Adjuvant therapy in pancreatic cancer
Monotherapy for whom ?

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Efficacy Parameters in adjuvant mono-chemotherapy

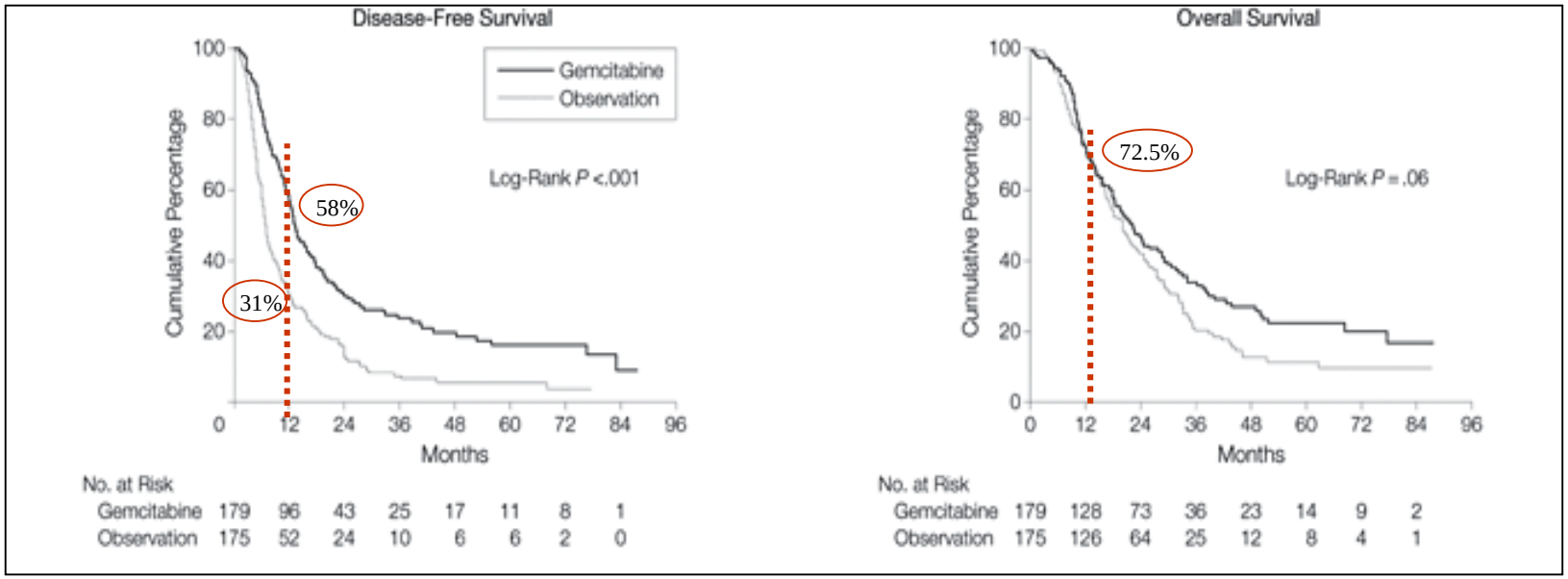
Randomized studies in resectable PDAC

	Regimen	DFS	HR (p)	OS	HR (p)	5-yr-OS
ESPAC-1	No chemo 5-FU	9.4 15.3	(p=0.02)	15.5 **20.1**	0.71 (p=0.009)	8% **21%**
CONKO-001	Observation Gem	6.9 13.4	(p<0.001)	20.2 **22.1**	(0.06)	10.4% **20.7%**
ESPAC-3	5-FU Gem	14.1 14.3	ns	23.0 **23.6**	0.96 ns	15.9% **17.5%**
JASPAC	Gem **S1**	11.3 **22.9**	0.60 (<0.001)	25.5 **46.5**	0.57 (p<0.0001)	24.4% **44.1%**

BEFORE ASCO 2018 : STANDARD STATEMENTS

- GEM=5FU 6 months EU/US long-term benefit :☺
- S1 >> GEM 6 months Japan DFS/5y OS ! ☺☺? West?
- GEM/cape (>) GEM 6 months DFS☹ OS ☺☹ →additional option >new SOC + more side effects
- GEM/erlotinib : failed
- Toxicity/tolerance: good tolerance profile for S1 (< 5% gr ¾)☺
  5FU/LV bolus :stomatitis/diarrhea
- GEM: hematologic tox
- JAMA 2010-Lancet 2016-Lancet 2017

→Before ASCO ,Surgery + adjuvant mono-chemo was the « usual » standard but..



- 20% survival at 5 y and 10% at 10 y
- 25% of pts died within first year
- 50% of pts recurred within first year
- 30-40% did not complete adjuvant chemo

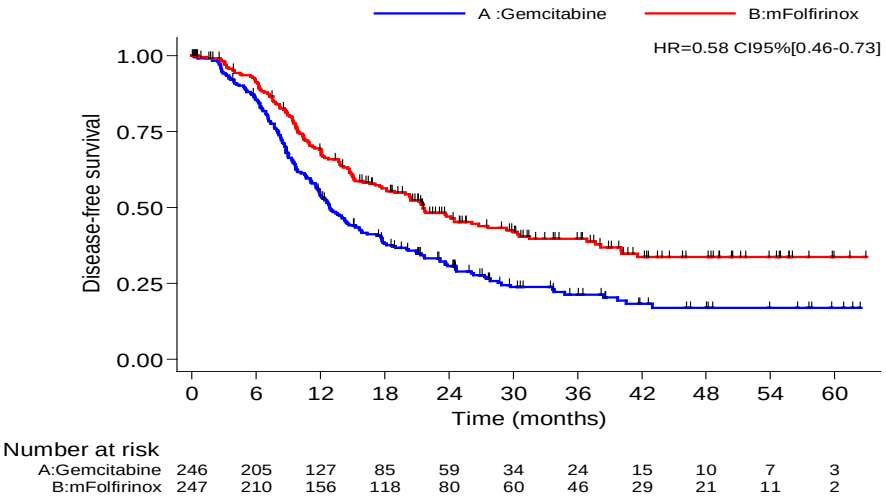
Oettle, H. et al. JAMA 2007,JAMA 2013

KEY ONGOING PHASE III ADJUVANT PC TRIALS

Trial	Estimated Enrollment	Experimental Arm	Comparator Arm	Primary Endpoint
ITALIAN	310	FOLFOXIRI	Gem	DFS
PACT-15 (NCT01150630)[2]	370[a]	Adj PEXG ± neoadj PEXG	Gem	OS
NCT01072981[2]	722	Gem ± CRT + algenpantucel-L immunotherapy	Gem ± CRT	OS
PRODIGE 24/ ACCORD 24 (NCT01526135)[2]	490	mFOLFIRINOX	Gem	DFS
RTOG 0848, first rand RTOG 0848, second rand (NCT01013649)[2]	950	Gem + Erl	Gem	OS
		Gem ±Erl	Gem ±Erl + CRT	OS
APACT (NCT01964430)[2]	800	*nab*-P + Gem	Gem	DFS

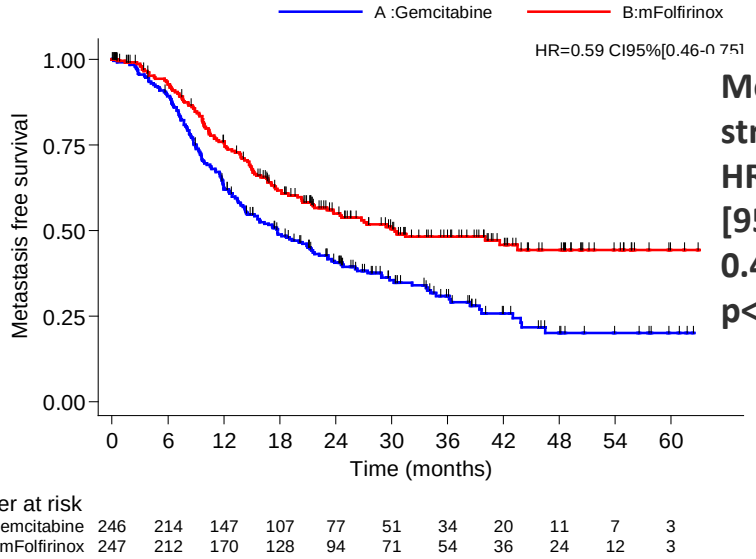
DFS as end point
Post op CA 19.9 > 150 excluded!
Strict and planned follow-up mandatory

AFTER ASCO 2018 : FOLFIRINOX IS THE WINNER BY KO



DFS
stratified HR=0.58 [95%CI: 0.46-0.73],
p<0.0001

DFS
Metastatic-free survival
OS
Specific survival

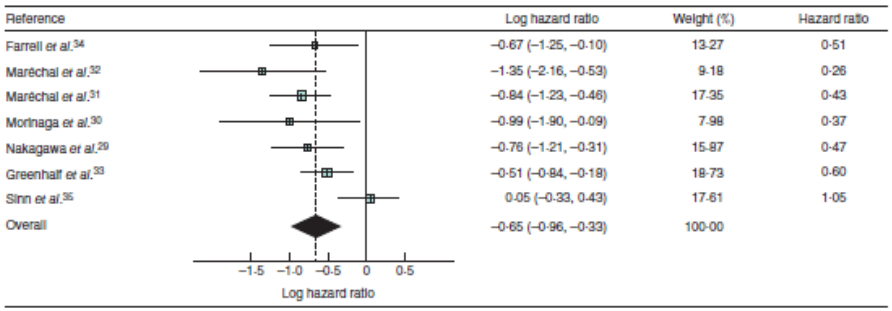


Meta-free S
stratified HR=0.59, [95%CI: 0.46-0.75], p<0.0001

Conroy, ASCO 2018

EFFICACY BENEFIT OF ADJUVANT THERAPY OVER TIME

Trial	Therapy		DFS(PFS/RFS) (months)	5 yr survival (%)	mOS (months)
ESPAC - 1/CONKO	Surgery		6.9-9.4	10%	15-20
ESPAC 1+3	5FU/LV=G		14-15	17%	20-23
CONKO	GEM		13.4	20%	22.8
ESPAC 4	GEM/cape		13.9	28%	28
JASPAC	S1		23	44% 59% at 3	46.5
PRODIGE 24	mFolfirinox		21.6	NA 63% at 3y	54.4
	GEM		13	NA 48% at 3y	35
hENT1 data with GEM*	GEM (retro)				50 (high) 24 (low)
« «	ESPAC 3				26 (high) 17 (low)



- *Maréchal, Gastroenterology 2012
- *Bird, BJS 2017
- *Greenhalf, JNCI 2014

GEM BENEFIT OVER TIME IS INCREASING BUT ONLY FOR OS!

STUDY		DFS	mOS(months)	5Y OS (%)
CONKO 001		13.4	22.8	21%
ESPAC 3		14	23.6	17.5%
ESPAC 4		14	25	28%
JASPAC		11.3	25.5	24.4%
PRODIGE 24		13	35	NA 48% at 3Y
hENT1 based		24	26-50	NA

Better selection of pts?

Improved surgery?

More adapted chemo

More active chemo at recurrence

INCLUSION/SELECTION CRITERIA FOR MFOLFIRINOX IN PRODIGE 24

- PS 0-1
- Age <80 (threshold for folfirinox?)
- No heart coronary disease/failure
- No severe comorbidities
- Post op recovery
- No IBD-post op diarrhea or subocclusion

- Tolerance – treatment exposure/completion

SIX-MONTH TREATMENT COMPLETION IN PRODIGE 24

	mFolfirinox No = 238	Gemcitabine No = 243	P
All cycles of chemotherapy	**66.4%**	**79.0%**	**0.002**
Planned administrations	**12**	**18**	–
Median No. administrations	**12** [1-12]	**18** [1-18]	
No. administrations delayed	**14.4%**	**3.9%**	**< 0.001**
Relative dose-intensity > 0.70	**48.7%**	**91.4%**	**< 0.001**
Early stop	**80** (33.6%)	**51** (21.0%)	**0.002**
due to :			
- **relapse**	**15** (6.3%)	**26** (10.7%)	
- **toxicity**	**21** (8.8%)	**11** (4.5%)	
- **Principal Investigator's decision**	**7** (2.9%)	**2** (0.8%)	
- **patient decision**	**13** (5.4%)	**2** (0.8%)	

TOLERANCE PROFILE IN PRODIGE 24

Grade 3-4 tox	mFolfirinox	GEM	P-value
diarrhea	18.6% (12.7%)*	3.7% (1.2%)*	<0.001
fatigue	11% (23%)*	4.6% (14.2%)*	0.003
vomiting	5%	1.2%	<0.001
neuropathy	9.3%	0%	<0.001
mucositis	2.5%	0%	<0.001
Febrile neutropenia	2.9% (5.4%)*	3.7% (1.2%)*	0.65
thrombopenia	1.3%	4.5%	0.03

- *Data from mPDAC trial with original Folfirinox (Conroy et al, NEJM 2011)
- Grade 3-4 diarrhea is significantly related to a higher number of lymph nodes examined!
- mFolfirinox=no bolus of 5FU, CPT11=150 mg/m2
- Use of G-CSF in 60 % in the mFolfirinox arm

From: **Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer ResectionA Randomized Controlled Trial**

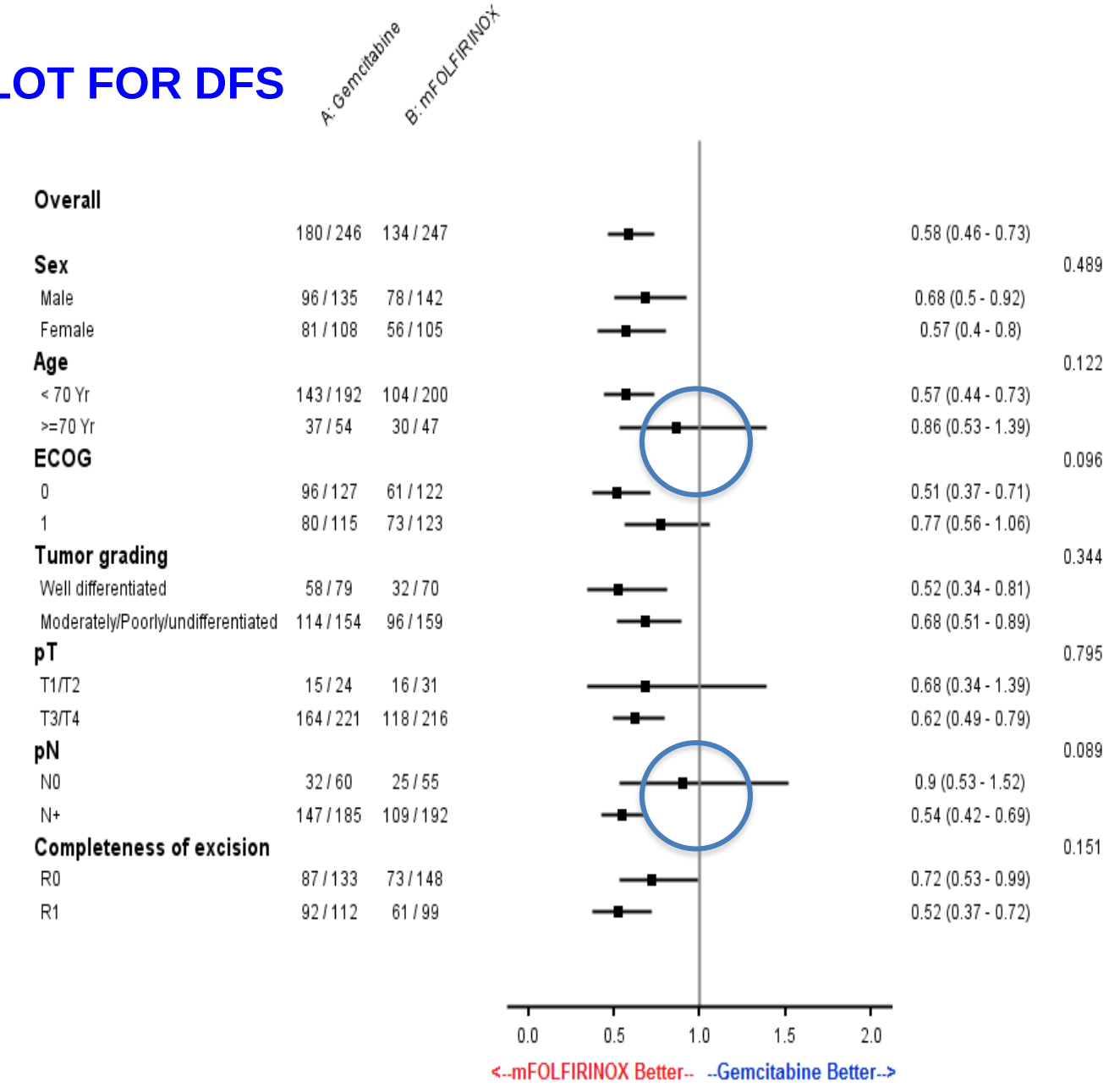
JAMA. 2010;304(10):1073-1081. doi:10.1001/jama.2010.1275

Table 2. Reported Toxicity

Toxicity Variable	Reported NCI CTC Version 2 Toxicity[a]				
	Fluorouracil + Folinic Acid (n = 551)		Gemcitabine (n = 537)		
	Grade 1/2, No.	Grade 3/4, No. (%)	Grade 1/2, No.	Grade 3/4, No. (%)	*P* Value[b]
WBC count	154	32 (6)	262	53 (10)	.01
Neutrophils	180	121 (22)	270	119 (22)	.94
Platelets	57	0	170	8 (1.5)	.003
Nausea	292	19 (3.5)	282	13 (2.5)	.37
Vomiting	159	17 (3)	131	11 (2)	.34
Stomatitis	304	54 (10)	96	1 (0)	<.001
Alopecia	189	1 (0)	135	1 (0)	>.99
Tiredness	340	45 (8)	351	32 (6)	.16
Diarrhea	333	72 (13)	194	12 (2)	<.001
Other	262	67 (12)	290	43 (8)	.03

Abbreviations: CTC, Common Terminology Criteria; NCI, National Cancer Institute; WBC, white blood cell.
[a] Toxicity grades defined per CTC Version 2.0.[22]
[b] From Fisher exact test with significance level set to $P < .005$ and with Bonferroni adjustment to account for multiple testing.

FOREST PLOT FOR DFS

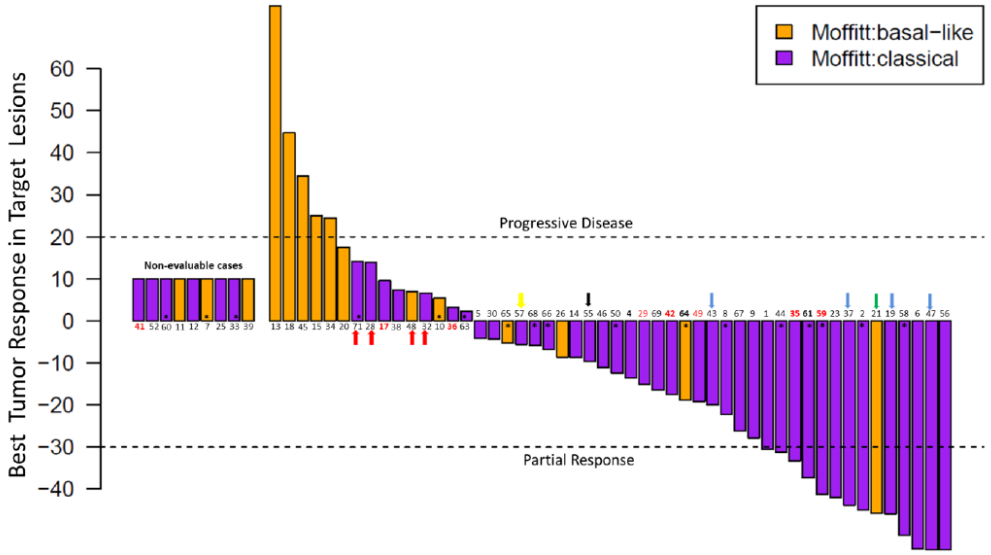


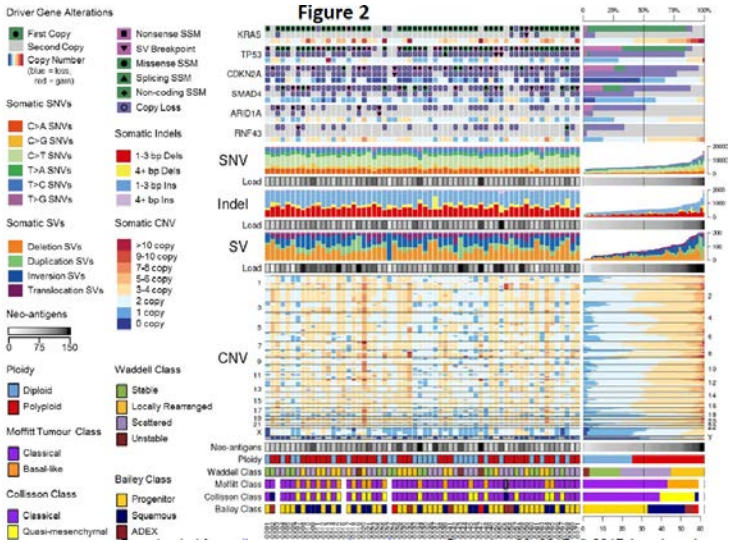
The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

INDICATION/SELECTION OF REGIMEN

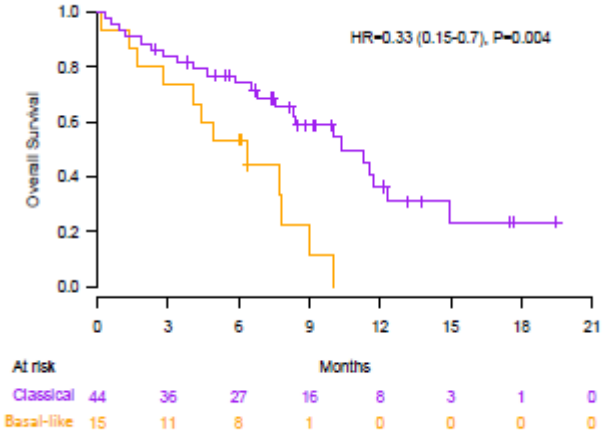
- Patient
  - PS (<>1- age (70?) – nutritional status - postop recovery
  - Comorbidities (coronary heart disease)-bowel disorders
  - Personal choice -convenience
- Setting
  - Neoadjuvant therapy or not (+/- RT)- long sequence
  - Neoadjuvant therapy efficace or not (ypTNM,TRG?)→perioperative
- Tumour
  - High risk of recurrence (grade-N1-R1)
  - Persistant elevated CA 19.9?
  - Ct DNA ?
- Molecular
  - Fluoropyrimidines biomarkers
  - GEM biomarkers/signature
  - Folfirinox signature ..? Classical vs basal-like molecular profile

CLINICAL APPLICATION OF GENOMICS



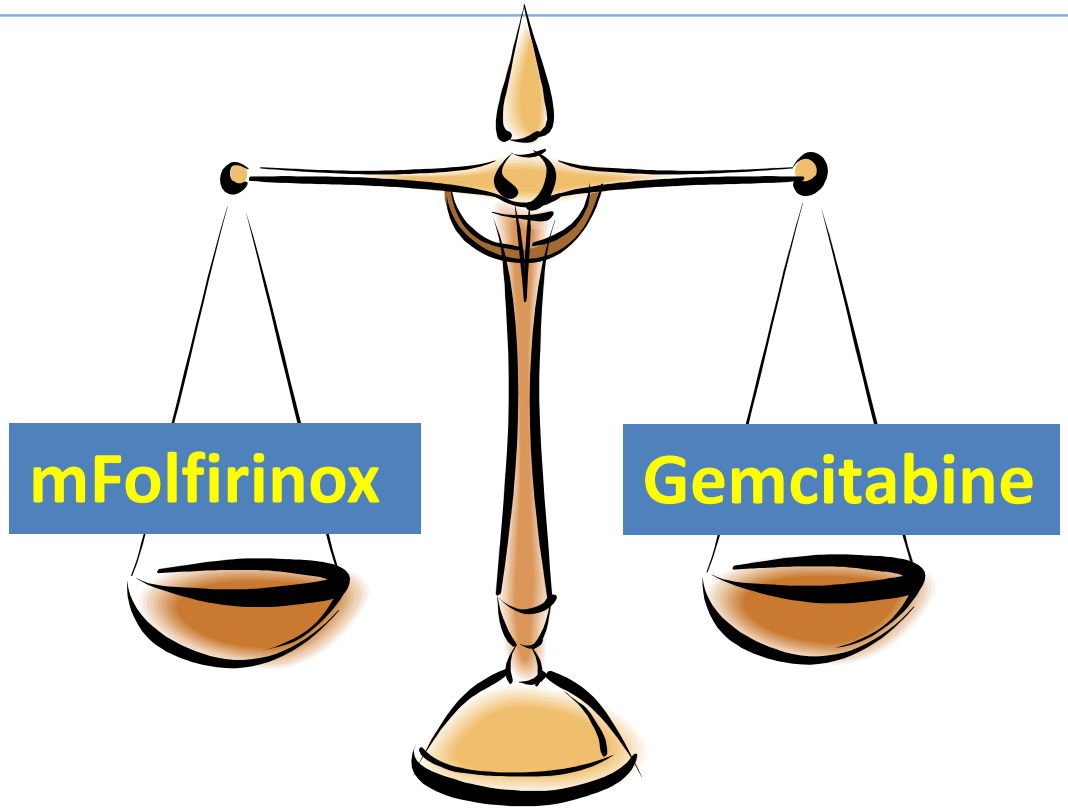


Response to chemo
Mainly Folfirinox



Aung KL, CCR 2017

HOW TO CHOOSE?



Efficacy even reduced
Tolerance manageable
Fit pts after surgery

Lesser survival benefit
Better tolerance (convenience)
Lesser fit pts (> 70,PS1-2, diarrhea)
“Lower” risk (N0)?

Genomics?

MY CONCLUSIONS

- mFOLFIRINOX is the new SOC unless contraindic

- Gemcitabine (or fluoropyrimidines) remains a valuable option for less fit patients (after surgery !) with proven long term benefit over surgery alone- S1 in western?

- Adjuvant approach deserves future molecular studies for using these drugs (mono vs polychemo) based on gene signature and precision medecine