p=0.97)
SEQUOIA[4]	568	Metastatic (2L)	FOLFOX	FOLFOX + **pegilodekan**	Median OS 6.3 mo (no pegilodekan) vs. 5.8 mo (with pegilodekan)(HR 1.0; p=0.66)

[1]Tempero et al ASCO 2019 abstr 4000; [2]Tempero et al ESMO GI 2019 abstract O-002; [3]Tempero et al ASCO GI 2020 abstr 638; [4]Hecht et al ASCO GI 2020 abstr 637

Recent notable results | positive

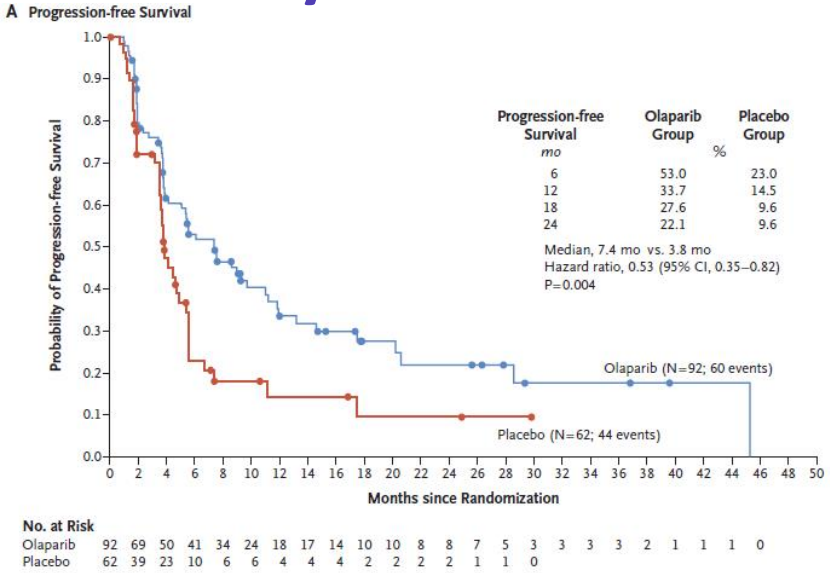
POLO study

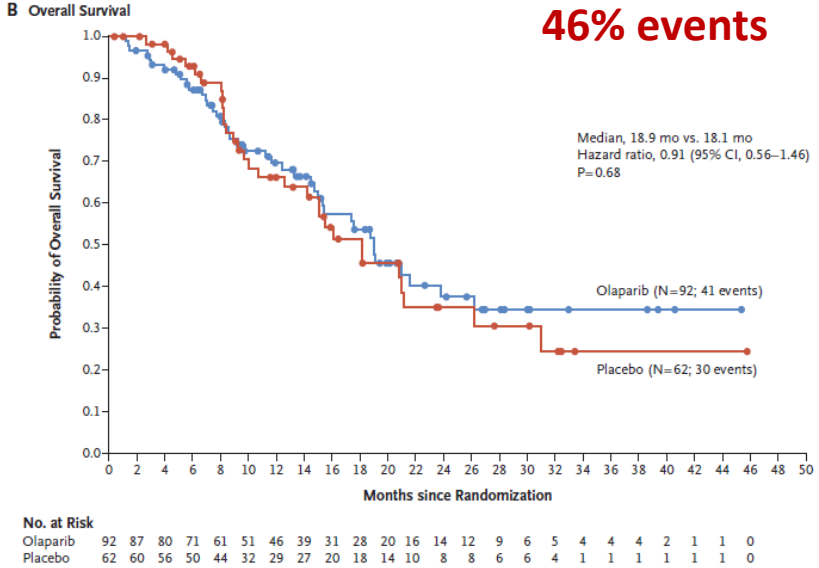


Golan et al N Engl J Med. 2019 Jul 25;381(4):317-327

Notable results | positive

POLO study





Improved progression-free survival

7.4 vs 3.8 months

HR 0.53; 95%CI 0.35 to 0.82; p=0.004

Overall survival data not mature

18.9 vs 18.1 months

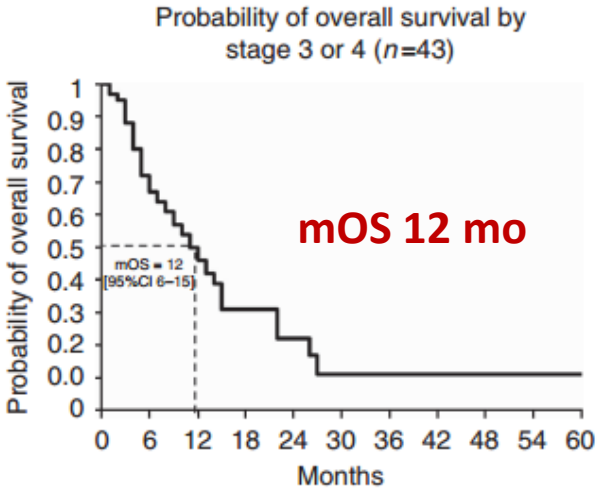
HR 0.91; 95%CI 0.56 to 1.46; p=0.68

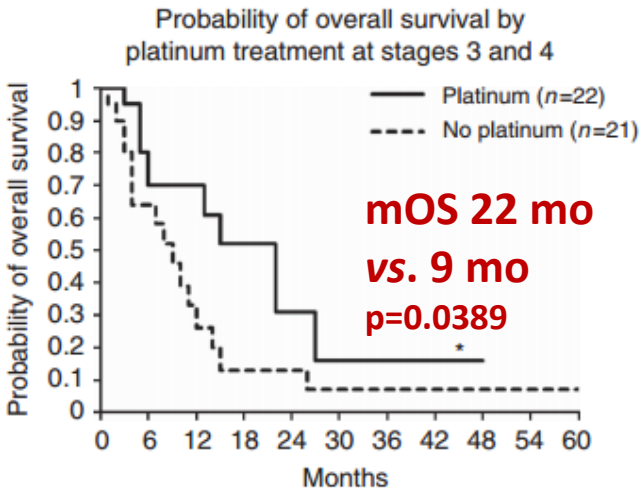
Golan et al N Engl J Med. 2019 Jul 25;381(4):317-327

Identification of important subgroups

1. BRCA-mutated patients benefit from ***olaparib*** (vs placebo) – POLO study[1]

2. BRCA-mutated patients benefit from ***platinum-based chemotherapy***[2]



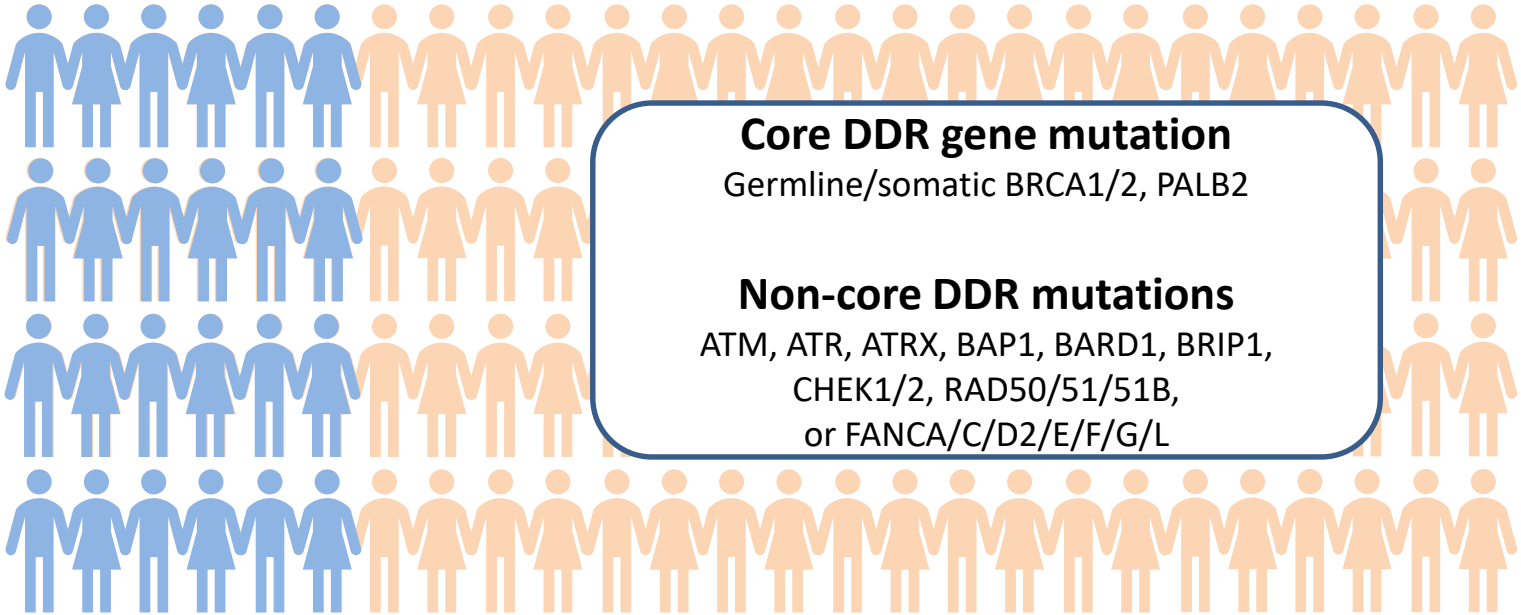


[1]Golan et al N Engl J Med 2019; 381:317-327; [2]Golan Br J Cancer 2014; 111:1132–1138

Identification of important subgroups

However, <7% of patients with pancreatic cancer have an inherited BRCA1 and/or BRCA2 mutation

Identification of important subgroups



This group is bigger if we include other DNA damage repair (DDR) mutations

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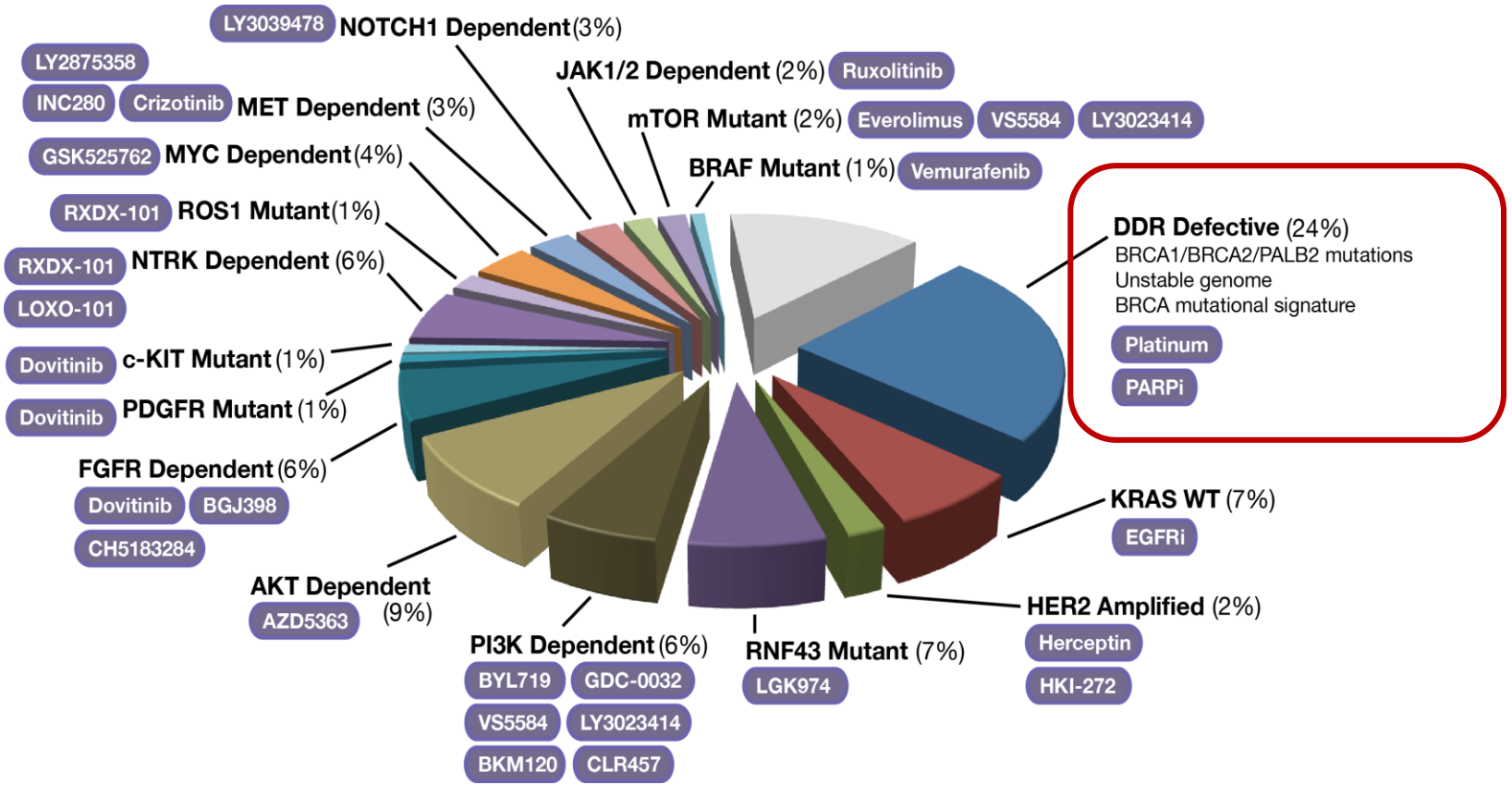
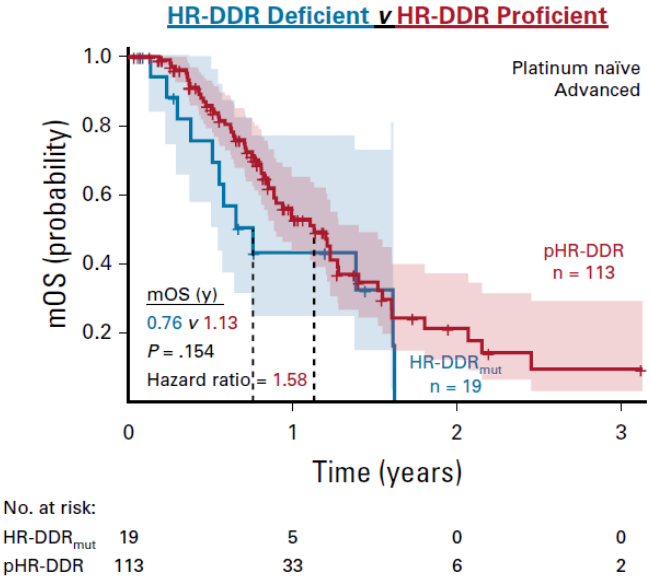
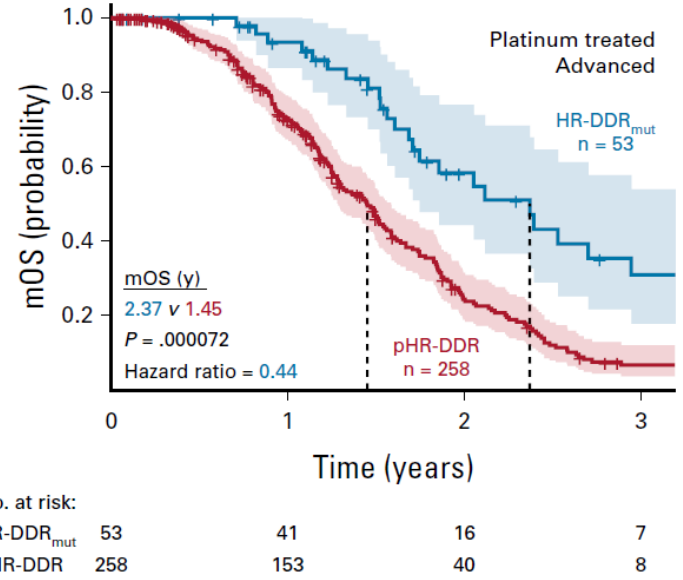
Identification of important subgroups



Bailey Nature 2016

DDR response to platinum | not just BRCA





No difference without platinum

0.76 vs 1.13 yrs

HR 1.58; p=0.154

OS advantage if platinum used

2.37 vs 1.45 yrs

HR 0.44; p=0.000072

Pishvaian et al JCO Precision Oncology 2019; online Oct23

FOLFIRINOX | locally-advanced disease

Lancet Oncol 2016; 17: 801–10

FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis

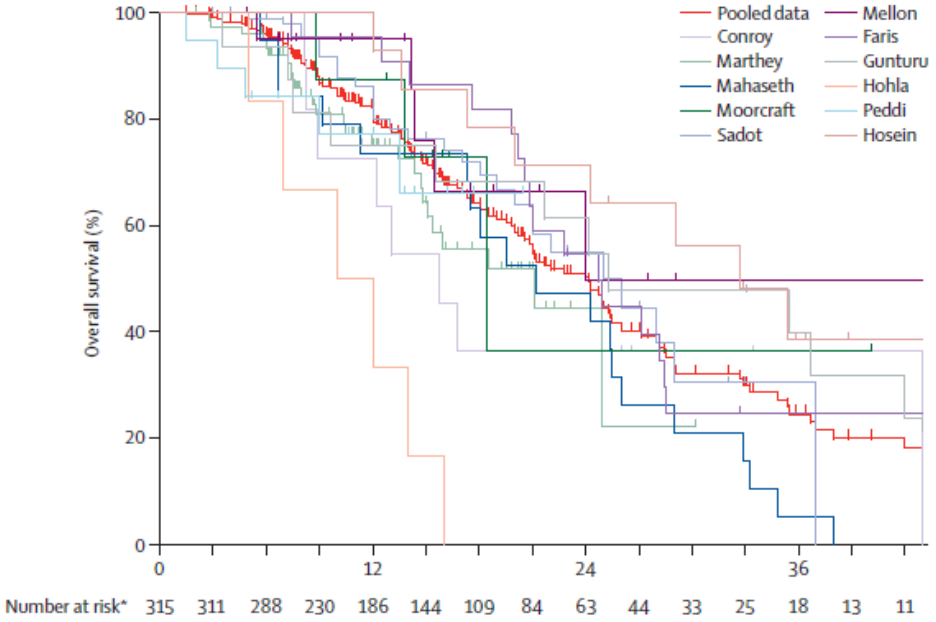
Mustafa Suker, Berend R Beumer*, Eran Sadot, Lysiane Marthey, Jason E Faris, Eric A Mellon, Bassel F El-Rayes, Andrea Wang-Gillam, Jill Lacy, Peter J Hosein, Sing Yu Moorcraft, Thierry Conroy, Florian Hohla, Peter Allen, Julien Taieb, Theodore S Hong, Ravi Shridhar, Ian Chau, Casper H van Eijck, Bas Groot Koerkamp*

13 studies, 355 patients with LAPC
11 studies, 315 patients with data for patient-level survival analysis

63.5% of patients received (chemo)-radiotherapy after FOLFIRINOX

Median OS: 24.2 mo (95%CI 21.7–26.8)

Median PFS: 15.0 mo (95%CI 13.7–16.3)



Median overall survival ranged from 10.0 months to 32.7 months across studies

FOLFIRINOX | locally-advanced disease

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After FOLFIRINOX 28% of patients with LAPC underwent resection (range 0-43%)

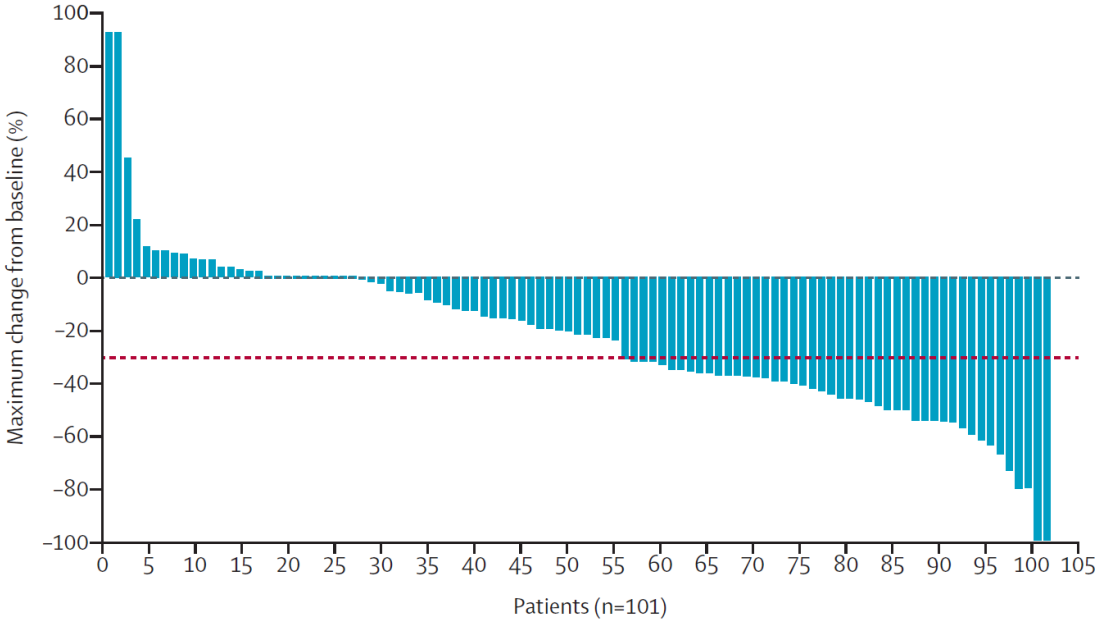
Of these, 74% were R0 resections

"There was no significant correlation across studies between the proportion of patients who underwent resection and overall survival"

	Number of patients	Radiotherapy or chemoradiotherapy	Resection	R0 resection
Boone[22]	10	5 (50%)	2 (20%)	1 (50%)
Conroy[12]	11	NR	0	NA
Faris[21]	22	20 (91%)	5 (23%)	5 (100%)
Gunturu[24]	16	NR	2 (13%)	NR
Hohla[18]	6	2 (33%)	2 (33%)	NR
Hosein[23]	14	9 (64%)	6 (43%)	5 (83%)
Mahaseth[19]	20	10 (50%)	4 (20%)	3 (75%)
Marthey[25]	77	24 (31%)	28 (36%)	25 (89%)
Mellon[28]	21	21 (100%)	5 (24%)	5 (100%)
Moorcraft[26]	8	NR	2 (25%)	NR
Peddi[20]	19	NR	4 (21%)	NR
Sadot[29]	101	63 (62%)	31 (31%)	16 (52%)
Total	325	154 (57%)	91 (28%)	60 (74%)

Gem-*nab*-paclitaxel| locally-advanced disease

LAPACT study



N=107 patients; phase II

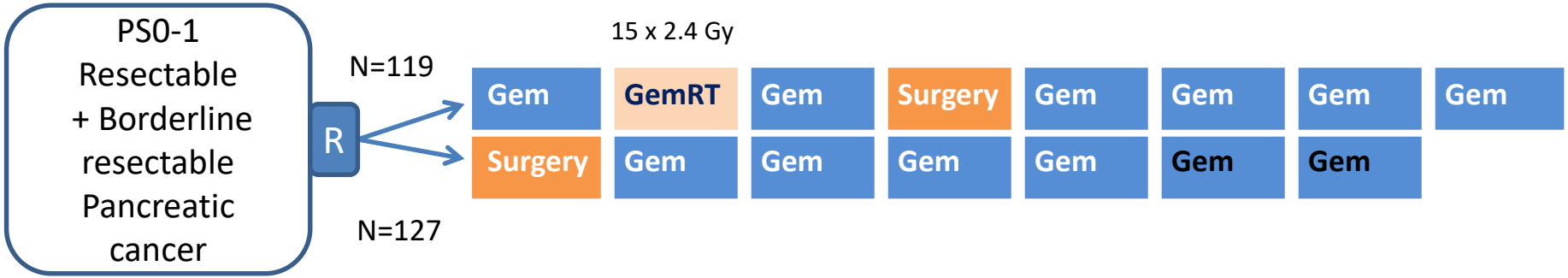
Primary endpoint:
TTF: *9 mo (90% CI 7.3 – 10.1)*

Secondary Endpoints:
DCR: 77.6%
ORR: 33.6%
PFS: 10.9 mo (90% CI 9.3 – 11/6)
OS: 18.8 mo (90% 15.0 – 24.0)

"a chemotherapy regimen option" in LAPC (unlicensed indication)

Philip et al 2020 Mar;5(3):285-294

Neoadjuvant | PREOPANC study



Primary endpoint not met

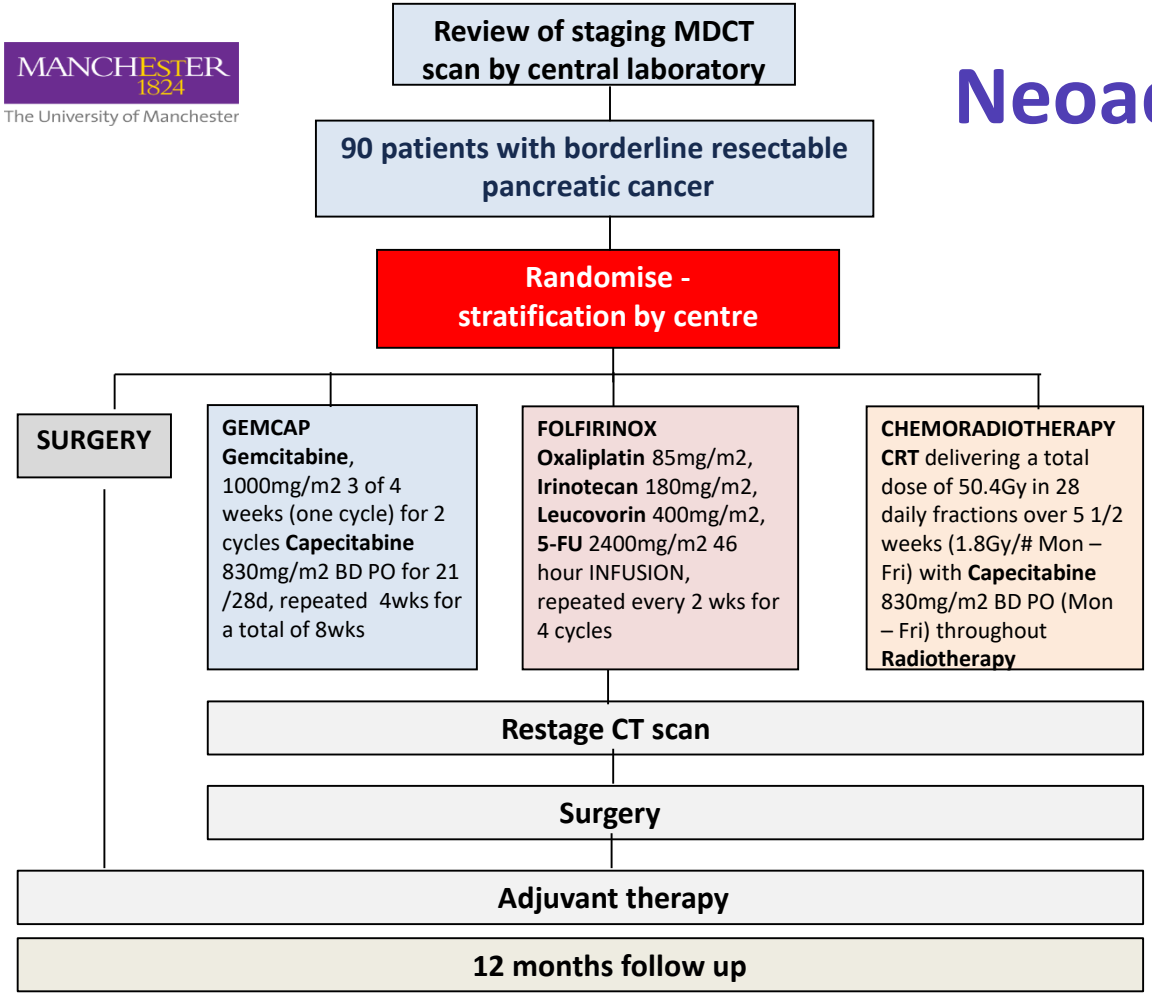
- Median OS (ITT): 16.0 (pre-op CRT) vs 14.3 mo (up-front surgery)(HR 0.78; 95%CI 0.58 to 1.05; p=0.096)

Secondary endpoints – pre-op CRT:

- Improved R0 resection rate 71% (51 of 72) vs 40% (37 of 92) (p<0.001)
- Improved disease-free survival: 8.1 vs 7.7 mo; HR 0.73 (95%CI 0.55 to 0.96); p=0.0320
- Had lower rates of pathologic lymph nodes, perineural invasion, and venous invasion.
- The proportion of patients who suffered serious adverse events was 52% versus 41% (p=0.096).

Versteijne et al J Clin Oncol 2020;38:1763-1773

Neoadjuvant | ESPAC-5F



Primary

1. Recruitment rate
2. Resection rate (R1 + R0)

Secondary

1. R0 resection margin rate
2. Toxicity
3. Overall survival
4. Post operative complication rate
5. Post operative mortality rate
6. Response rate
7. Disease free survival rate
8. Local disease free survival rate
9. Quality of life

- Two patients excluded from the Full Analysis Set (one Immediate surgery, one CRT)
- Some data cleaning ongoing

Ghaneh et al ASCO 2020 abstr 4505

Neoadjuvant | ESPAC-5F study

Primary endpoint (R0+R1)

Resection rate:

Immediate Surgery

- 62% (95%CI 44% - 79%)

Neoadjuvant treatment

- 55% (95%CI 41% - 69%)

P=0.668

Secondary endpoint (R0)

Resection rate:

Immediate Surgery

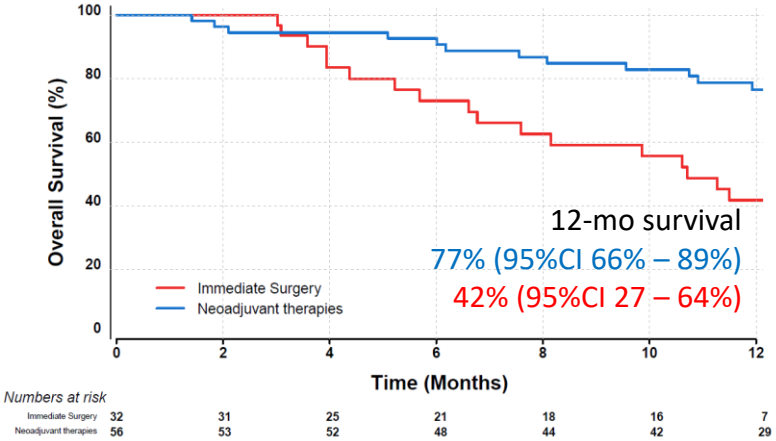
- 15% (95%CI 3% - 38%)

Neoadjuvant treatment

- 23% (95%CI 10% - 41%)

P=0.721

Secondary endpoint (OS)



HR = 0.28 [95%CI, 0.14 – 0.57]

χ^2 (1) = 13.77, *P*<0.001

Ghaneh et al ASCO 2020 abstr 4505

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Neoadjuvant | consistent findings

Study	N	Phase	Stage	Treatment	OS Hazard ratio
PREOPANC[1]	246	3	Resectable / borderline	Gem/XRT	0.78
ESPAC-5F[2]	88	2	Borderline	FOLFIRINOX/GemCap/CRT	0.28
Prep-02/JSAP05[3]	364	2/3	Resectable	Gem + S1	0.72

All in favour of up-front systemic therapy

[1]Versteijne et al J Clin Oncol 2020;38:1763-1773; [2]Ghaneh et al ASCO 2020 abstr 4505; [3]Unno et al ASCO-GI 2019 abstr189

Neoadjuvant | much more data to come

Major Ongoing Studies

- Perioperative versus adjuvant
  - NEOPAC[a], NEPAFOX[b], NEONAX[c], PACT-15[d]
- Perioperative FOLFIRINOX vs adjuvant FOLFIRIONX
  - ALLIANCE[e]
- Preoperative FOLFIRINOX vs preop gem/xrt followed by adjuvant gem
  - PREOPANC-2[f]
- Role of preop XRT
  - A021501[g], PANDAS-PRODIGE 44[h]

a. Clinicaltrial.gov. NCT01521702; b. Clinicaltrial.gov. NCT02172976; c. Clinicaltrial.gov. NCT02047513; d. Clinicaltrial.gov. NCT01150630.
e. Clinicaltrial.gov. pending. f. EudraCT number 2017-002036-17; g. Clinicaltrial.gov. NCT02839343. h. Clinicaltrial.gov. NCT02676349;

Presented by Dr Philip – ESMO GI congress 2020

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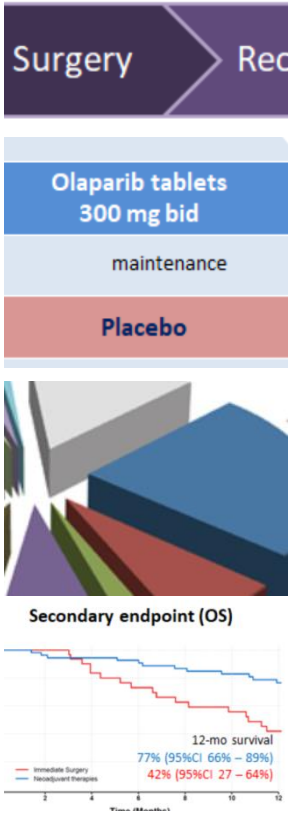
Summary



- Pancreatic cancer remains an area of unmet need
- Adjuvant chemotherapy reduces risk of recurrence and death – scope to improve starting and completing chemotherapy
- The principle of molecular subgroups has been established (germline BRCA)
- DNA damage repair as a broader group under active investigation (e.g. Precision Panc)
- Other molecular subgroups also under investigation
- Survival outcomes of surgery after induction systemic therapy are promising with many studies ongoing