2019 AIOM REVIEW:
FROM CHICAGO TO VERONA
Verona, 14-15 Giugno 2019

Gastrointestinal (no colorectal)

POSTER REVIEW

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Agenda

- **Esophageal**
  - PET-guided therapy in GEJ adenocarcinoma: #4018
- **Gastric**
  - Molecular selection for ramucirumab: #3143, #4064
  - Combining anti-HER2 therapy and ICIs: #4011
  - Refining clinical selection of frial/elderly patients: #4006, #4051
- **Pancreatic**
  - BRCA, HRD and PARP inhibitors in mPC: #4014, #4015, #4132, #4132
  - Neoadjuvant CT in resectable disease: #4126, #4128, #4137
- **Hepatobiliary**
  - ICIs in BTC: #4074, #4079, #4082, #4097
  - New targets in BTC and molecular selection in HCC: #4085, #4075

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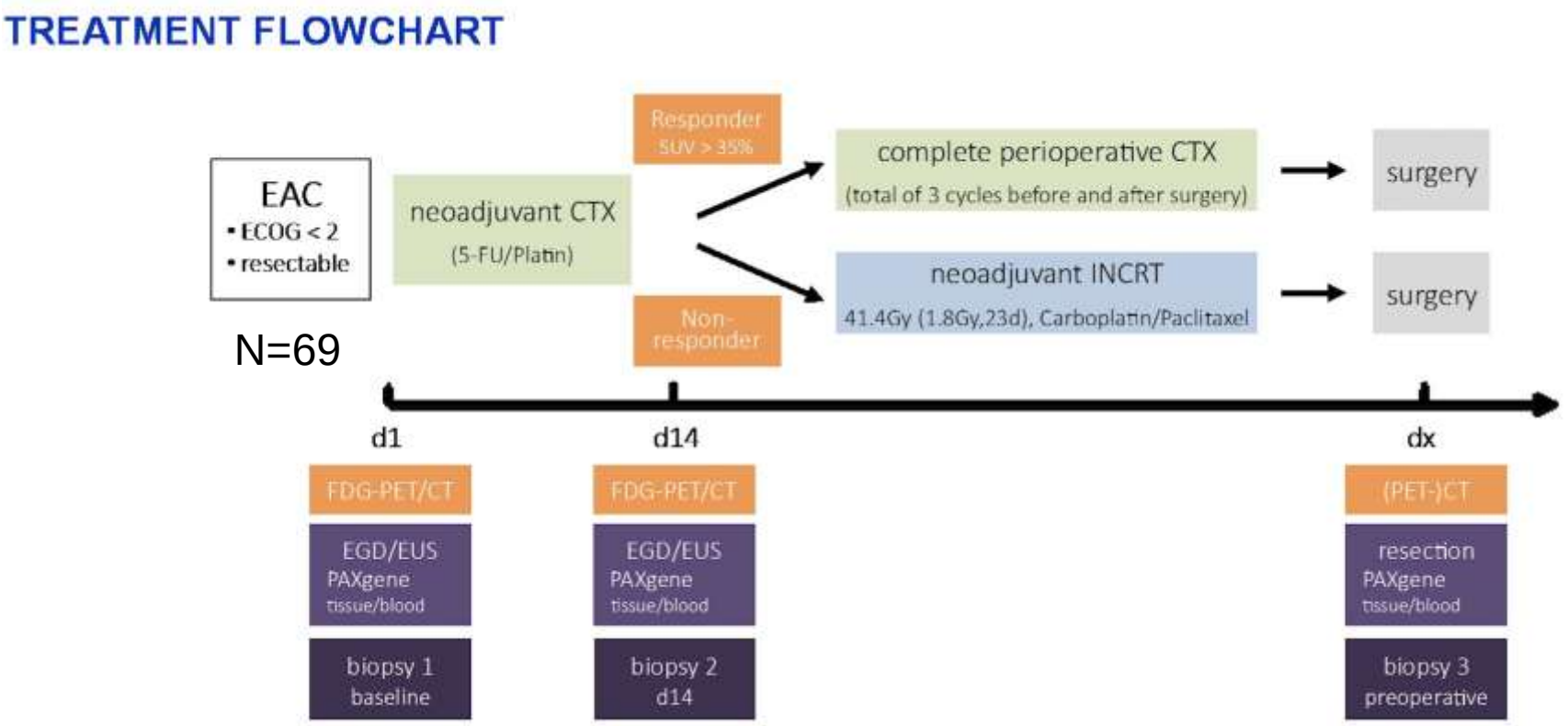
MEMORI: PET-guided therapy in GEJC



- ✓ GEJ adenocarcinoma staged uT3NxM0
- ✓ Metabolic response defined as at least 35% decrease in SUV mean value
- ✓ Chemotherapy: physician's choice EOX, XP or mFOLFOX6
- ✓ Primary endpoint: R0 resection in PET-non responders >70%

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MEMORI: PET-guided therapy in GEJC

PRIMARY ENDPOINT: RESECTION RATE

Residual tumor	
R0	64 (93%)
R1	5 (7%)

	PET-Responder	PET-Non-responder
R0	**94%** (n=44)	**91%** (n=20)
R1	**6%** (n=3)	9% (n=2)

PATHOLOGY

	PET-Responder (n=47)	PET-Non Responder (n=22)
Complete remission (1a) 0% residual tumor	2% (n=1)	9% (n=2)
Subtotal remission (1b) < 10% residual tumor	28% (n=13)	50% (n=11)
Moderate remission (2) 10-50% residual tumor	38% (n=18)	27% (n=6)
No remission (3) > 50% residual tumor	32% (n=15)	14% (n=3)
Major remission (1a + 1b) **0 - 10% residual tumor**	**30%** (n=14)	**59%** (n=13)

Primary endpoint met

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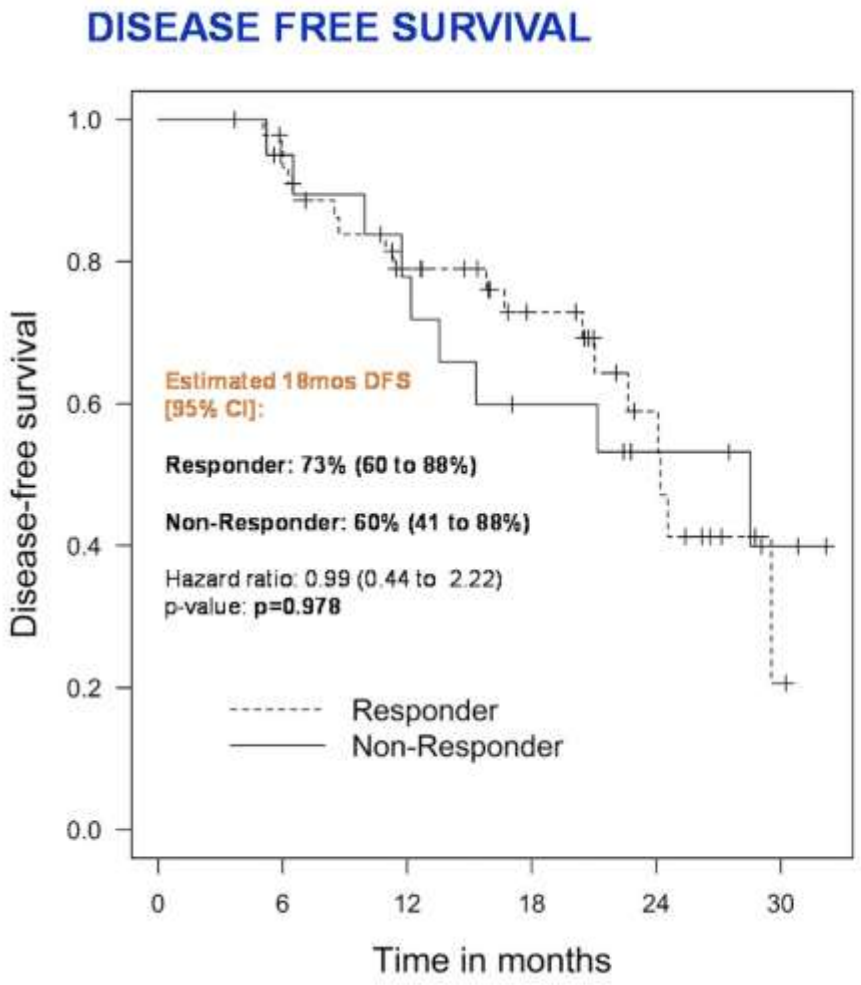
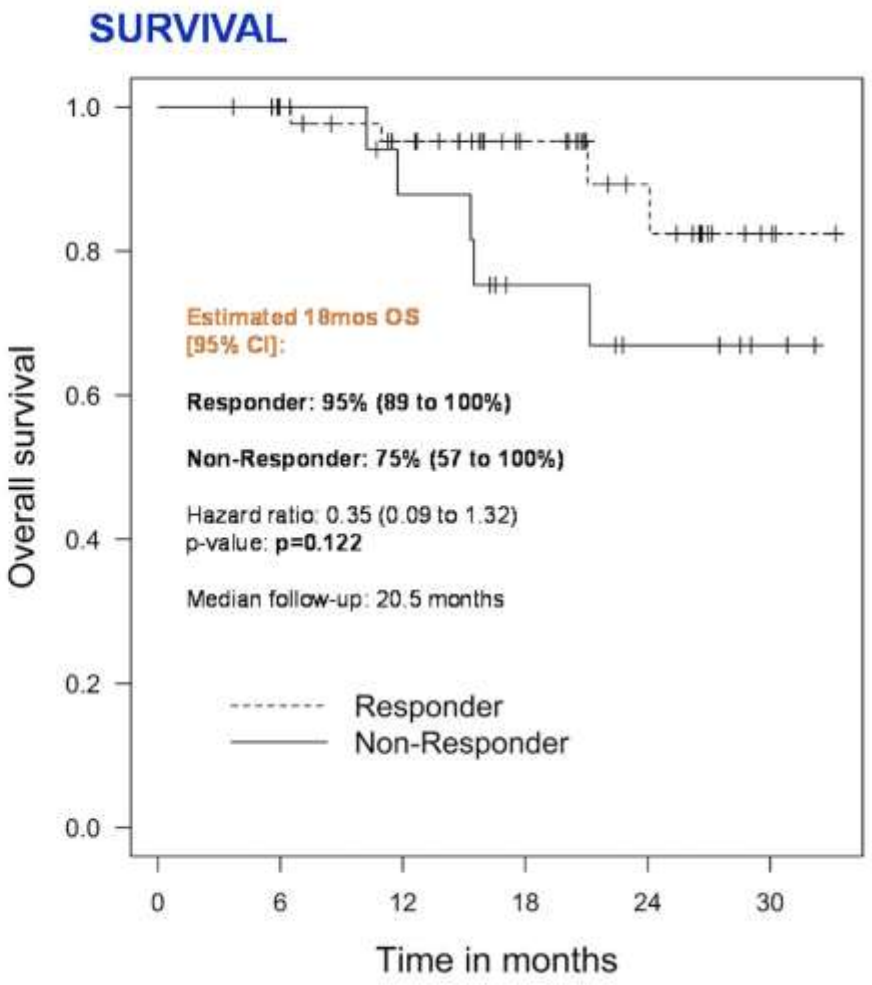
MEMORI: PET-guided therapy in GEJC





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VERA: VEGF-A amplification and Ramucirumab

mGC patients were included in the study according to the following criteria:

1) complete (CR) or partial response (PR) to single-agent ramucirumab

2) >6 months PFS to single-agent ramucirumab

3) >10 months PFS to ramucirumab plus paclitaxel

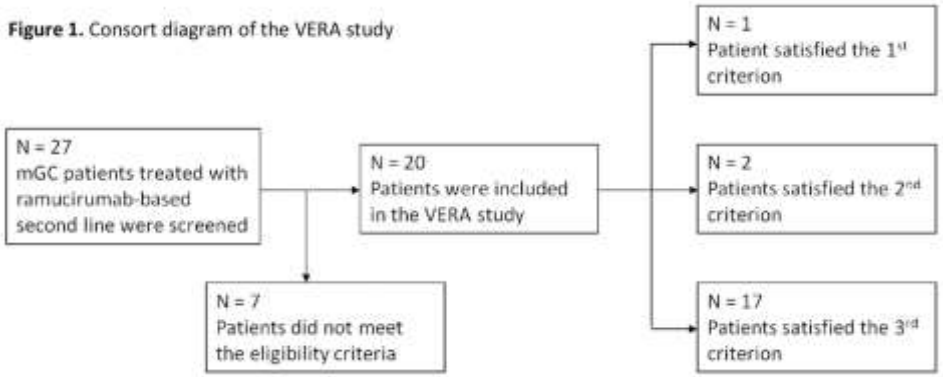
Statistical Plan

According to a Fleming single-stage design, hypothesizing a prevalence of *VEGF-A* amplification of 1% and 15% among all-comers and exceptional responders, 20 patients were required to reject the null hypothesis of low prevalence of *VEGF-A* amplification, with alpha- and beta- errors of 0.05 and 0.10, respectively.

Molecular analysis

VEGF-A amplification (defined as >10% tumor cells with ≥10 *VEGF-A* copies, variably sized signal clusters or a ratio of *VEGF-A* gene to centromere of ≥2) was centrally assessed through fluorescent in situ hybridization (FISH) on pre-treatment FFPE tumor tissue.

Figure 1. Consort diagram of the VERA study



Patient ID	FISH result	Average *VEGF-A* copy number	Average CEP copy number	*VEGF-A*/CEP Ratio	% of cells with ≥10 signals
1	Negative	2.2	2.1	1	/
2	**Amplified**	**Large clusters**	**/**	**/**	**/**
3	Negative	2.3	2.2	1	/
4	Not evaluable	Not evaluable	Not evaluable	Not evaluable	Not evaluable
5	Polysomy	3.6	3.3	1	/
6	Negative	2.4	2.3	1	/
7	Not evaluable	Not evaluable	Not evaluable	Not evaluable	Not evaluable
8	Negative	2.05	1.9	1	/
9	Negative	2.0	2.0	1	/
10	Negative	2.1	2.0	1	/
11	Negative	1.9	1.8	1	/
12	**Amplified**	**7.8 (small clusters)**	**3.9**	**2.0**	**30**
13	Negative	2.1	2.0	1	/
14	Negative	2.0	2.0	1	/
15	Negative	2.0	1.9	1	/
16	**Amplified**	**4.0**	**3.7**	**1.2**	**11**
17	Negative	2.4	2.1	1.1	/
18	Negative	2.1	2.0	1	/
19	Negative	2.2	2.1	1	/
20	Negative	2.0	2.0	1	/

Best response: 10 PR, 10 SD

Median PFS: 15.6 mos

Median OS: 25.7 mos

Raimondi A et al. abstr. 3143

CT + Trastuzumab + Pembrolizumab: Phase 2 study

1st line Stage IV EG Cancer
HER2 IHC 3+ or IHC 2+/FISH>2.0
MSK confirmation not required prior to Rx

RECIST measurable or evaluable disease

N=37

CT Scan ctDNA analysis

"induction"

Trastuzumab 8mg/kg
Pembrolizumab 200mg
x 1 cycle

CT Scan ctDNA analysis q 9 weeks

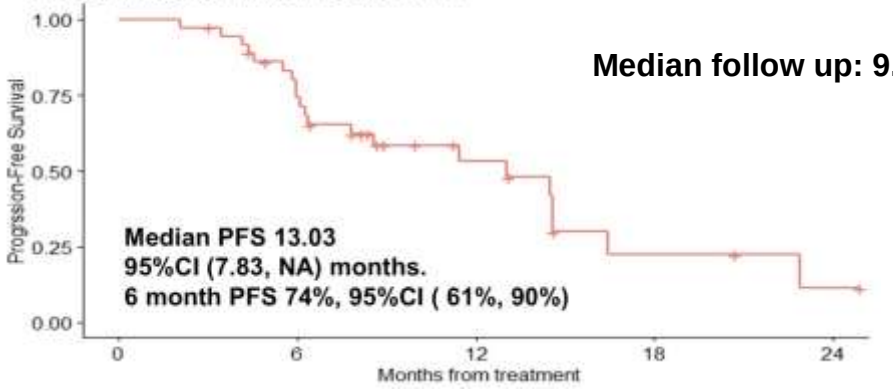
*Capecitabine 850mg/m2 bid day 1-14
Oxaliplatin 130 mg/m2 Trastuzumab 6 mg/kg Pembrolizumab 200 mg q21 days
* (5-FU and Cisplatin permitted)

***Primary endpoint**: 6-months PFS, 26 or more patients progression free at 6 months*

Secondary endpoints:

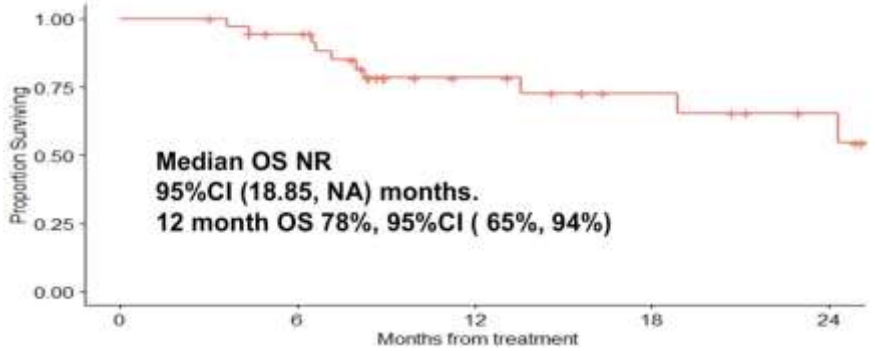
- *OS*
- *ORR & DCR by RECIST 1.1*

PROGRESSION FREE SURVIVAL



Median follow up: 9.9 mos

OVERALL SURVIVAL



Best response to PEMBRO/TRAS/CAPEOX in RECIST 1.1measurable disease (n=35)

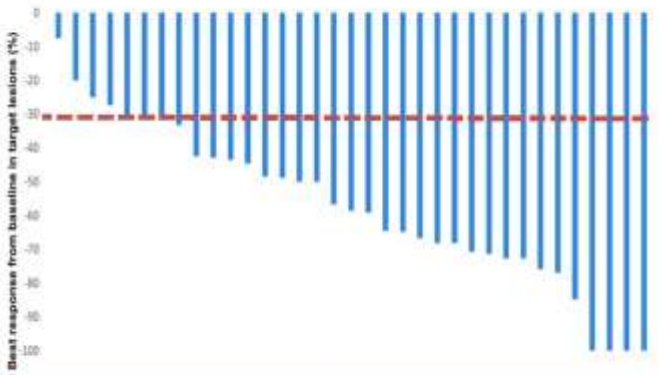
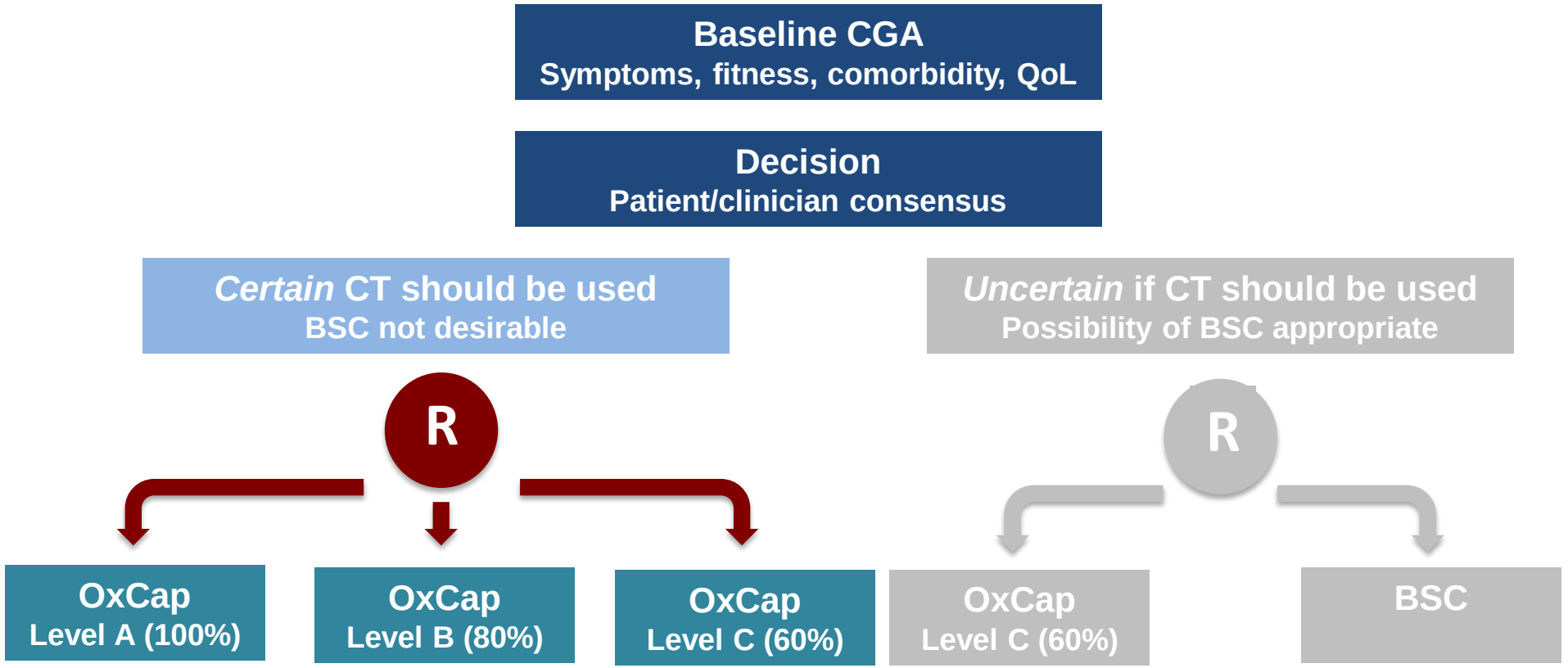


Table 4. Best Response (n=37)	Patients, n (%)
ORR, n (%)	28 (89%) 95% CI (71%; 91%)
CR PR SD PD Non-measurable	4 (11) 27 (77) 4 (11) 0 2
Disease Control Rate	100%

Random phase 3 study KEYNOTE 811 ongoing…

Janjigian YY et al. abstr. 4011

GO2: Optimising CT in frial and elderly mEGC



- ✓ Phase 3, randomized, open-label, non-inferiority
- ✓ Eligibility: not fit for full dose 3-drug regimens
- ✓ Level A: LOHP 130 mg/sqm d1 + Cape 625 mg/sqm/bid continuously (q21 days)

Hall PS et al. abstr. 4006

GO2: Frialty assessment and study design

Domains	Assessment
Weight loss	Weight loss (> 3kg in 3m) | BMI (<18.5)
Mobility	Timed up and go test (>10 seconds)
Falls	2 or more falls in 6m (EORTC G8)
Neuropsychiatric	Dementia/depression diagnosis
Function	One or more impairment in IADL
Social	Place of residence (Requires 24 hour care)
Mood	EQ5D question (feelings today)
Fatigue	EORTC QLQ Fatigue Score
Polypharmacy	Prescribed regular medications (>4)

Definition	
Not frail	- impairment in 0 domains
Mildly frail	- impairment in 1-2 domains
Severely frail	- impairment in ≥3 domains

OBJECTIVES

✓ Assess non-inferiority in terms of PFS of lower doses *vs*. level A
[HR 1.34, 1-sided alpha 0.05, power 80% ➔ approximately 34 days median PFS]

✓ Assess patient experience with lower doses
[OTU]

✓ Assess whether optimum dose differs with baseline factors
[OTU according to baseline age, frialty, PS]

Hall PS et al. abstr. 4006

GO2: OTU definition

"Overall Treatment Utility" (OTU) scored after 9 weeks:

good OTU	intermediate OTU	poor OTU
all of: • clinician score "benefit"* *and* • patient satisfied *and* • no major toxicity *and* • no drop in QL¶	*either:* • clinician score "no benefit" • (but patient satisfied and no major toxicity or QL drop) *or* • either patient dissatisfied or major toxicity or QL drop • (but clinician scores benefit)	*both:* • clinician score "no benefit" *and any of* • patient dissatisfied • major toxicity • QL deterioration *or* • patient has died

NB: decision rules to ensure OTU can be scored in 100% patients

*clinician score of "benefit": no clinical/radiological evidence of cancer progression and no general health deterioration

¶ drop in QL defined as ≥16% fall (≥2 on the 12-point EORTC global QL scale). Cocks, K et al., Eur J Cancer (2012) 48, 1713-21

https://blogs.ed.ac.uk/canceroutcomes/overall-treatment-utility/

Hall PS et al. abstr. 4006

GO2: Patients

Patients

		Level A (n=170)	Level B (n=171)	Level C (n=173)	Total (n=512)
Median age (range)		76	76	77	76 (51 - 96)
Male gender		77%	75%	72%	75%
Site of primary	Oesophagus	32%	42%	39%	38%
	GO junction	29%	19%	22%	23%
	Gastric	38%	37%	37%	37%
Squamous histology		12%	11%	12%	11%
Trastuzumab treated		4%	6%	6%	5%
Distant metastases		68%	69%	70%	69%
Performance Status ≥2		31%	32%	31%	31%
Severely frail (≥3 domains)		61%	56%	58%	58%

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GO2: Reduced dose CT not inferior *vs*. full dose CT

Results: step 1 - non-inferiority is confirmed

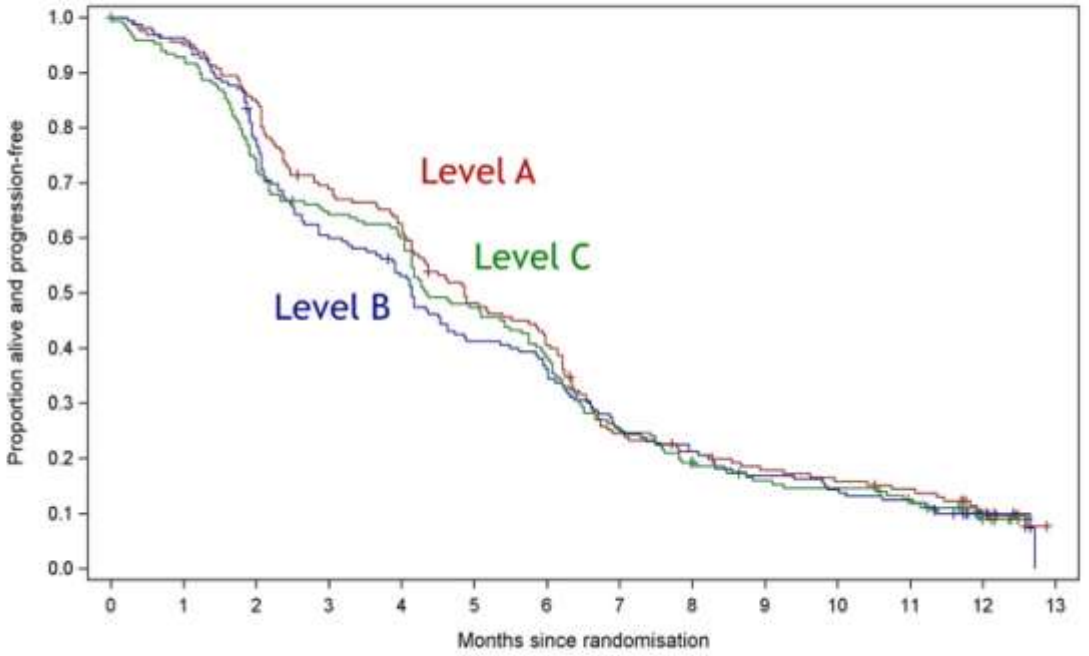
Primary endpoint

Progression Free Survival

Adjusted hazard ratios

Level B vs A 1.09 [95% CI 0.89 - 1.32]

Level C vs A 1.10 [95% CI 0.90 - 1.33]



The non-inferiority boundary of 1.34 is excluded, so non-inferiority is confirmed

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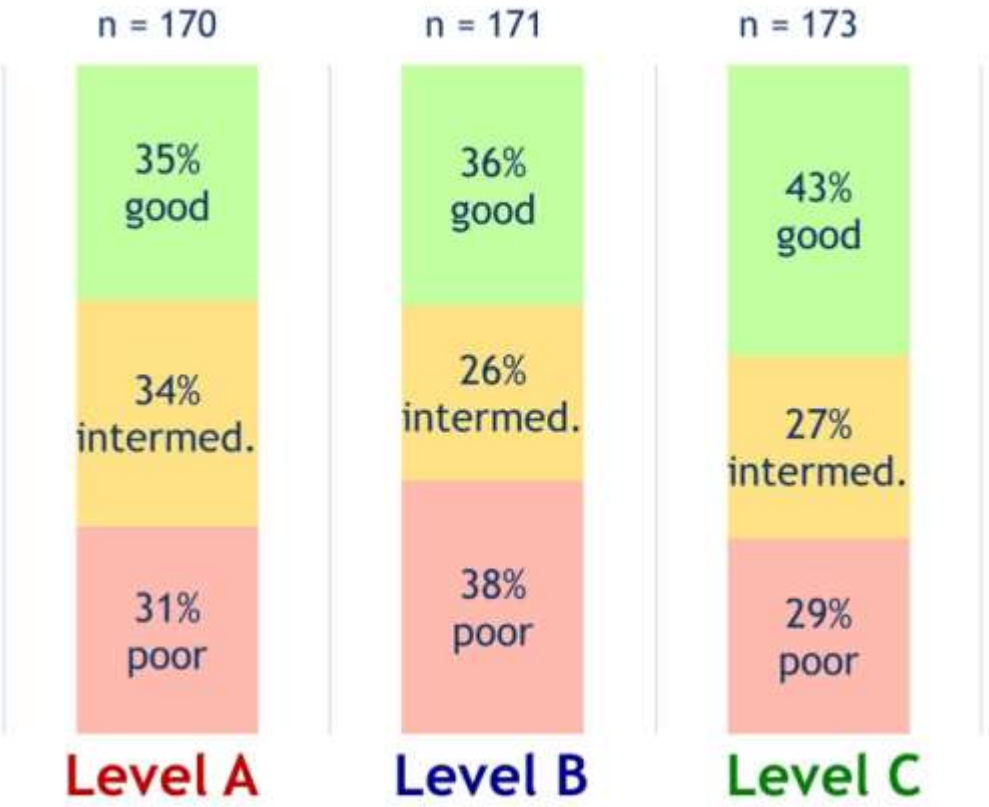
GO2: Trend for better OTU with reduced dose CT

Results step 2: the patient experience

Overall Treatment Utility

Overall treatment utility favours **Level C**, which had the highest percentage of Good and lowest percentage of Poor OTU scores



Adjusted odds ratios (trend for better OTU)

Level B vs A 0.87 [95% CI 0.59 - 1.29]

Level C vs A 1.24 [95% CI 0.84 - 1.84]

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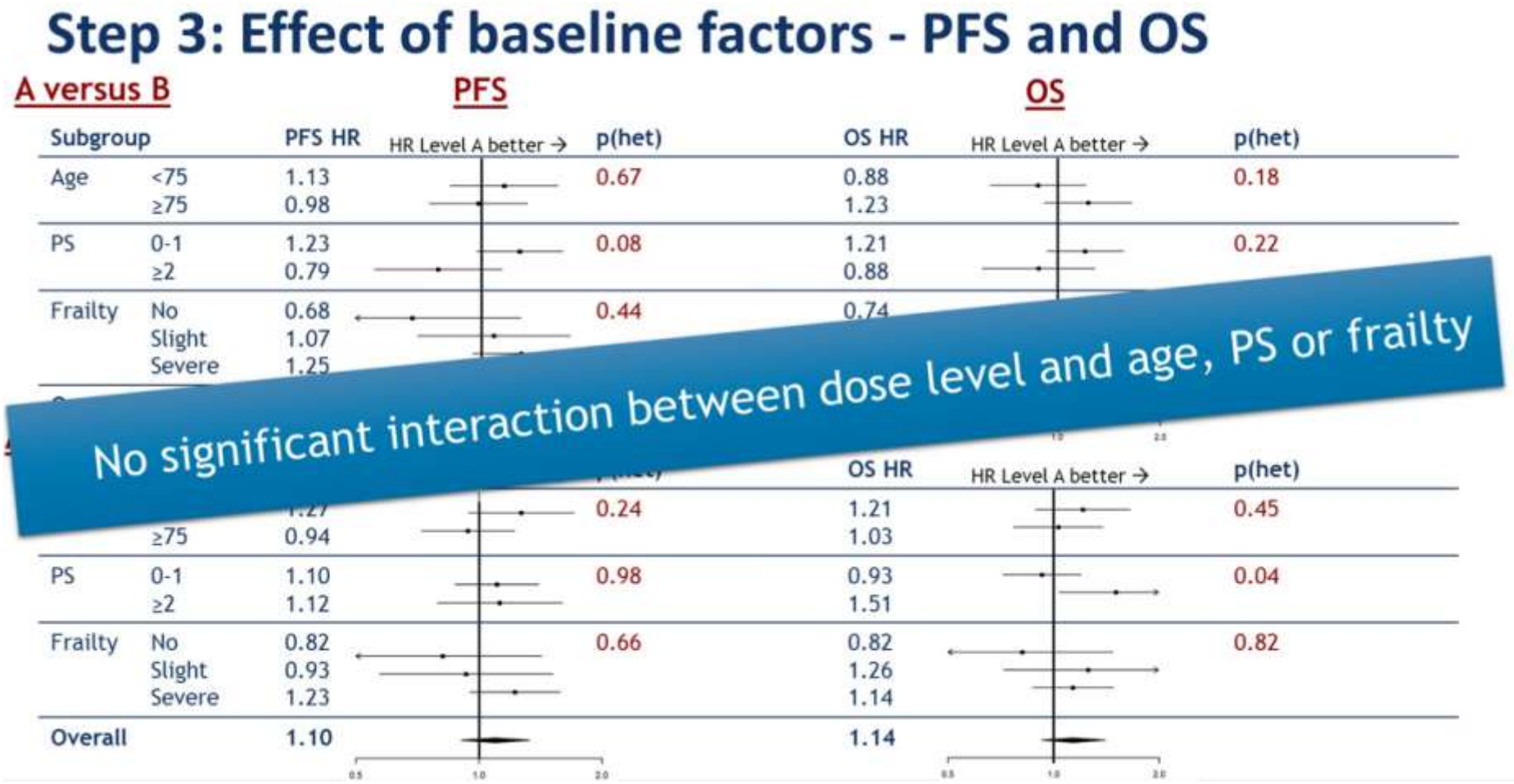
GO2: No subgroup clearly benefit from full dose CT



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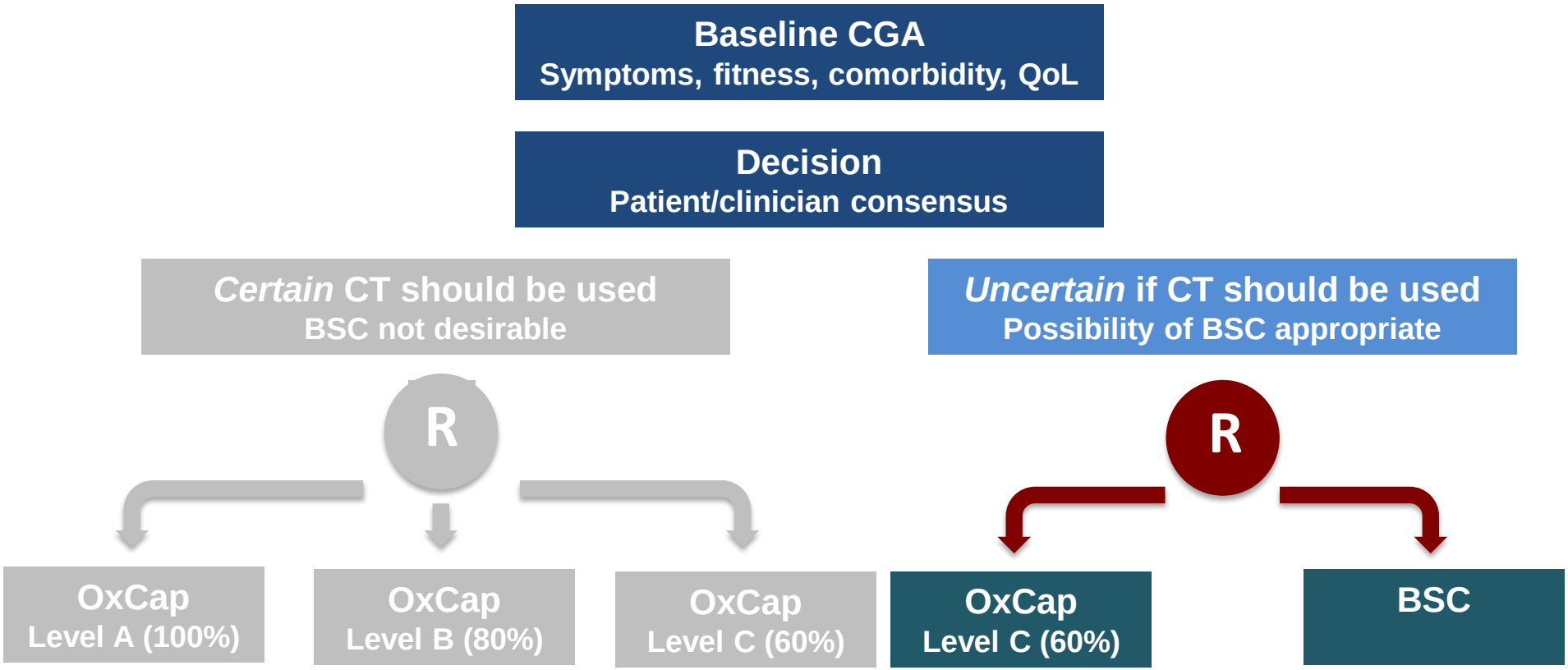
GO2: Uncertain randomization cohort

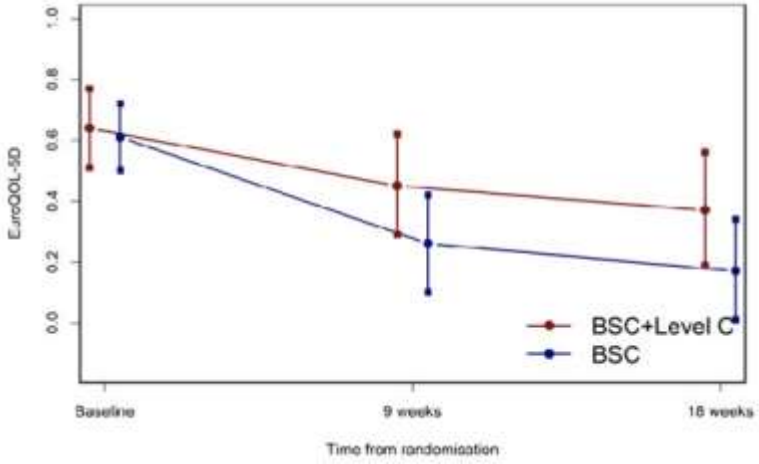


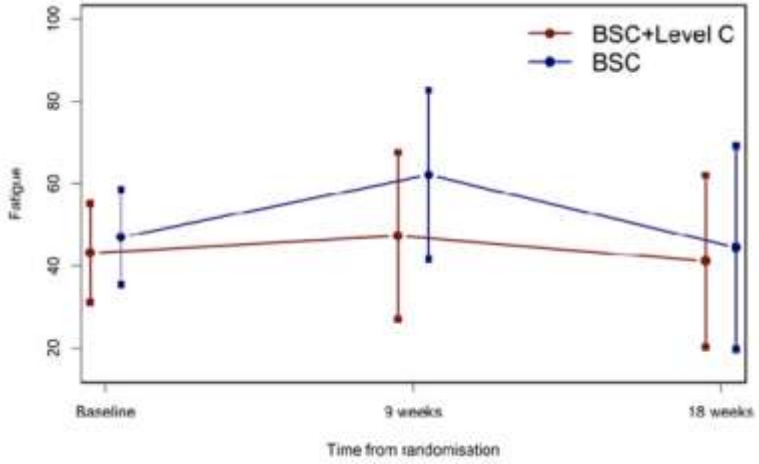
- ✓ Randomized 1:1
- ✓ Eligibility: if clinician and patient agreed the indication for CT was uncertain
- ✓ Sample size was not pre-set, but around 60 patients were anticipated

Swinson D et al. abstr. 4051

GO2: No definitive benefit from CT *vs*. BSC

Findings (4): Outcomes with Chemotherapy				
Cox regression analysis adjusted for stratification factors		HR	95% CI	P-value
Allocation	Chemo + SC vs SC	0.69	0.32-1.48	0.35
Age group	>=75 vs <75	1.32	0.52-3.33	0.56
Presence of distant metastases	No vs Yes	0.44	0.2-0.93	0.03
Histology	Squam CC vs other	1.36	0.52-3.54	0.53
WHO PS				0.006
	2 vs 0-1	1.89	0.84-4.27	0.13
	>2 vs 0-1	8.78	2.33-33.1	0.001
Was trastuzumab administered	Yes vs No	0.54	0.1-2.78	0.46





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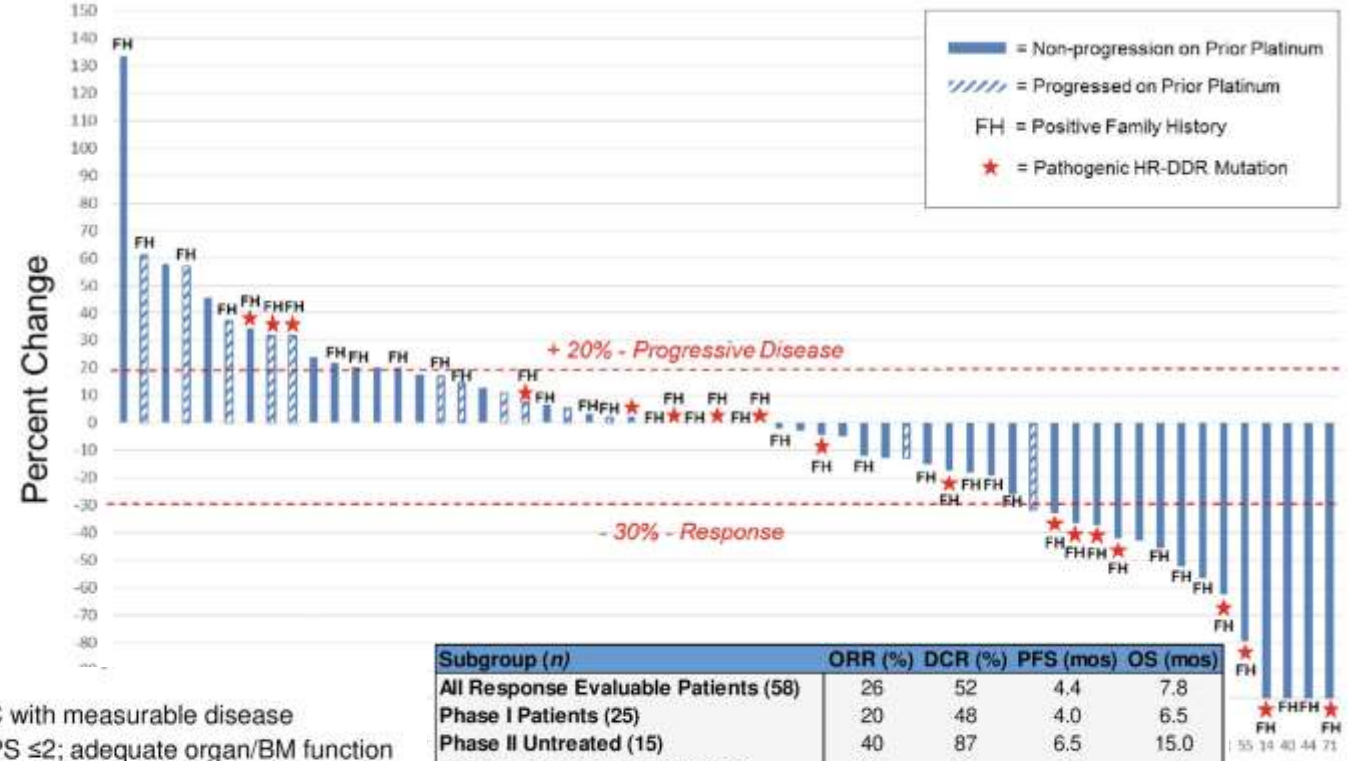
FOLFOX + Veliparib: Phase I/II



Patient Eligibility

- Metastatic PDAC with measurable disease
- ≥18 y.o; ECOG PS ≤2; adequate organ/BM function
- For Phase I - no patient selection
- For Phase II - 2 cohorts
  - ➢ No prior systemic therapy (Cohort A)
  - ➢ Previously treated (Cohort B)
- For Phase II, patients selected if they had a family history suggestive of a breast or ovarian cancer syndrome (per NCCN guidelines), or a known pathogenic germline/somatic mutation in an HR-DDR gene

Subgroup (*n*)	ORR (%)	DCR (%)	PFS (mos)	OS (mos)
All Response Evaluable Patients (58)	26	52	4.4	7.8
Phase I Patients (25)	20	48	4.0	6.5
Phase II Untreated (15)	40	87	6.5	15.0
Phase II Previously Treated (18)	22	28	1.8	4.6
Prior Platinums				
Proggression on Prior Platinum (*14*)	7	14	2.1	5.3
No Prior Platinum (*44*)	32	64	5.5	8.8
Family History (FH)				
(+) FH (*43*)	30	53	5.4	9.5
No FH (*15*)	13	47	3.8	5.5
HR-DDR Mutations				
HR-DDR mutated (*18*)	44	61	6.0	10.4
Non-Mutated/Unknown (40)	18	48	3.6	6.9
HR-DDR Mutated, No progression on prior platinum (*14*)	57	79	8.4	11.2

Pishvaian MJ et al. abstr. 4015

SWOG S1513: FOLFIRI +/- Veliparib random phase II

METHODS

Inclusion Criteria

- no prior irinotecan or PARPi
- 1 prior treatment for metastatic disease
- eligible if nab-P/gem for local disease and PD ≤ 3 mo
- able/willing to undergo pre-treatment biopsy
- ECOG PS 0-1,
- ANC ≥ 1500, Hb ≥ 9, Plt ≥ 100K, Tbili ≤ 1.5 x ULN

RESULTS

Table 1: Patient Characteristics

	mFOLFIRI Veliparib N=59	FOLFIRI N=58
Age (median) yrs range	67.3 (45-85)	66.9 (39-84)
Sex males females	31 (53%) 28 (47%)	33 (57%) 25 (43%)
Race white black other	52 (88%) 4 (6%) 3 (6%)	47 (81%) 5 (9%) 6 (10%)
Prior 1L chemo for mPC: yes no	 53 (90%) 6 (10%)	 52 (90%) 6 (10%)
HRD Groups	**N=59**	**N=56**
Group 1 BRCA1/2	3	1
Group 2 non-BRCA core HRD ATM, PALB2, CDK12, RAD51C/D, BARD1, BRIP1	2	5
Group 3 non-core HRD BLM, FANC, CHEK2, SLX4, ERCC, RIF1	7	4
Group 4 HRD wild type	47	46

Fig 2. Overall Survival All Patients (n=117)

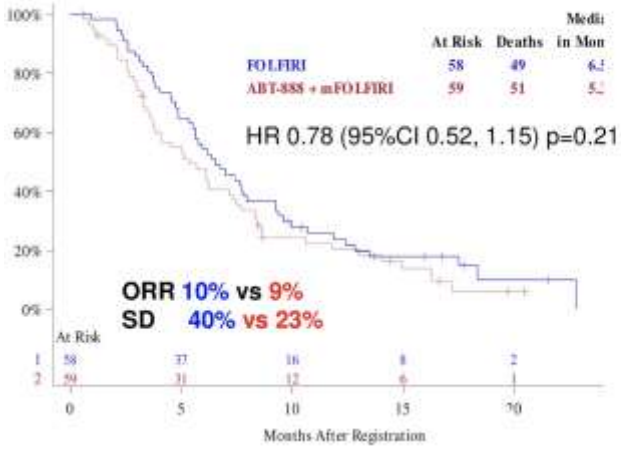


Fig 3. PFS All Patients (n=117)

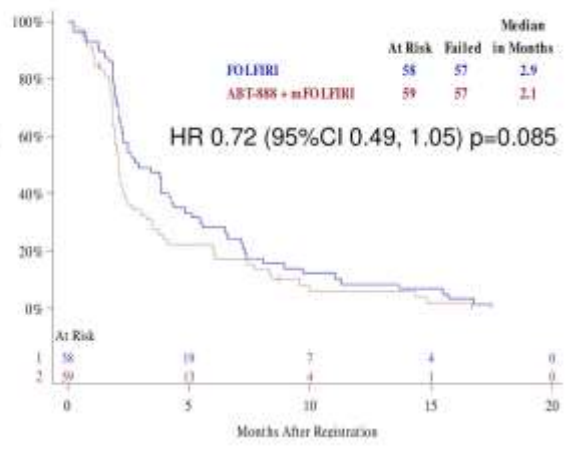


Fig 4. OS by HRD Study Arms Combined (n=107)

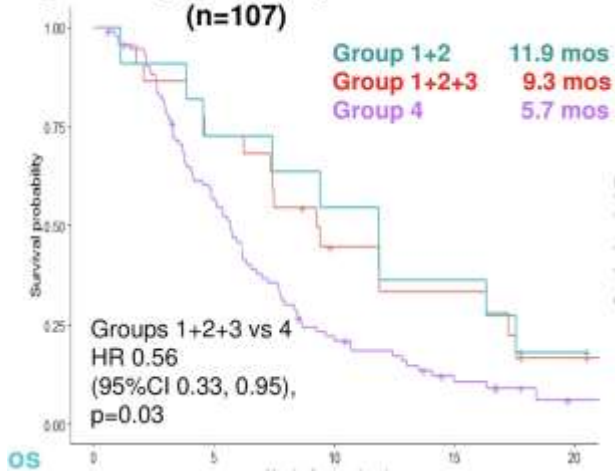
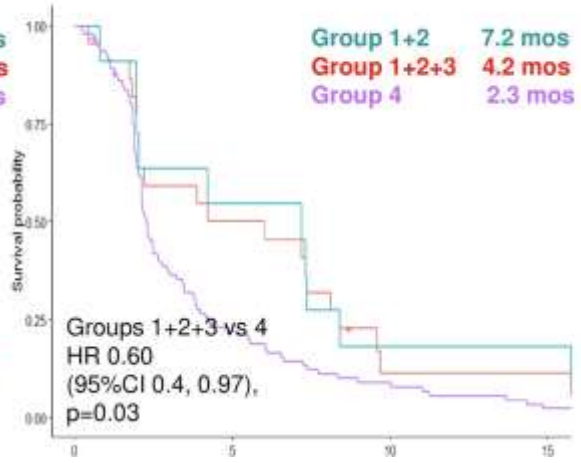


Fig 5. PFS by HRD Study Arms Combined



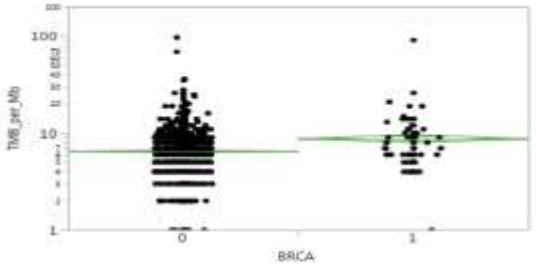
Chiorean EG et al. abstr. 4014

BRCA1-2 mutations in PC

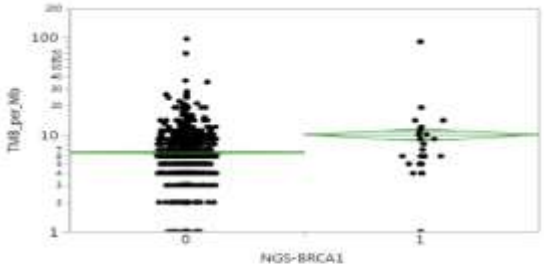
Frequency of BRCA mutations				
	BRCA 1		BRCA 2	
Results	N	%	N	%
Wild-type	2,818	98.7	2,754	96.9
Pathogenic	37	**1.3**	89	**3.1**

BRCA mutant ➔ Higher TMB

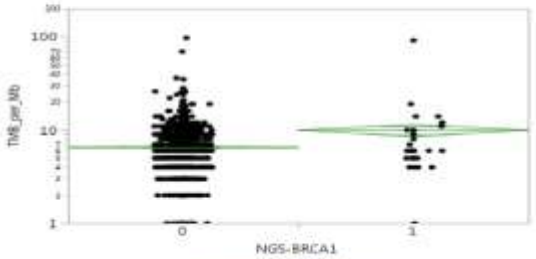
BRCA mutant ➔ Higher rate MSI^{high}/PD-L1+



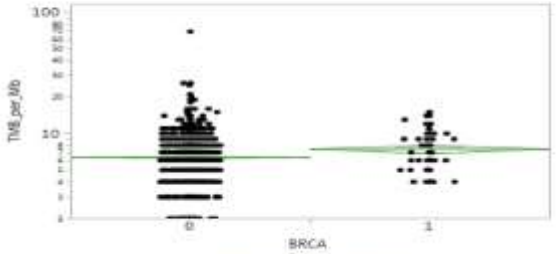
TMB in MSI, BRCA1/2



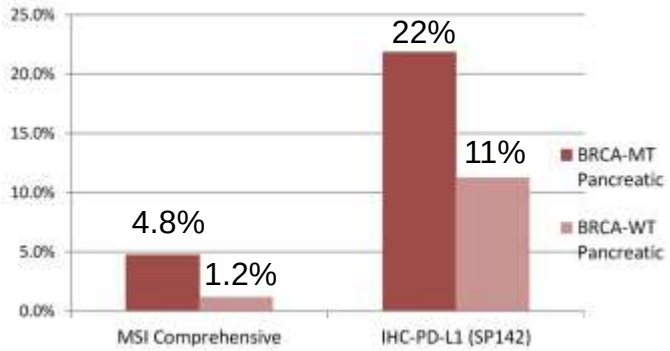
TMB in MSI, BRCA2



TMB in MSI, BRCA1



TMB in MSS, BRCA1/2



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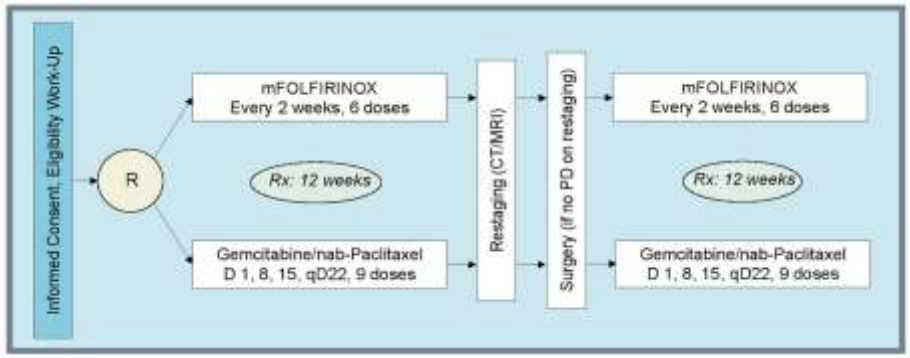
SWOG S1505: Neoadj mFOLFIRINOX *vs*. Gem-Nab



		Total (n=147)	
ELIGIBLE		104	71%
INELIGIBLE		43	29%
	Reasons for ineligibility*:		
	No primary mass seen	4	10%
	No RECIST 1.1 measurable disease	4	10%
	Venous involvement ≥ 180°	14	33%
	Arterial involvement	22	52%
	Metastatic disease	29	69%

	Total (n=102)	
Started Chemotherapy	99	96%
Completed Chemotherapy	86	84%
Any Grade 3/4 Toxicity (n=99)	60	61%
Anemia	4	4%
Neutropenia	22	22%
Thrombocytopenia	3	3%
Febrile Neutropenia	2	2%
Fatigue	7	7%
Nausea/Vomiting	5	5%
Diarrhea	8	8%
Sensory Neuropathy	2	2%
Death	1	1%

		Total (n=99)	
REACHED PROTOCOL SURGERY			
Yes		76	77%
No		23	23%
REASONS FOR NOT REACHING PROTOCOL SURGERY (n=23)			
	Progression	8	35%
	Chemotherapy related toxicity	9	39%
	Symptomatic deterioration	1	4%
	Patient refusal	2	9%
	Other	3	13%

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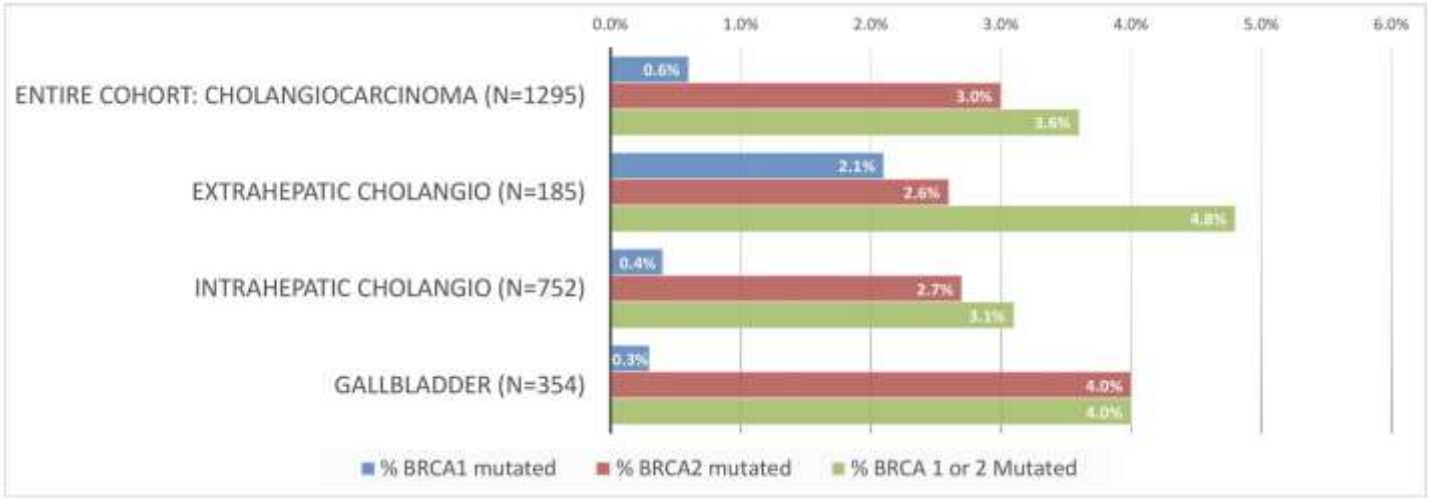
Agenda

- **Esophageal**
  - PET-guided therapy in GEJ adenocarcinoma: #4018
- **Gastric**
  - Molecular selection for ramucirumab: #3143, #4064
  - Combining anti-HER2 therapy and ICIs: #4011
  - Refining clinical selection of frial/elderly patients: #4006, #4051
- **Pancreatic**
  - BRCA, HRD and PARP inhibitors in mPC: #4014, #4015, #4132, #4132
  - Neoadjuvant CT in resectable disease: #4126, #4128, #4137
- **Hepatobiliary**
  - ICIs in BTC: #4074, #4079, #4082, #4097
  - New targets in BTC and molecular selection in HCC: #4085, #4075

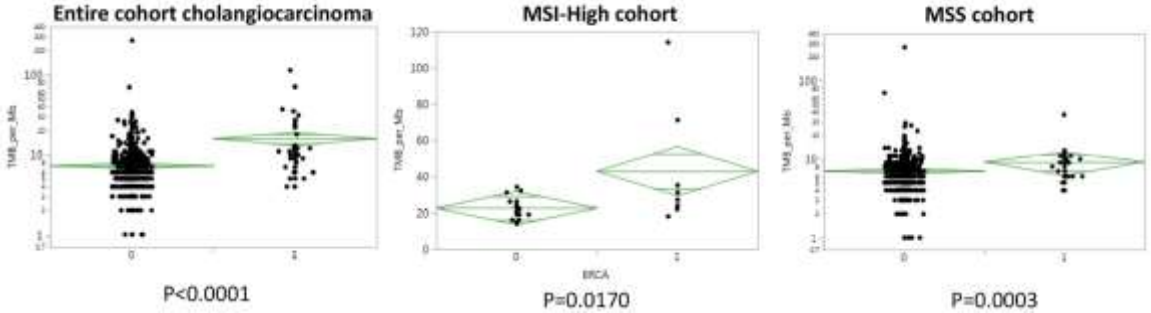
ICIs in BTC: Results

	Agent	N	Setting	RR	DoR (mos)	PFS (mos)
#4074	Camrelizumab +FOLFOX/GEMOX	81	HCC and BTC	7% (DCR 67.4%)	5.3	Not reached
#4079	Pembrolizumab	104+24	>1 line	5.8%-13%	Not reached	1.8-2.0
#4082	Pembrolizumab	39	>1 line	11.1%	NR	1.5
#4097	Nivolumab	54	>1 line	22%	NR	3.98

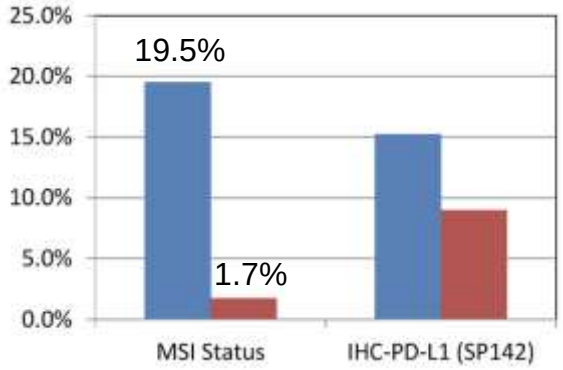
BRCA1-2 mutations in BTC



BRCA mutant ➔ Higher TMB



BRCA mutant ➔ Higher rate MSI^{high}



Seeber A et al. abstr. 4085

INNOVATE-1: eNOS SNP and benefit from Sorafenib

✓ Endothelial nitric oxide synthase (*eNOS*) and angiopoietin-2 (*ANGPT2*) SNPs (NOS3-786 and rs55633437) were retrospectively found associated with outcome in HCC patients treated with Sorafenib

✓ **DESIGN**

- prospective, translational, multicenter study (12 Oncology Units in Italy)
- N=165 patients included

✓ **ELIGIBILITY**

- advanced or intermediate stage HCC not eligible for locoregional treatments (surgical resection, percutaneous ablation, TACE) or liver transplantation
- ECOG performance status score of 2 or less
- Child–Pugh liver function class A or B7 with biliruibin <2
- life expectancy of 12 weeks or more
- adequate bone marrow, liver and kidney function

✓ **PRIMARY OBJECTIVE**

- progression-free survival (PFS)

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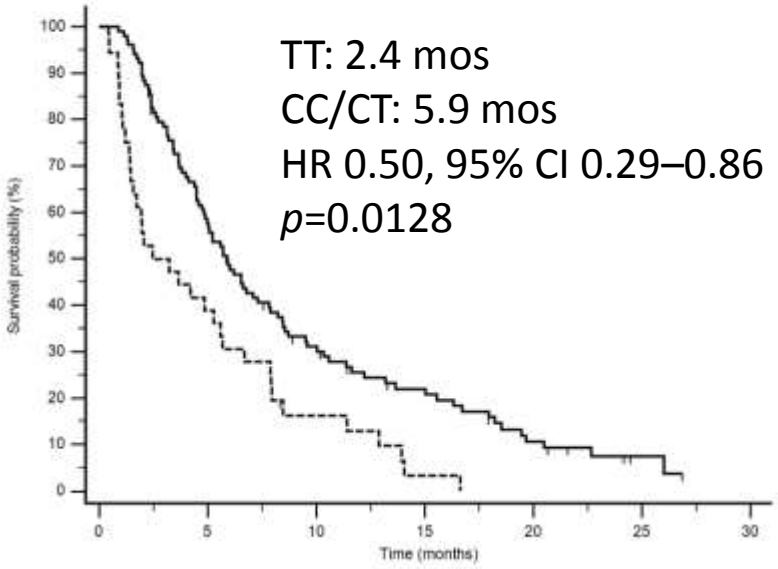
INNOVATE-1: *NOS3-786* CC+CT *vs*. TT

Significance confirmed at multivariate analysis

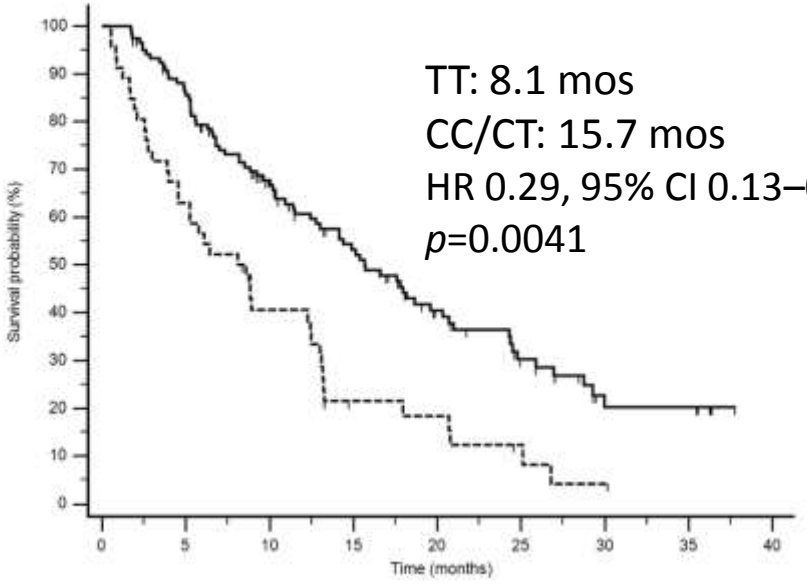
(Child Pugh, PLR, BCLC, Gender, Portal Vein Thrombosis, LDH, aetiology)

PFS



TT: 2.4 mos
CC/CT: 5.9 mos
HR 0.50, 95% CI 0.29–0.86
p=0.0128

OS



TT: 8.1 mos
CC/CT: 15.7 mos
HR 0.29, 95% CI 0.13–0.68
p=0.0041

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Thank you!

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