



SISTEMA SANITARIO REGIONALE

AZIENDA OSPEDALIERA
SAN CAMILLO FORLANINI

Roma, 02.12. dicembre 2019



Tumori Gastro Intestinali

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Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

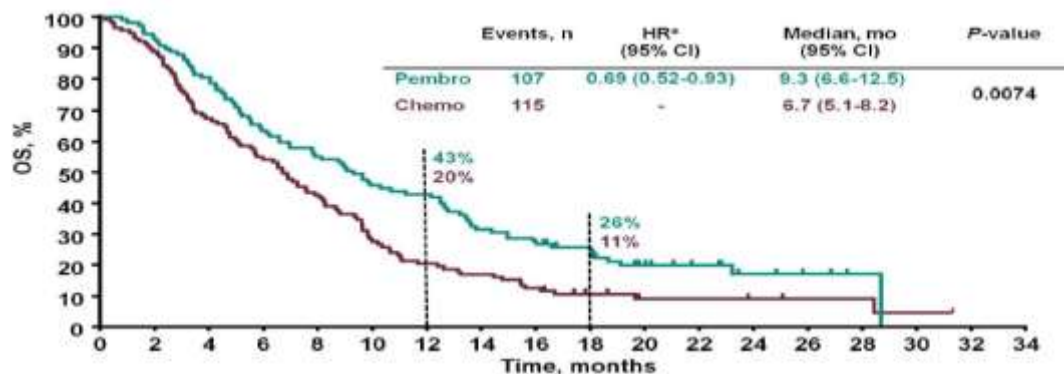
- Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco
- Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	Company/Organization
Meeting sponsorship, Board	Merck, Servier
Board	MSD
Meeting Organization	ROCHE

Truly "Practice Changing" Studies

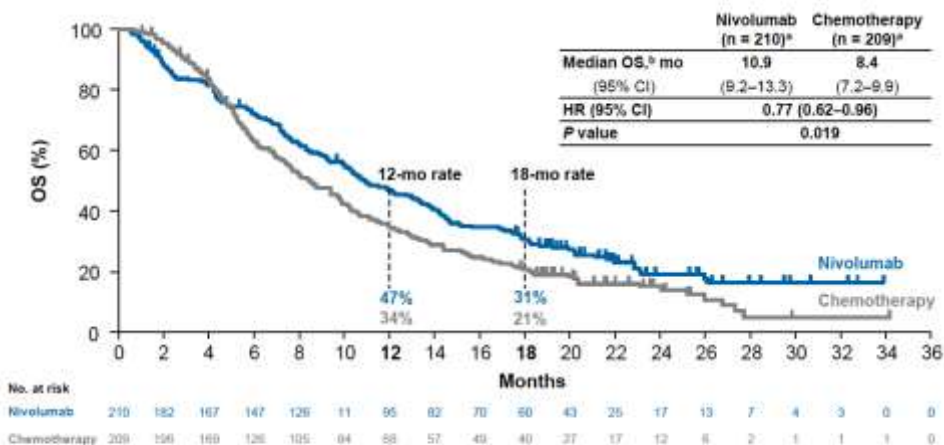
- Addressing unmet needs
- Study design that compare experimental arm to a "standard" practice
- Positive outcomes that are clinical meaningful
- Reproducive results
- *Practices accessible to the community*

Esophageal Cancer 2nd line



Kojima et al ASCO GI 2019

PD-L1
CPS ≥ 10 subgroup
n= 222 (35%)
Overall survival



Cho et al, ESMO 2019

- Nivolumab provided superior OS, with a 23% reduction in the risk of death and a 2.5-month improvement in median OS, versus chemotherapy

*Intent-to-treat population; ^bMaximum follow-up: 17.6 months; CI, confidence interval; mo, months.

Treatment paradigm in advanced/ metastatic SCC oesophagus 2019

CHECKMATE 648¹

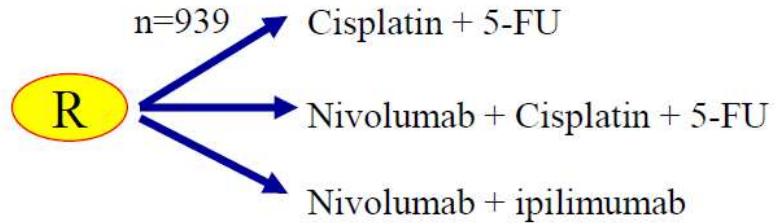
Inoperable/
metastatic/ recurrent
SCC

Platinum + FP- based
chemotherapy

Nivolumab

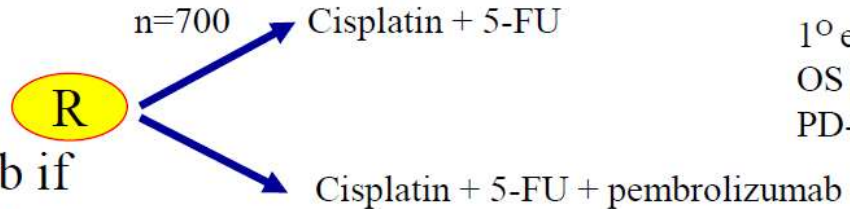
Pembrolizumab if
PD-L1 CPS ≥ 10

Taxanes or irinotecan



1^o endpoint:
OS and PFS in
PD-L1 TPS ≥ 1

KEYNOTE 590²



1^o endpoint:
OS and PFS in
PD-L1 CPS ≥ 10

¹Ajani et al ASCO GI 2019 NCT03143153;

²Kato et al Future Oncol 2019 NCT03189719

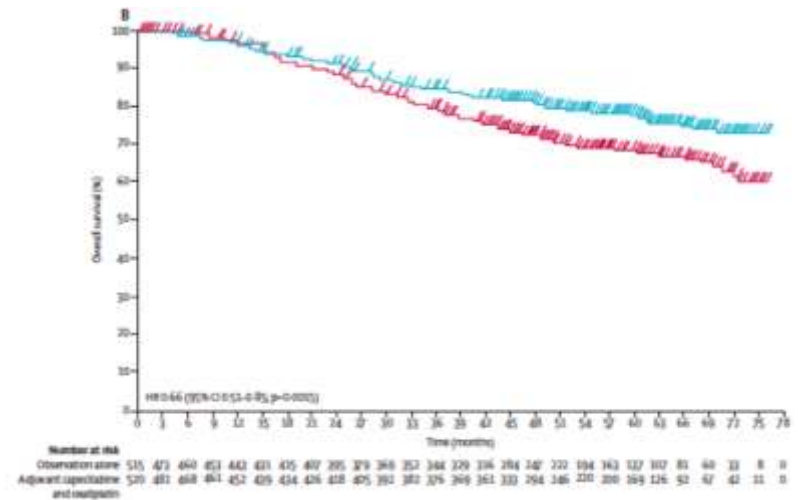
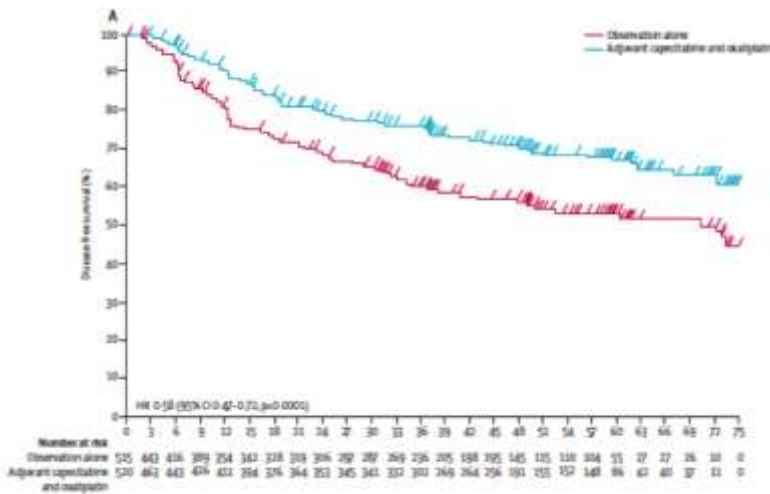
CLASSIC TRIAL

D2 resected,
stage II-IIIB
GC patients

R

Arm A: 8 cycles of XELOX

Arm B: Observation



5-yr OS improved by 9% (78% vs 69%) which corresponds to a NNT of 11.1

Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

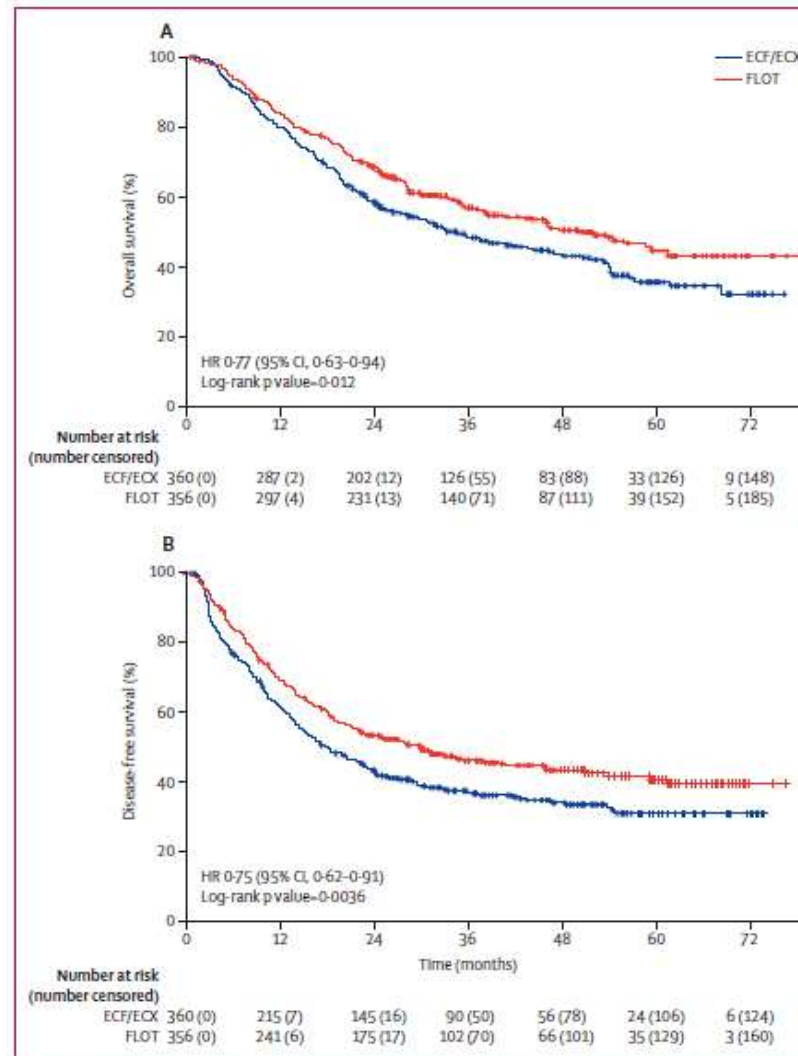
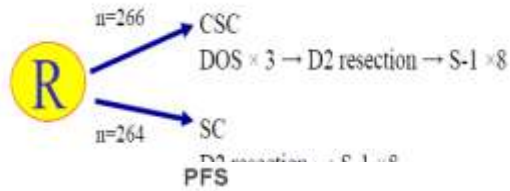


Figure 2: Kaplan-Meier estimates of overall survival (A) and disease-free survival (B)
 (A) Overall survival in the intention-to-treat population in the ECF/ECX group versus the FLOT group.
 (B) Disease-free survival in the intention-to-treat population in the ECF/ECX group versus the FLOT group.
 (ECF/ECX= epirubicin and cisplatin plus either fluorouracil or capecitabine. FLOT= fluorouracil plus leucovorin, oxaliplatin and docetaxel. HR=hazard ratio. CI=confidence interval.

PRODIGY: Randomised phase III study in gastric and GEJ adenocarcinoma of peri-op vs. post-op chemotherapy

Histologically confirmed cT2, 3 / N(+), or cT4N_{any} gastric or GEJ adenocarcinoma

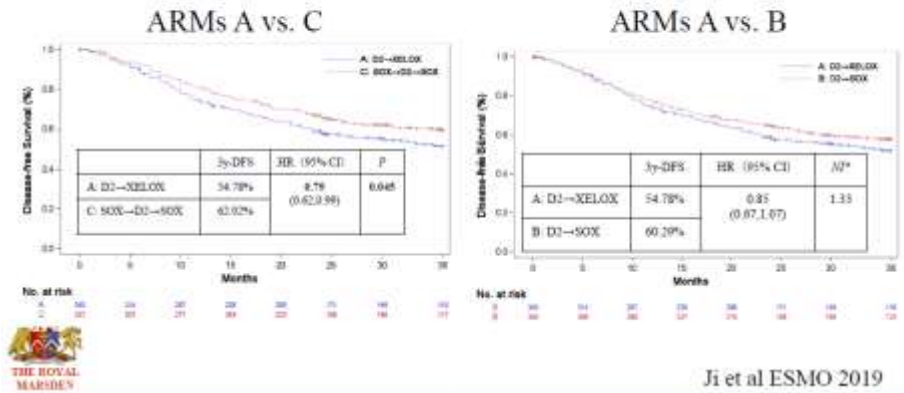


Kang Y-K, et al. Ann Oncol 2019;30(suppl):abstr LBA41



GASTRIC CANCER: WHICH STRATEGY IN OPERABLE DISEASE (In Asia)?

RESOLVE Primary comparisons



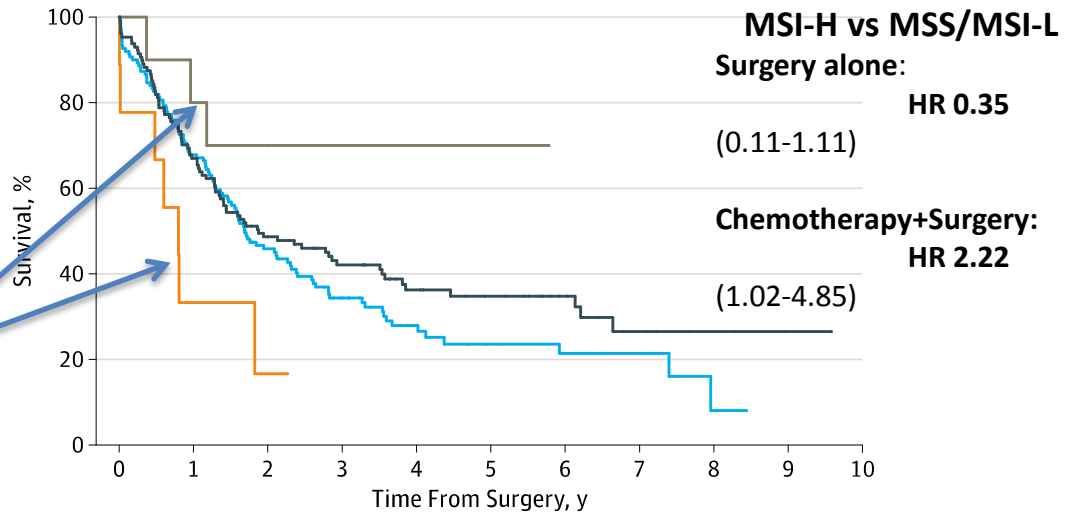
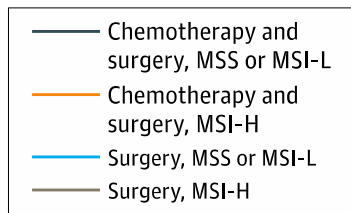
Ji et al ESMO 2019

R0 resection 214 (96.4) 211 (85.8)

Mismatch Repair Deficiency, Microsatellite Instability, and Survival

An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

Elizabeth C. Smyth, MB, BCH, MSc; Andrew Wotherspoon, MD; Clare Peckitt, MSc; David Gonzalez, PhD; Sanna Hulkki-Wilson, BSc, MSc; Zakaria Eltahir, PhD; Matteo Fassan, MD, PhD; Massimo Rugge, MD, FACC; Nicola Valeri, MD, PhD; Alicia Okines, MD; Madeleine Hewish, MD, PhD; William Allum, MD; Sally Stenning, MSc; Matthew Nankivell, MSc; Ruth Langley, MD, PhD; David Cunningham, MD, FMedSci



Patients with MSI-H may not benefit or may have a detrimental effect !!

No. at risk

Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1
Chemotherapy and surgery, MSI-positive patients	9	3	1							
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	
Surgery, MSI-positive patients	10	8	6	3	1	1				

MSI-GC-01: Individual patient data meta-analysis of microsatellite instability (MSI) and gastric cancer from four randomized clinical trials.

Pietrantonio et al, ASCO 2019

- Data from MAGIC, CLASSIC, ITACA-S, ARTIST (1552 patients)

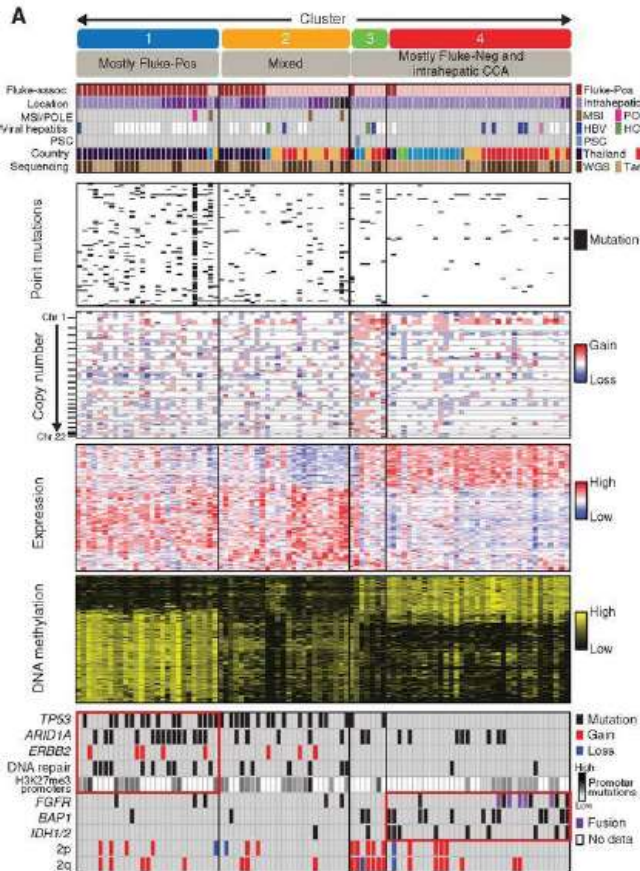
4 RCT

MAGIC + CLASSIC

**Perioperative or adjuvant chemotherapy may not be helpful for pts with MSI-H GC
Immune checkpoint blockade should be prospectively investigated in this population.**

	5y-OS %	HR (95% CI)	Interaction test		5y-OS %	HR (95% CI)	Interaction test
MSS: Chemo vs surgery	62 vs 53	0.73 (0.61-0.86)			62 vs 53	0.71 (0.58-0.88)	
MSI: Chemo vs surgery	75 vs 83	1.49 (0.56-3.96)	0.141		63 vs 83	2.46 (0.84-7.2)	0.027

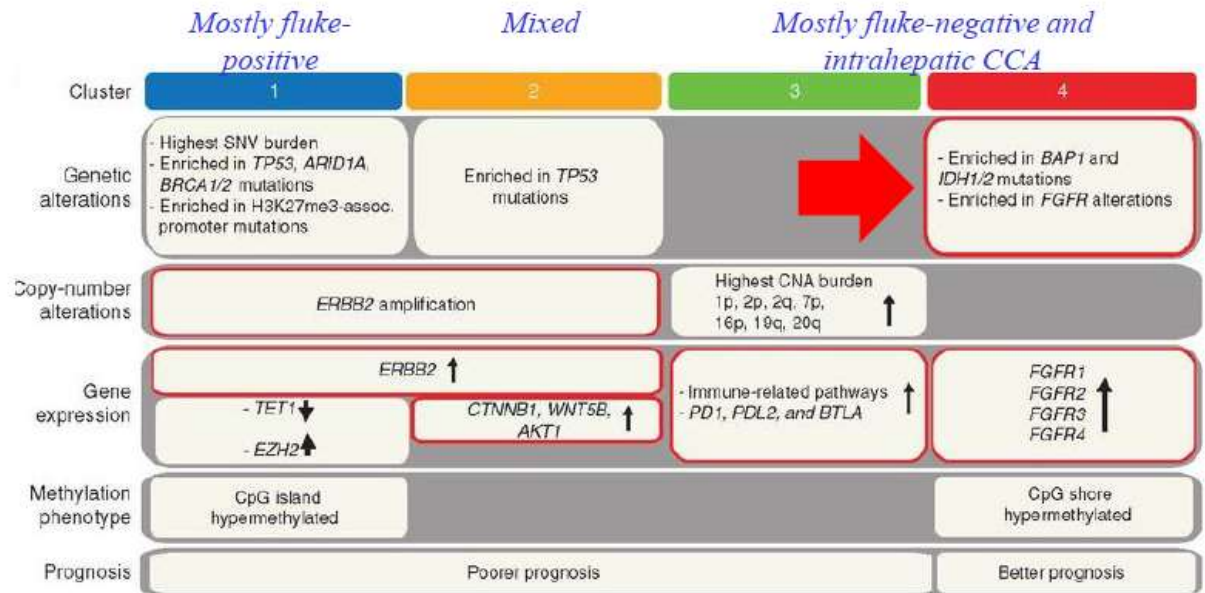
Molecular Classification of Cholangiocarcinoma



Liver Flukes:

Clonorchis sinensis – China, Korea, Vietnam

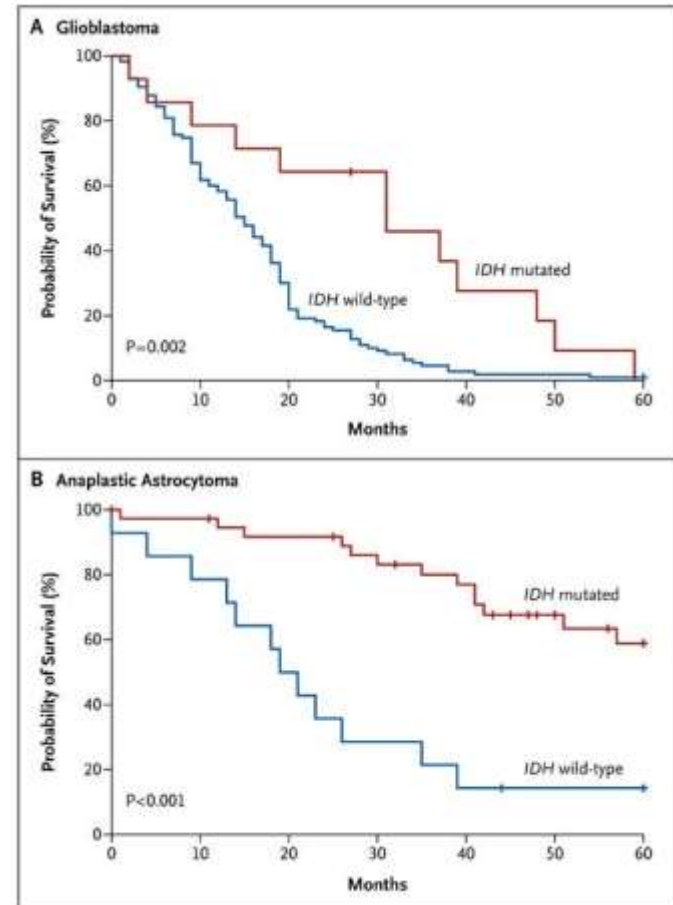
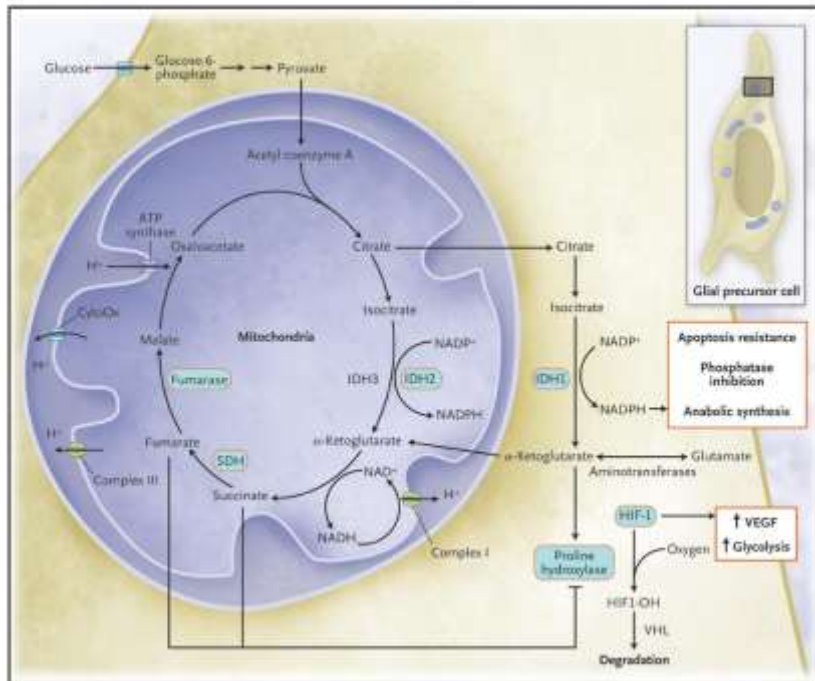
Opisthorchis viverrini: Thailand, Cambodia, Laos



Jusakul et al Cancer Discov 2017

Survival of Adult Patients with Malignant Gliomas with or without *IDH* Gene Mutations.

The Roles of IDH1, IDH2, Succinate Dehydrogenase, and Fumarase in Cellular Metabolism.



FGF/FGFR signaling pathway plays a central role in multiple cellular processes

23 ligands (FGF1-23)

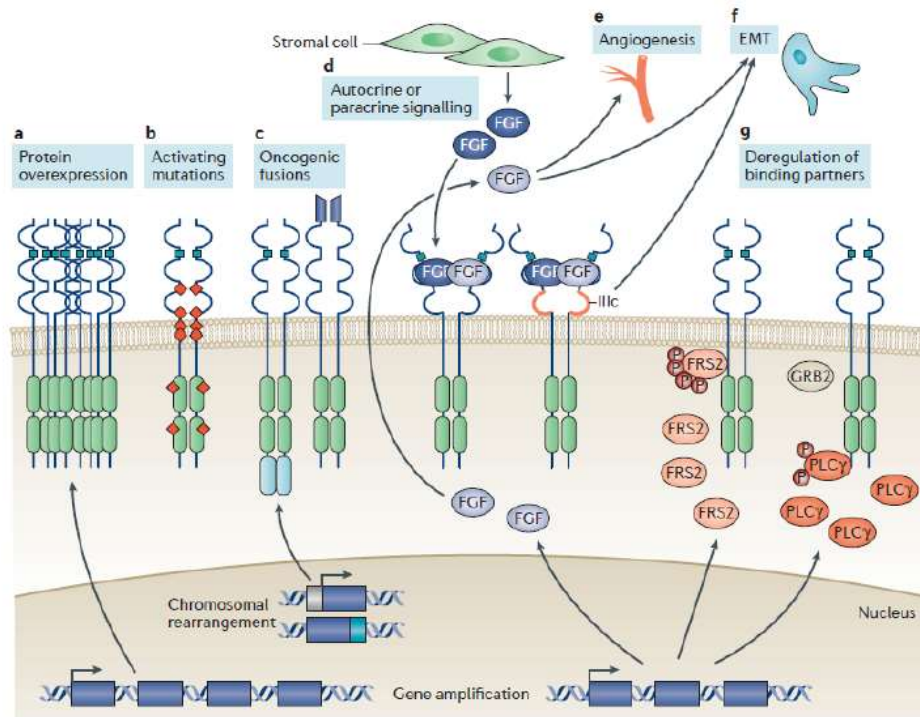
4 FGFR family members

- FGFR1, FGFR2, FGFR3, and FGFR4

FGFR signaling stimulates proliferation, cell migration, angiogenesis

Different FGFR alterations lead to constitutive signalling:

- Gene amplification
- Activating mutations
- Protein overexpression
- Fusions/rearrangements



Targeted therapy in molecularly-altered advanced cholangiocarcinoma

	Ivosidenib ¹	Infigratinib ²	Pemigatinib ³	Dabrafenib + Tremetinib ⁴
N	124	71	107	35
Target	IDH	FGFR	FGFR	BRAF
ORR	2%	25.4%	35.5%	36%
DCR	53%	83.6%	82%	75%
mPFS	2.7 months	6.8 months	6.9 months	9.2 mmonths
mOS	10.8 months	12.5 months	21.1 months	11.7 months

¹Abou-Alfa et al ESMO 2019; ²Javle et al ESMO 2018

³Vogel et al ESMO 2019; ⁴Wainberg et al ASCO GI 2019

Epatocarcinoma: ESMO clinical Practice Guidelines for diagnosis, treatment and Follow up

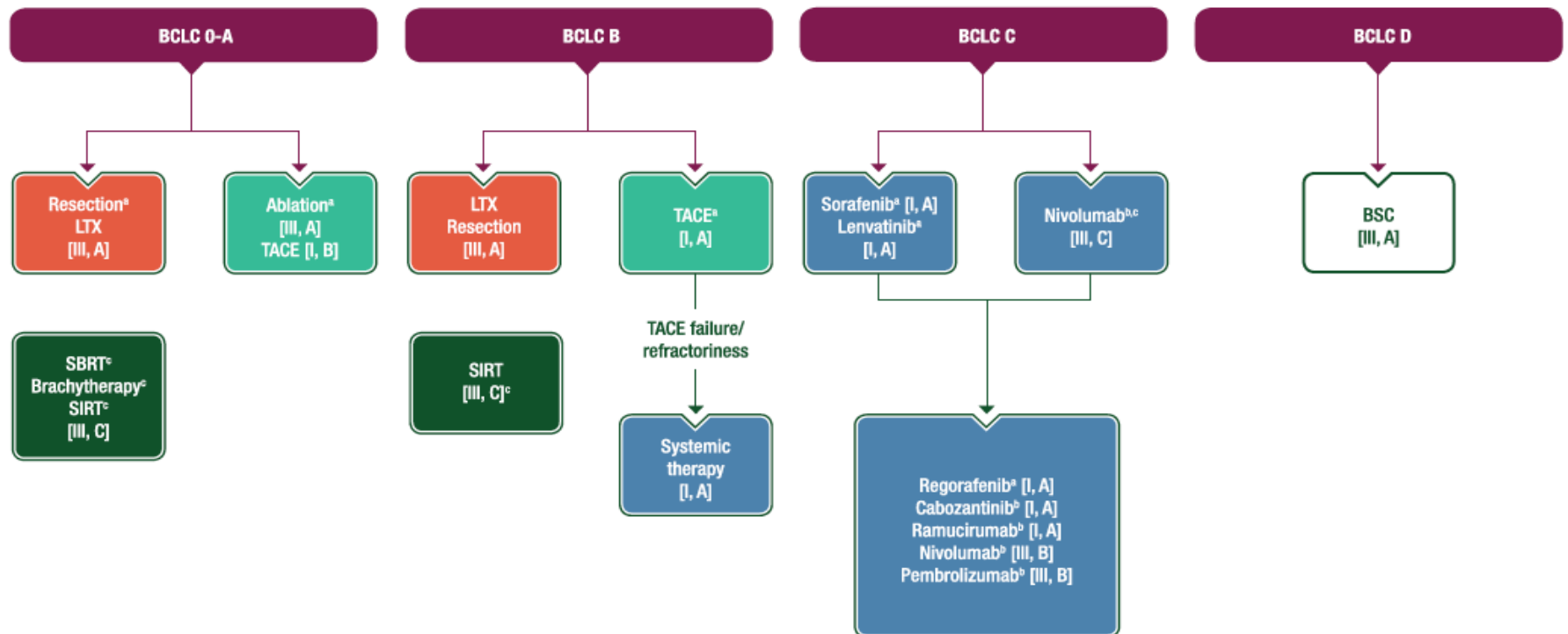


Figure 1. HCC treatment options depending on BCLC stage.

^aSee Table 4 for indication constraints based on tumour burden and liver function.

^bNot EMA-approved as of August 2018.

BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; LTX, liver transplantation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation.

HCC

LBA38_PR: CheckMate 459: A randomized, multi-center phase 3 study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC) – Yau T, et al

Study objective

- To investigate the efficacy and safety of nivolumab compared with sorafenib as a 1L treatment for patients with advanced HCC

Key patient inclusion criteria

- Advanced HCC
 - Ineligible for surgery and/or loco-regional therapy or PD after surgery and/or loco-regional therapy
 - Child-Pugh class A
 - Systemic therapy naïve
 - ECOG PS 0-1
- (n=743)



Stratification

- Aetiology (HCV vs. non-HCV)
- Vascular invasion and/or extrahepatic spread (present vs. absent)
- Geography (Asia vs. non-Asia)

PRIMARY ENDPOINT

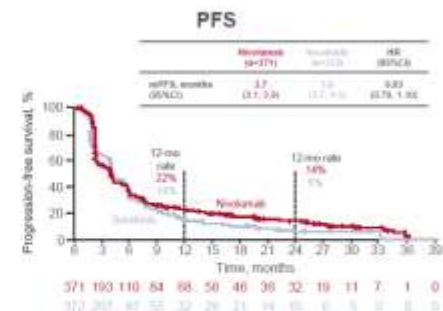
- OS

SECONDARY ENDPOINTS

- ORR, PFS, efficacy by PD-L1 status, safety

Yau T, et al. Ann Oncol 2019;30(suppl):abstr LBA38_PR

Key results



Yau T, et al. Ann Oncol 2019;30(suppl):abstr LBA38_PR

In patients with advanced HCC, 1L nivolumab did not provide a significant improvement in OS compared with sorafenib although had a manageable safety profile

LBA39: Randomised efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC) – Lee M, et al

Study objective

- To investigate the efficacy and safety of atezolizumab + bevacizumab as a 1L treatment in patients with unresectable HCC

Key patient inclusion criteria

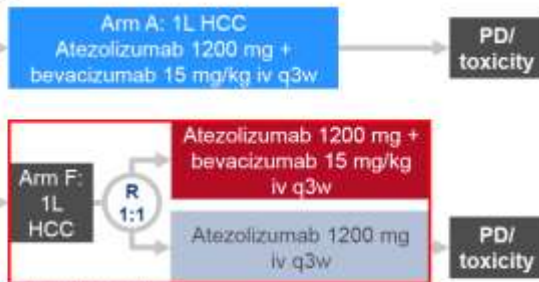
- Advanced HCC
- Child-Pugh up to class B7 for Arm A and class A for Arm F
- Systemic therapy naïve
- ECOG PS 0-1
- (n=743)

Stratification

- AFP level (<400 vs. ≥400 ng/mL)
- Macrovascular invasion and/or extrahepatic spread (present vs. absent)
- Geography (Asia excluding Japan vs. rest of world)

PRIMARY ENDPOINTS

- Arm A: ORR (RECIST v1.1)
- Arm F: PFS (RECIST v1.1)

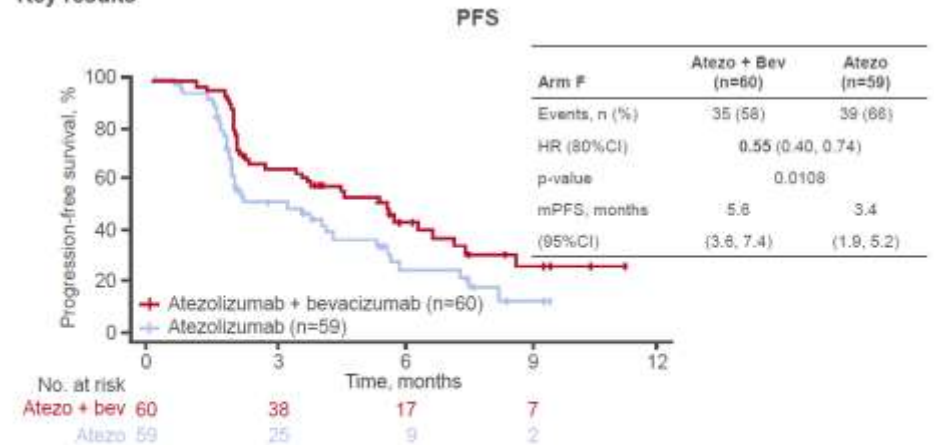


SECONDARY ENDPOINTS

- OS, safety

Lee M, et al. Ann Oncol 2019;30(suppl):abstr LBA39

Key results



Lee M, et al. Ann Oncol 2019;30(suppl):abstr LBA39

NEOLAP – combination chemotherapy in LAPC

What do we know in PC ?

- Pancreatic cancer (PC) is projected to become the second leading cause of cancer-related death world-wide by 2030
 - 4 mill GI cancer - 338,000 PC
- The clinical landscape of pancreatic cancer is currently divided into four subgroups
 - Resectable PC
 - Borderline resectable PC
 - **Locally advanced PC (combination chemotherapy)**
 - Metastatic PC

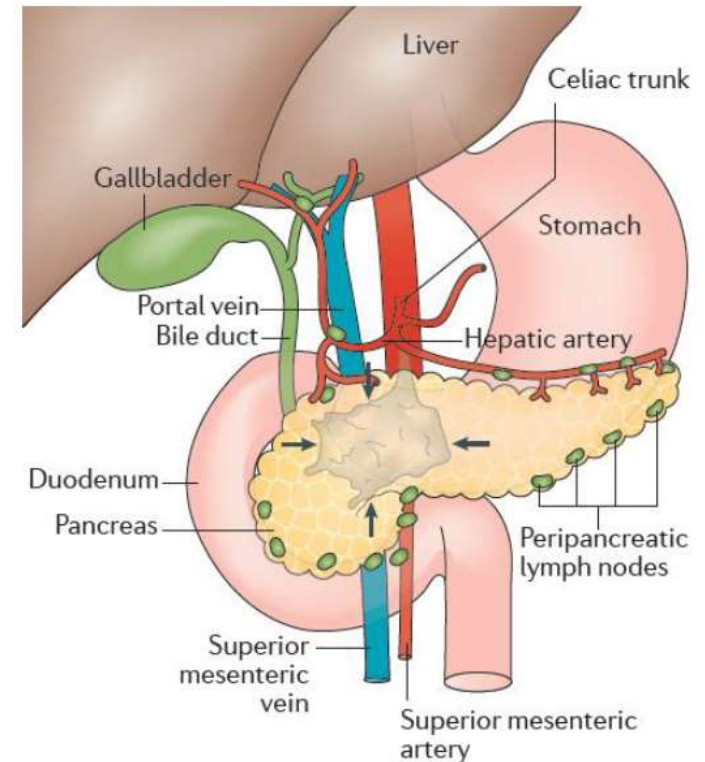




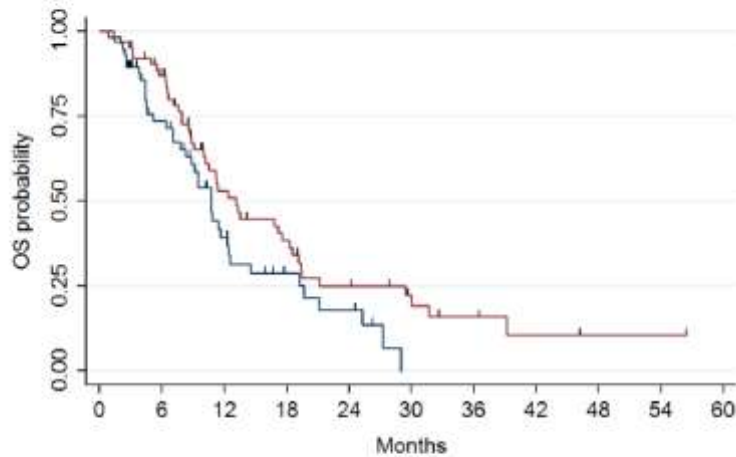
Table 1. Comparison of CT-based criteria distinguishing resectable, borderline resectable, and locally advanced disease

		MD Anderson [8, 15]	AHPBA/SSAT/SSO [19]	NCCN (Version 2.2016) [22]	Alliance [23]
Celiac	Resectable	No involvement	No involvement	No arterial tumor contact	No involvement
	Borderline	No involvement	No involvement	Solid tumor ^a contact $\leq 180^\circ$, or $>180^\circ$ without involvement of the aorta and with intact and uninvolved gastroduodenal artery ^b (body/tail only)	Tumor-vessel interface $< 180^\circ$
	Locally Advanced	Any involvement	Any involvement	$>180^\circ$ solid tumor contact (any portion of pancreas), or any degree of solid tumor contact with aortic involvement (body/tail only)	Tumor-vessel interface $\geq 180^\circ$
SMA	Resectable	No involvement	No involvement	No arterial tumor contact	No involvement
	Borderline	Abutment $\leq 180^\circ$	Abutment $\leq 180^\circ$	Solid tumor contact $\leq 180^\circ$	Tumor-vessel interface $< 180^\circ$
	Locally Advanced	$>180^\circ$ involvement	$>180^\circ$ involvement	$>180^\circ$ solid tumor contact (any portion of pancreas), or any solid tumor contact with the first jejunal branch off SMA (head/uncinate only)	Tumor-vessel interface $\geq 180^\circ$
CHA	Resectable	No involvement	No involvement	No arterial tumor contact	No involvement
	Borderline	Short segment abutment $< 180^\circ$ or encasement $\geq 180^\circ$ amenable to reconstruction	Short segment abutment $< 180^\circ$ or encasement $\geq 180^\circ$ amenable to reconstruction	Solid tumor contact without extension to celiac axis or hepatic bifurcation, allowing for safe/complete reconstruction	Any degree of reconstructible involvement
	Locally Advanced	Involvement not amenable to reconstruction	Involvement not amenable to reconstruction	Any solid tumor contact with extension to celiac axis or hepatic bifurcation	Nonreconstructible involvement
SMV/PV	Resectable	Any involvement without occlusion	No involvement	No tumor contact with the SMV/PV or $\leq 180^\circ$ contact without vein contour irregularity	Tumor-vessel interface $< 180^\circ$, no occlusion
	Borderline	Short segment occlusion only, with patent vein above and below the occlusion amenable to surgical reconstruction	Abutment, encasement, and/or occlusion amenable to surgical reconstruction (any involvement)	Solid tumor contact with the SMV/PV of $> 180^\circ$, contact of $\leq 180^\circ$ with contour irregularity of the vein, or thrombosis of the vein but with suitable vessel proximal and distal to the site allowing for safe and complete reconstruction	Tumor-vessel interface $\geq 180^\circ$ and/or occlusion amenable to surgical reconstruction
	Locally Advanced	Non-reconstructible occlusion	Any non-reconstructible involvement or major venous thrombosis extending for several cm	Unreconstructible SMV/PV due to tumor involvement or occlusion (tumor or bland thrombus) <i>Head/uncinate only:</i> Contact with most proximal draining jejunal branch into SMV	Any non-reconstructible involvement

Criteria TC per definizione BLPC e LAPC

GAP and NEOLAP in locally advanced pancreatic cancer

GAP¹

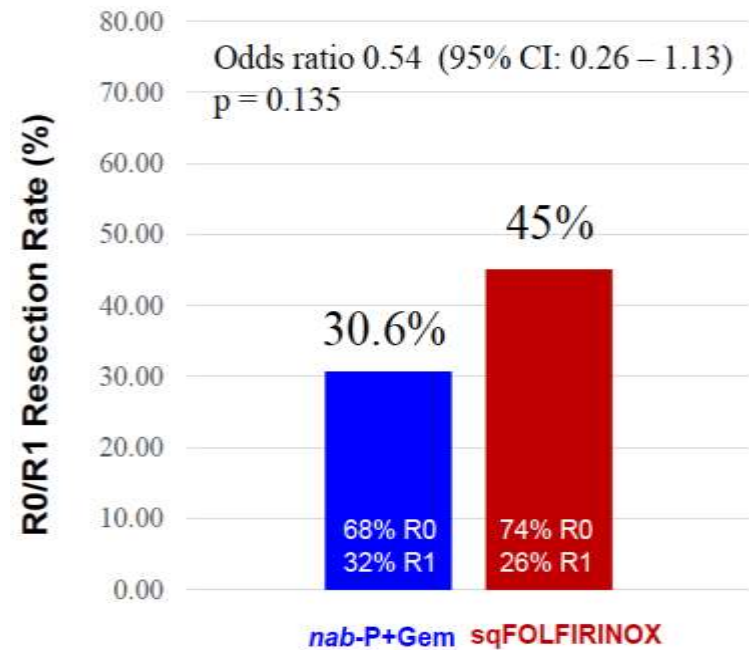


Number at risk		0	6	12	18	24	30	36	42	48	54	60
Gem	57	36	16	8	5	0	0	0	0	0	0	0
Gem/NabP	63	51	26	18	11	7	4	2	1	1	0	0

Arm	Events	Median	95%CI
Gem	39	10.7 months	8.3 – 12.4
Gem/NabP	43	13.1 months	10.0 – 18.3

HR 0.65; 90%CI 0.44-0.94, one-tailed p=0.03

NEOLAP²

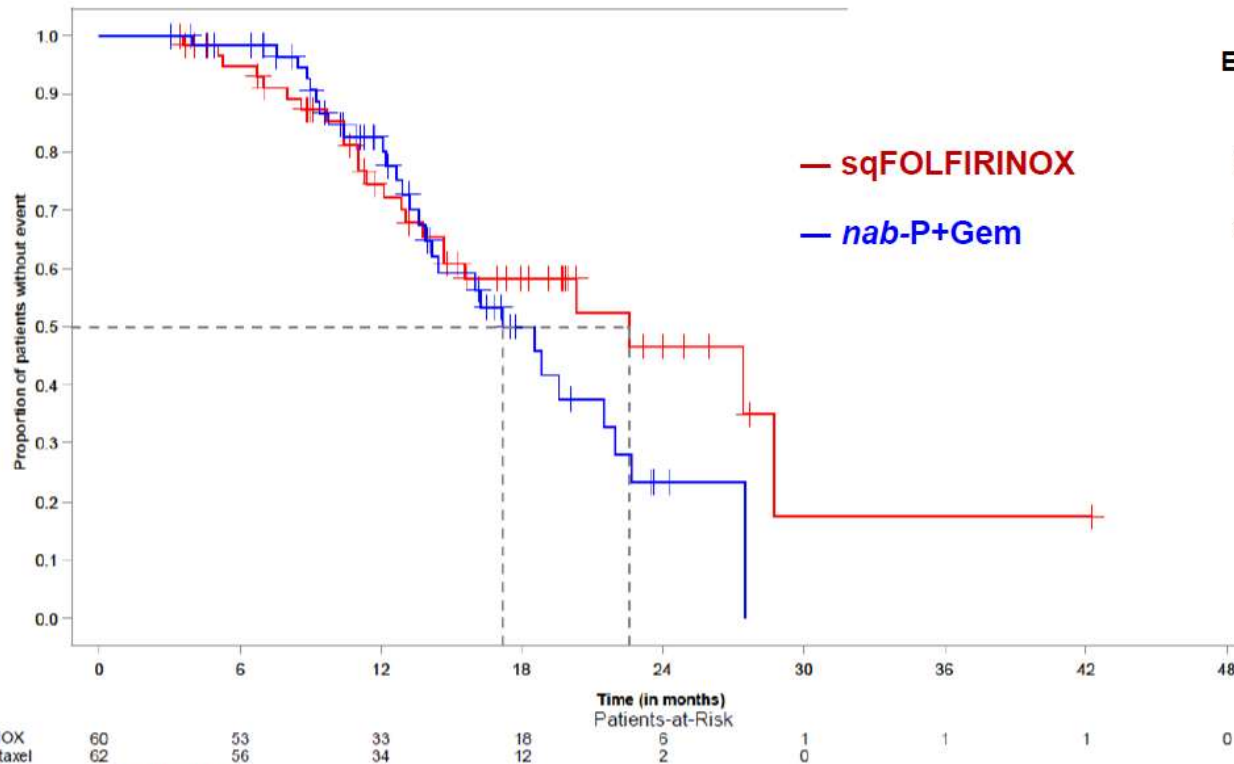


¹Cascinu et al ESMO 2019:
²Kunzmann et al ESMO 2019

GAP and NEOLAP in locally advanced

OVERALL SURVIVAL

AIO



Events/ N	Median (months)	95% CI
24/60	22.5	14.7 – 28.7
28/62	17.2	14.2 – 21.9

HR 0.73 (95% CI: 0.42 – 1.28)
 p (log-rank) = 0.268

Median follow-up: 13.8 months



assessed by local MD 1

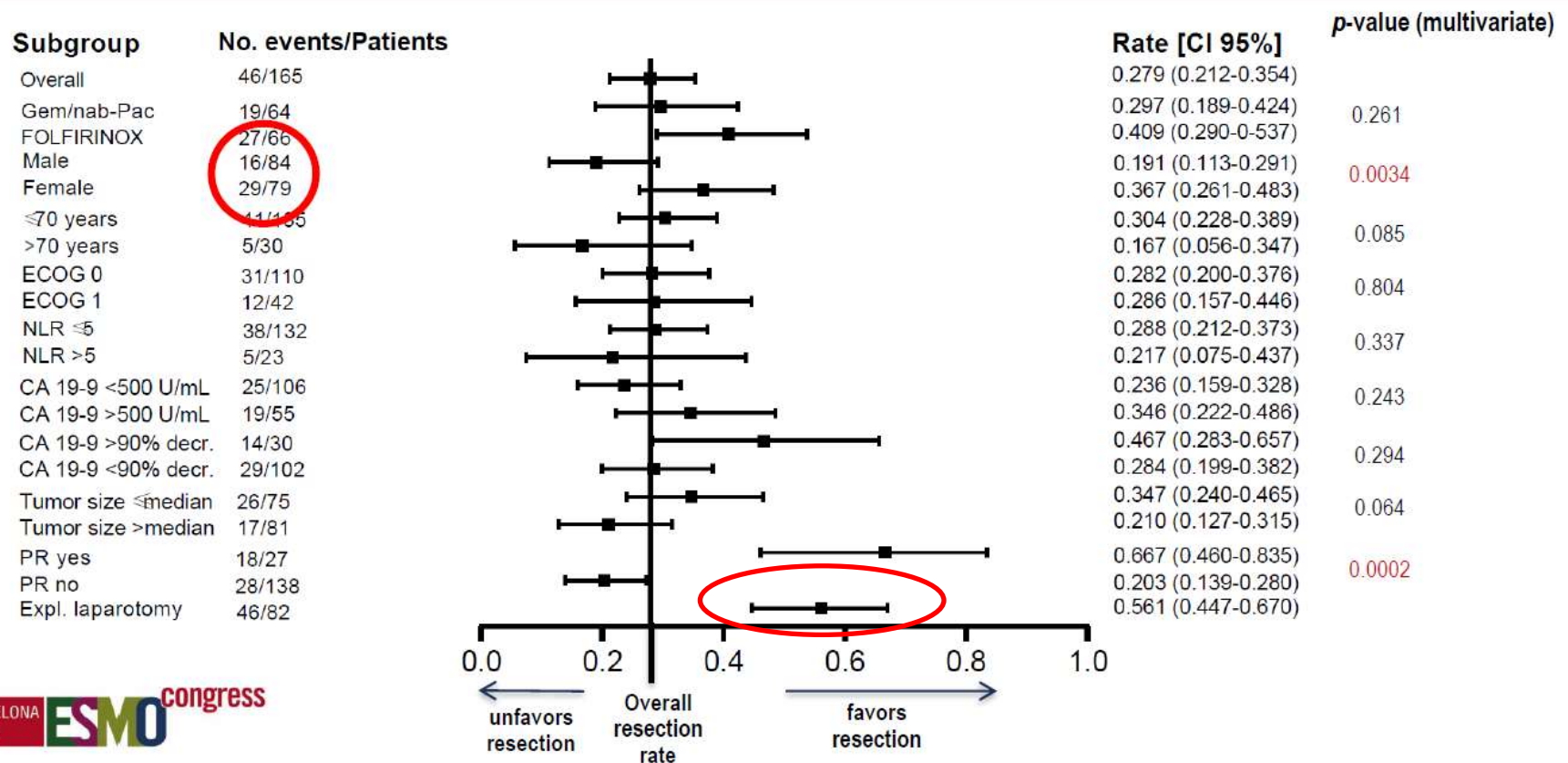
p = Log-rank test (2-sided, $\alpha=0.05$)

¹Caschini et al ESMO 2019.

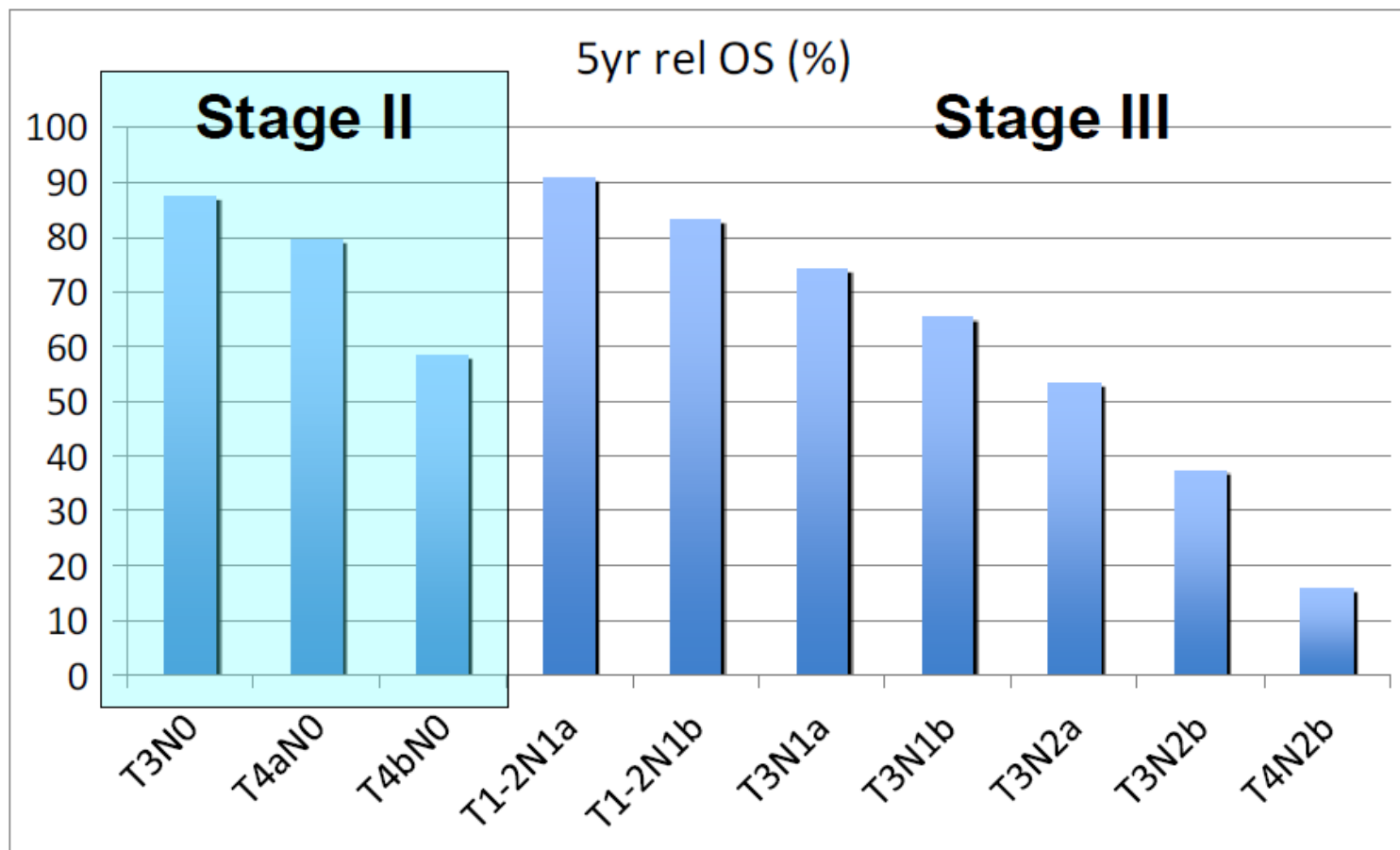
²Kunzmann et al ESMO 2019

SUBGROUP ANALYSIS FOR RESECTION (ITT-POPULATION)

AIO



Stage II AJCC v7



Clinical Prognostic Factors for Stage II Colon Cancer

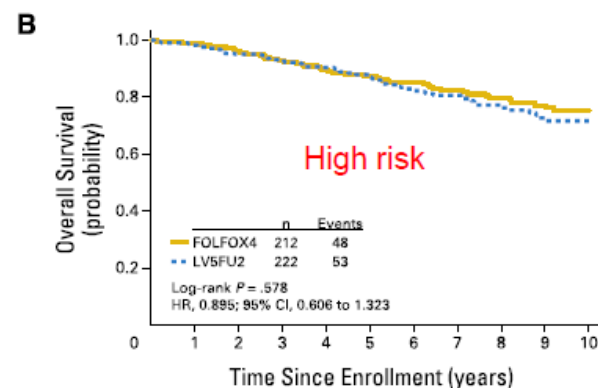
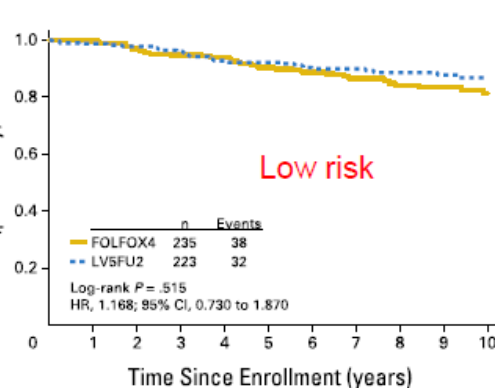
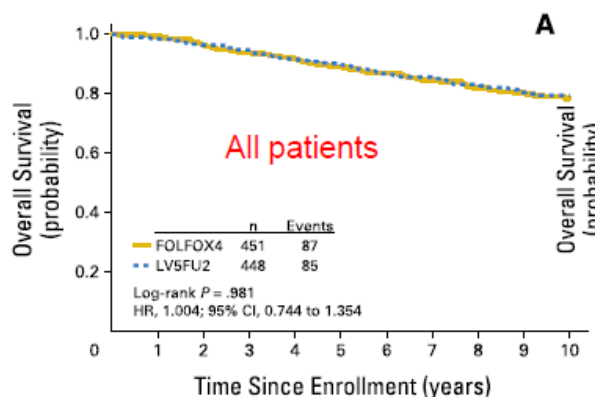
Definition of High Risk Stage II Disease

- T4
- Poorly differentiated
- Invasion (vascular/lymphatic/perineural)
- Inadequate nodal harvest (<10 SCOT, <12 TOSCA, HORG, ACHIEVE)
- Obstruction
- Perforation

Although no consensus exists on the definition of high-risk stage II colon cancer, the European Society for Medical Oncology and American Society of Clinical Oncology guidelines include T4 lesions, perforation, and number of analyzed lymph nodes fewer than 10 or 12 as high-risk characteristics.

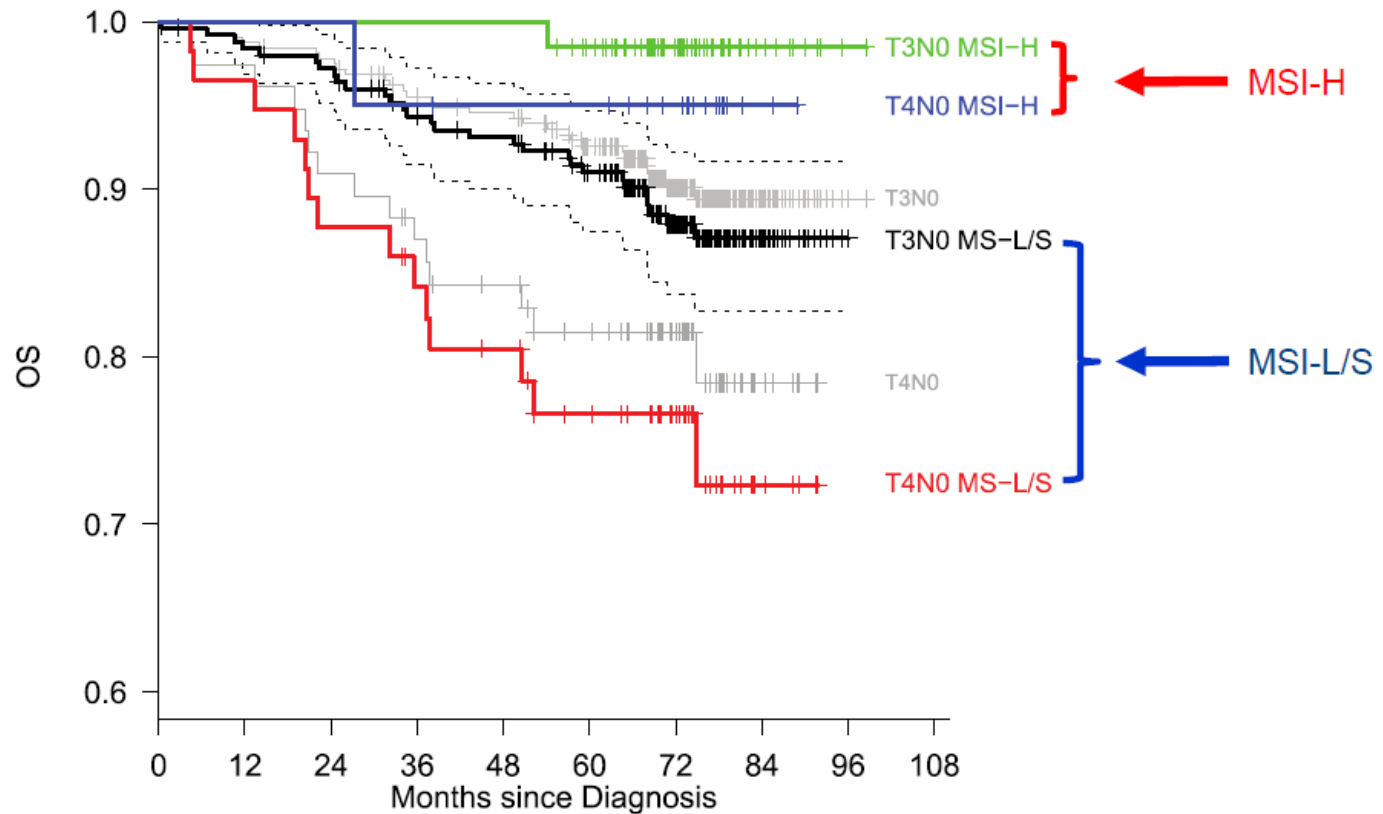
Tournigant et al. JCO 2015

Updated MOSAIK Data Low Risk & High Risk Stage II FOLFOX vs. FU/LV



		5 y DFS		6y OS	
	N Pat	HR	P-value	HR	P-value
high risk	569	0.72 0.51-1.01	.062	0.91 0.66-.97	.648
low risk	330	1.36 0.76-2.45	1.01	1.36 0.67-2.5	.399

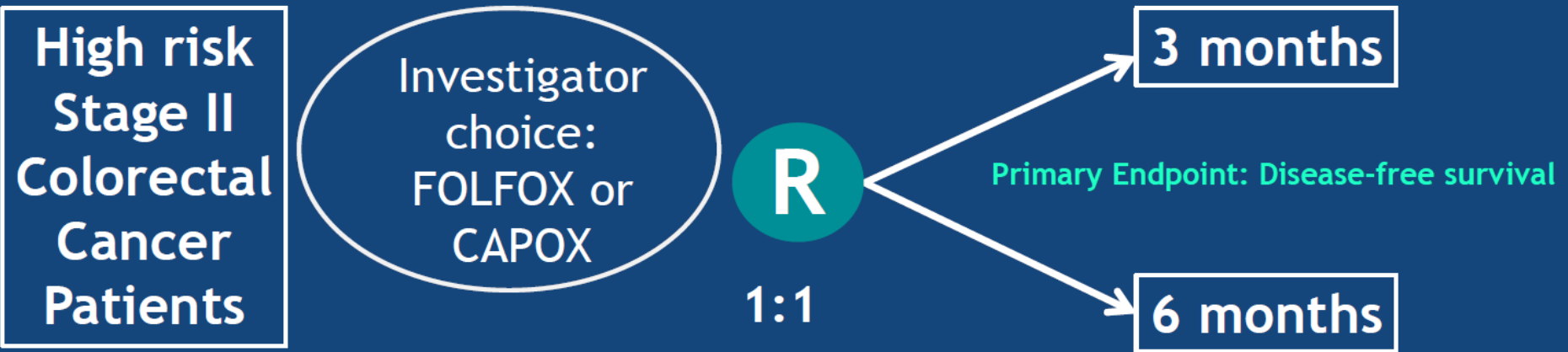
Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II Colon Cancer



	At risk:							Number of events		
	T3N0 MS-L/S	251	246	242	230	225	209	138	31	29
	T3N0 MSI-H	66	66	66	66	66	61	35	9	1
→	T4N0 MS-L/S	57	55	50	46	43	37	26	5	14
	T4N0 MSI-H	20	20	20	19	18	18	14	2	1



Study Schema To evaluate the *non-inferiority* of 3m vs 6m



Prospective analysis of *four* concurrently conducted phase III randomized trials



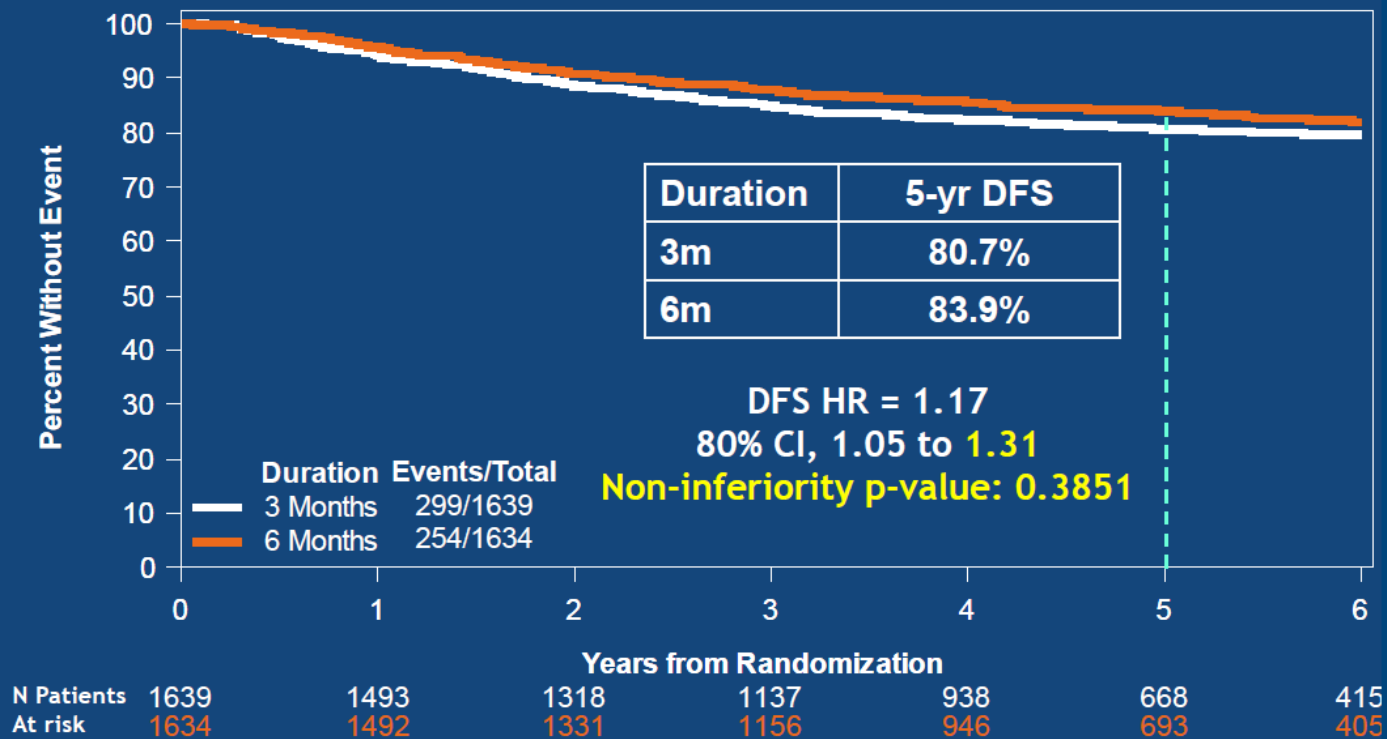
IDEA Trials Summary (High Risk Stage II)

Trial	Regimen(s)	HR stage II Colorectal Cancer Patients	Enrolling Country
TOSCA	CAPOX or FOLFOX4	1268	Italy
SCOT	CAPOX or mFOLFOX6	1078*	UK, Denmark, Spain, Australia, Sweden
HORG	CAPOX or FOLFOX4	413	Greece
ACHIEVE2	CAPOX or mFOLFOX6	514	Japan

*Included 130 rectal patients

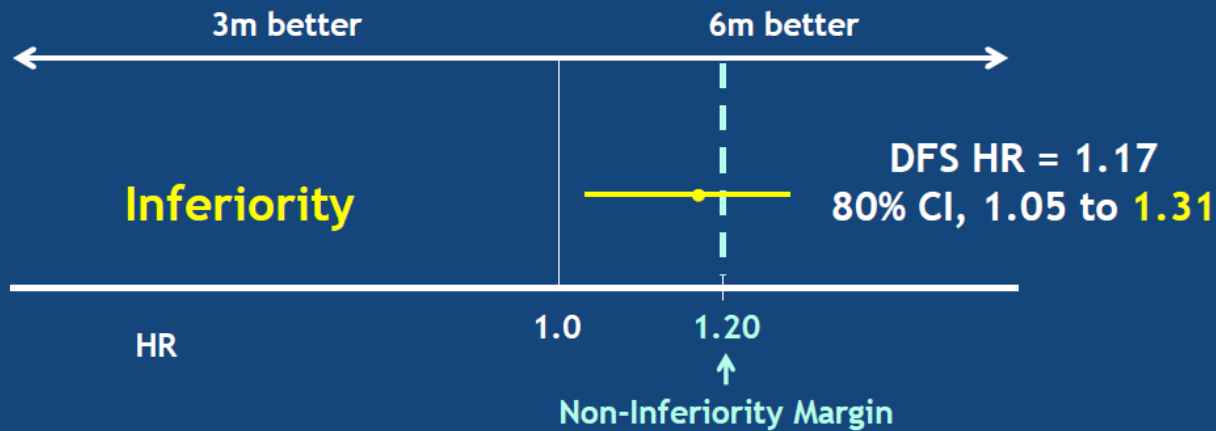


Results: Primary DFS Analysis (mITT)



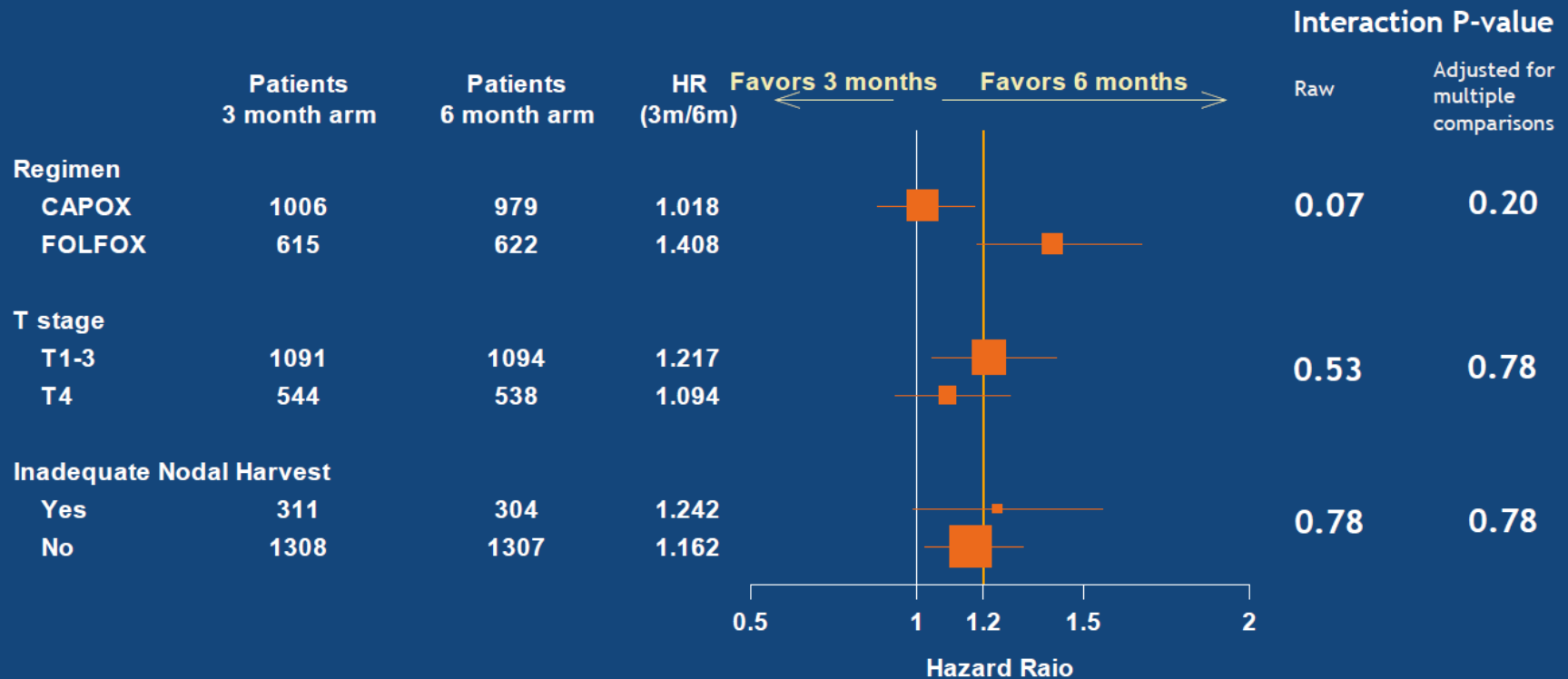


Results: Primary DFS Analysis: Statistical Conclusions





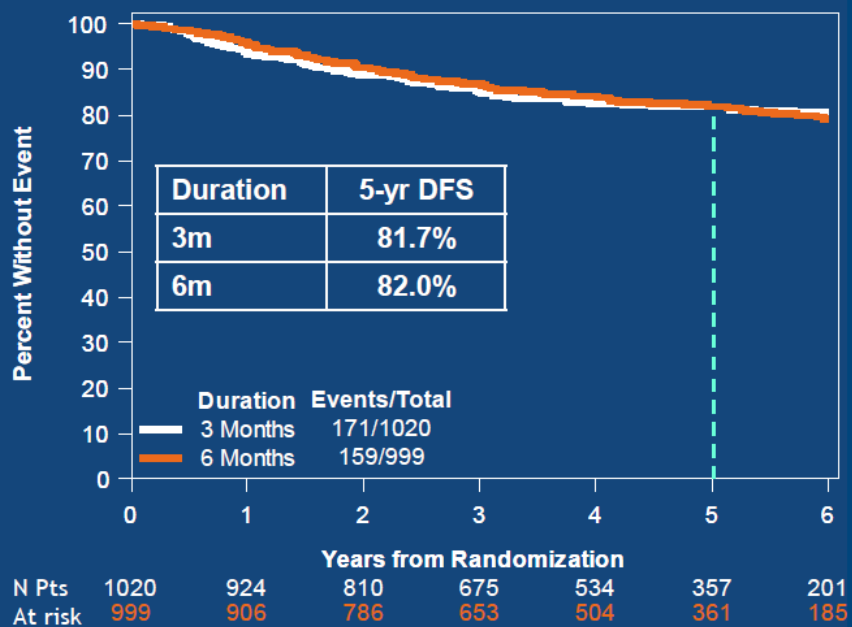
Results: DFS Comparison by Regimen and risk



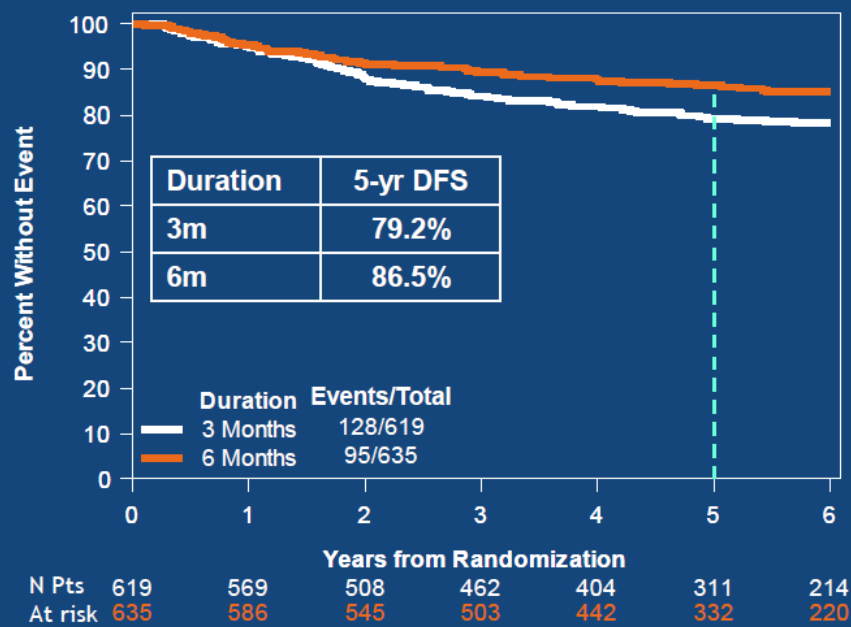


Results: DFS Comparison by Regimen

CAPOX



FOLFOX



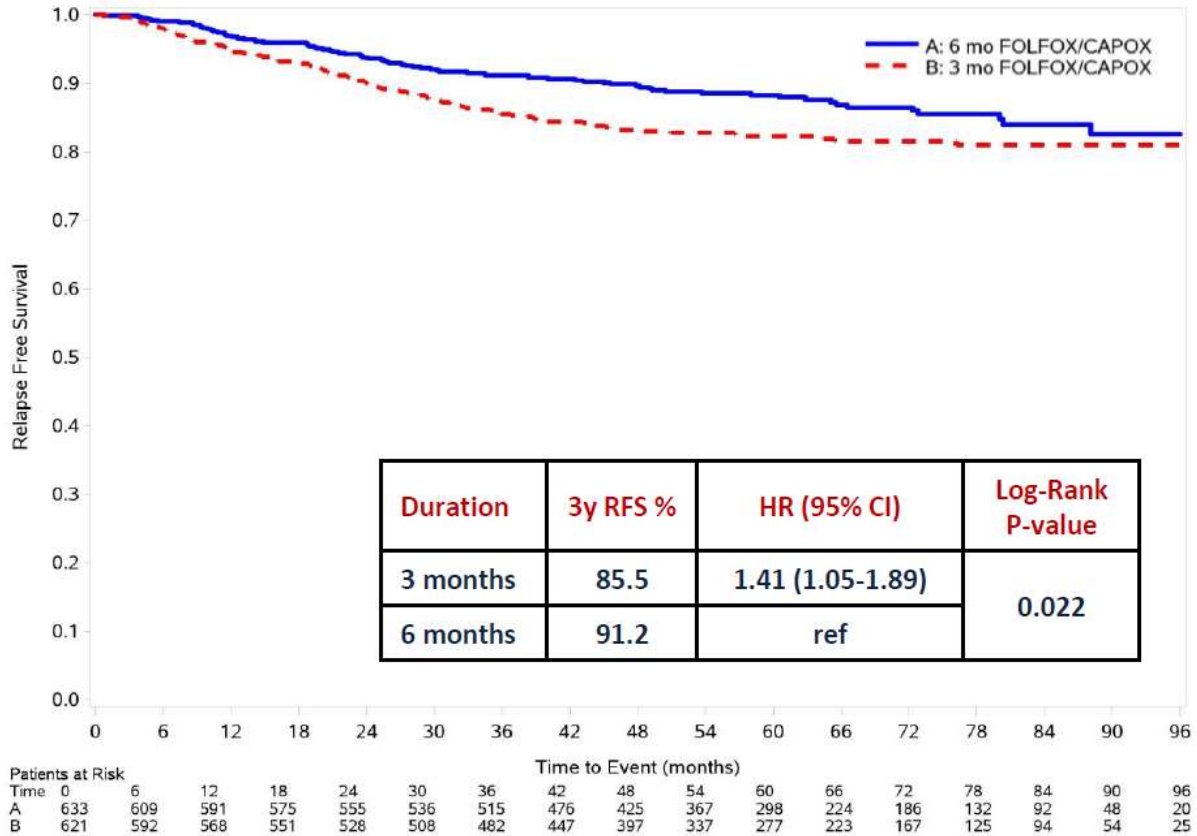


Conclusions

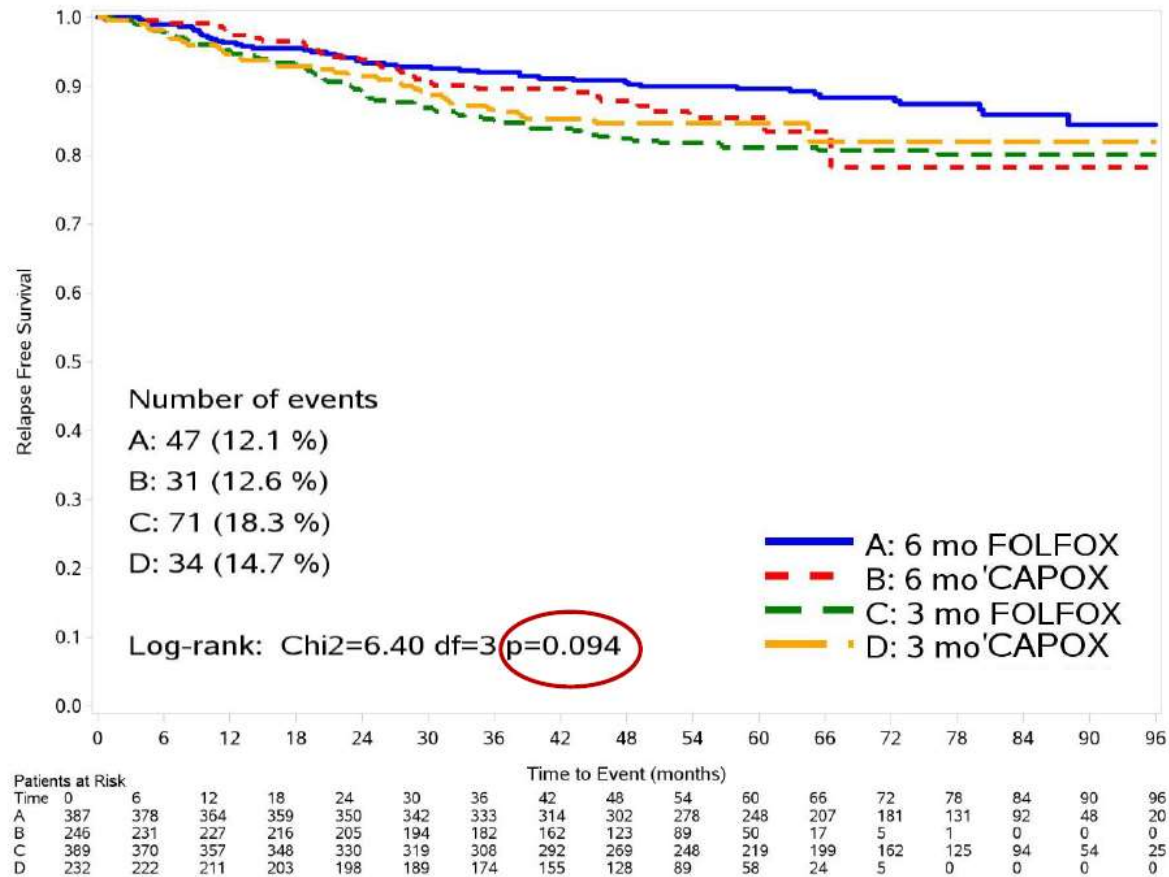
- Overall non-inferiority was not shown for 3 months
- 3 months treatment results in significantly less toxicity
- Similar regimen effect as in stage III disease
 - **Strongly suggests non-inferiority for 3 months CAPOX**
 - **Strongly suggests inferiority for 3 months FOLFOX**

**SUPERIORITY OF 6 MONTHS FOLFOX
(Garufi)**

Relapse-Free Survival



RFS by treatment duration and regimen



eUpdate: Early Colon Cancer Treatment Recommendations



eUpdate - Early Colon Cancer Treatment Recommendations

Published: 23 September 2019. Authors: ESMO Guidelines Committee

HIGH-RISK

T4

<12 lymph nodes

perforation/obstruction

tumour grade 3,

in the absence of MSI:

6 months fluoropyrimidine

VS

VERY HIGH-RISK

MSS and T4 or more than one

validated risk factor,

consider addition of oxaliplatin:

3 months of CAPOX

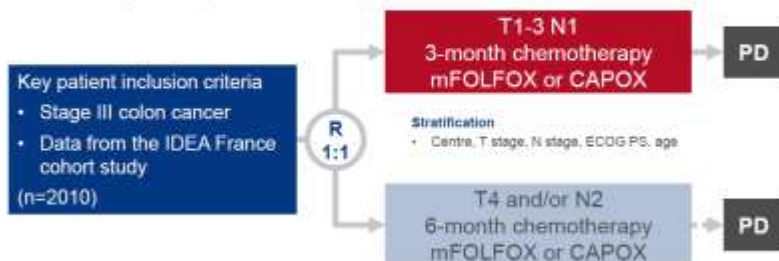
6 months of FOLFOX

LIQUID BIOPSY

LBA30_PR: Analysis of circulating tumor DNA (ctDNA) from patients enrolled in the IDEA-FRANCE phase III trial; prognostic and predictive val for adjuvant treatment duration – Taieb J, et al

Study objective

- To investigate whether ctDNA can be used as a prognostic or predictive marker for determining intensity and duration of adjuvant treatment



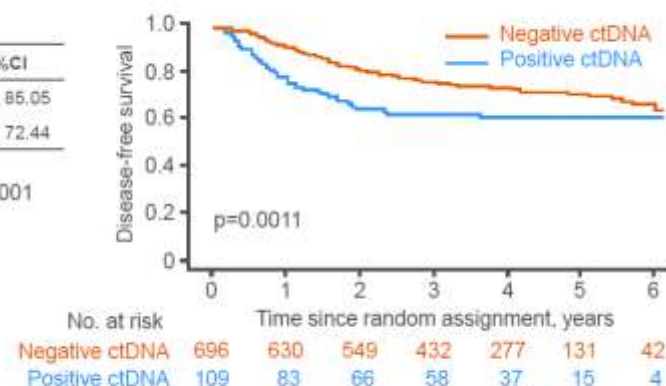
*Digital pathology is used to quantify the densities of CD3+ and cytotoxic CD8+ T cells in core tumour and invasive margin and converted to predefined cut-offs and grouped as either low, intermediate or high or as low or intermediate + high or as a continuous score

Taieb J, et al. Ann Oncol 2019;30(suppl):abstr LBA30_PR

	DFS rate, %	95%CI
Negative ctDNA	82.39	79.32, 85.05
Positive ctDNA	64.12	54.19, 72.44

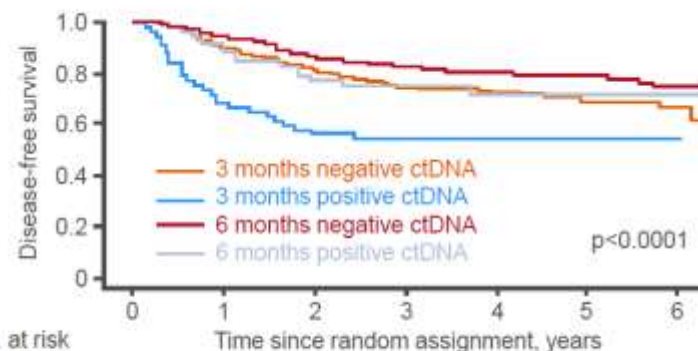
Positive vs. negative
HR 1.85 (95%CI 1.31, 2.61); p<0.001

DFS



Taieb J, et al. Ann Oncol 2019;30(suppl):abstr LBA30_PR

DFS



	0	1	2	3	4	5	6
3-mo negative ctDNA	346	309	269	204	134	60	19
3-mo positive ctDNA	56	37	30	27	18	4	1
6-mo negative ctDNA	350	321	280	228	143	71	23
6-mo positive ctDNA	53	46	36	31	19	11	3

ESMO 2019 – GI Cancers

- **Esophagus**: established IO 2nd line
- **Gastric**: confirmed perioperative approach
- **HCC**: still unmet need (Sorafenib, Lenvatinib, Nivolumab)
- **Intrahepatic Colangio**: molecular testing possible (IDH1, FGFR, BRAF and MSI)
- **Pancreatic**: LAPC doublet standard, triplet possible
- **Colon**: new triplet for BRAF patients; Stage II still Fluoropyrimidines. Liquid Biopsy: very near