TUMORI GASTROINTESTINALI

Nuove Prospettive: tumori NON colon-retto

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Antonia Strippoli

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

Nuove Prospettive: tumori non COLON-RETTO

EPATOCARCINOMA

- CHECKMATE 459 Nivolumab vs Sorafenib
- GO30140 Bevacizumab +/- Atezolizumab

COLANGIOCARCINOMA

- ClarIDHY Ivosidenib vs placebo
- Pemigatinib

CARCINOMA PANCREATICO LOCALMENTE AVANZATO

- GAP gemcitabina vs gemcitabina+Nab paclitaxel
- NEOLAP gemcitabina+Nab paclitaxel vs FOLFIRINOX

CARCINOMA GASTRICO LOCALIZZATO

- PRODIGY chemioterapia peri-operatoria vs chemioterapia post-operatoria
- RESOLVE SOX peri-operatorio vs CAPOX post-operatorio vs SOX post-op

CARCINOMA ESOFAGO-GASTRICO METASTATICO

- ATTRACTION 3 Nivolumab vs Taxani
- KEYNOTE 062 MSI CT vs Pembrolizumab vs CT+Pembrolizumab
- ANGEL Rivoceranib vs Placebo

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

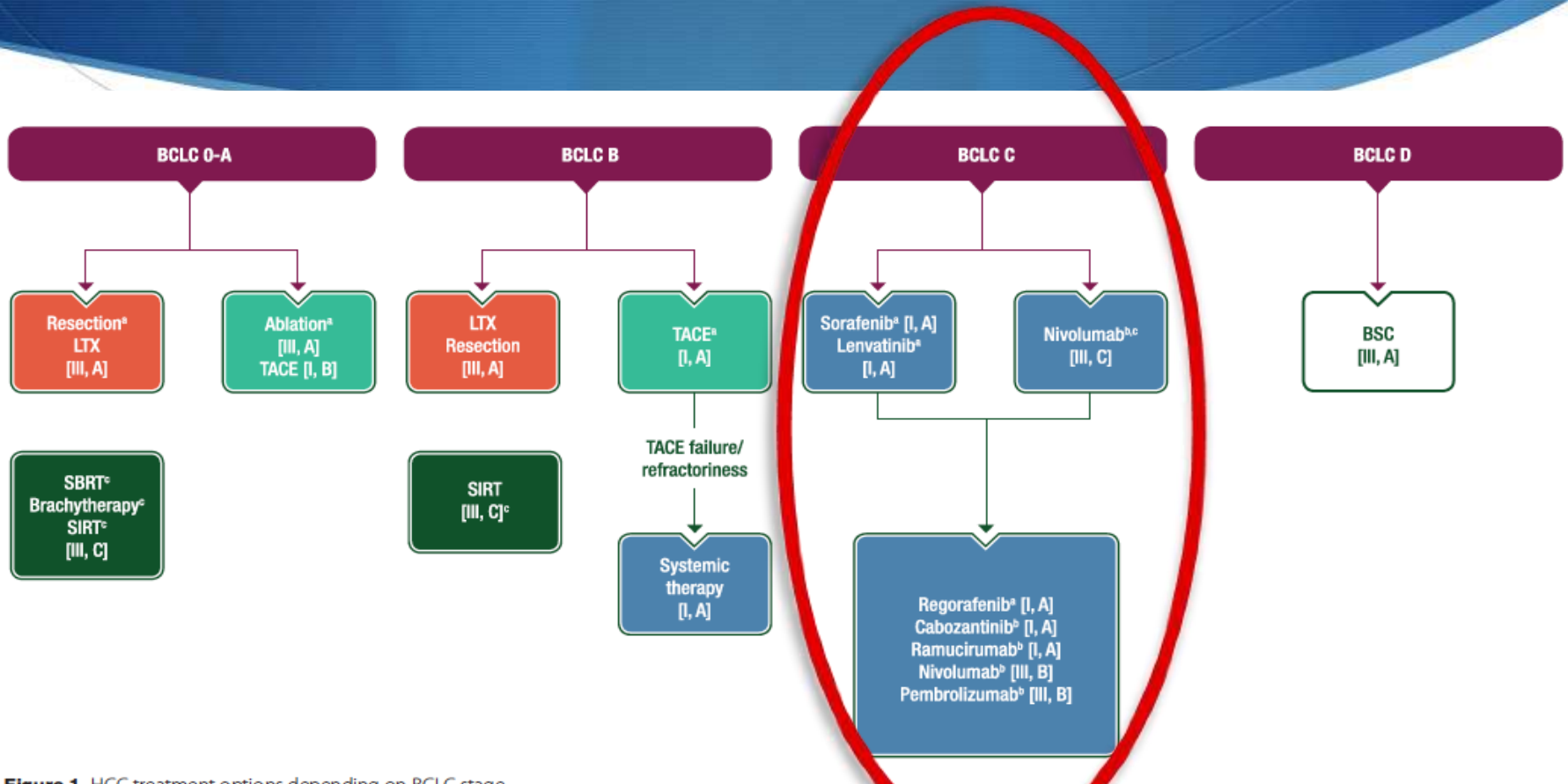


Figure 1. HCC treatment options depending on BCLC stage.
[a]See Table 4 for indication constraints based on tumour burden and liver function.
[b]Not EMA-approved as of August 2018.
BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; LTX, liver transplantation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation.

Vogel et al. 2018, Annals of Oncology

CHECKMATE 459: FIRST LINE PHASE III RCT OF NIVOLUMAB VS SORAFENIB IN ADVANCED HCC

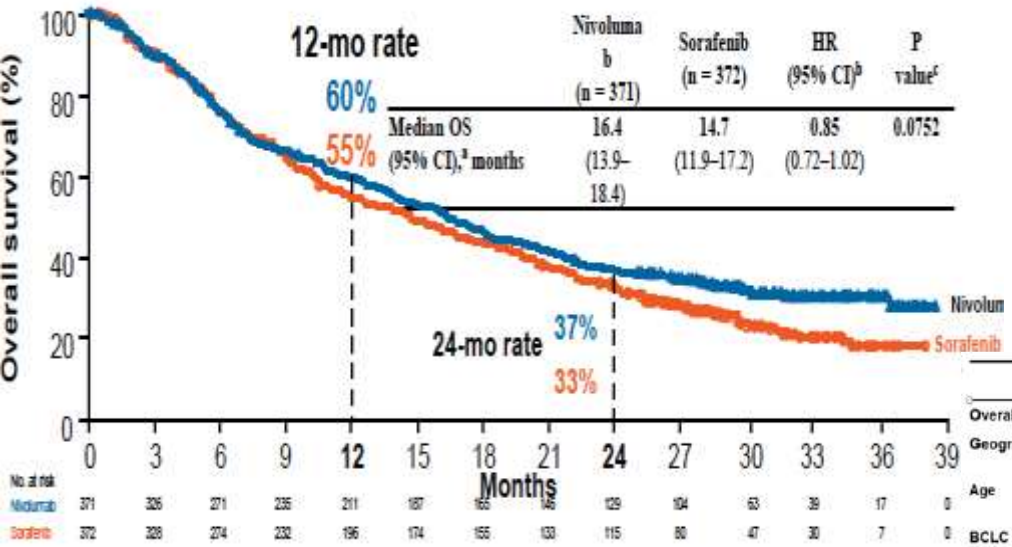
Histologically proven advanced HCC
Not eligible or progressed on surgery ± locoregional treatment
Child Pugh Class A

R

n=371 → Nivoluamb

n=372 → Sorafenib

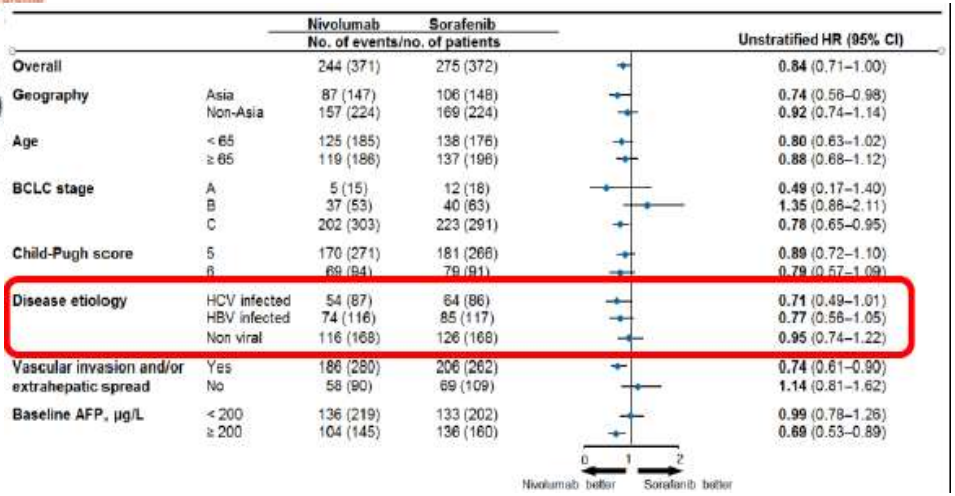
HBV: 31% pts
HCV: 23%
tPD-L1: 18%



	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)[b]	P value[c]
Median OS (95% CI),[a] months	16.4 (13.9–18.4)	14.7 (11.9–17.2)	0.85 (0.72–1.02)	0.0752

	Niv	Sor
CR	4%	1%
PR	12%	6%

OR: 2.41 (95% CI: 1.48, 3.92)



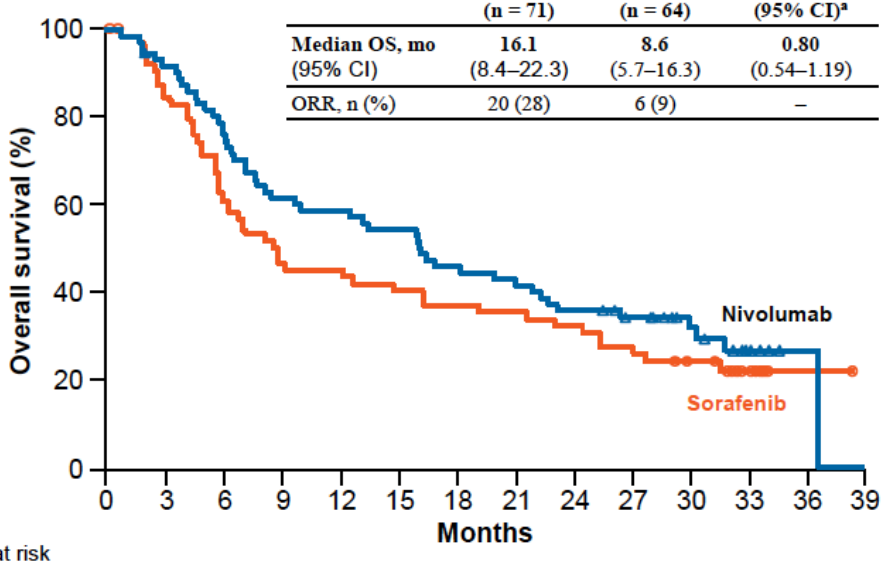
Primary endpoint: OS

Yau et al ESMO 2019

CHECKMATE 459: TREATMENT EFFECT IN PREDEFINED SUBSETS

Tumor cell PD-L1 expression ≥ 1%

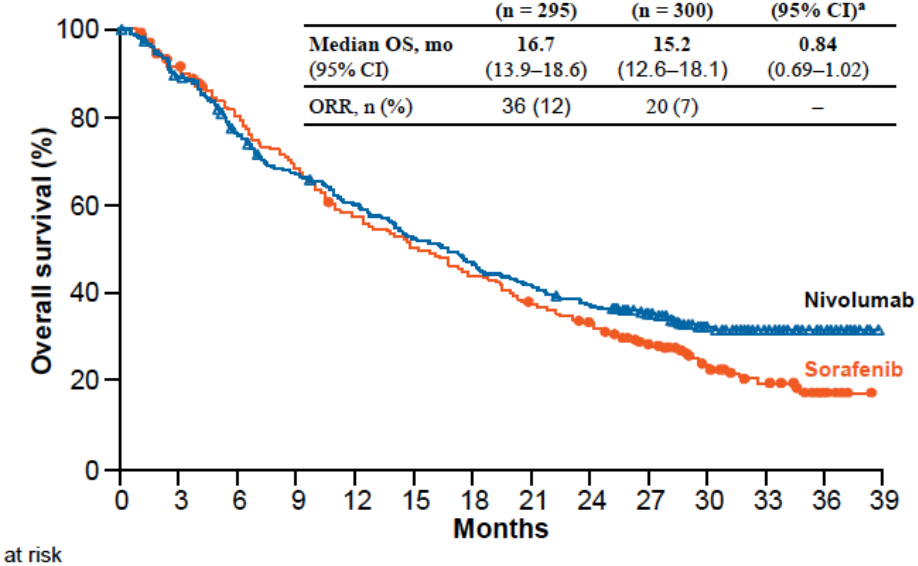
	Nivolumab (n = 71)	Sorafenib (n = 64)	HR (95% CI)[a]
Median OS, mo (95% CI)	16.1 (8.4–22.3)	8.6 (5.7–16.3)	0.80 (0.54–1.19)
ORR, n (%)	20 (28)	6 (9)	–



No. at risk														
Nivolumab	71	64	53	43	41	38	32	29	25	21	13	7	1	0
Sorafenib	64	53	37	29	28	25	23	22	20	17	13	7	1	0

Tumor cell PD-L1 expression < 1%

	Nivolumab (n = 295)	Sorafenib (n = 300)	HR (95% CI)[a]
Median OS, mo (95% CI)	16.7 (13.9–18.6)	15.2 (12.6–18.1)	0.84 (0.69–1.02)
ORR, n (%)	36 (12)	20 (7)	–



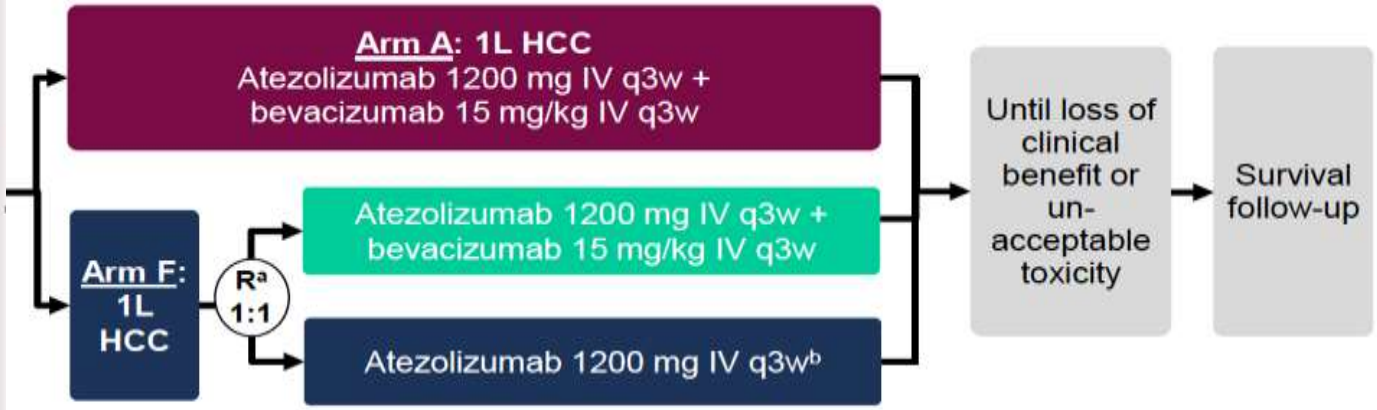
No. at risk														
Nivolumab	295	257	214	188	167	146	131	115	103	82	50	32	16	0
Sorafenib	300	269	231	197	163	144	127	106	92	63	34	23	6	0

Yau et al ESMO 2019

PHASE Ib GO30140

Eligibility Criteria:

- Measurable disease per RECIST 1.1
- ECOG PS 0/1
- Adequate haematologic and organ function
- Child-Pugh score up to B7 for Arm A and Child-Pugh A for Arm F
- No prior systemic therapy
  - No prior treatment with anti–CTLA-4, anti–PD-1 or anti–PD-L1 antibodies



- This study includes the first randomised analysis of an immune checkpoint inhibitor + VEGF inhibitor versus an immune checkpoint inhibitor alone

[a] Stratification factors were geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP level (< 400 ng/mL vs ≥ 400 ng/mL). [b] Crossover was permitted
Data cutoff: 14 June 2019.

Lee et al ESMO 2019

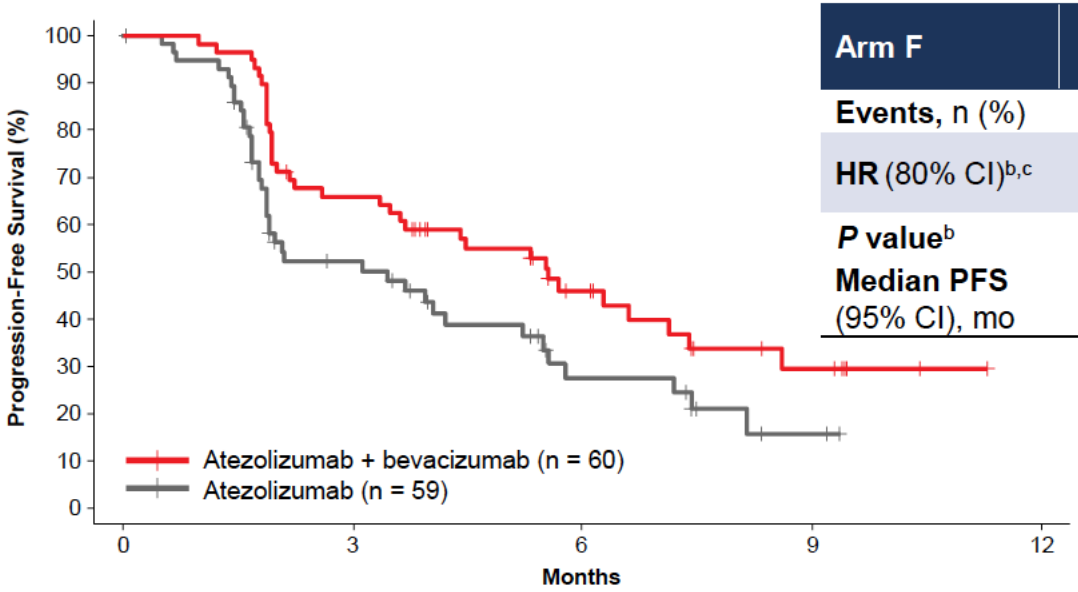
PHASE Ib GO30140: EFFICACY

	Cohort A	Cohort F	
	Atezo + Bev	Atezo + Bev	Atezo
N	104	60	59
Median FU	12.4 months	6.6 months	6.6 months
ORR	36%	20%	17%
mPFS	7.3 months	5.6 months	3.4 months
mOS	17.1 months	NR	NR

Lee et al ESMO 2019

GO30140 ARM F primary Endpoint: PFS[a]

Objective: Assess the safety and efficacy of atezolizumab + bevacizumab vs atezolizumab monotherapy in patients with unresectable HCC



No. at risk				
Atezolizumab + bevacizumab	60	38	17	7
Atezolizumab	59	25	9	2

Arm F	Atezo + Bev (n = 60)	Atezo (n = 59)
Events, n (%)	35 (58)	39 (66)
HR (80% CI)[b,c]	**0.55** (0.40 – 0.74)	
***P* value**[b]	0.0108	
Median PFS (95% CI), mo	5.6 (3.6 – 7.4)	3.4 (1.9 – 5.2)

[a] IRF RECIST 1.1. [b] Stratification factors included for analysis are geographic region (Asia excluding Japan vs rest of world) and AFP level (< 400 vs ≥ 400 ng/mL) at baseline. [c] Hypothesis testing performed under pre-specified 2-sided α level of 0.2. Data cutoff: 14 June 2019.

Atezo + bev vs atezo in HCC: presented by MS Lee

https://bit.ly/2ZAsVBM

Lee et al ESMO 2019

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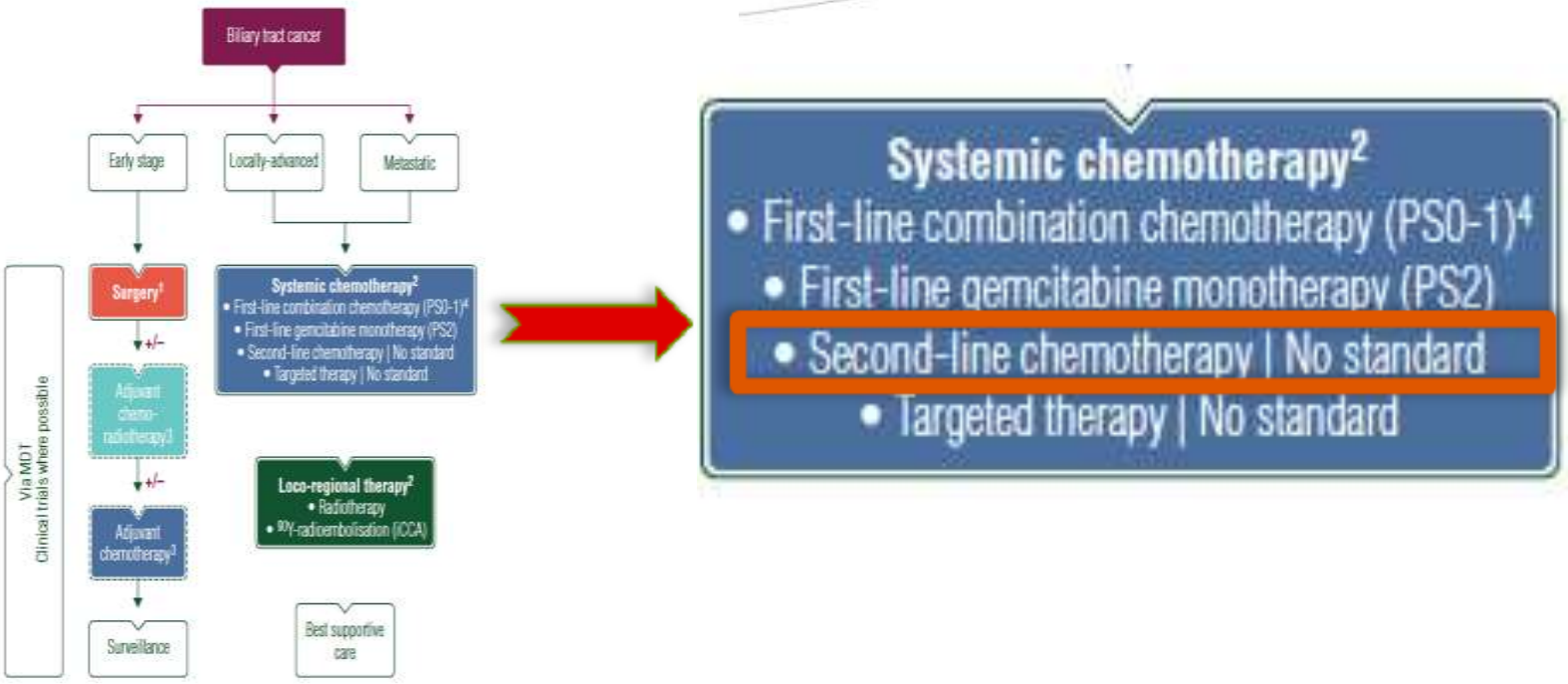
ESMO guidelines for biliary tract cancer management



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

Valle et al Ann Oncol 2016

Randomized second line phase III study of FOLFOX vs active symptom control in advanced biliary tract cancer

Advanced BTC
Disease progression on 1st line GemCis
Max 6 weeks progression to randomisation

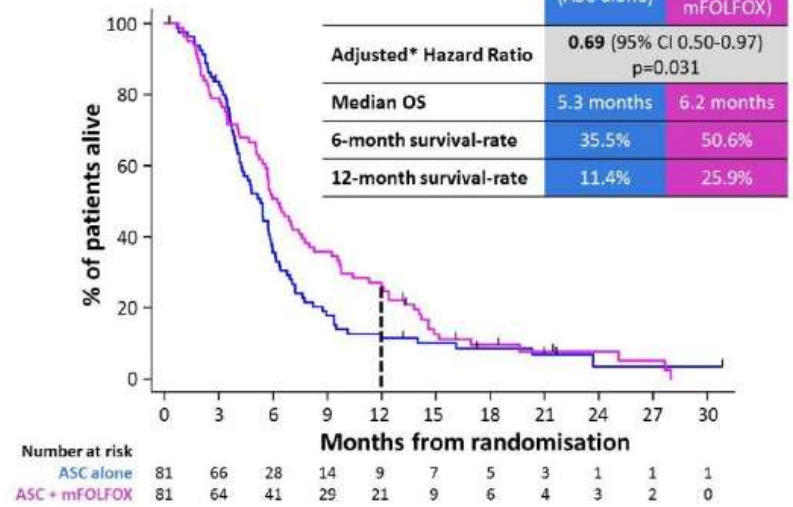
R

n=81 → Active symptom control (ASC)

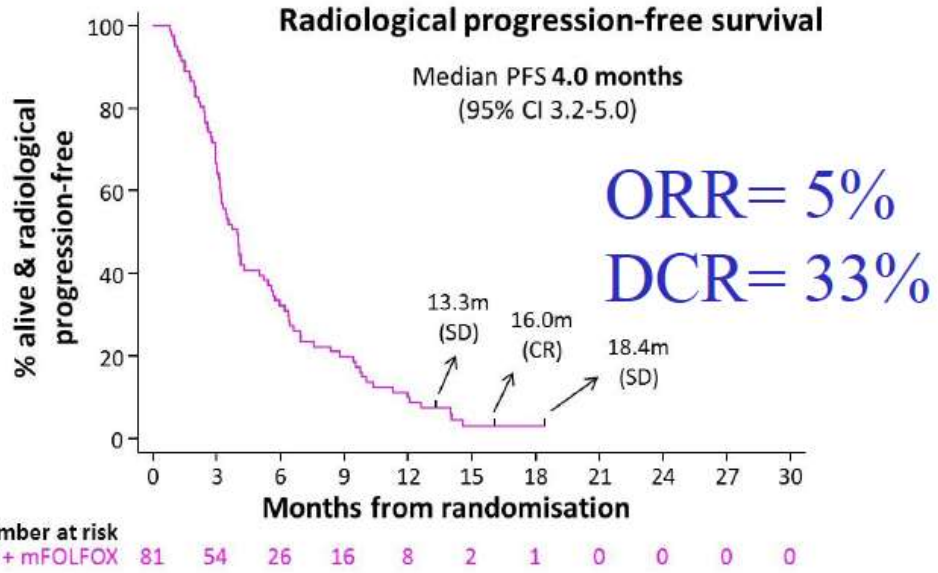
IHC: 44% pts
EHC: 28%
GB: 21%

n=81 → FOLFOX + ASC

Overall survival by trial arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

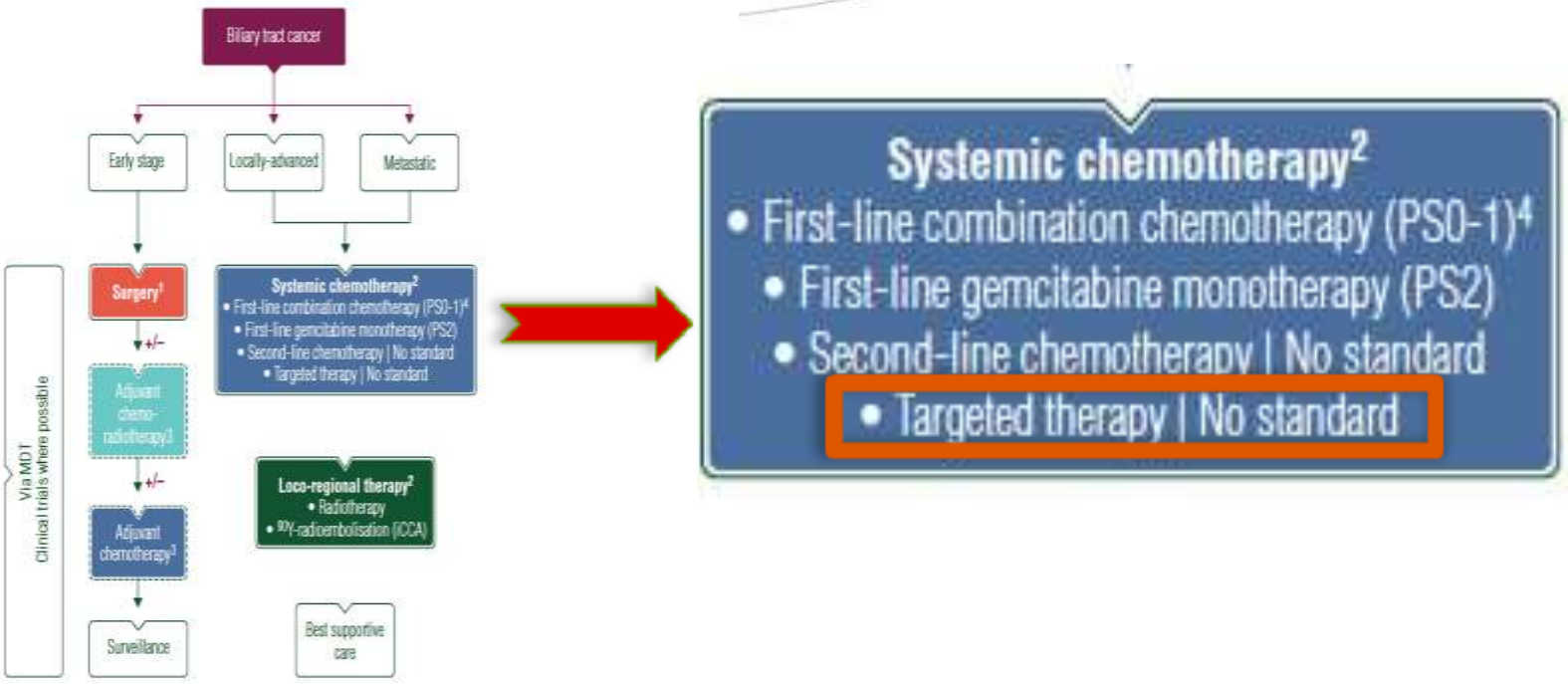


ORR= 5%
DCR= 33%

Primary endpoint: Overall survival

Lamarca et al ASCO 2019

ESMO guidelines for biliary tract cancer management



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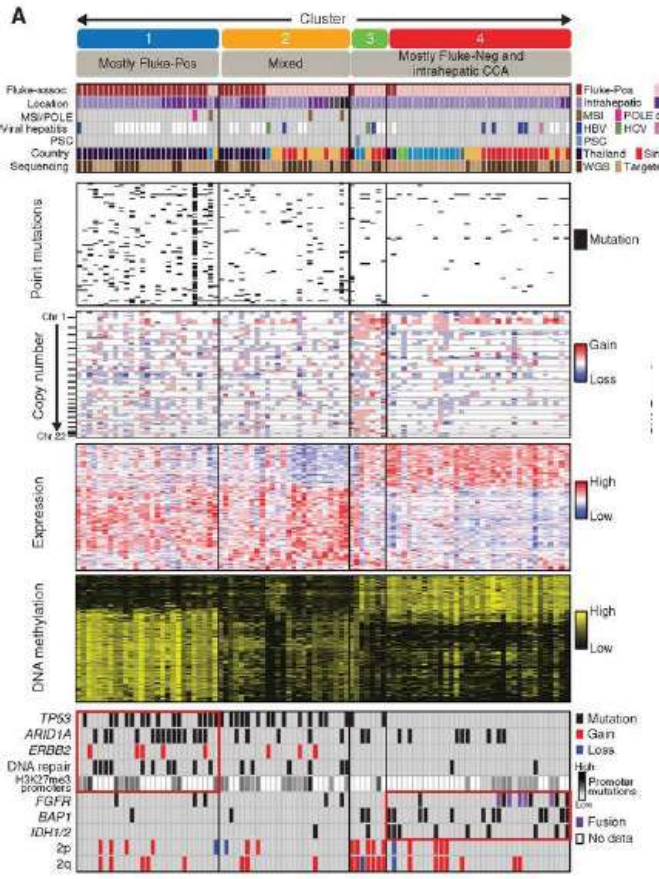
Valle et al Ann Oncol 2016

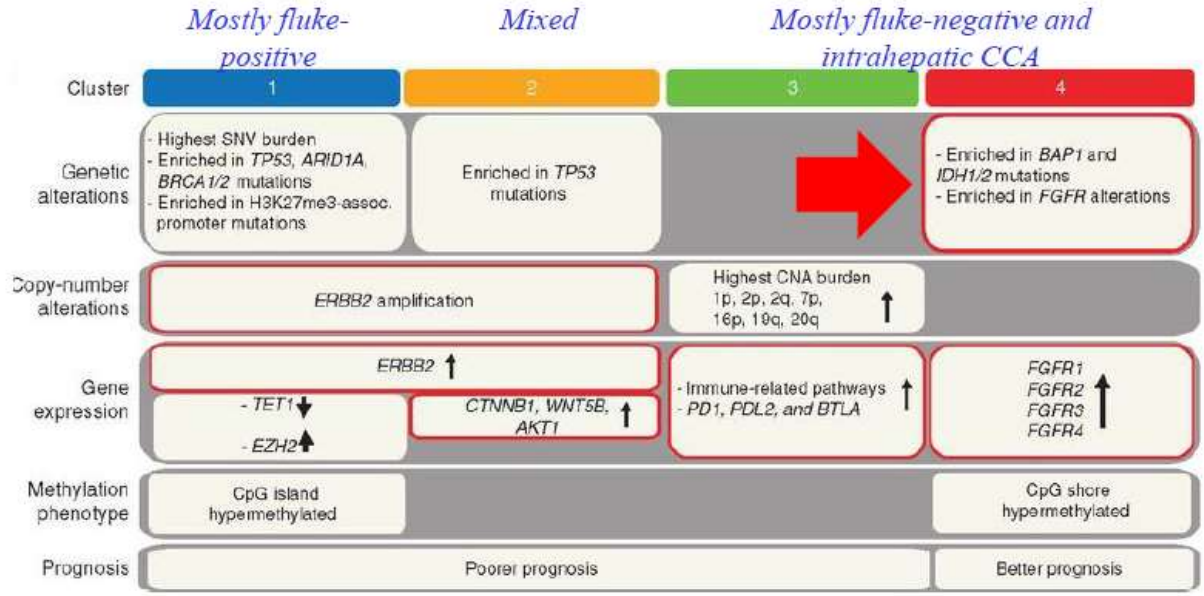
Integrated genomic and epigenomic characterisation of biliary tract cancer (BTC)



Liver Flukes:

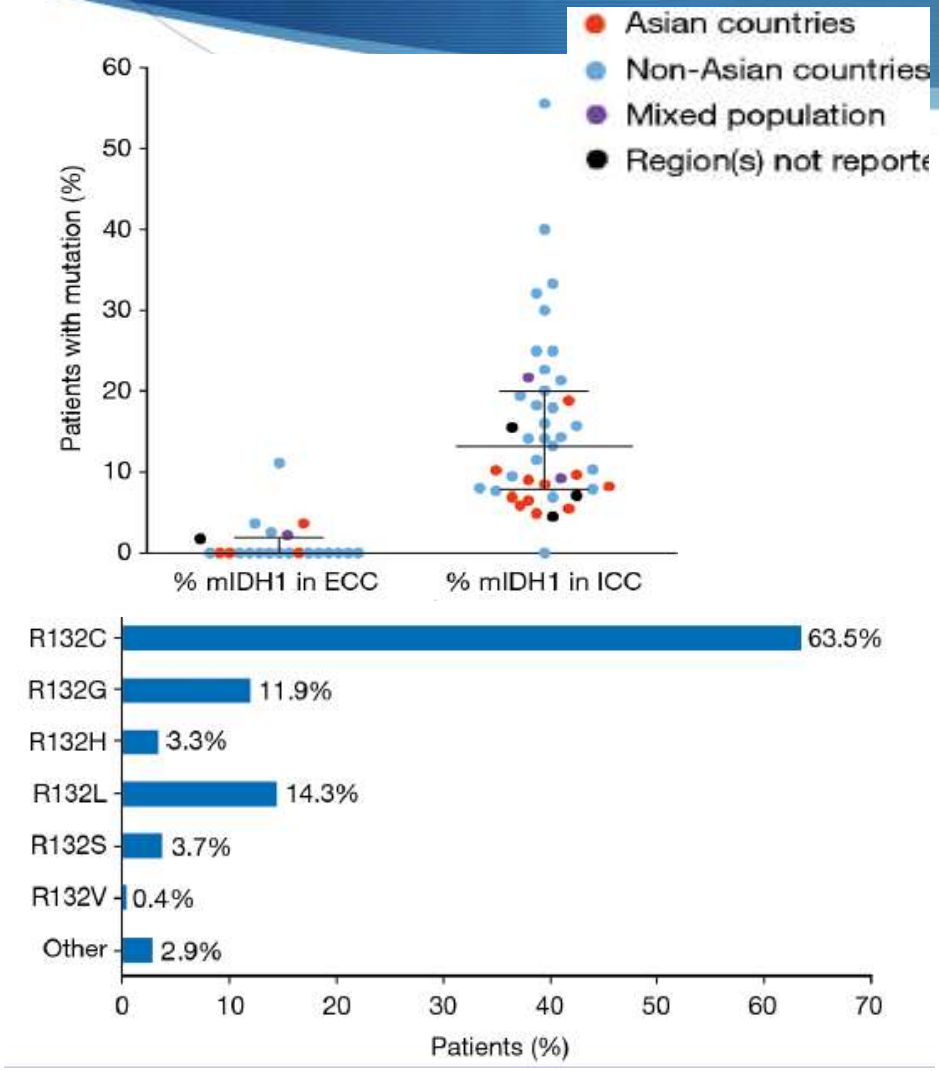
Clonorchis sinesis – China, Korea, Vietham

Opisthorchis viverrini: Thailand, Cambodia, Laos



Jusakul et al Cancer Discov 2017

IDH1 mutations in cholangiocarcinoma Systematic Review



- 45 publications
- Patient n=5,393
- IDH1 mutation found in IHC 13.1% EHC 0.8%
- Higher in non-Asian centres compared to Asian centres (16.5% vs. 8.8%; OR= 2.06)
- Most common mutation is R132C
- Most frequent co-mutations were ARID1A (22%), BAP1 mutation or loss (15.5%) and PBRM1 (13.3%)
- mIDH1 was not a prognostic factor (OS, PFS or TTP)

Boscoe et al J Gastrointest. Oncol 2019

ClarIDHdy: phase III study of Ivosidenib vs placebo in advanced mIDH1 biliary tract cancer

2: 1 randomisation

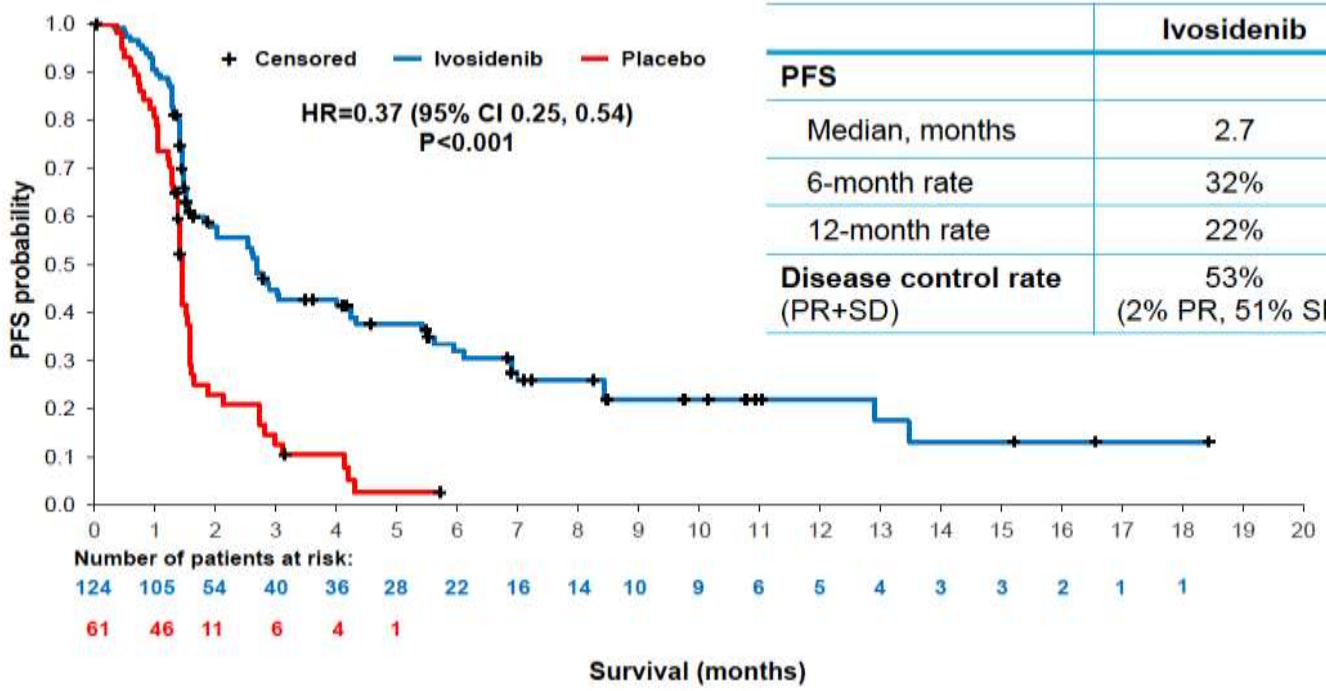
Advanced cholangiocarcinoma
mIDH1 status by NGS
1-2 prior therapy (≥1 GEM or 5-FU based)

R

n=124 → Ivosidenib 500mg QD orally continuous

n=61 → Placebo

Crossover permitted at radiological disease progression

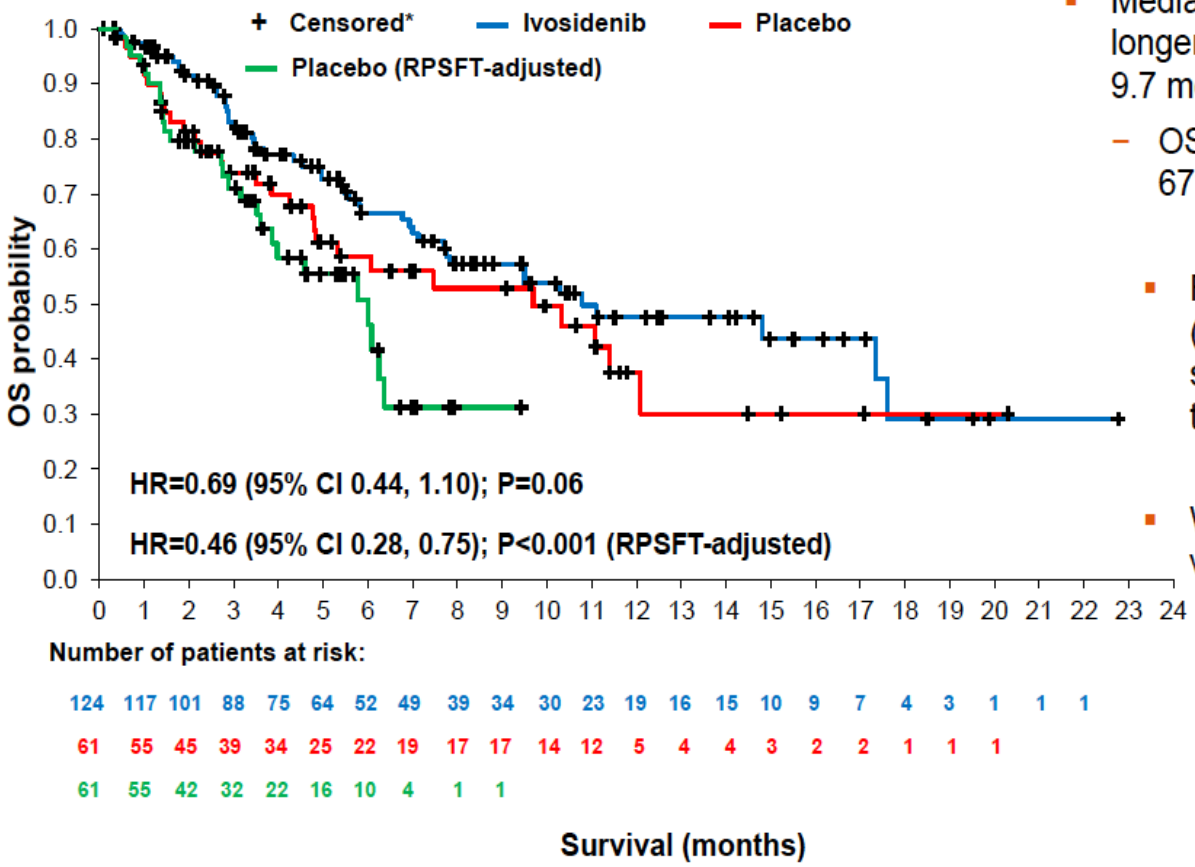


	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

IHC: 91% pts
EHC: 3%
Unknown: 5%

Abou-Alfa et al, ESMO 2019

ClarIDHdy: Overall Survival



- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
- Rank-preserving structural failure time (RPSFT)[1,2] method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
- With the RPSFT method, the median OS with placebo adjusts to 6 months

Abou-Alfa et al, ESMO 2019

Targeted therapy in molecularly-altereted advanced cholangiocarcinoma

BARCELONA 2019 ESMO congress

FIGHT-202: A PHASE 2 STUDY OF PEMIGATINIB IN PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA

Vogel A,[1] Sahai V,[2] Hollebecque A,[3] Vaccaro G,[4] Melisi D,[5] Al-Rajabi R,[6] Paulson AS,[7] Borad MJ,[8] Gallinson D,[9] Murphy AG,[10] Oh D-Y,[11] Dotan E,[12] Catenacci DV,[13] Van Cutsem E,[14] Lihou C,[15] Zhen H,[15] Féliz L,[15] Abou-Alfa GK[16,17]

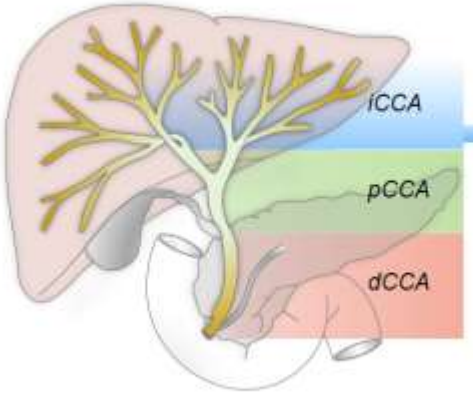
[1]Hannover Medical School, Hannover, Niedersachsen, Germany; [2]University of Michigan, Ann Arbor, MI, USA; [3]Gustave Roussy, Villejuif, France; [4]Providence Cancer Center Oncology and Hematology Care Clinic, Portland, OR, USA; [5]Università degli studi di Verona, Verona, Italy; [6]University of Kansas Cancer Center, Kansas City, KS, USA; [7]Baylor Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA; [8]Mayo Clinic Cancer Center, Scottsdale, AZ, USA; [9]Morristown Memorial Hospital, Carol Cancer Center, Morristown, NJ, USA; [10]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [11]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; [12]Fox Chase Cancer Center, Philadelphia, PA, USA; [13]University of Chicago Medicine, Chicago, IL, USA; [14]University Hospitals Leuven and KU Leuven, Leuven, Belgium; [15]Incyte Corporation, Wilmington, DE, USA; [16]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [17]Weill Medical College at Cornell University, New York, NY, USA

esmo.org

FIGHT 202

BACKGROUND

Cholangiocarcinoma



iCCA, pCCA, and dCCA correspond to intrahepatic, perihilar, and distal cholangiocarcinoma, respectively.

- Several actionable oncogenic alterations have been identified in CCA, including alterations involving FGFR2[1–3]
- *FGFR2* fusions or rearrangements are
  - Almost exclusively found in iCCA
  - Present in 10–16% of patients with iCCA in the United States and Europe[4–6]
- Pemigatinib is a selective, potent, oral inhibitor of FGFR1, 2, and 3[7]

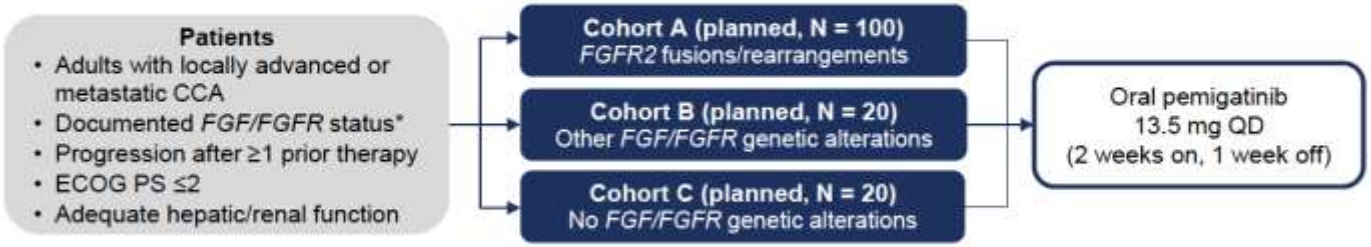
1. Lowery MA, et al. *Clin Cancer Res.* 2018;24:4154–61. 2. Nakamura H, et al. *Nat Genet.* 2015;47:1003–10. 3. Pellino A, et al. *Transl Gastroenterol Hepatol.* 2018;3:40. 4. Ross JS, et al. *Oncologist.* 2014;19:235–42. 5. Farshidfar F, et al. *Cell Rep.* 2017;19:2878–80. 6. Graham RP, et al. *Hum Pathol.* 2014;45:1630–8. 7. Liu PCC, et al. *Cancer Res.* 2015;75(15 Suppl):771 [abstract].

Vogel et al, ESMO 2019

FIGHT 202

FIGHT-202 STUDY DESIGN

- Phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA (NCT02924376)
  - Sites opened in the United States, Europe, Middle East, and Asia



Primary endpoint:	Confirmed ORR in cohort A by independent central review
Secondary endpoints:	ORR in cohorts B, A + B, and C; duration of response, disease control rate, PFS, OS, and safety in all cohorts

* Patients prescreened for *FGF/FGFR* status, documented either centrally (FoundationOne®, Foundation Medicine), based on local assessment, or an existing Foundation Medicine report. Retrospective central confirmation of locally documented *FGF/FGFR* status was required.

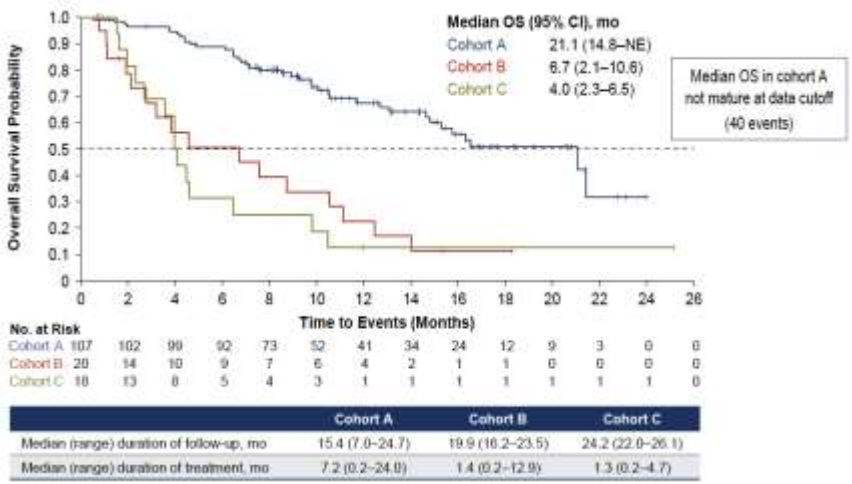
Vogel et al, ESMO 2019

FIGHT 202: response

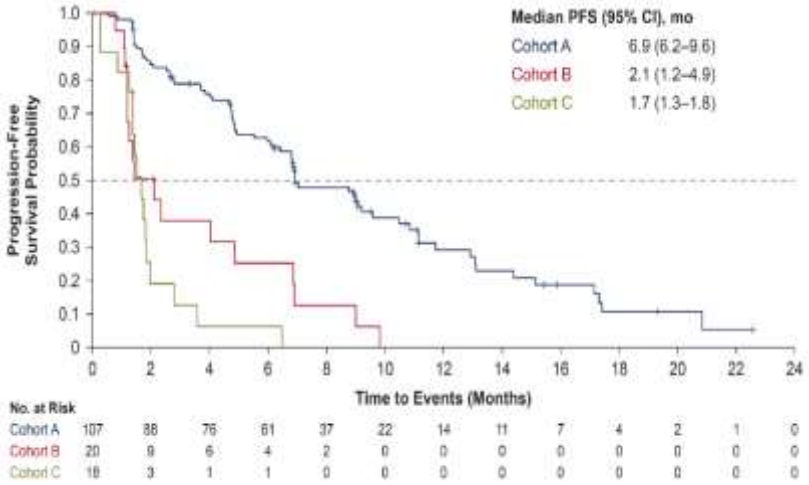
Variable	Cohort A (n = 107) *FGFR2* Fusions/ Rearrangements	Cohort B (n = 20) Other *FGF/FGFR* Genetic Alterations	Cohort C (n = 18) No *FGF/FGFR* Genetic Alterations
ORR (95% CI), %	**35.5 (26.50–45.35)**	0	0
Best OR,* n (%)			
CR	3 (2.8)	0	0
PR	35 (32.7)	0	0
SD	50 (46.7)	8 (40.0)	4 (22.2)
PD	16 (15.0)	7 (35.0)	11 (61.1)
Not evaluable†	3 (2.8)	5 (25.0)	3 (16.7)
Median DOR (95% CI), mo	7.5 (5.7–14.5)	—	—
DCR (CR + PR + SD) (95% CI), %	82 (74–89)	40 (19–64)	22 (6–48)

Vogel et al, ESMO 2019

FIGHT: OS e PFS



	Cohort A	Cohort B	Cohort C
Median (range) duration of follow-up, mo	15.4 (7.0–24.7)	19.9 (16.2–23.5)	24.2 (22.0–26.1)
Median (range) duration of treatment, mo	7.2 (0.2–24.0)	1.4 (0.2–12.9)	1.3 (0.2–4.7)



The study was not designed to compare cohorts.

Vogel et al, ESMO 2019

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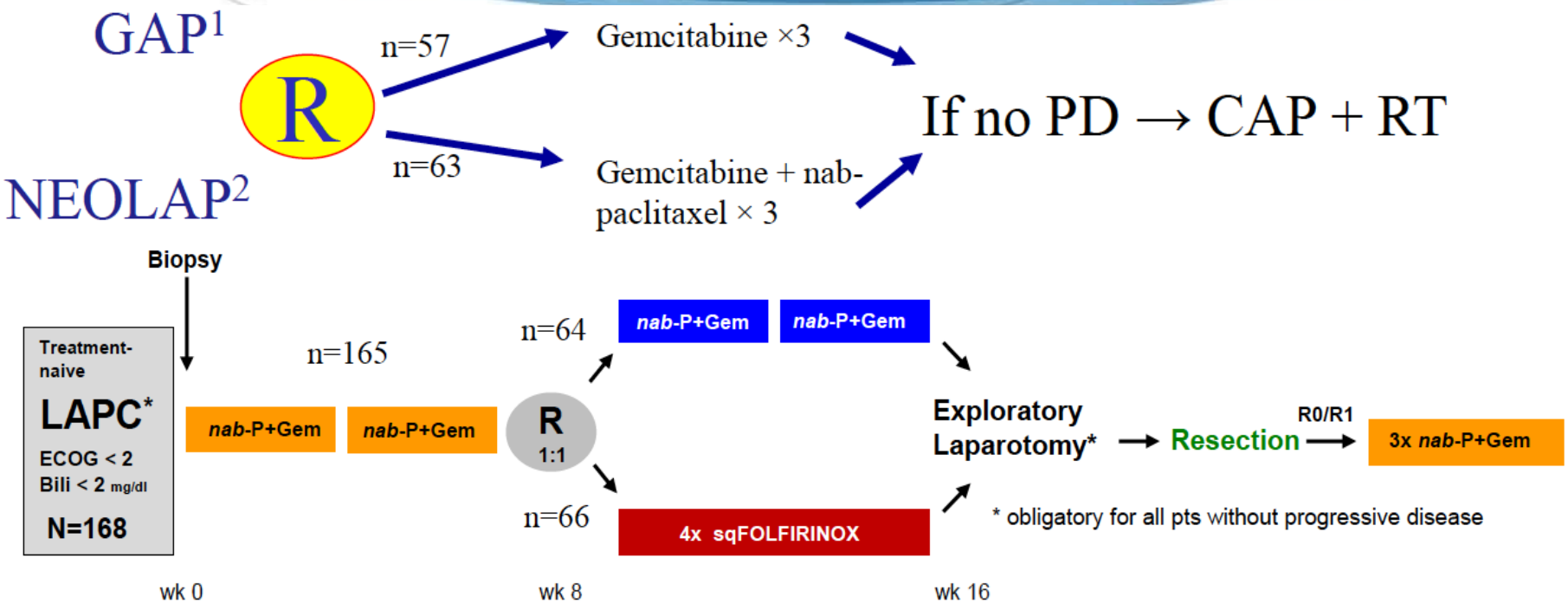
- ANGEL Rivoceranib vs Placebo

GAP and NEOLAP in locally advanced pancreatic cancer

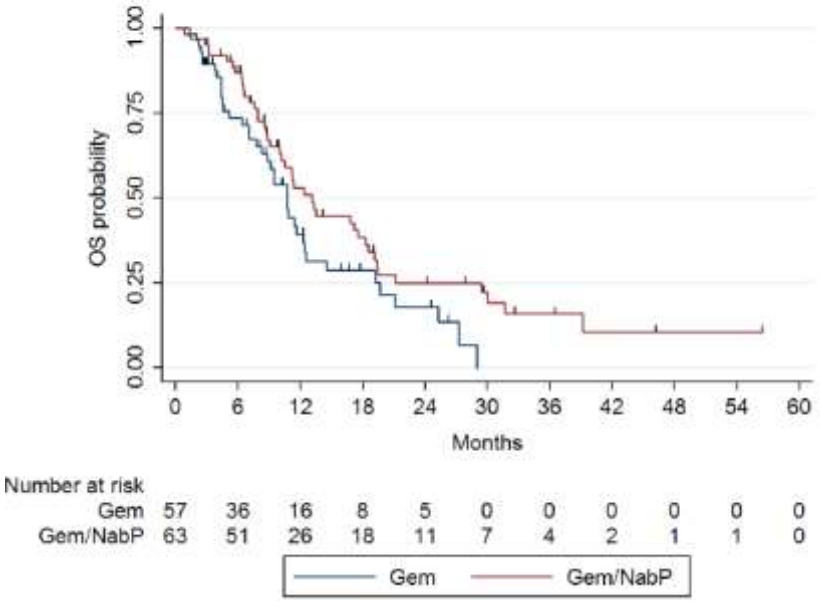


* assessed by local MDT

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

GAP and NEOLAP in locally advanced pancreatic cancer

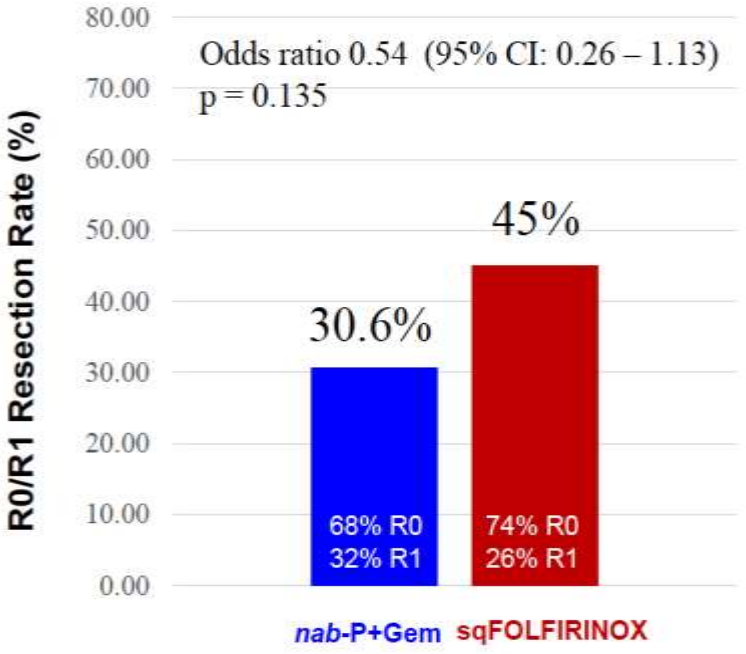
GAP[1]



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

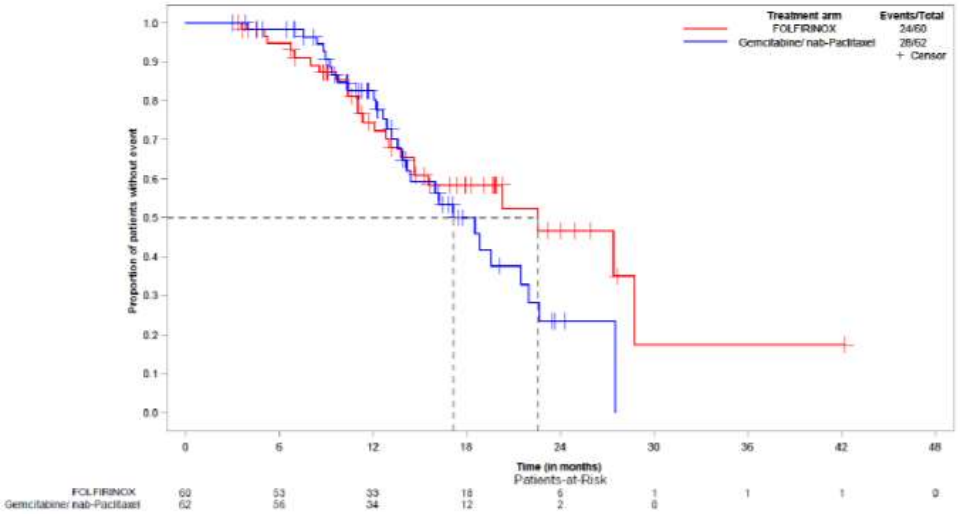
HR 0.65; 90%CI 0.44-0.94, one-tailed p=0.03

NEOLAP[2]



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

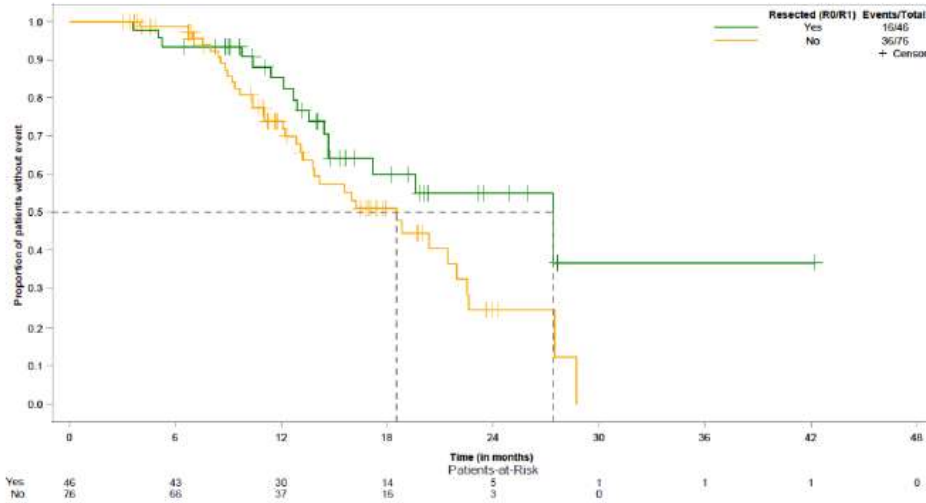
NEOLAP Overall Survival



	Events/ N	Median (months)	95% CI
— sqFOLFIRINOX	24/60	22.5	14.7 – 28.7
— *nab*-P+Gem	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



		Events/ N	Median (months)	95% CI
— Resected (R0/R1)		16/46	27.4	14.7 – n.r.
— Not resected		60/119	14.2	12.2 – 18.8
Overall	76/165		17.2	13.8 – 20.3

HR 0.45 (95% CI: 0.26 – 0.78)
p (log-rank) = 0.0035

Median follow-up: 13.8 months

Kunzmann et al ESMO 2019

Nuove Prospettive: tumori non COLON-RETTO

EPATOCARCINOMA

- CHECKMATE 459 Nivolumab vs Sorafenib
- GO30140 Bevacizumab +/- Atezolizumab

COLANGIOCARCINOMA

- ClarIDHY Ivosidenib vs placebo
- Pemigatinib

CARCINOMA PANCREATICO LOCALMENTE AVANZATO

- GAP gemcitabina vs gemcitabina+Nab paclitaxel
- NEOLAP gemcitabina+Nab paclitaxel vs FOLFIRINOX

CARCINOMA GASTRICO LOCALIZZATO

- PRODIGY chemioterapia peri-operatoria vs chemioterpia post-operatoria
- RESOLVE SOX peri-operatorio vs CAPOX post-operatorio vs SOX post-op

CARCINOMA ESOFAGO-GASTRICO METASTATICO

- ATTRACTION 3 Nivolumab vs Taxani
- KEYNOTE 062 MSI CT vs Pembrolizumab vs CT+Pembrolizumab
- ANGEL Rivoceranib vs Placebo

BARCELONA 2019 ESMO congress

A PHASE III OPEN LABEL RANDOMIZED STUDY OF NEOADJUVANT CHEMOTHERAPY WITH DOCETAXEL, OXALIPLATIN AND S-1 (DOS) FOLLOWED BY SURGERY AND ADJUVANT S-1, VS SURGERY AND ADJUVANT S-1 FOR RESECTABLE ADVANCED GASTRIC CANCER (PRODIGY STUDY)

Y.-K. Kang, J.H. Yook, Y.-K. Park, Y.-W. Kim, J.Y. Kim, M.-H. Ryu, S.Y. Rha, I.-J. Chung, I.-H. Kim, S.C. Oh, C.-H. Yoo, J.-H. Choi, D.Y. Zang, G.J. Kim, Y.J. Lee, S.-H. Noh

Presenter: Professor Yoon-Koo Kang

Department of Oncology, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, South Korea

Contact: ykkang@amc.seoul.kr

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

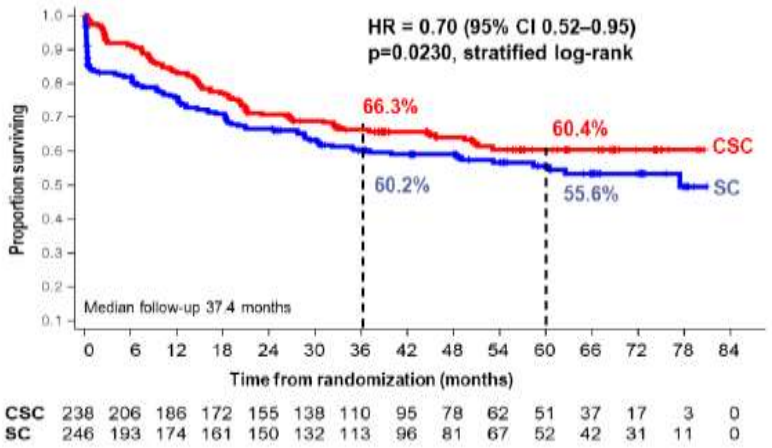
Histologically confirmed cT2, 3 / N(+) or $cT4N_{any}$ gastric or GEJ adenocarcinoma

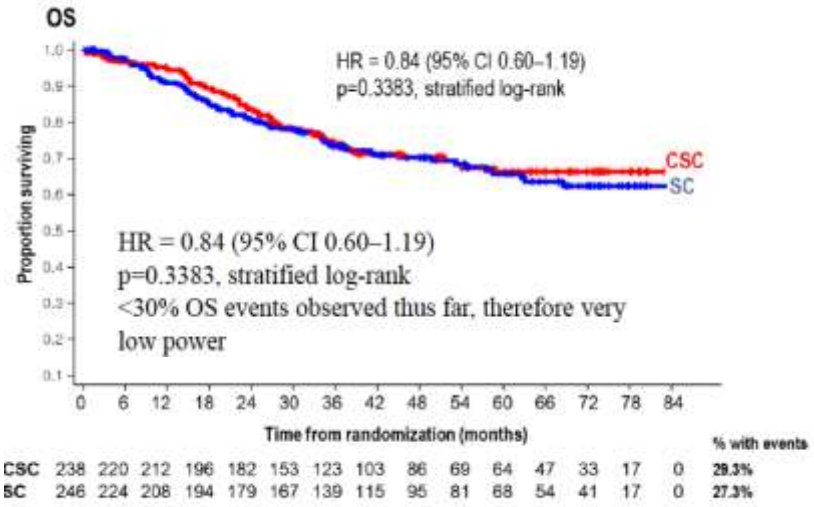
R

n=266 → CSC
DOS × 3 → D2 resection → S-1 ×8

n=264 → SC
D2 resection → S-1 ×8

Primary endpoint: 3years PFS





Kang et al ESMO 2019

RESOLVE STUDY

BARCELONA 2019 ESMO congress

PERIOPERATIVE CHEMOTHERAPY OF OXALIPLATIN COMBINED WITH S-1 (SOX) VERSUS POSTOPERATIVE CHEMOTHERAPY OF SOX OR OXALIPLATIN WITH CAPECITABINE (XELOX) IN LOCALLY ADVANCED GASTRIC ADENOCARCINOMA WITH D2 GASTRECTOMY: A RANDOMIZED PHASE III TRIAL (RESOLVE TRIAL)

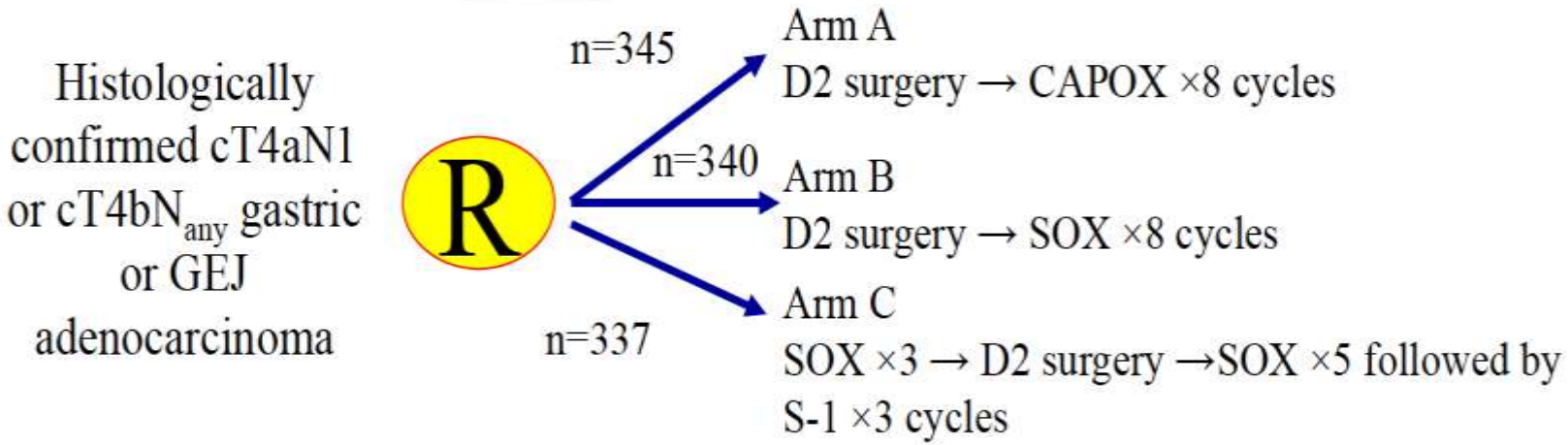
J.Ji, L.Shen, Z.Li, X.Zhang, H.Liang, Y.Xue, Y.Wang, Z.Zhou, J.Yu, L.Chen, Y.Du, G,Li, G.Xiao, D.Wu, Y.Zhou, C.Dang, Y.He, Z.Zhang, Y.Sun, Y. Li,

Peking University Cancer Hospital, Beijing, China

Abstract 3635, LBA-42

on behalf of the RESOLVE Investigators

RESOLVE: Randomised phase III study in gastric and GEJ adenocarcinoma of peri-op SOX vs post-op SOX vs post-op CAPOX



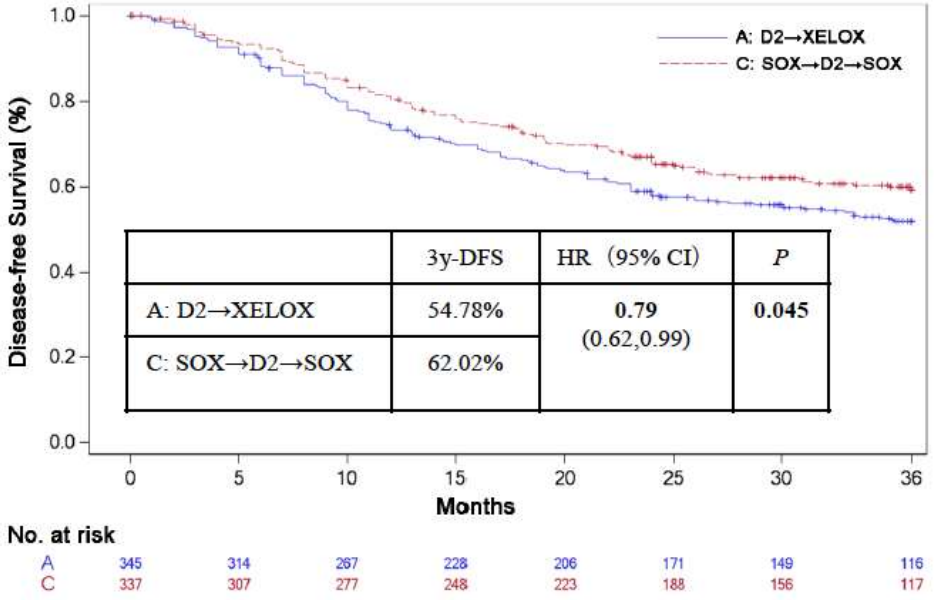
Primary endpoint: 3-year DFS

Arms A vs. C: superiority; A vs. B: non-inferiority

Ji et al ESMO 2019

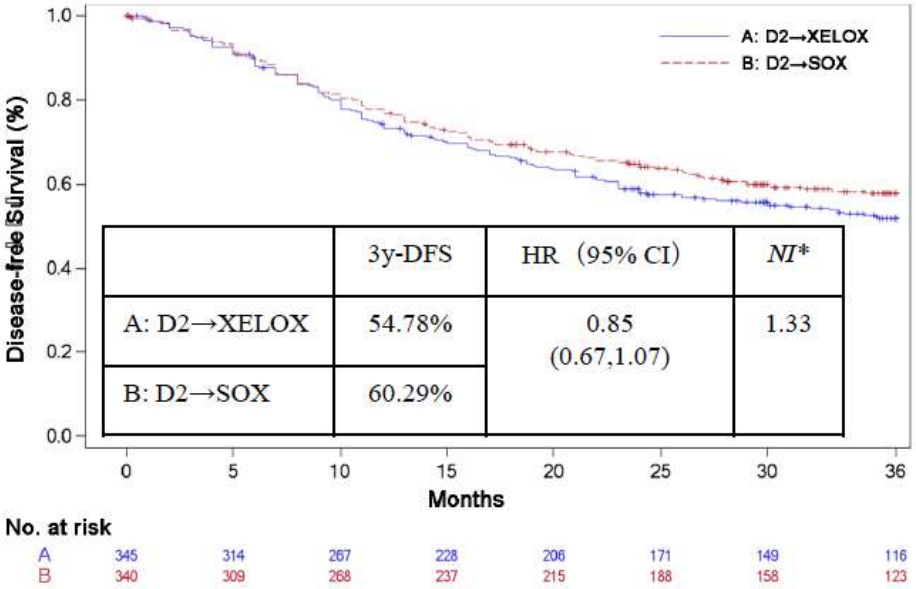
RESOLVE primary comparisons

ARMs A vs. C



	3y-DFS	HR (95% CI)	*P*
A: D2→XELOX	54.78%	**0.79** (0.62,0.99)	**0.045**
C: SOX→D2→SOX	62.02%		

ARMs A vs. B



	3y-DFS	HR (95% CI)	*NI**
A: D2→XELOX	54.78%	0.85 (0.67,1.07)	1.33
B: D2→SOX	60.29%		

Ji et al ESMO 2019

Nuove Prospettive: tumori non COLON-RETTO

EPATOCARCINOMA

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- ANGEL Rivoceranib vs Placebo
- KEYNOTE 062 MSI CT vs Pembrolizumab vs CT+Pembrolizumab
- ATTRACTION 3 Nivolumab vs Taxani

Apatinib in gastric cancer

BARCELONA 2019 ESMO congress

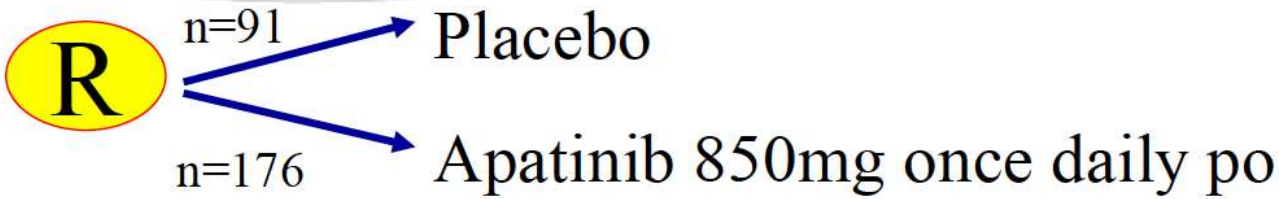
Randomized phase 3 ANGEL study of rivoceranib (apatinib) + best supportive care (BSC) vs placebo + BSC in patients with advanced/metastatic gastric cancer who failed ≥2 prior chemotherapy regimens

Kang Y-K, Kang WK, Di Bartolomeo M, Chau I, Yoon H, Cascinu S, **Ryu M-H,** Kim JG, Lee K-W, Oh SC, Takashima A, Kryzhanivska A, Chao Y, Vladimirov V, Evesque L, Schenker M, McGinn A, Sankar N, Wyrwicz L, Boku N

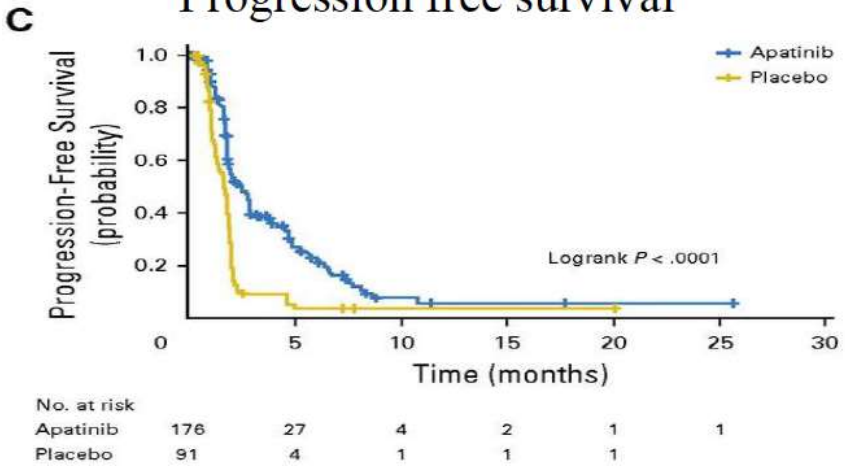
Presenting author: *Professor Min-Hee Ryu, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Kang et al, ESMO 2019

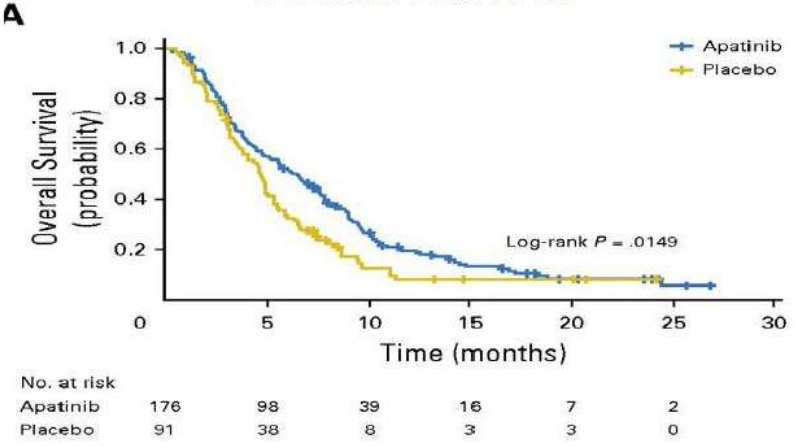
Background



Progression free survival

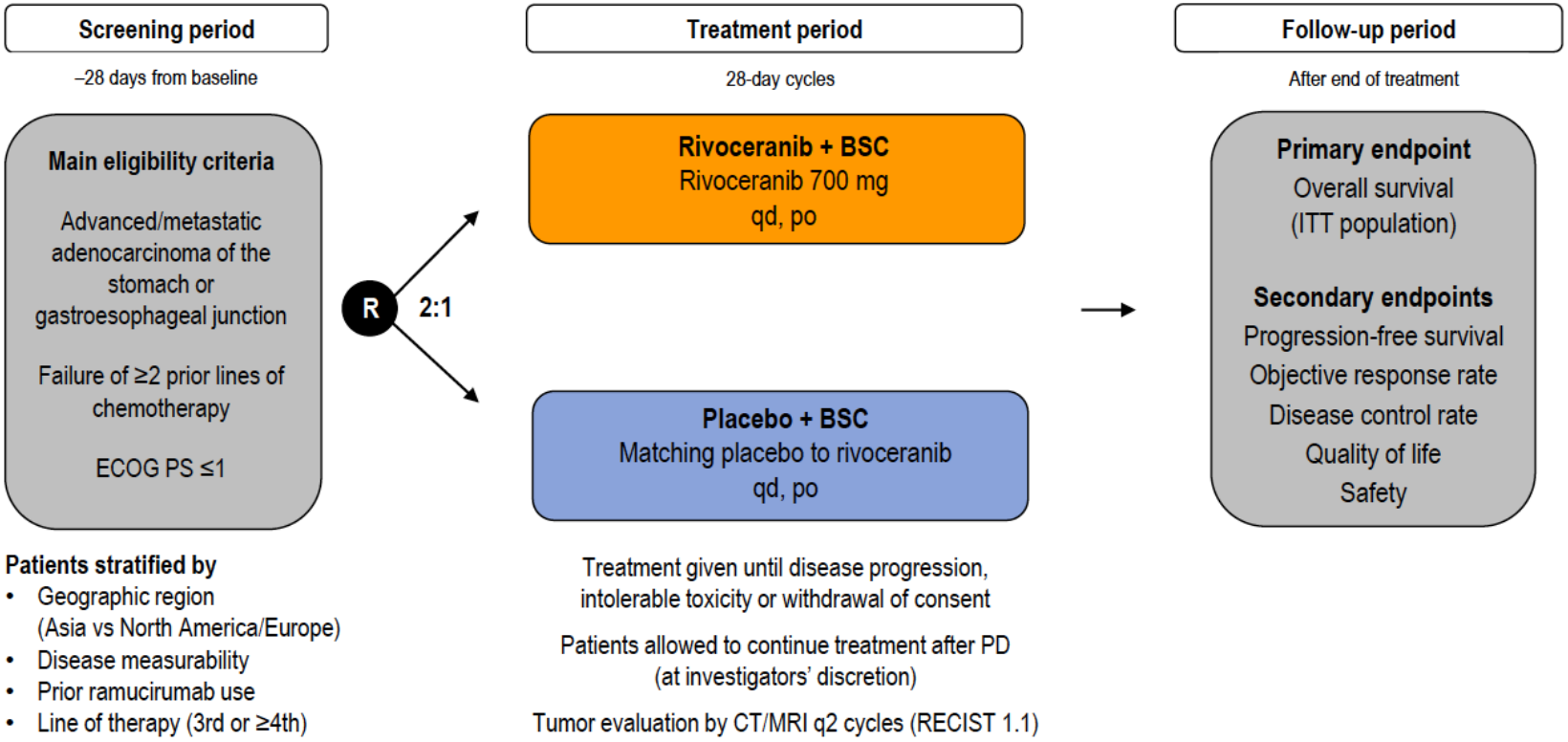


Overall survival



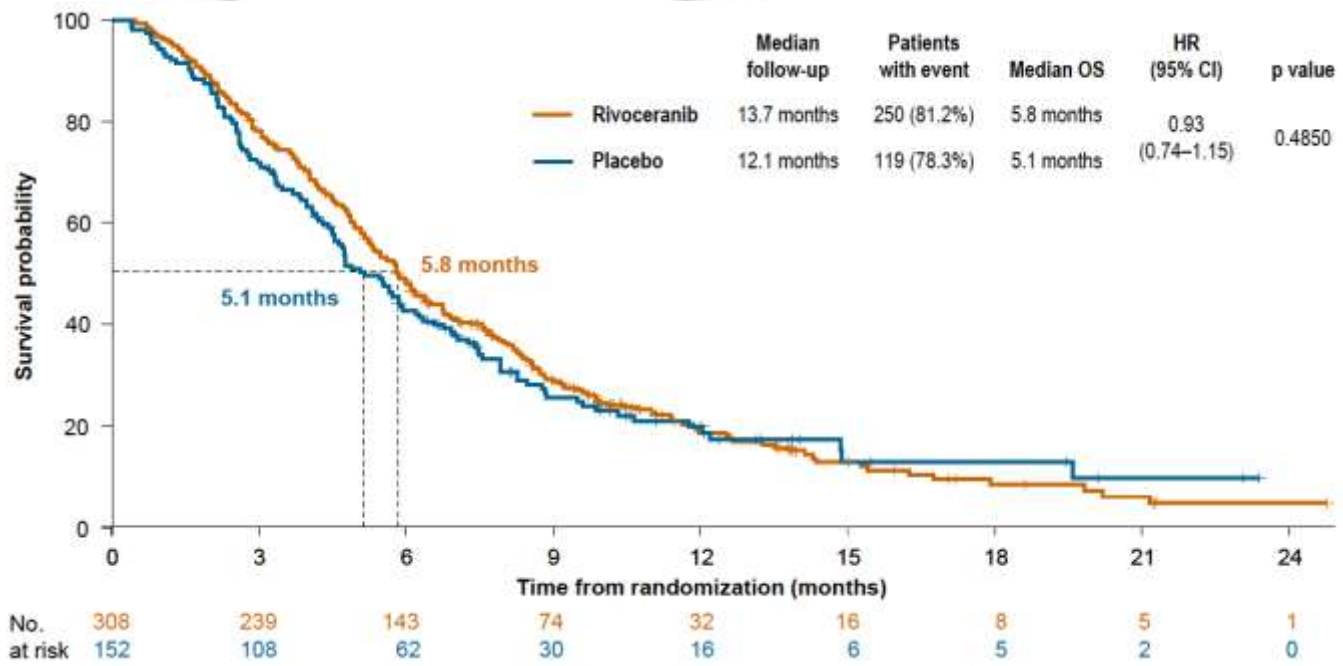
Li et al J Clin Oncol 2016

ANGEL: a global randomized phase III study



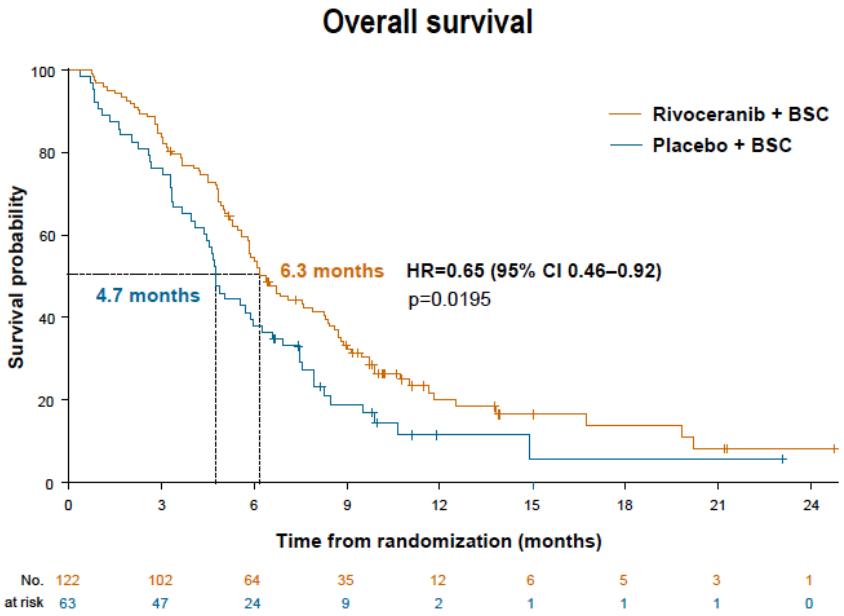
Kang et al ESMO 2019

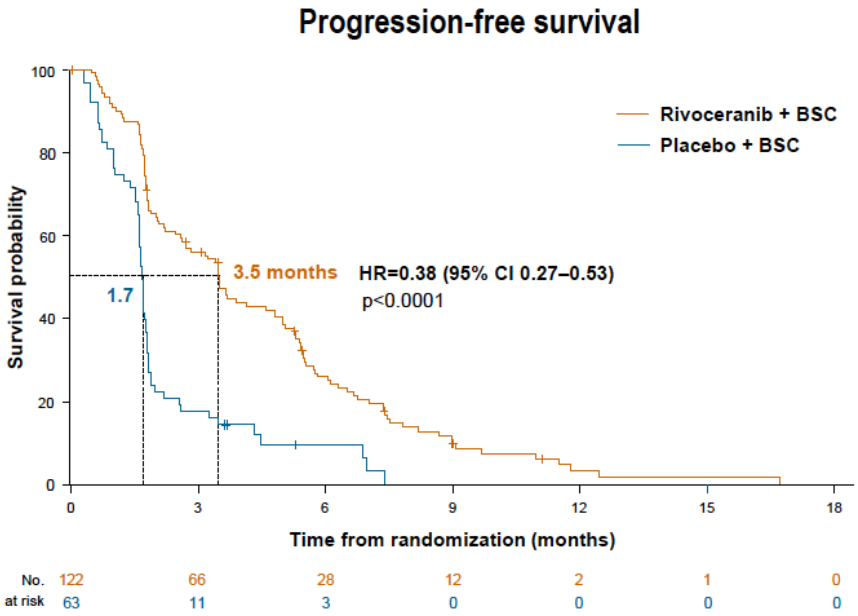
ANGEL: OS



Kang et al ESMO 2019

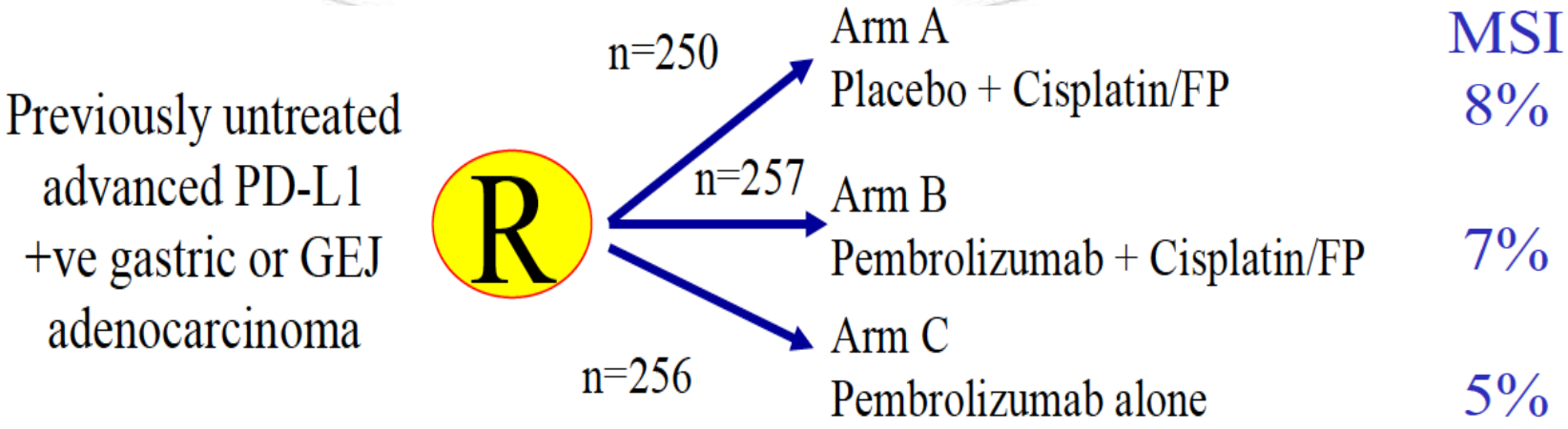
ANGEL: OS and PFS in ≥ 4 line patients





Kang et al ESMO 2019

Randomized first line phase III Pembrolizumab study in gastric and GEJ adenocarcinoma KEYNOTE-062 MSI subgroup



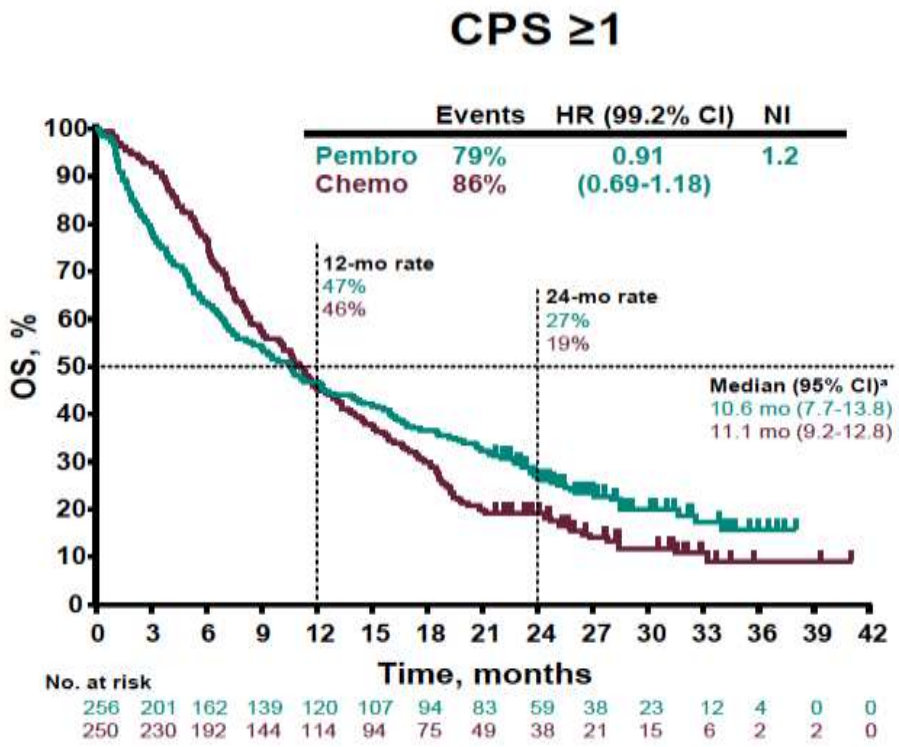
Primary endpoint: PD-L1 CPS ≥1 PFS and OS

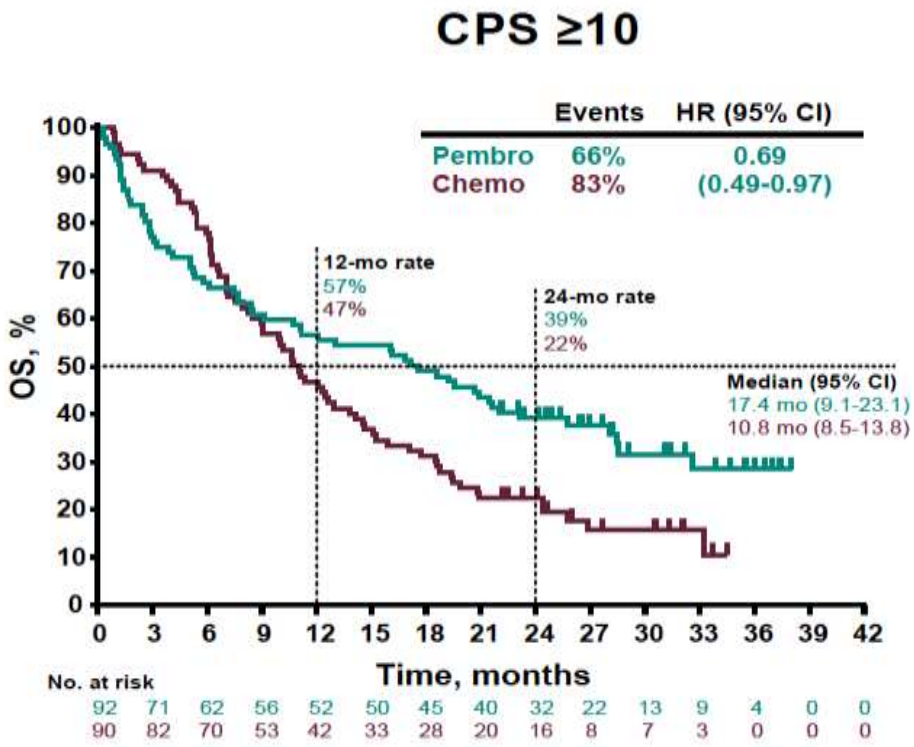
Co- endpoint: PD-L1 CPS ≥10 PFS and OS

Arms A vs. B: superiority; A vs. C: non-inferiority

Shitara et al ESMO 2019; Tabernero et al ASCO 2019

Pembro vs CT: OS in ITT

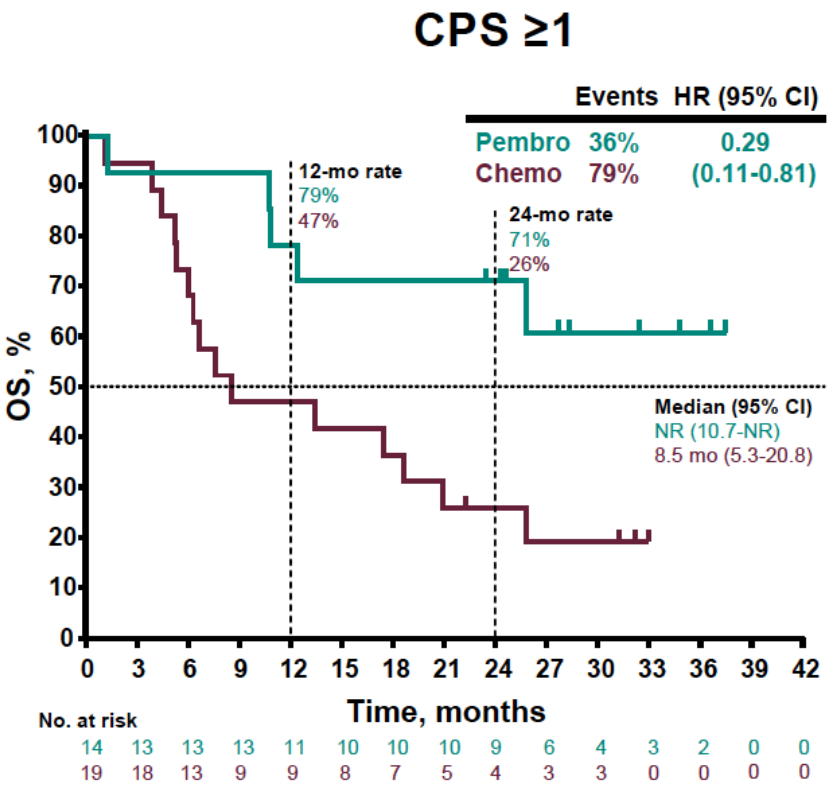


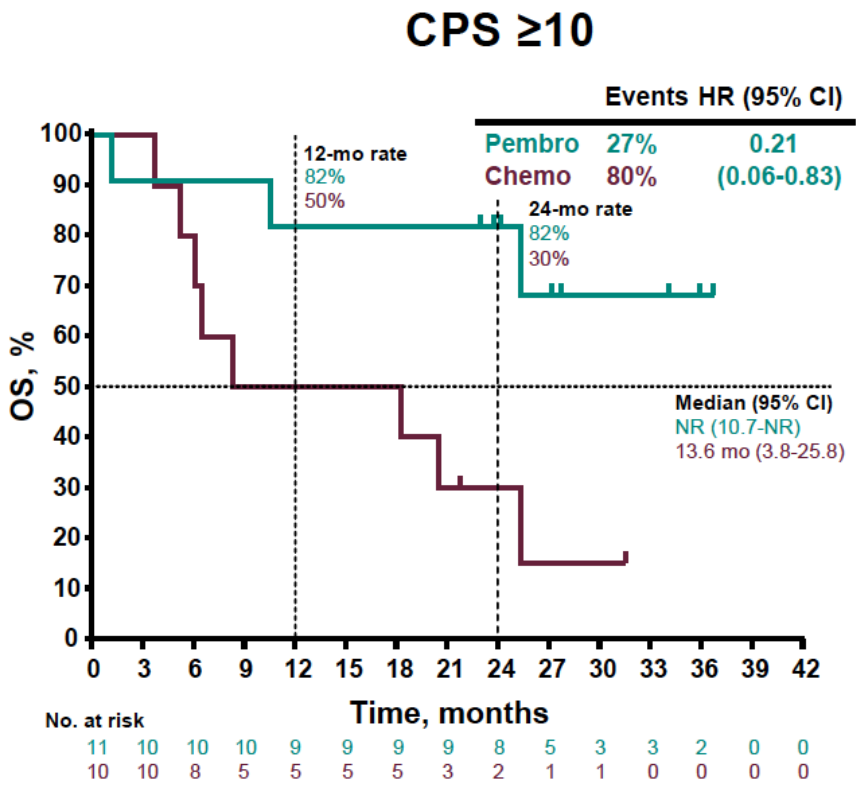


NI, non-inferiority margin. aHR (95% CI), 0.91 (0.74-1.10), $P = 0.162$ for superiority of pembro vs chemo Data cutoff: March 26, 2019.

Shitara et al ESMO 2019; Tabernero et al ASCO 2019

Pembro vs CT: OS in MSI-H group

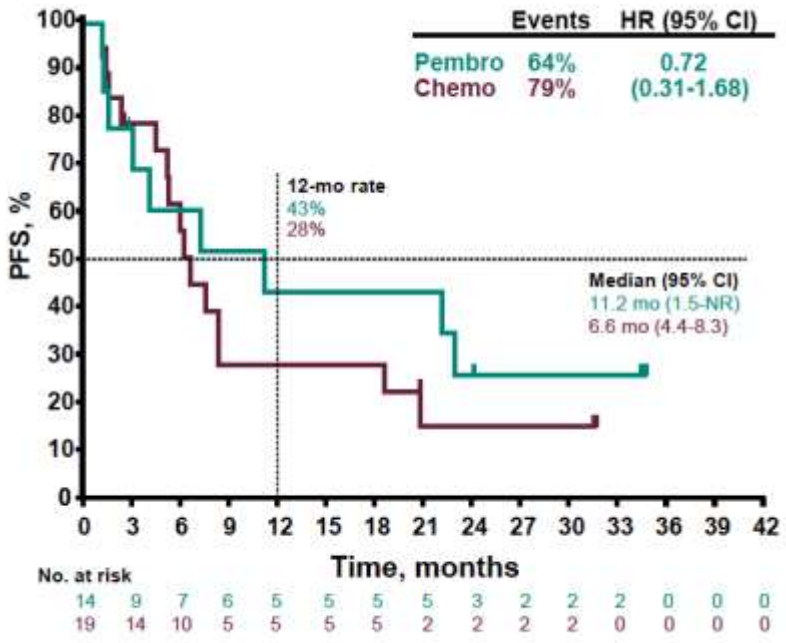


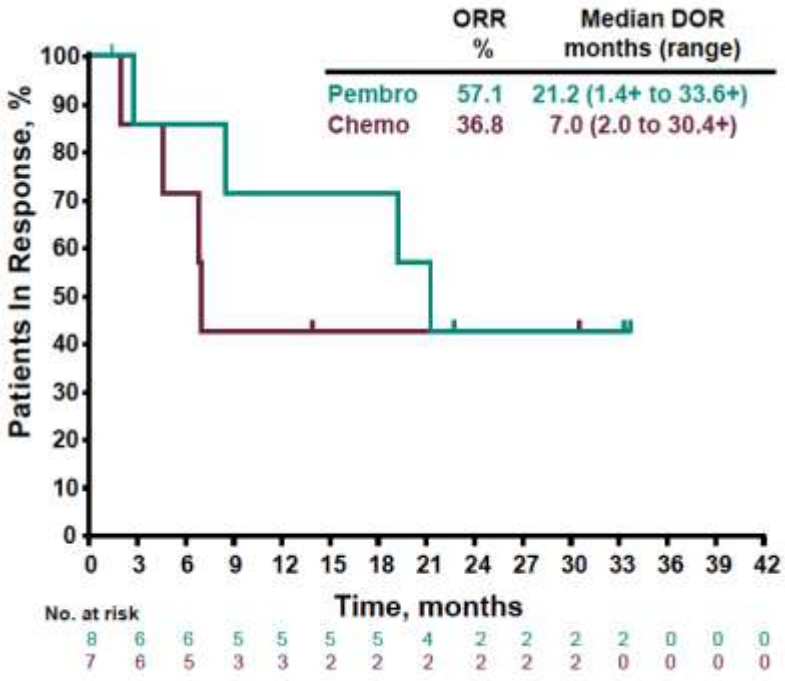


Data cutoff: March 26, 2019.

Shitara et al ESMO 2019

Pembro vs CT: PFS and DOR in MSI-H group (CPS≥1)

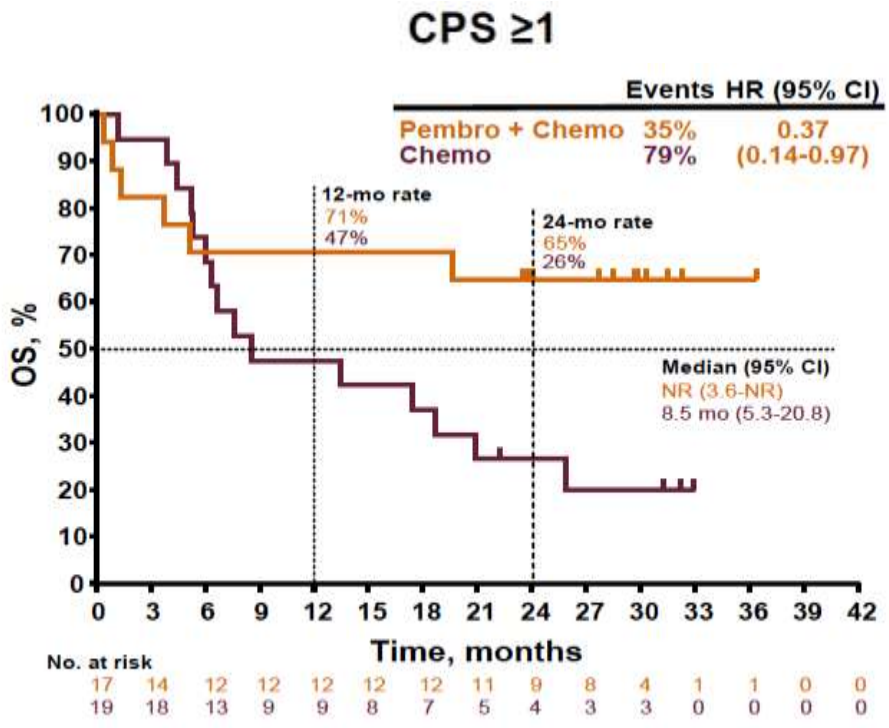


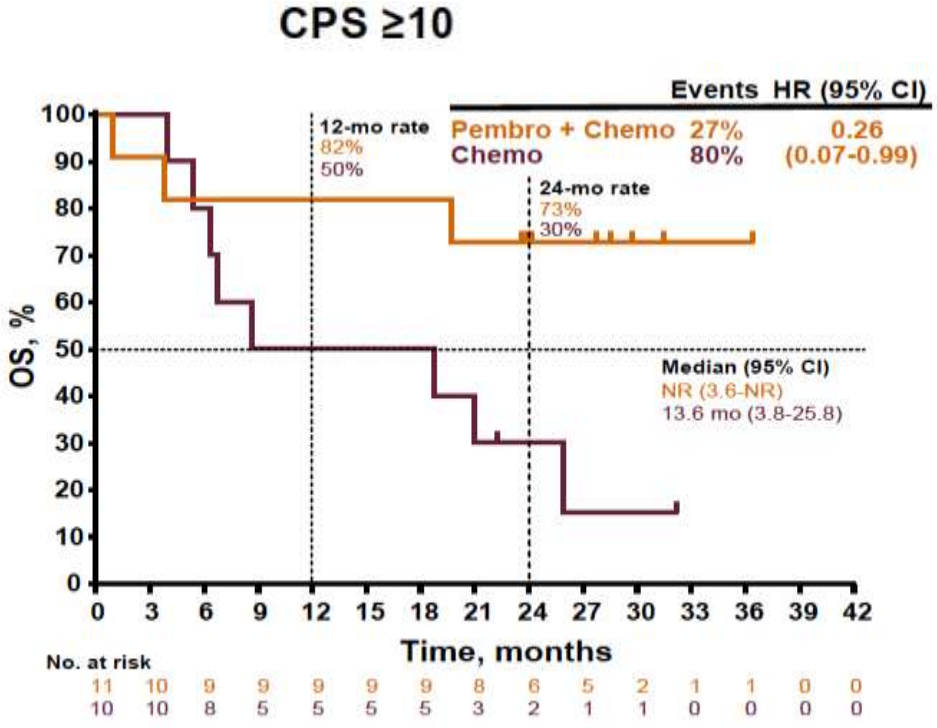


PFS and response assessed per RECIST v1.1 by blinded independent central review; Data cutoff: March 26, 2019.

Shitara et al ESMO 2019

Pembro+CT vs Pembro: OS in MSI-H group





Data cutoff: March 26, 2019.

Shitara et al ESMO 2019

ATTRACTION-3: Randomized second line phase III study in squamous oesphageal carcinoma (SCC) with Nivolumab

Unresectable advanced or recurrent SCC oesophagus
Refractory to or intolerant to 1 prior line platinum + FP therapy

R

n=209 → Taxane (docetaxel or paclitaxel)

n=210 → Nivolumab 240 mg every 2 weeks

FIRST ENDPOINT: OS

	Nivolumab (n = 210)[a]	Chemotherapy (n = 209)[a]
Median OS,[b] mo	10.9	8.4
(95% CI)	(9.2–13.3)	(7.2–9.9)
HR (95% CI)	0.77 (0.62–0.96)	
P value	0.019	

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

[a]Intent-to-treat population; [b]Minimum follow-up: 17.6 months.
CI, confidence interval; mo, months.

Cho et al, ESMO 2019

Treatment Paradigm in advanced/metastatic SCC oesophagus 2019

Inoperable/metastatic/recurrent SCC

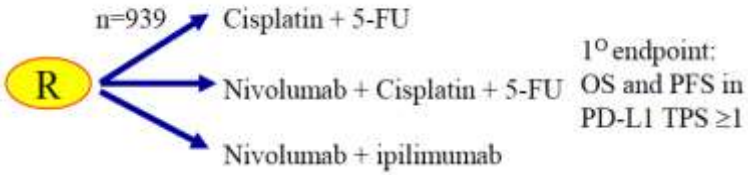
Platinum+FP based CT

Nivolumab

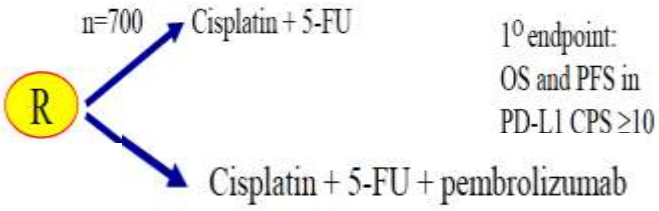
Pembrolizumab if PDL1 CPS>10

Taxanes or Irinotecan

CHECKMATE 648[1]



KEYNOTE 590[2]



[1]Ajani et al ASCO GI 2019 NCT03143153;
[2]Kato et al Future Oncol 2019 NCT03189719

TUMORI GASTROINTESTINALI

Nuove Prospettive: tumori NON colon-retto

Grazie

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

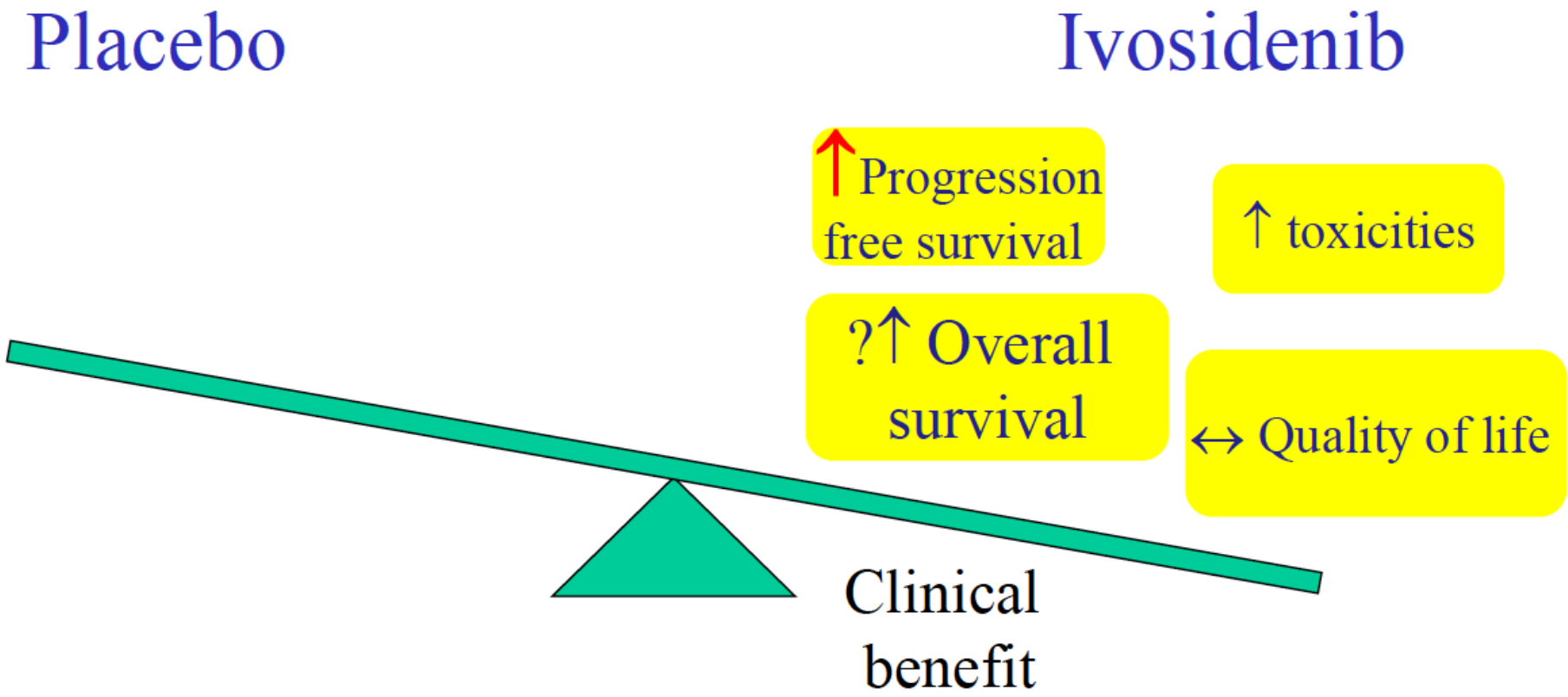
Antonia Strippoli

ClarIDHy: Baseline characteristics

Characteristic	Ivosidenib (n=124)	Placebo (n=61)
Randomization strata, n (%)		
1 prior line of therapy	66 (53.2)	33 (54.1)
2 prior lines of therapy	58 (46.8)	28 (45.9)
IDH1 mutation, n (%)		
R132C	84 (67.7)	45 (73.8)
R132L/G/S/H	21 (16.9); 17 (13.7); 2 (1.6); 0	7 (11.5); 6 (9.8); 1 (1.6); 2 (3.3)
ECOG PS score at baseline,* n (%)		
0	49 (39.5)	19 (31.1)
1	74 (59.7)	41 (67.2)
Cholangiocarcinoma type at diagnosis, n (%)		
Intrahepatic	111 (89.5)	58 (95.1)
Extrahepatic/Perihilar	5 (4.0)	1 (1.6)
Unknown	8 (6.5)	2 (3.3)
Extent of disease at screening		
Local/regional	9 (7.3)	5 (8.2)
Metastatic	115 (92.7)	56 (91.8)

*Two (2) patients had an ECOG worsen to 2 (placebo) and 3 (ivosidenib) at baseline assessment upon study start.

ClarIDHdy: phase III study of Ivosidenib vs placebo in advanced mIDH1 biliary tract cancer



Abou-Alfa et al, ESMO 2019

FIGHT 202: AE

Adverse Event, n (%)	Any AEs (N = 146)*	
	All Grades	Grade ≥3
Hyperphosphatemia†	**88 (60)**	**0**
Alopecia	72 (49)	0
Diarrhea	68 (47)	4 (3)
Fatigue	**62 (42)**	**7 (5)**
Nail toxicities†	62 (42)	3 (2)
Dysgeusia	59 (40)	0
Nausea	58 (40)	3 (2)
Constipation	51 (35)	1 (1)
Stomatitis	**51 (35)**	**8 (5)**
Dry mouth	49 (34)	0
Decreased appetite	48 (33)	2 (1)
Vomiting	40 (27)	2 (1)
Dry eye	37 (25)	1 (1)
Arthralgia	36 (25)	9 (6)

- **Hyperphosphatemia†** managed with a low phosphate diet, phosphate binders, and diuretics, or dose reduction/interruption
  - All grade 1 or 2
  - Few (n = 3) required dose reductions/interruptions
- **Hypophosphatemia†** occurred in 23% of patients
  - Most common grade ≥3 AE (12%)
  - None clinically significant/serious; none led to discontinuation/dose reduction
- **Serous retinal detachment†** occurred in 4% of patients
  - Mostly grade 1/2 (grade ≥3, 1%)
  - None resulted in clinical sequelae

Vogel et al, ESMO 2019

FIGHT 202: ORR

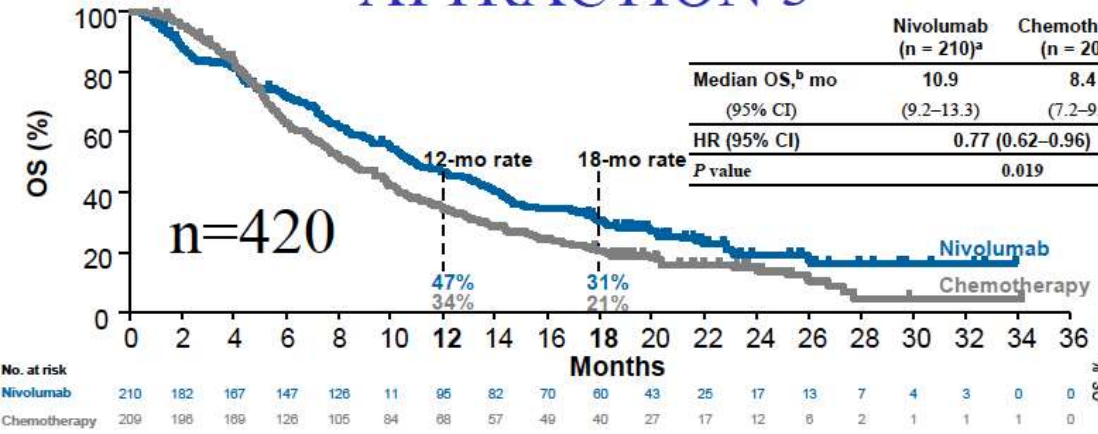
ORR BY SUBGROUP (COHORT A)

Subgroup	No. of Patients	Objective Response Rate (95% CI)
All patients	107	35.5 (26.50–45.35)
Age group		
<65 years	82	34.1 (24.03–45.45)
65–<75 years	20	40.0 (19.12–63.95)
≥75 years	5	40.0 (5.27–85.34)
Sex		
Male	42	31.0 (17.62–47.09)
Female	65	38.5 (26.65–51.36)
Race		
White	79	34.2 (23.87–45.71)
Asian	11	36.4 (10.93–69.21)
Other	17	41.2 (18.44–67.08)
Region		
North America	64	35.9 (24.32–48.90)
Western Europe	32	40.6 (23.70–59.36)
Rest of world	11	18.2 (2.28–51.78)
ECOG status		
0	45	48.9 (33.70–64.23)
1 or 2	62	25.8 (15.53–38.50)
Metastatic disease present		
Yes	88	33.0 (23.30–43.79)
No	16	50.0 (24.65–75.35)
Lines of prior therapy		
1 line	65	36.9 (25.28–49.80)
2 lines	29	34.5 (17.94–54.33)
≥3 lines	13	30.8 (9.09–61.43)
FGFR2 rearrangement partner		
BICC1	31	32.3 (16.68–51.37)
Other	76	36.8 (26.06–48.69)

Vogel et al, ESMO 2019

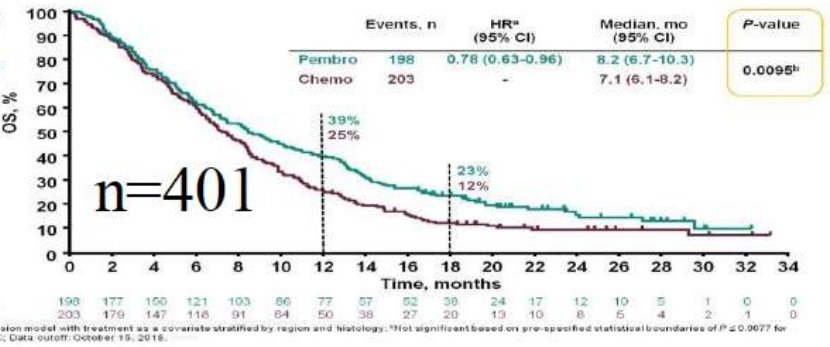
PD-1 antibody has a consistent beneficial OS effect in SCC oesophagus

ATTRACTION 3[1]



	Nivolumab (n = 210)[a]	Chemotherapy (n = 209)[a]
Median OS,[b] mo	10.9	8.4
(95% CI)	(9.2–13.3)	(7.2–9.9)
HR (95% CI)	0.77 (0.62–0.96)	
P value	0.019	

KEYNOTE 181[2]



	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	198	0.78 (0.63-0.96)	8.2 (6.7-10.3)	0.0095[b]
Chemo	203	-	7.1 (6.1-8.2)	

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology. [b]Not significant based on pre-specified statistical boundaries of $P \leq 0.0077$ for superiority of OS in SCC; Data cutoff: October 15, 2018.

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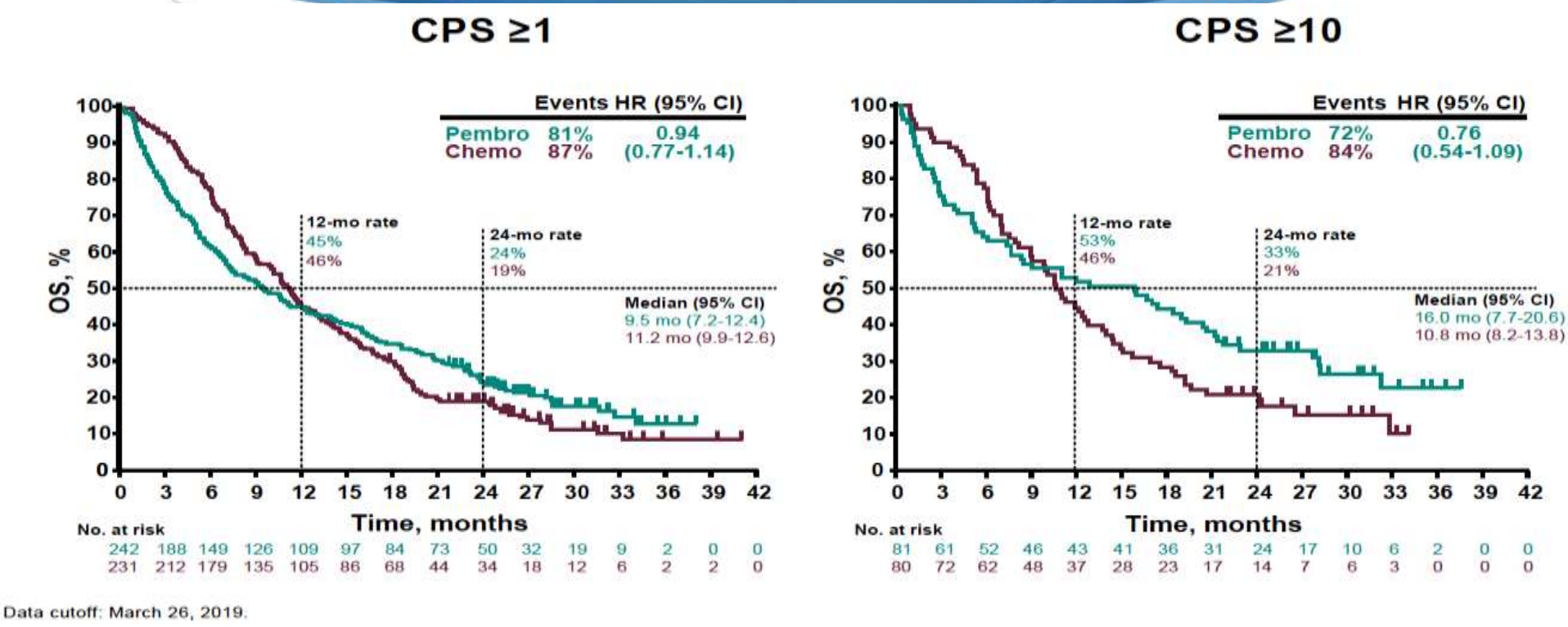
[1]Cho et al ESMO 2019; [2]Kojima et al ASCO GI 2019

Pembro vs CT: OS in non MSI-H group



Data cutoff: March 26, 2019.

Shitara et al ESMO 2019

(ACTS-GC)

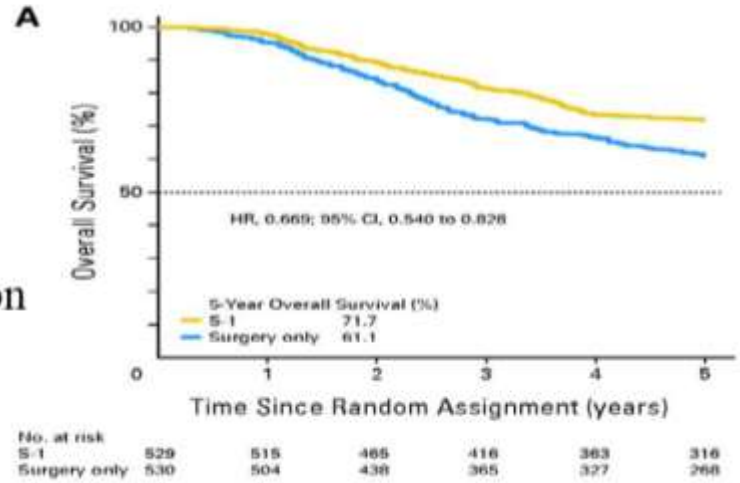
Patients with stage II & III gastric cancer; D2 or more dissection

R

n=529 S-1

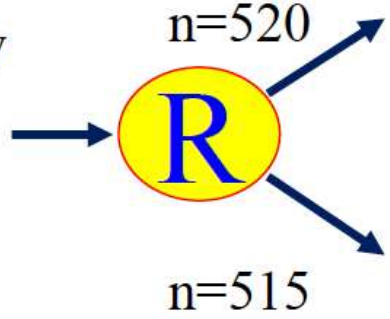
Observation n=530

Overall survival (total population)



CLASSIC: trial design

Patients with surgically resected GC, stage II, IIIa or IIIb disease.
D2 dissection



CAPOX
Oxaliplatin 130mg/m^2
Capecitabine 2,000mg/m^2/day for 14 days
q 3 weeks for 8 cycles

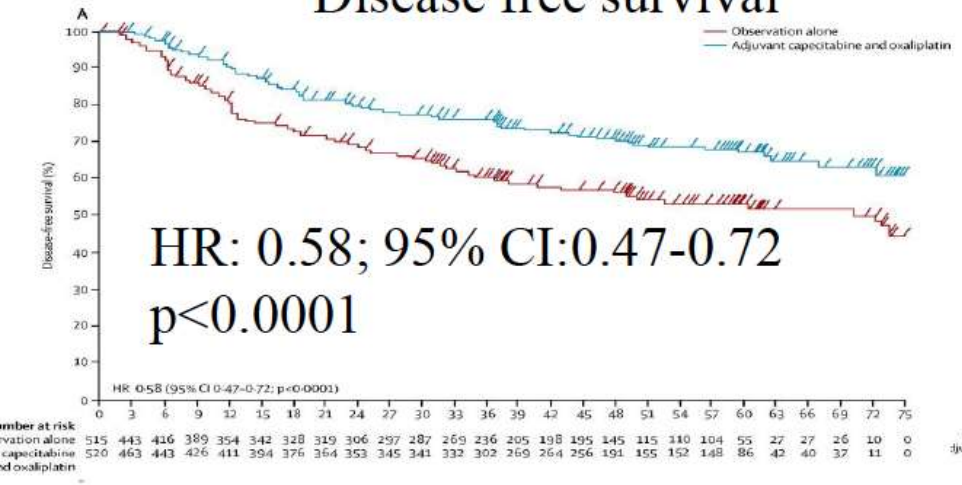
Observation

- Primary outcome: 3-year DFS
- Secondary endpoints: overall survival, response rate, safety
- To increase 3-year DFS from 56.2% to 65% (HR=0.75) with adjuvant CAPOX, 512 patients required per arm to observe 385 DFS events (80% power; 2-sided p=0.05)

Bang et al. Lancet 2012

CLASSIC: survival outcome

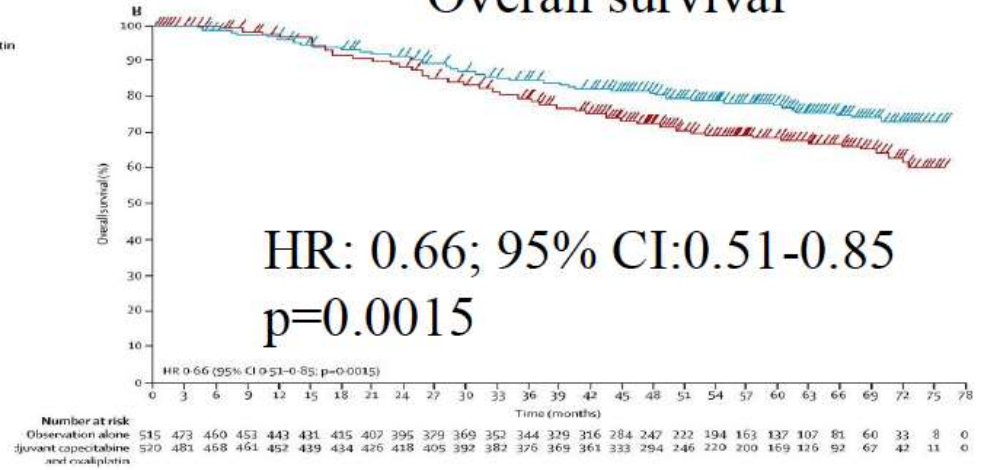
Disease free survival



HR: 0.58; 95% CI:0.47-0.72

p<0.0001

Overall survival



HR: 0.66; 95% CI:0.51-0.85

p=0.0015

	5 year DFS
Surgery alone	53%
Adjuvant CAPOX	68%

	5 year OS
Surgery alone	69%
Adjuvant CAPOX	75%

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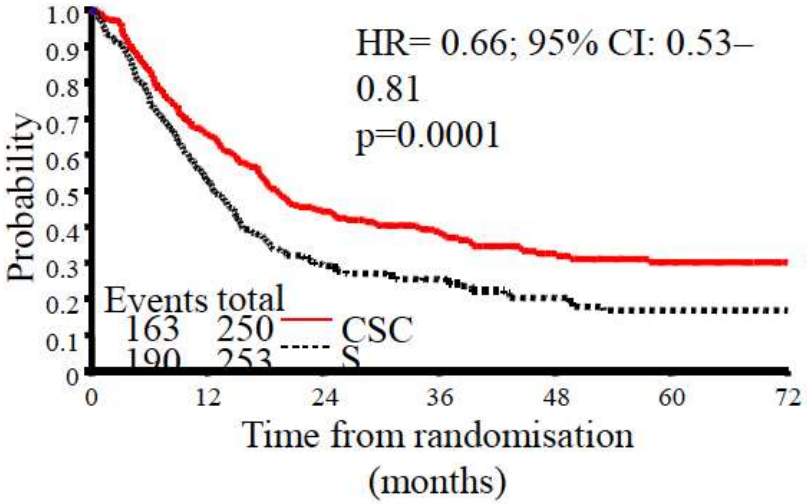
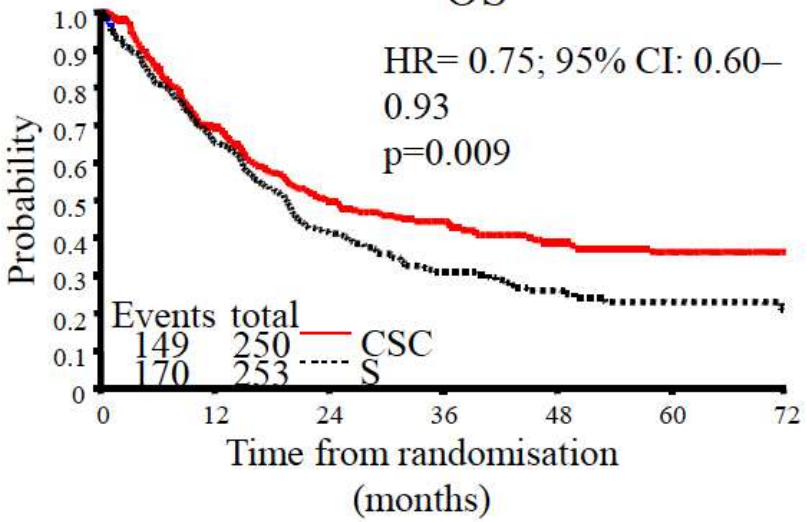
Noh et al Lancet Oncol 2014

MRC MAGIC study

PFS



OS



	2-year survival (%)	5-year survival (%)	Median survival (months)
CSC	50	36	24
S	41	23	20
Benefit to CSC arm	9	13	4

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CSC = peri-operative ECF; S = surgery alone

Cunningham et al N Engl J Med 2006