Neoplasie colorettali ed epato-bilio-pancreatiche

FABIO FULFARO
POLICLINICO UNIVERSITARIO
PAOLO GIACCONE
PALERMO

Neoadjuvant - Colon– NeoCol trial

Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer: The NeoCol trial

Lars Henrik Jensen, Monica Linda Kjaer, Finn Ole Larsen, Niels Henrik Hollander, Hans B. Rahr, Frank Pfeffer, Laura Diness, Jan Lindebjerg, Soeren Rafael Rafaelsen, Torben Hansen, Signe Timm, Inger Marie Løes, Ismail Go¨ genur, Kim Wedervang, Fahimeh Andersen, Lone Nørga° rd Petersen, Elinor Bexe Lindskog, Laurids Poulsen, Olav Dahl;

Backgroud

- Neoadjuvant chemotherapy is accepted in different cancers with the potential benefits of reducing tumor size, eliminating micrometastasis, and reducing adjuvant cht

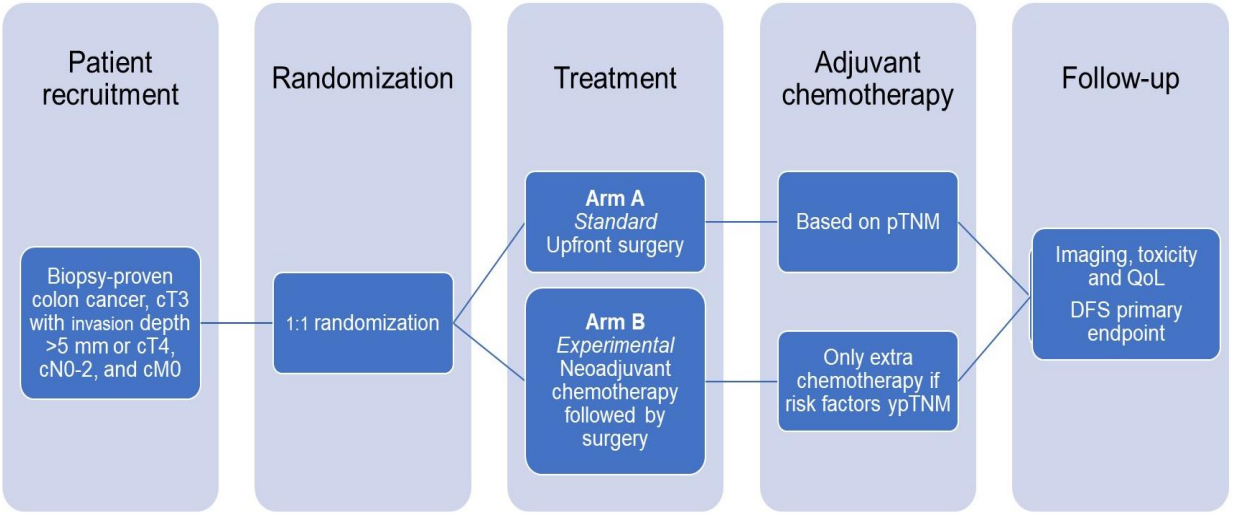
Primary endpoint

- DFS

Secondary endpoints

- OS, toxicity, QoL, rate of patients fullfiling the critieria for adjuvant chemotherapy

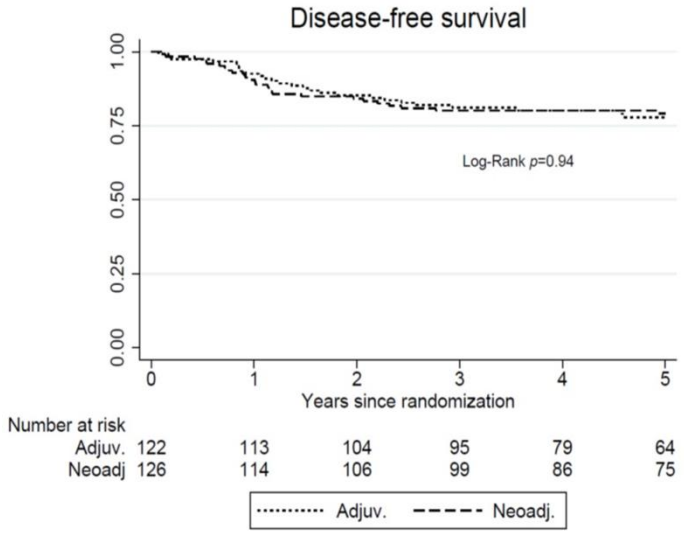
Study design

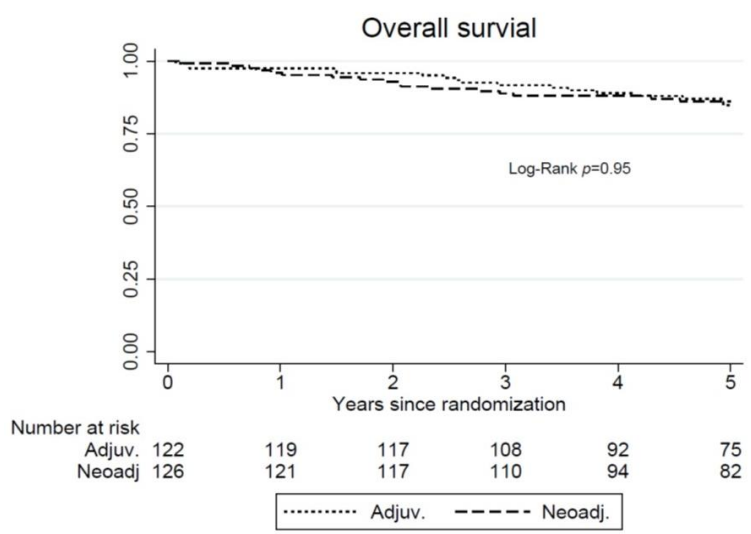


Neoadjuvant - Colon– NeoCol trial

Results

- 122 pts standard group vs 126 pts in neoadjuvant group (tot 248 pz)
- 73 % of T3 tumors, 26% T4 on the baseline CT scan.
- DFS was similar in the two arms (p = 0.95), as well as OS (p = 0.95).
- The median number of chemotherapy cycles was lower in the neoadjuvant group, 3 (IQR 1-7) vs. 4 (0-8).
- More patients in the standard arm had an indication of adjuvant chemotherapy, 88 vs. 72 (p = 0.02).





		Upfront surgery (standard), N=82	Neoadj. Treatment (experimental), N=126
During treatment	Nausea	3 (4%)	7 (7%)
Toxicity grade 3-4, N (%yes)	Vomiting	3 (4%)	3 (2%)
	Stomatitis	1 (1%)	-
	Diarrhea	11 (14%)	16 (13%)
	Sensory neuropathy	9 (11%)	9 (7%)
	Motor neuropathy	2 (2%)	2 (2%)
	Hand-foot syndrome	4 (5%)	-
	Obstipation	-	1 (1%)
	Pain	3 (4%)	3 (2%)
	Other	7 (7%)	12 (9%)
During follow-up			
Toxicity grade 3-4, N (%yes)	Sensory neuropathy	4 (5%)	2 (2%)
	Motor neuropathy	2 (3%)	1 (1%)
	Hand-foot syndrome	-	-
	Pain	2 (3%)	-

- Surgical complication regarding ileus and anastomotic leakage were more common in the standard group (ileus 8 vs 3%, anastomotic leakage 8 vs 2%)
- There were more p/ypT0-2 at surgery for the neoadjuvant group, as well as p/ypN0, suggesting more favorable outcomes in terms of downsizing and downstaging

Conclusions

- No significant difference in DFS and OS in patients with colon cancer.
- More favorable outcomes in terms of number of chemotherapy cycles, postoperative complications, downstaging and downsizing.

PROSPECT: A randomized phase III trial of neoadjuvant chemoradiation versus neoadjuvant FOLFOX chemotherapy with selective use of chemoradiation, followed by total mesorectal excision (TME) for treatment of locally advanced rectal cancer (LARC) (Alliance N1048).

Deborah Schrag, Qian Shi, Martin R. Weiser, Marc J Gollub, Leonard B. Saltz, Benjamin Leon Musher, Joel Goldberg, Tareq Al Baghdadi, Karyn A. Goodman, Robert R. McWilliams, Jeffrey M. Farma, Thomas J. George, Hagen Fritz Kennecke, Alan P. Venook, Eileen Mary O'Reilly, Jeffrey A. Meyerhardt, Amylou C. Dueck, Ethan Basch, George J. Chang, Harvey J. Mamon

Backgroud

- Radiation with sensitizing fluoropyrimidine (5FUCRT) is a standard curative intent treatment for LARC.
- Pelvic chemoradiation has highly long term toxicity

Primary endpoint

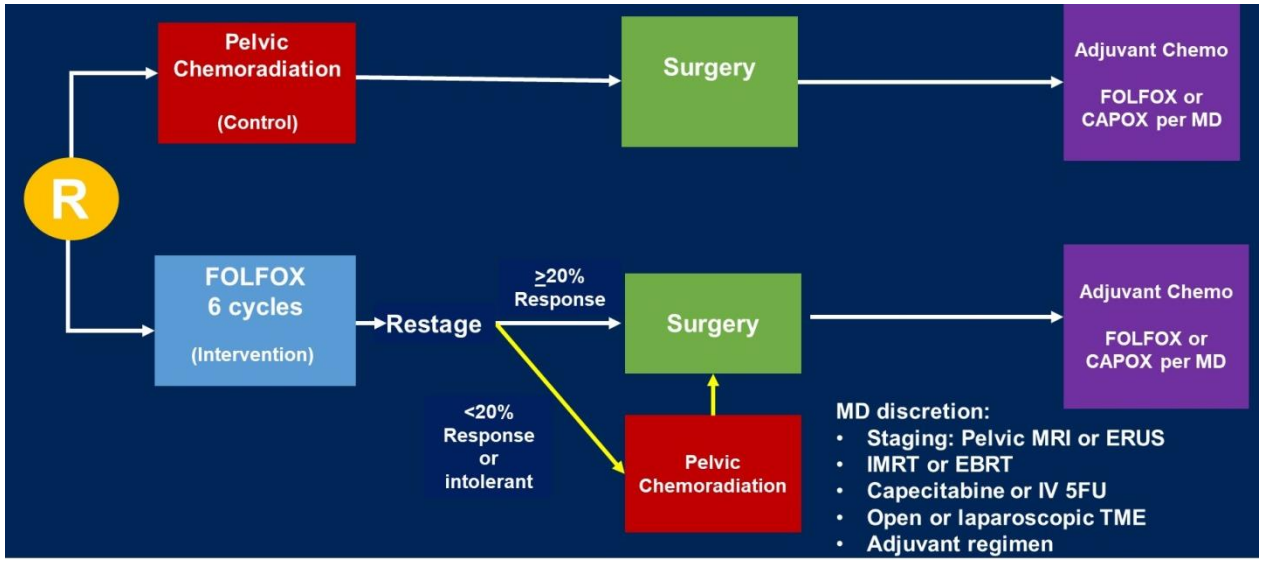
- DFS

Secondary endpoints

- OS, local recurrence free survival, R0 resection, pCR, toxicity-CTCAE, toxicity PRO-CTCAE, QoL

Study design

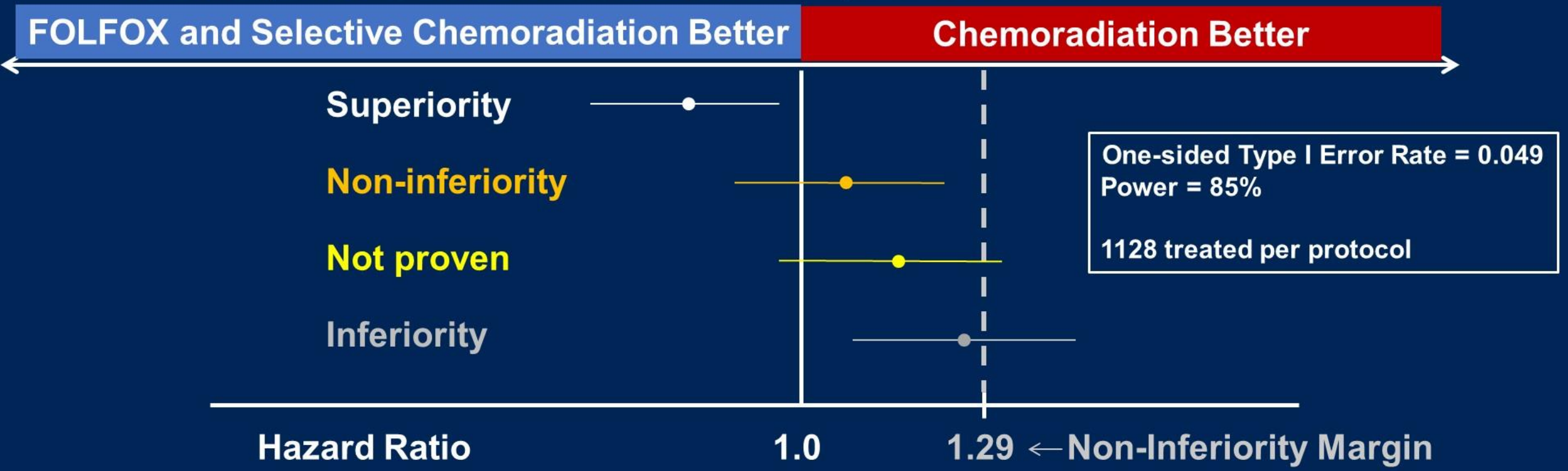
- cT2N+, cT3N-, cT3N+ rectal cancer pts eligible for neoadjuvant treatment



Non-inferiority Hypothesis for Disease Free Survival

Non-inferiority could be claimed if the upper limit of the two-sided 90.2% confidence interval of the hazard ratio (HR) did not exceed 1.29.

This corresponds to an absolute difference in 5-year DFS of <5%

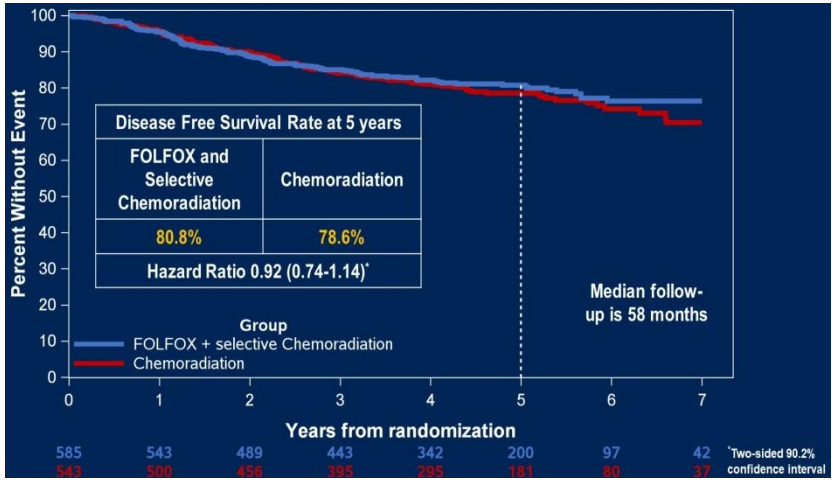


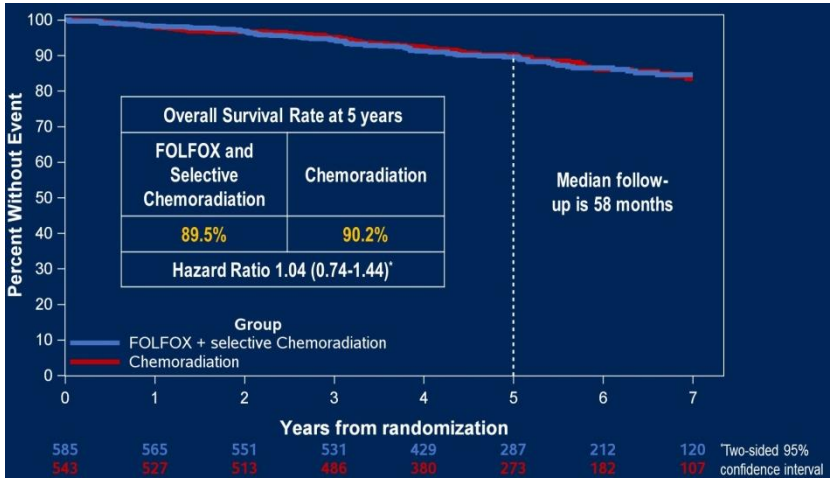
Neoadjuvant – Rectum – PROSPECT trial

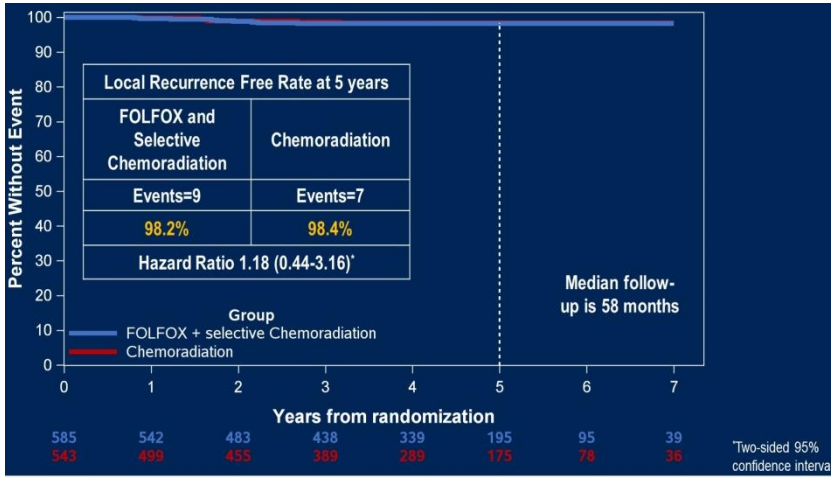
Results

Recruitment: 264 Centers	FOLFOX and Selective Chemoradiation	Chemoradiation
N	585	543
Age Mean (SD)	57 (11)	57(11)
Sex		
Female	37%	32%
Male	63%	68%
Tumor location from the anal verge in cm (SD)	8 (3)	8 (3)
Baseline Staging Performed with MRI	84%	84%
Clinical Stage at Baseline		
cT2N+	11%	7%
cT3N-	39%	37%
cT3N+	50%	56%

- DFS at five years was non inferior for the experimental arm vs chemoradiation arm (80.8% vs 78,6% HR 0,92 (0,74-1,14)
- OS, local recurrence free rate were similar in both arms
- pCR were 22% in the FOLFOX and selective chemoradiation vs 24% in the chemoradiation group
- 9% of pts randomized to FOLFOX received neoadjuvant chemoradiation either for a clinical response <20% or lack of chemotherapy tolerability







Neoadjuvant – Rectum – PROSPECT trial

Results

- Neoadjuvant G 3 AEs were 41% in the experimental arm vs 23% in the control arm.
- No significant difference but a trend in favor of FOLFOX and selective chemoradiation regarding the QoL
- Significant difference in maintaining bowel function and sexual function in favor of the experimental arm

	Neoadjuvant Treatment	
% Reporting Severe PRO-CTCAE Scores	FOLFOX and Selective Chemoradiation 12 weeks (22 weeks if also 5FUCRT)	Chemoradiation 6 weeks
Anxiety	11%	6%
Appetite Loss	22%	9%
Constipation	27%	11%
Depression	10%	3%
Diarrhea	6%	20%
Dysphagia	12%	1%
Dyspnea	7%	1%
Edema	2%	2%
Fatigue	42%	20%
Mucositis	11%	2%
Nausea	21%	7%
Neuropathy	19%	5%
Pain	22%	18%
Vomiting	4%	2%

	Severe Adverse Symptoms at 12 months	
% Reporting Severe PRO-CTCAE Scores	FOLFOX and Selective Chemoradiation	Chemoradiation
Anxiety	3%	2%
Appetite Loss	1%	1%
Constipation	3%	4%
Depression	2%	3%
Diarrhea	2%	4%
Dysphagia	1%	0%
Dyspnea	0%	0%
Edema	1%	1%
Fatigue	3%	7%
Mucositis	0%	0%
Nausea	1%	0%
Neuropathy	3%	8%
Pain	5%	4%
Vomiting	0%	0%

Conclusion

- FOLFOX chemotherapy with selective use of 5FUCRT is non-inferior to 5FUCRT for neoadjuvant treatment of LARC prior to low anterior resection with TME.
- FOLFOX with selective chemoradiation could represent an alternative neoadjuvant treatment for cT2N+, cT3N-, cT3N+ rectal cancer pts

Limitations

- Excluded high risk patients: distal, T4 tumors, multiple enlarged nodes
- Not all patients had MRI staging
- We may still be overtreating some patients

Caveat: *While conducting this trial, new approaches have emerged*

- Shorter courses of adjuvant FOLFOX[1]
- Short course radiation[2]
- Total neoadjuvant therapy[3]
- Non-operative management[4]
- Immuno-ablative therapy for MSI-high patients[5]

1. Grothey A NEJM 2018
2. Bahdoer R Lancet 2001
3. Cercek A Jama Oncol 2022
4. Habr-Gama A, Dis Colon Rectum 1998
5. Cercek A, NEJM 2022

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

Thierry Conroy, Pierre-Luc Etienne, Emmanuel Rio, Ludovic Evesque, Nathalie Mesgouez-Nebout, Veronique Vendrely, Xavier Artignan, Olivier Bouche, Alice Boileve, Matthieu Delaye, Dany Gargot, Valerie Boige, Nathalie Bonichon-Lamichhane, Christophe Louvet, Christelle De La Fouchardiere, Clotilde Morand, Veronica Pezzella, Eric Rullier, Florence Castan, Christophe Borg

Backgroud

- TNT significantly improved short-term outcomes in pts with locally advanced rectal cancer compared with pts who received standard CRT, surgery, and adjuvant chemotherapy (RAPIDO and PRODIGE 23) with higher QoL scores

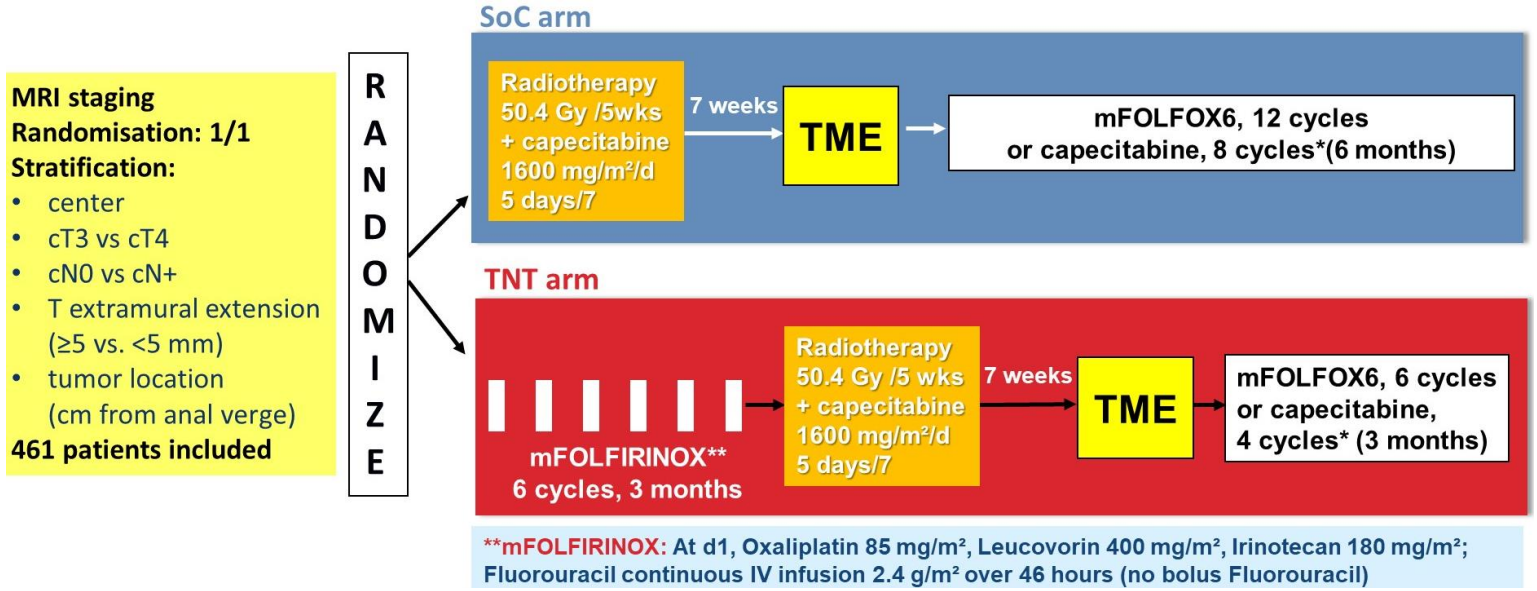
Primary endpoint

- DFS

Secondary endpoints

- OS, metastasis free survival, pCR, toxicity, QoL

Study design



Neoadjuvant – Rectum – Prodige 23 trial

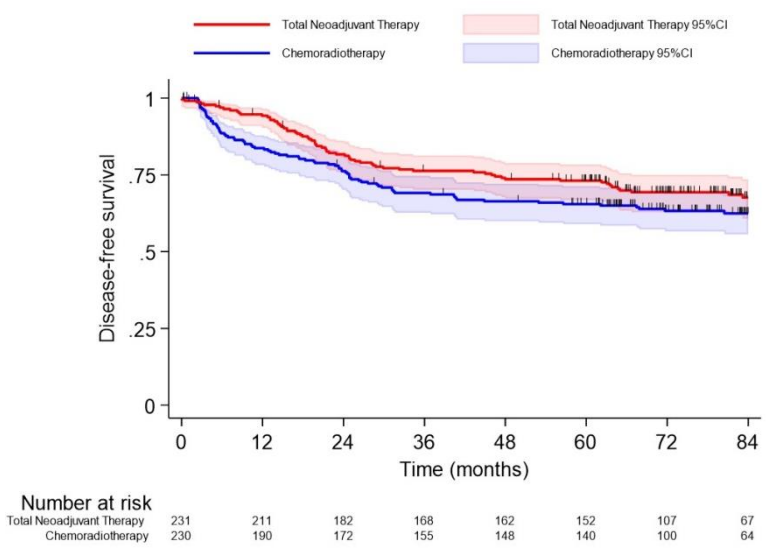
Characteristics	TNT N=231	SoC N=230	p
Distance to anal verge			
≤5 cm	37.7%	36.1%	0.92
5.1-10 cm	49.3%	51.3%	
10.1-15 cm	13.0%	12.6%	
mrT stage			
T2/T3	1.3%/80.9%	0.9%/83.6%	0.70
T4	17.8%	15.6%	
cN stage			
N+	89.1%	90.0%	0.52
Predicted lateral margin			
≤1 mm	26.0%	27.7%	0.70

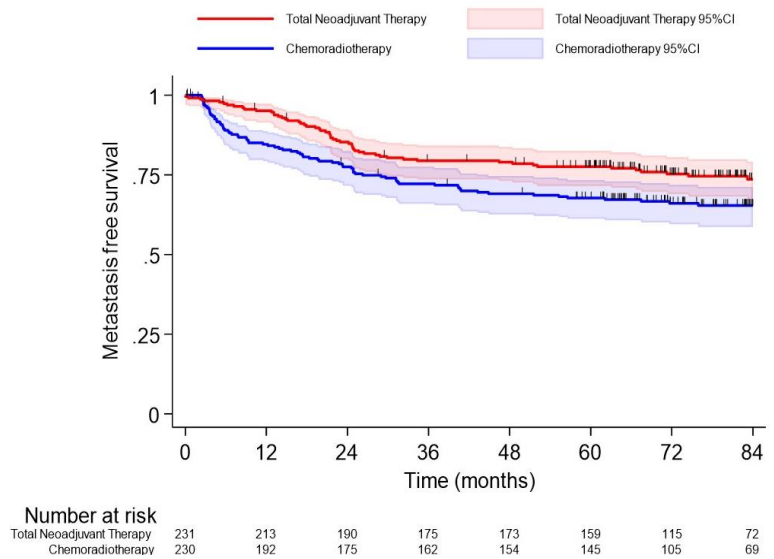
Results

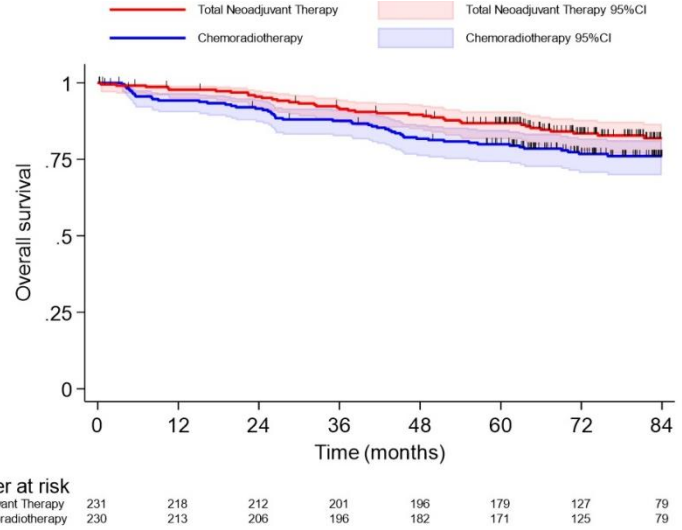
- 7-year DFS rate was 67,6% for TNT compared to 62,5% of the control arm (p.0048)
- 7 year OS rate was significantly better for TNT (81.9% vs 76.1%, p 0.003)
- 7 year Metastasis-Free Survival rate was 73,6% for TNT compared to 65,4% of the control arm (p.0011)

Conclusions

- NACT with mFOLFIRINOX followed by CRT, surgery, and ACT significantly improved all outcomes, including OS in pts with LARC vs those who received standard CRT, surgery and ACT.







Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-overexpressing/amplified (HER2+) metastatic colorectal cancer (mCRC): Primary results from the multicenter, randomized, phase 2 DESTINY-CRC02 study.

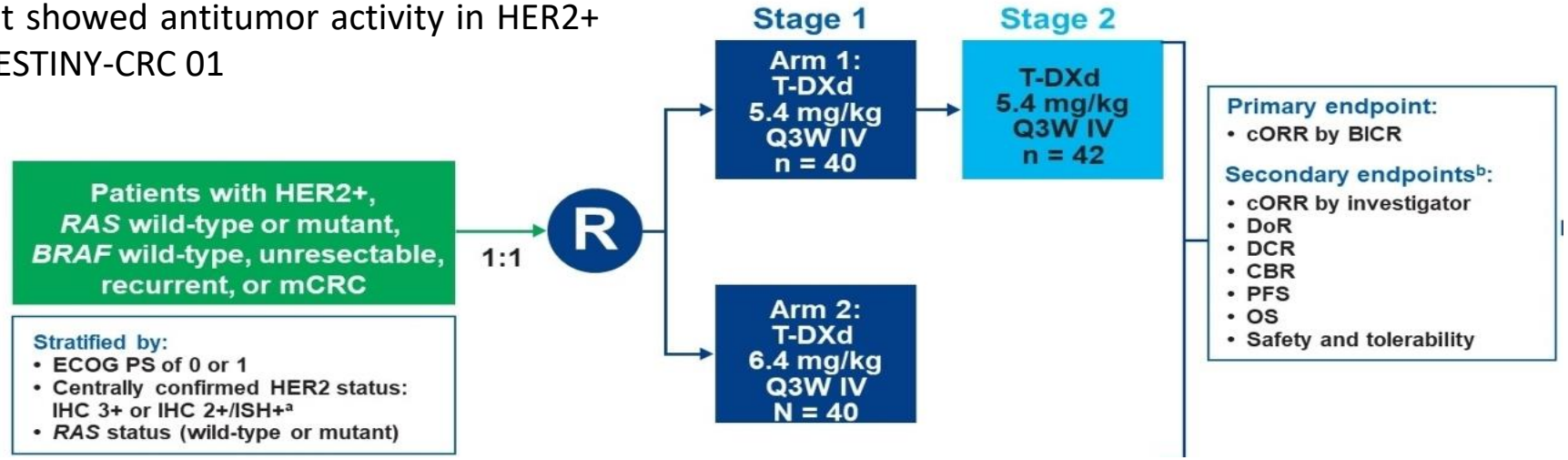
Kanwal Pratap Singh Raghav, Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Cristina Gravalos Castro, John H Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

Background

- HER2+ mCRC associated with resistence to EGFR-targeted therapy.
- T-DXd is an ab-drug conjugate with humanized anti-HER2 IgG1 mAb, a topoisomerase inhibitor payload and a cleavable linker that showed antitumor activity in HER2+ mCRC patients in DESTINY-CRC 01

Study design

- Randomized, blinded, multicenter phase II trial,not powered To statistically compare the two arms



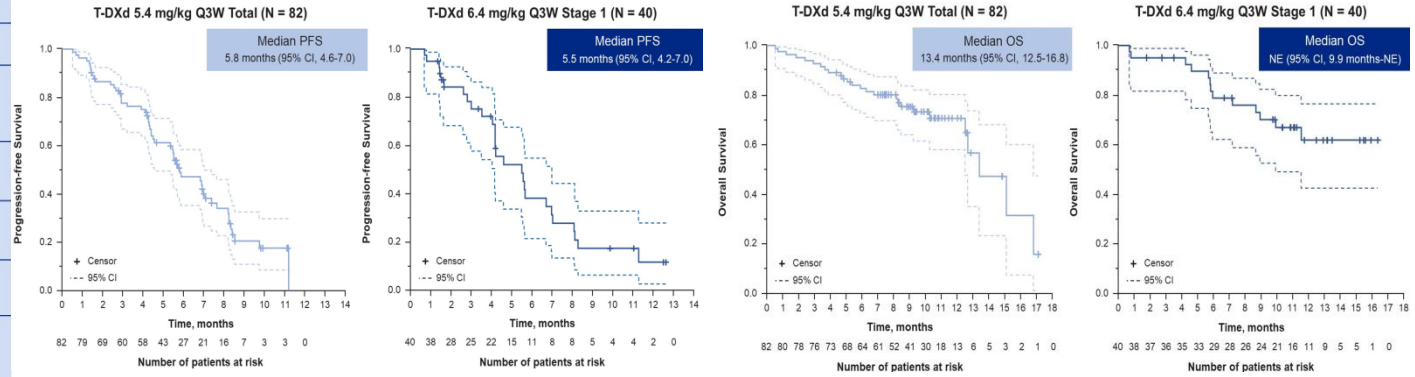
J Clin Oncol 40, 2022 (suppl 16; abstr 4022)

mCRC – Targeted therapy – DESTINY CRC 02 trial

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median age, years (range)	58.2 (26-78)	60.6 (30-84)	59.1 (26-84)	62.3 (35-81)
Sex, n (%)				
Male	21 (52.5)	24 (57.1)	45 (54.9)	19 (47.5)
Region, n (%)				
Asia-Pacific	25 (62.5)	22 (52.4)	47 (57.3)	24 (60.0)
US	5 (12.5)	1 (2.4)	6 (7.3)	2 (5.0)
Europe	10 (25.0)	19 (45.2)	29 (35.4)	14 (35.0)
HER2 status, n (%)				
IHC 3+	32 (80.0)	32 (76.2)	64 (78.0)	34 (85.0)
IHC 2+/ISH+	8 (20.0)	10 (23.8)	18 (22.0)	6 (15.0)
ECOG PS, n (%)				
0	22 (55.0)	24 (57.1)	46 (56.1)	22 (55.0)
1	18 (45.0)	18 (42.9)	36 (43.9)	18 (45.0)
***RAS* status, n (%)**				
Wild-type	34 (85.0)	34 (81.0)	68 (82.9)	34 (85.0)
Mutant	6 (15.0)	8 (19.0)	14 (17.1)	6 (15.0)
HER2/*RAS* status, n (%)				
IHC 2+ ISH+/wild-type	7 (17.5)	5 (11.9)	12 (14.6)	6 (15.0)
IHC 2+ ISH+/mutant	1 (2.5)	5 (11.9)	6 (7.3)	0
IHC 3+/wild-type	27 (67.5)	29 (69.0)	56 (68.3)	28 (70.0)
IHC 3+/mutant	5 (12.5)	3 (7.1)	8 (9.8)	6 (15.0)
Liver metastases at baseline, n (%)	29 (72.5)	30 (71.4)	59 (72.0)	26 (65.0)
CNS metastases at baseline, n (%)	3 (7.5)	0	3 (3.7)	1 (2.5)
Primary tumor site, n (%)				
Left colon[a]	32 (80.0)	29 (69.0)	61 (74.4)	34 (85.0)
Rectum	15 (37.5)	12 (28.6)	27 (32.9)	19 (47.5)
Right colon[b]	8 (20.0)	13 (31.0)	21 (25.6)	6 (15.0)

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

Results



	T-DXd 5.4 mg/kg Q3W Total N = 83[b]		T-DXd 6.4 mg/kg Q3W Stage 1 N = 39	
n (%)	**Any-grade**	**Grade ≥3**	**Any-grade**	**Grade ≥3**
Any TEAEs	82 (98.8)	41 (49.4)	39 (100)	23 (59.0)
Nausea	48 (57.8)	7 (8.4)	22 (56.4)	0
Fatigue[c]	38 (45.8)	8 (9.6)	18 (46.2)	2 (5.1)
Neutropenia[d]	25 (30.1)	14 (16.9)	18 (46.2)	11 (28.2)
Decreased appetite	25 (30.1)	2 (2.4)	6 (15.4)	0
Anemia[e]	22 (26.5)	8 (9.6)	16 (41.0)	9 (23.1)
Thrombocytopenia[f]	21 (25.3)	5 (6.0)	14 (35.9)	5 (12.8)
Alopecia	20 (24.1)	0	11 (28.2)	0
Constipation	20 (24.1)	0	5 (12.8)	0
Diarrhea	19 (22.9)	2 (2.4)	11 (28.2)	0
Vomiting	17 (20.5)	4 (4.8)	3 (7.7)	0

Conclusions

- T-DXd showed promising antitumor activity in pts with HER2+ mCRC at both 5.4 and 6.4 mg/kg doses.
- Antitumor efficacy was observed irrespective of RAS mutation status at 5.4 mg/kg T-DXd, and in those with prior anti-HER2 therapy.
- Safety was consistent with the known safety profile of T-DXd
- Safety favored 5.4 mg/Kg doses

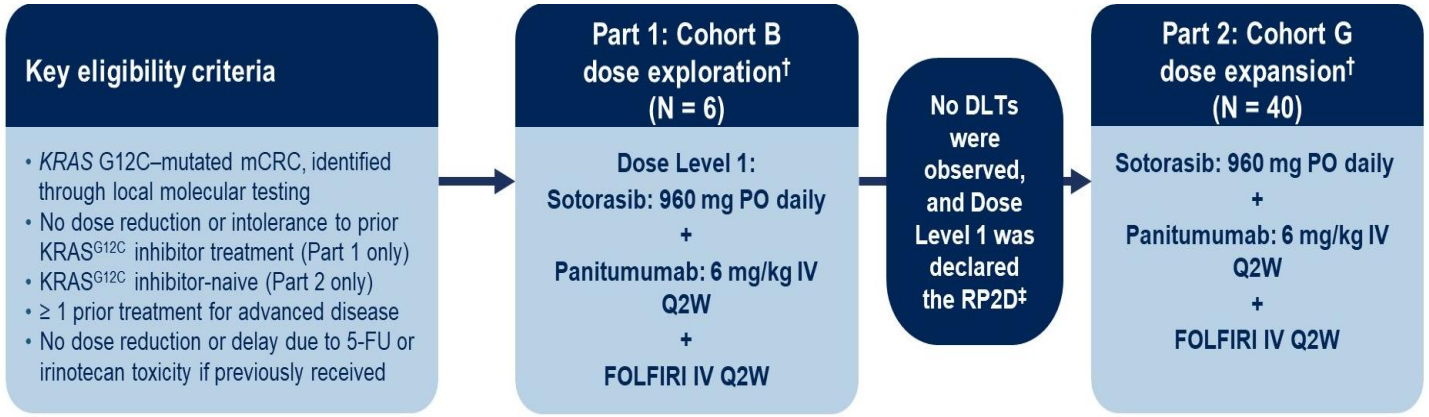
Sotorasib (Soto) plus panitumumab (Pmab) and FOLFIRI for previously treated KRAS G12Cmutated metastatic colorectal cancer (mCRC): CodeBreaK 101 phase 1b safety and efficacy.

David S. Hong, Yasutoshi Kuboki, John H Strickler, Marwan Fakih, He´ le` ne Houssiau, Timothy Jay Price, Elena Elez, Salvatore Siena, Emily Chan, Jane Nolte-Hippenmeyer, Panli Cardona, Qui Tran, Toshiki Masuishi

Backgroud

- Approximately 3% of CRC pts have an oncogenic KRAS G12 mutation.
- Sotorasib showed a 9.7% ORR as monotherapy for chemorefractory pts with KRAS G12C-mutated mCRC.
- Combined with Panitumumab, ORR increased to 30%, supporting the model that the doublet mitigates Soto-related feedback reactivation of the RAS-MAPK pathway and accumulation of activated

Study design



Primary endpoint

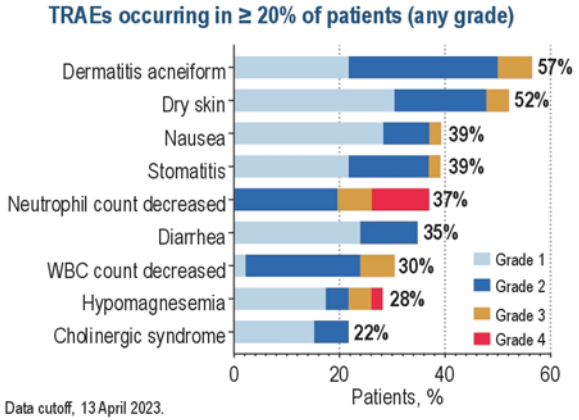
- Safety and tolerability

Secondary endpoints

- ORR, DCR, DOR, TTR, PFS

mCRC – Targeted therapy – CodeBreaK 101 trial

TRAE	N = 46 n (%)
TRAE, any grade	44 (96)
Grade 3	13 (28)
Grade 4*	7 (15)
Serious	2 (4)
Fatal	0
TRAE leading to ≥ 1 dose interruptions/reductions	34 (74)
Attributed to sotorasib	6 (13)
Attributed to panitumumab	20 (43)
Attributed to FOLFIRI (any component)	30 (65)
TRAE leading to discontinuation of ≥ 1 agent	12 (26)
Sotorasib†	1 (2)
Panitumumab	2 (4)
FOLFIRI (any component)‡	11 (24)
TRAE leading to discontinuation of all agents	1 (2)

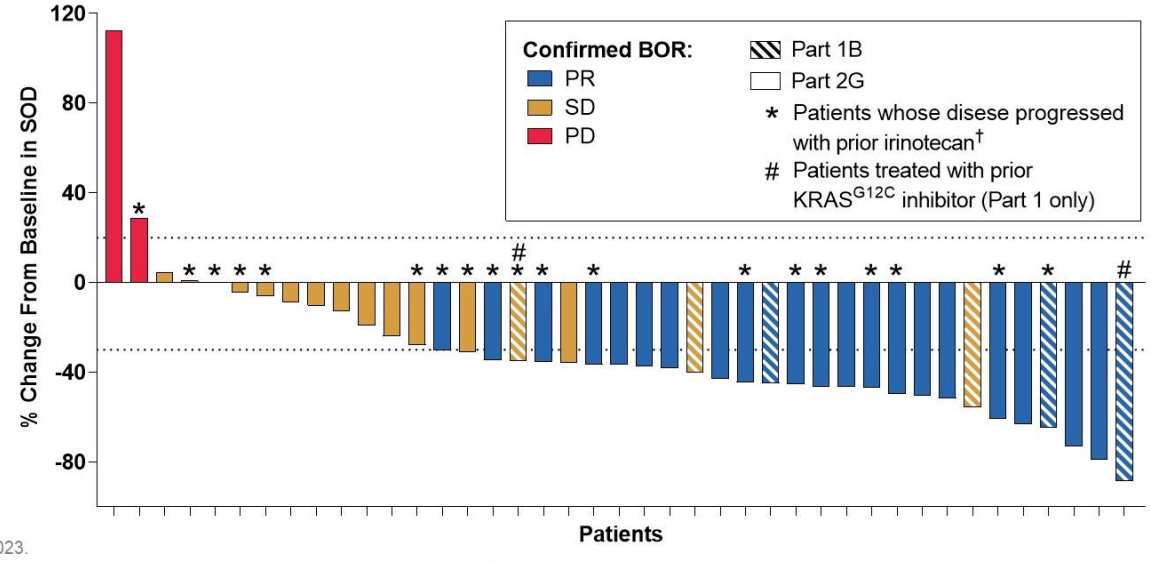


Data cutoff, 13 April 2023.
*Grade 4 TRAEs were neutrophil count decreased (n = 5, 11%), blood creatine phosphokinase increased (n = 1, 2%), and hypomagnesemia (n = 1, 2%).
†Sotorasib discontinuation was required in 1 patient due to grade 3 alanine aminotransferase increase attributed to all components of treatment.
‡The most common component discontinued due to TRAE was 5-FU, occurring in 11 (24%) of patients. Discontinuation of 5-FU bolus while continuing 5-FU continuous infusion did not count as discontinuation of one component.

Response by investigator assessment*	Part 1 Sotorasib + Panitumumab + FOLFIRI (n = 6)	Part 2 Sotorasib + Panitumumab + FOLFIRI (n = 36)	Total (N = 42*)
ORR confirmed (95% CI)	3 (50) (11.8, 88.2)	20 (56) (38.1, 72.1)	**23 (55)** (38.7, 70.2)
CR	0	0	0
PR	3 (50)	20 (56)†	23 (55)†
SD	3 (50)	13 (36)	16 (38)
PD	0	2 (6)	2 (5)
Unavailable	0	1 (3)	1 (2)
DCR (95% CI)	6 (100) (54.1, 100.0)	33 (92) (77.5, 98.3)	**39 (93)** (80.5, 98.5)

Results

- Median prior lines of systemic therapy was 2 (range: 1-6), 97% had prior fluoropyrimidine and 73% had prior irinotecan.
- Sotorasib (960 mg PO daily) plus Pmab (6 mg/kg IV Q2W) and FOLFIRI (IV Q2W) was the recommended phase 2 dose
- Safety findings were consistent with known profiles of Soto, Pmab, and FOLFIRI



Conclusions

- Sotorasib plus Pmab and FOLFIRI showed promising safety and efficacy in pretreated KRAS G12C-mutated mCRC.
- Adverse events were manageable and consistent with the expected safety profile of the drugs used

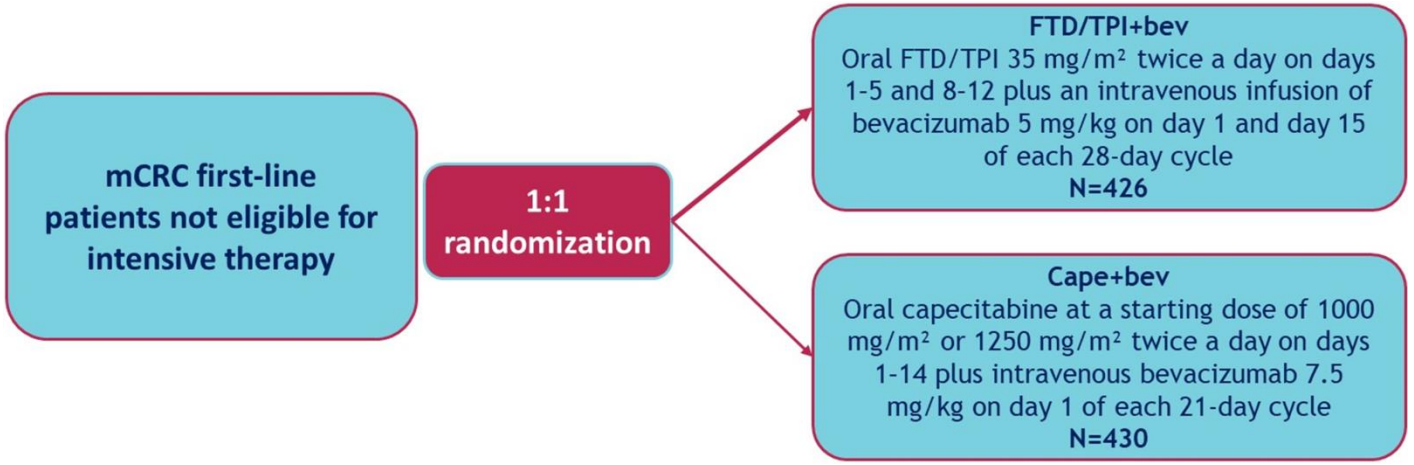
Overall survival results for trifluridine/tipiracil plus bevacizumab vs capecitabine plus bevacizumab: Results from the phase 3 SOLSTICE study.

Thierry Andre, Alfredo Falcone, Yaroslav V. Shparyk, Fedor Vladimirovich Moiseenko, Eduardo Polo, Tibor Csoszi, Arinilda Silva Campos Bragagnoli, Gabor Liposits, Ewa Chmielowska, Flore Delaporte, Hasnaa Hassan, Donia Skanji, Nadia Amellal, Mark P. Saunders;

Backgroud

- Approximally 25% of pts with CRC present with mts at initial diagnosis
- First-line treatment for unresectable metastatic CRC is flurorpirimidine with or without bevacizumab for pts that are not candidates for intensive chemotherapy.
- Results of a phase II trial evaluating safety and efficacy of FTD/TPI + Bevacizumab VS capecitabine + bevacizumab suggest potential benefits for this treatment.
- However SOLSTICE study did not meet the primary endpoint in the first analysis

Study design



Primary endpoint

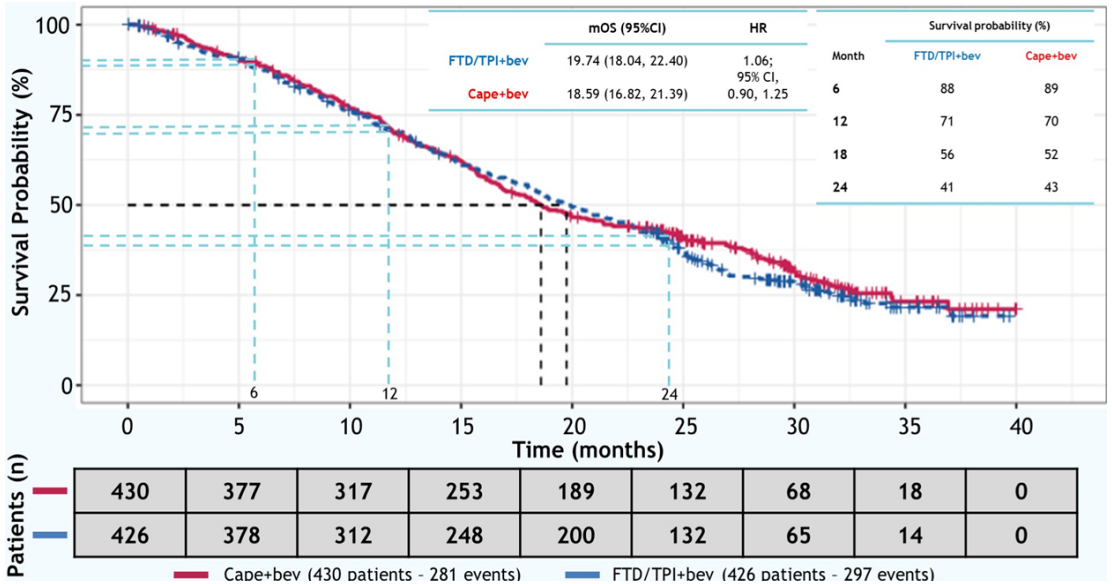
- PFS

Secondary endpoints

- OS

mCRC – SOLSTICE trial

	FTD/TPI+bev group (n=426) n (%)	Cape+bev group (n=430) n (%)
Sex		
Male	240 (56)	226 (53)
Female	186 (44)	204 (47)
ECOG performance status		
0	97 (23)	100 (23)
1	248 (58)	249 (58)
2	80 (19)	80 (19)
3	0 (0)	1 (<1)
Reason for non-eligibility for intensive therapy		
Clinical condition	290 (68)	286 (67)
Non-clinical condition	135 (32)	144 (33)
Primary tumor location		
Right-sided	129 (30)	127 (30)
Left-sided	296 (70)	303 (70)



Results

- No significant treatment effect was observed after adjustment for the prognosis factors (HR, 1.08; 95% CI, 0.92, 1.28)
- No new safety signal was identified.
- The most common severe emergent adverse events were neutropenia 54% vs 1%, anemia 16% vs 4%, hand-foot syndrome 0% vs 15%, and hypertension 9% vs 11% in FTD/TPI+bev vs cape+bev, respectively.

Factor	Levels	P-Value	Interaction P-Value	Missing value (n)
Treatment	FTD/TPI+bev (versus cape+bev)	0.3461	n/a	0
Age	<70 Years (versus ≥70 years)	0.0507	0.6037	0
Location of primary disease	Left (versus Right)	0.0477	0.3991	0
Surgical resection	Yes (versus No)	<000.1	0.5130	0
No of metastatic sites	1-2 (versus ≥3)	0.0078	0.2333	1
Presence of liver metastasis	No (versus Yes)	0.0005	0.4878	1
Neutrophils lymphocyte ratio	Nlr <3 (versus Nlr ≥3)	<000.1	0.6607	7
Charlson score	0 (versus 1-2) 1-2 (versus ≥3)	<000.1 0.3619	0.0210 0.7651	4 4
ECOG performance status	0 (versus 1) 1 (versus 2)	0.7652 0.0079	0.6294 0.0145	0 0

Conclusions

- FTD/TPI+bev was not superior to cape+bev in terms of PFS and OS.
- FTD/TPI+bev could represents an alternative to cape+bev in this population.

FOLFOXIRI plus bevacizumab and atezolizumab as upfront treatment of unresectable metastatic colorectal cancer (mCRC): Updated and overall survival results of the phase II randomized AtezoTRIBE study.

Carlotta Antoniotti, Daniele Rossini, Filippo Pietrantonio, Lisa Salvatore, Federica Marmorino, Margherita Ambrosini, Sara Lonardi, Maria Bensi, Roberto Moretto, Stefano Tamberi, Ilaria Toma, Alessandro Passardi, Maria Caterina De Grandis, Veronica Conca, Federica Palermo, Alessandro Cappetta, Aurelie Catteau, Luca Boni, Je´ roˆme Galon, Chiara Cremolini

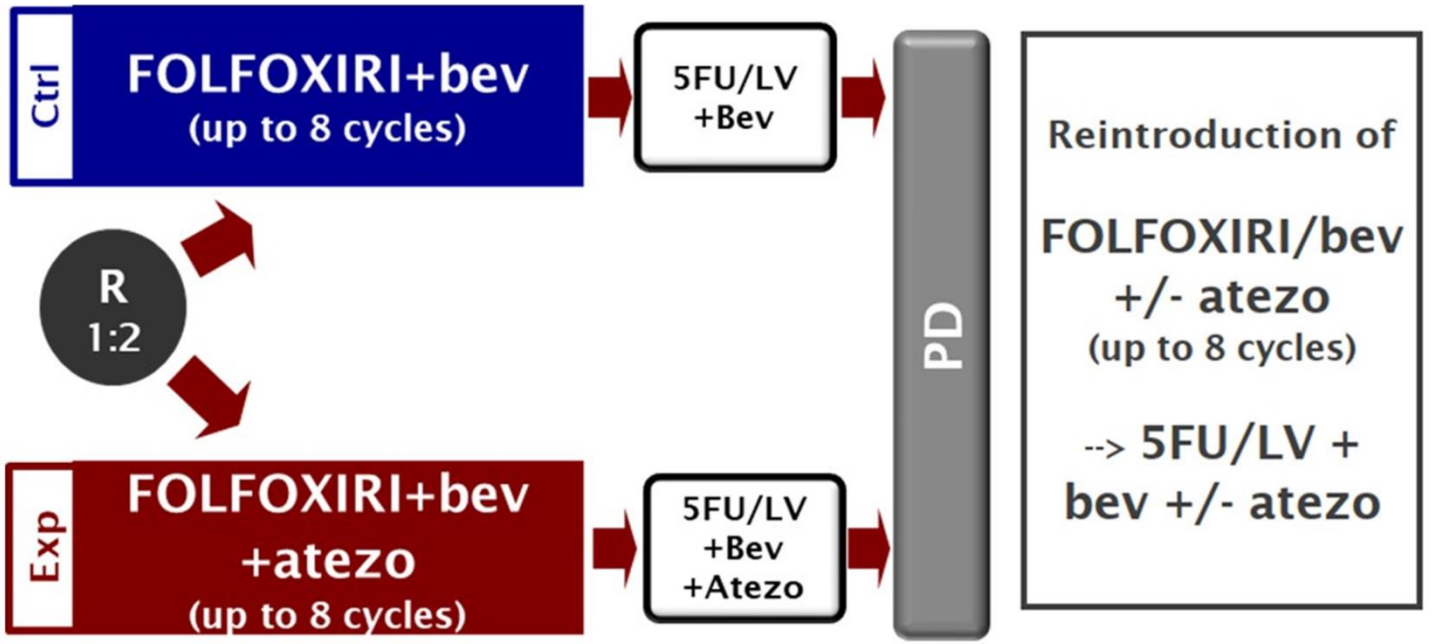
Background

- Adding atezolizumab to FOLFOXIRI/bev was safe and improved PFS (primary endpoint), with a modest benefit also among pts with pMMR tumors.
- Subgroup analyses suggest that TMB and Immunoscore IC (IS IC) -an IHC biomarker measuring CD8 and PD-L1 cell densities and their proximity- may identify pts with pMMR tumors deriving benefit from adding atezo to FOLFOXIRI/bev.

Primary endpoint

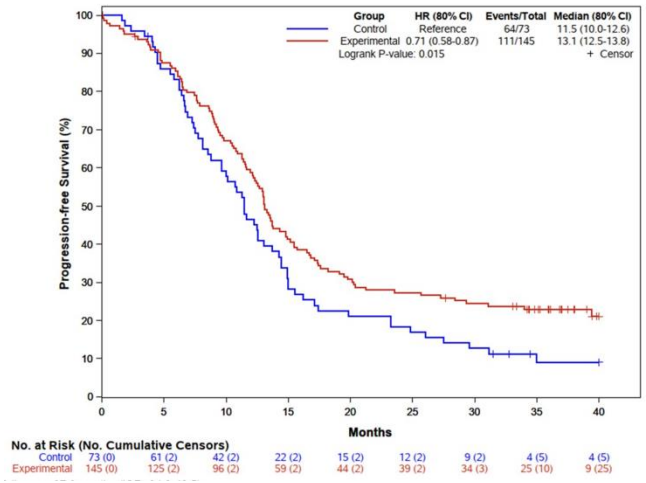
- PFS

Study design

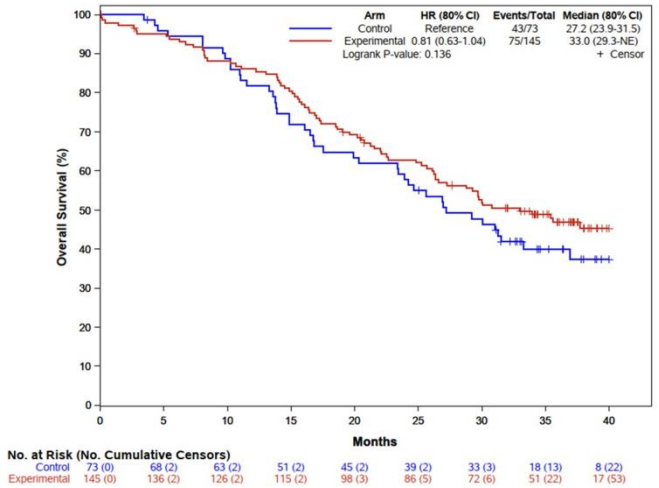


Biomarkers – mCRC – AtezoTRIBE trial

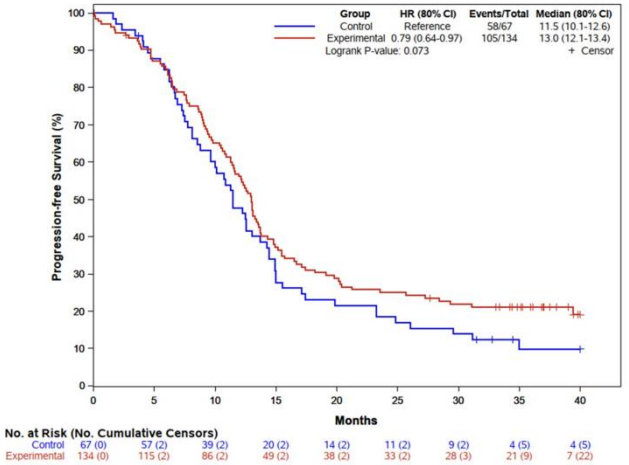
ITT PFS



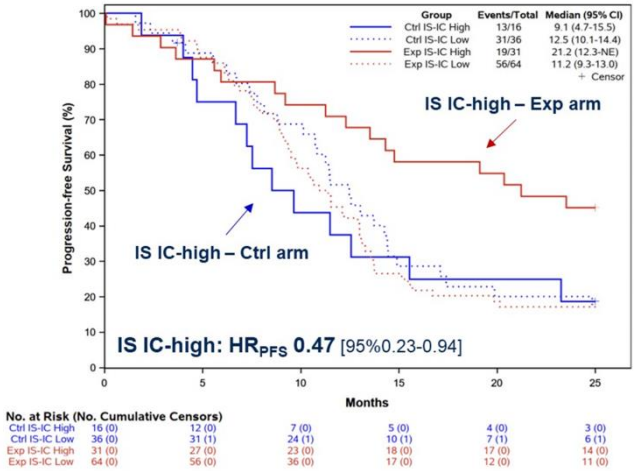
ITT OS



pMMR PFS



pMMR PFS and IS IC-High



Results

- In the ITT group, significant interactions between treatment and MMR status (Pint .011), TMB (Pint .008), and IS IC (Pint .037) were reported in terms of PFS.
- Only IS IC was associated with a differential OS benefit (Pint .065), with pts bearing IS IC-high tumors deriving benefit from adding atezo (HR 0.43, 95%CI 0.19-1.00)
- **In the pMMR group, significant interactions between treatment and TMB and IS IC were reported in terms of PFS (Pint .016 and .051, respectively) and OS (Pint .043 and .063, respectively). Pts bearing IS IC-high tumors derived higher OS benefit from adding atezo (HR 0.44, 95%CI 0.19-1.03**

Conclusions

- Pts with IS IC-high and/or TMB high pMMR mCRC seem to derive a survival benefit from adding atezolizumab to FOLFOXIRI/bev as upfront treatment

Modified FOLFOXIRI plus cetuximab and avelumab as initial therapy in RAS wild-type unresectable metastatic colorectal cancer: Results of the phase II AVETRIC trial by GONO.

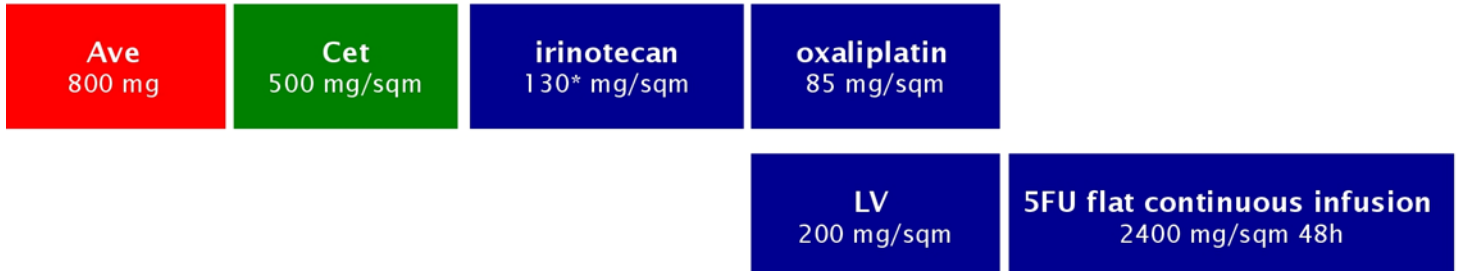
Veronica Conca, Carlotta Antoniotti, Francesca Bergamo, Filippo Pietrantonio, Daniele Rossini, Mario Scartozzi, Eleonora Perissinotto, Alberto Giovanni Leone, Pusceddu Valeria, Beatrice Borelli, Luigi Cavanna, Tiziana Pia Latiano, Daniele Santini, Gianluca Masi, Lisa Salvatore, Luca Frassineti, Francesco Leone, Stefano Tamberi, Luca Boni, Chiara Cremolini

Background

- mFOLFOXIRI in combination with an anti-EGFR agent showed a manageable safety profile and activity in RAS WT mCRC.
- The association of an active cytotoxic regimen with cetuximab may increase the exposure of tumour-associated neoantigens and induce immunogenic cell death and antibody-dependent cell-mediated cytotoxicity thus enabling the effect of ICIs

Study design

- Prospective, open label, multicenter, phase II, single arm trial in which initially unresectable and previously untreated RAS wt mCRC pts received mFOLFOXIRI) plus cetuximab and avelumab every 2 weeks up to 12 cycles followed by maintenance with 5FU/LV plus cet and ave until disease progression.



Primary endpoint

- PFS

Secondary endpoint

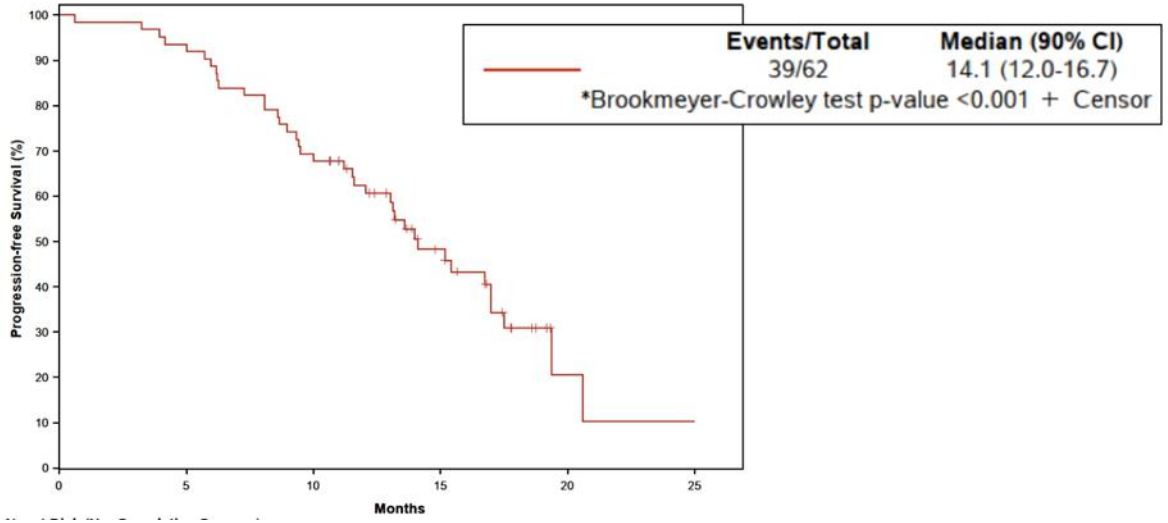
- RR, Safety

Results

Characteristic, n (%) patients	N = 62
Sex (M / F)	36 (58) / 26 (42)
Median Age (IQR)	56 (49-63)
ECOG PS (0 / 1-2)	54 (87) / 8 (13)
Synchronous Metastases (Y / N)	58 (94) / 4 (6)
Prior Adjuvant CT (Y / N)	0 / 62 (100)
Surgery on primary tumour (Y / N)	22 (35) / 40 (65)
Number Metastatic Sites (1 / >1)	30 (48) / 32 (52)
Liver Only Disease (Y / N)	26 (42) / 36 (58)
Primary Tumor Side (right / left or rectum)	7 (11) / 55 (89)
***BRAF* status** (wt / mut V600E)	62 (100) / 0
***MMR* status** (pMMR / dMMR)	62 (100) / 0
***HER2* status** (neg / pos / missing)	49 (79) / 4 (6) / 9 (15)

G3/4 adverse events, n (%) patients	*Safety run-in phase* N= 6	*Post-amendment* N = 56	N = 62
Any event	5 (83%)	36 (64%)	41 (66%)
Nausea	1 (17%)	6 (11%)	7 (11%)
Vomiting	-	1 (2%)	1 (2%)
Diarrhea	2 (33%)	15 (27%)	17 (27%)
Stomatitis	1 (17%)	4 (7%)	5 (8%)
Anemia	1 (17%)	1 (2%)	2 (3%)
Neutropenia	3 (50%)	15 (27%)	18 (29%)
Febrile neutropenia	-	1 (2%)	1 (2%)
Thrombocytopenia	-	2 (4%)	2 (3%)
Neurotoxicity	1 (17%)	3 (5%)	4 (6%)
Skin rash	1 (17%)	8 (14%)	10 (16%)
Asthenia	1 (17%)	7 (14%)	9 (15%)
Anorexia	1 (17%)	2 (4%)	3 (5%)

G3/4 immuno-related adverse events, n (%) patients	*Safety run-in phase* N= 6	*Post-amendment* N = 56	N = 62
Pancreatitis	-	1 (2%)	1 (2%)
Transaminases increase	-	1 (2%)	1 (2%)
Colitis	-	1 (2%)	1 (2%)
Infusion-related reactions	-	1 (2%)	1 (2%)
Immuno-related AEs	-	4 (7%)	4 (6%)



- mPFS was 14.1 months (90% CI 12.0-16.7, Brookmeyer-Crowley test p , 0.001).
- RR and DCR were 82% and 98%, respectively
- R0 resection rate was 21% (27% in liver-only subgroup).

Conclusions

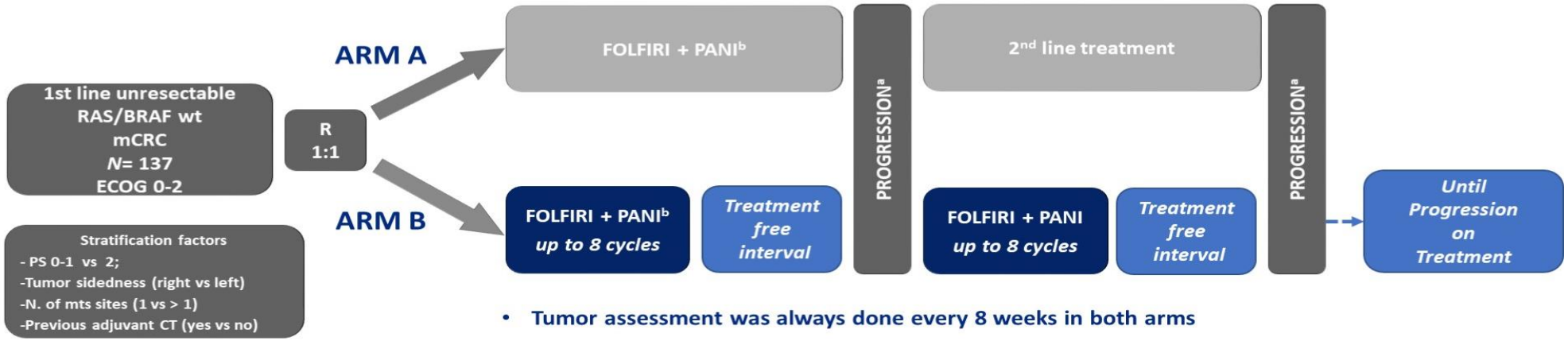
- Combining mFOLFOXIRI plus cet and ave achieves promising results in terms of PFS as well as response rate, in pts with pMMR RAS and BRAF wt mCRC.
- Safety profile feasible, but high rate of G3/G4 diarrhea

Intermittent or continuous panitumumab plus FOLFIRI (FOLFIRI/PANI) for first-line treatment of patients (pts) with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC): An update of survival/toxicity and preliminary results of genomic alterations from IMPROVE study

Antonio Avallone, Francesco Giuliani, Guglielmo Nasti, Vincenzo Montesarchio, Giuseppe Santabarbara, Silvana Leo, Umberto Malapelle, Alfonso De Stefano, Gerardo Rosati, Ivan Lolli, Emiliano Tamburini, Alfredo Colombo, Daniele Santini, Lucrezia Silvestro, Alessandra Leone, Carlo Vitagliano, Giancarlo Troncone, Alberto F. Sobrero, Diana Giannarelli, Alfredo Budillon

Study design

- Randomized, non-comparative multicenter, phase 2 study



- Tumor assessment was always done every 8 weeks in both arms

Primary endpoint

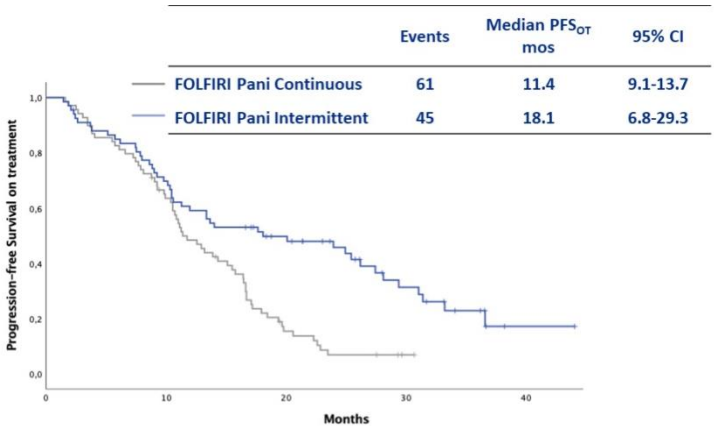
- PFS

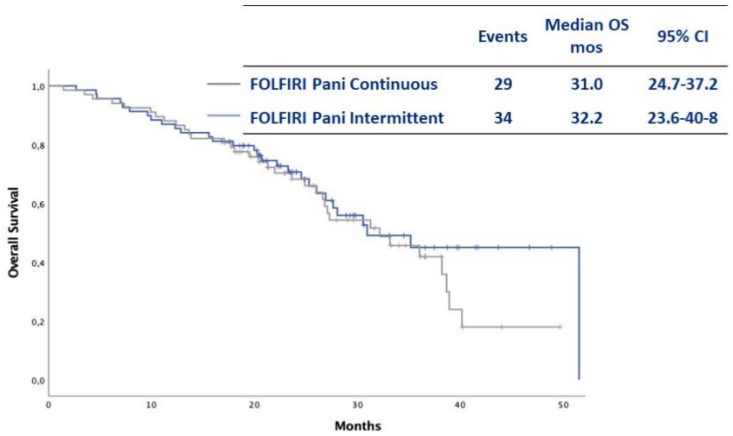
mCRC – IMPROVE trial

Baseline Characteristics	ARM A n = 69	ARM B n =68
Gender (M / F) %	**59** / 41	**60** / 40
Median age (years, IQR)	62 (55 - 71)	66 (61 - 73)
ECOG performance status (0/1/2) %	84 / 16 / 0	72 / 27 / 1
Prior adjuvant treatment (Y/N) %	**22** / 78	**31** / 69
Primary tumor resected (Y/N) %	52 / 48	62 / 38
Synchronous metastases (Y/N) %	55 / 45	46 / 54
Liver-limited disease (Y/N) %	**19** / 81	**12** / 88
Number of metastatic sites (1/>1) %	33 / **67**	26 / **74**
Primary tumor location (right/left) %	17 / **83**	15 / **85**

Results

- Median PFSOT in left sided tumors was 11.7 mo (95% CI: 9.1-14.3) in arm A and 18.1 mo (95% CI: 15.0-32.9) in arm B,
- in right sided pts PFSOT WAS 10.7 mo (95% CI: 7.3-14.1) and 7.9 mo (95% CI: 5.7-10.1, respectively.
- Main grade ≥ 3 toxicities were (arm A/B): skin 30/18%, neutropenia 25/24%; diarrhea 13/15%. Median STB score was 0.77/cycle (IQR: 0.20-1.06) in arm A and 0.36/cycle (IQR: 0-0.77) in arm B.
- GAs in baseline ctDNA were evidenced in 12/46 (26%) pts, persisting to PD in all but one pt. Among the 34 pts without baseline GAs, only 8 (23%) developed ≥ 1 acquired GAs (Acq-GAs) to PD.





Conclusions

- Intermittent FOLFIRI/PANI strategy produces a long PFSOT and a reduced skin severe and skin burden toxicity without any detrimental effect on OS.
- Preliminary data on Acq-GAs suggest that classical mutations associated with anti-EGFR resistance are infrequent with up-front use of anti-EGFR/chemotherapy.

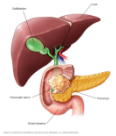
BIOMARKERS

Importanza ct Dna nel predirre la ricaduta di malattia in pazienti con ca colon retto operato GALAXY STUDY: impatto sulla DFS +++. Implicazioni nella pratica clinica

Le cellule RAS mut possono diventare WT: lo studio SCRUM JAPAN GOZILA mostra questa trasformazione nel 9.8 % dei casi trattati con CT. Questi pz potrebbero beneficiare di un trattamento con anti EGFR

Biopsia liquida nel FIRE-4: pazienti classificati come WT su analisi tissutale si sono invece mostrati con mutazioni RAS (13%) e BRAF (7%) alla biopsia liquida, queste mutazioni sono spesso frequenti quando la terapia con anti EGFR dura per molto tempo

PARADIGM trial conferma efficacia selezione pz ctDNA con Panitum nei tumori wt stabili e BRAF RAS wt



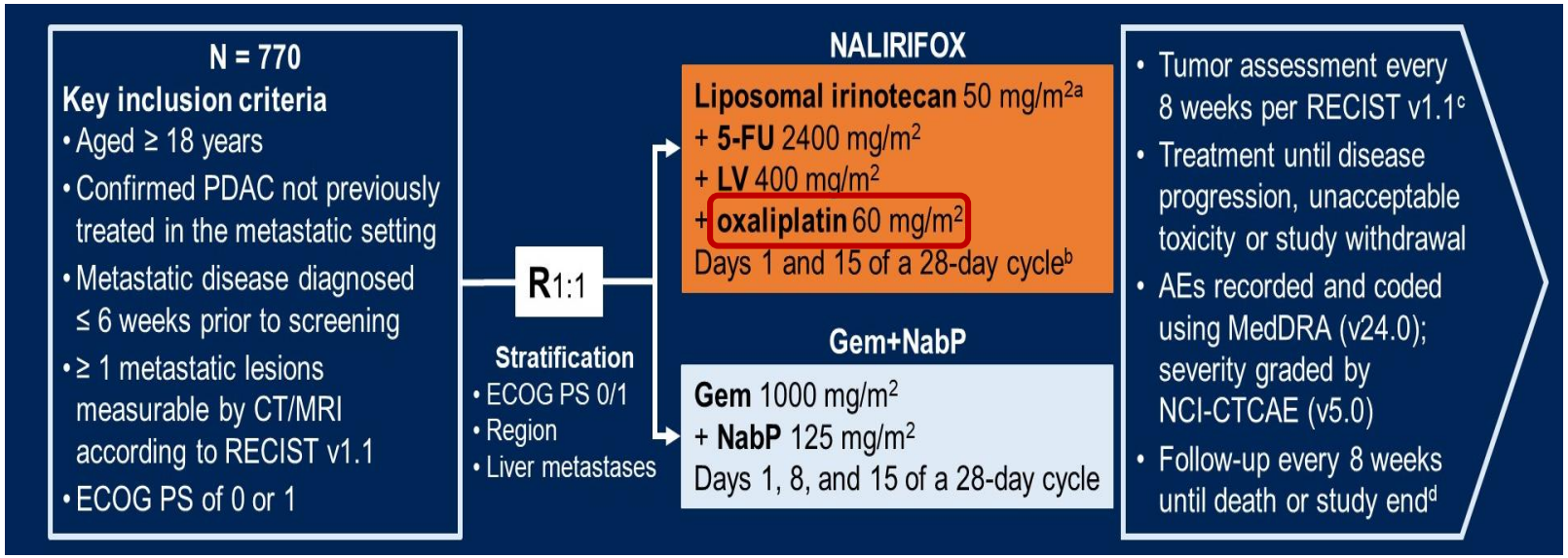
Pancreatic Ductal Adenocarcinoma (PDAC): NAPOLI 3

NALIRIFOX versus nab-paclitaxel + gemcitabine in treatment-naive patients with mPDAC: additional results from the phase 3 NAPOLI 3 trial

Eileen Mary O'Reilly, Davide Melisi, Teresa Macarulla, Roberto A. Pazo Cid, Sreenivasa R Chandana, Christelle De La Fouchardiere, Andrew Peter Dean, Igor Kiss, Woo Jin Lee, Thorsten Oliver Goetze, Eric Van Cutsem, Scott Paulson, Tanios S. Bekaii-Saab, Shubham Pant, Richard Hubner, Zhimin Xiao, Huanyu Chen, Fawzi Benzaghou, Zev A. Wainberg

NAPOLI-3: background and study design

- A phase 1/2 study (NCT02551991) demonstrated promising anti-tumor activity in patients with mPDAC who received first-line NALIRIFOX.
- First results of NAPOLI-3 were presented at ASCO Gastrointestinal Cancers Symposium 2023. The median OS was 11.1 months in the NALIFIROX arm as compared with 9.2 months in the Gem+NabP arm (HR 0.84 [95% CI 0.71–0.99]; p = 0.04); PFS was also significantly improved (7.4 months vs 5.6 months; HR 0.70 [0.59–0.84]; p = 0.0001).

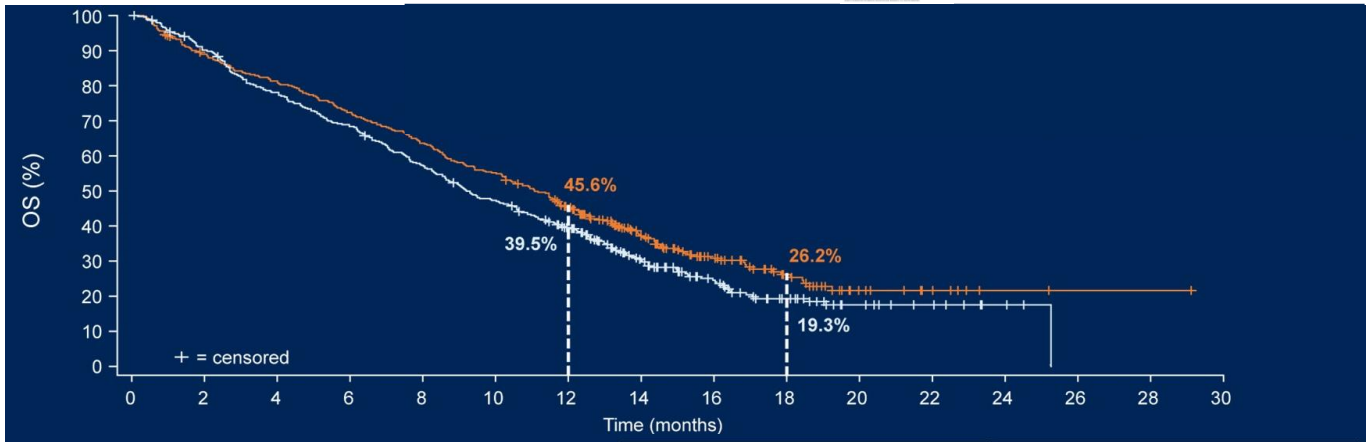


Primary endpoint: OS

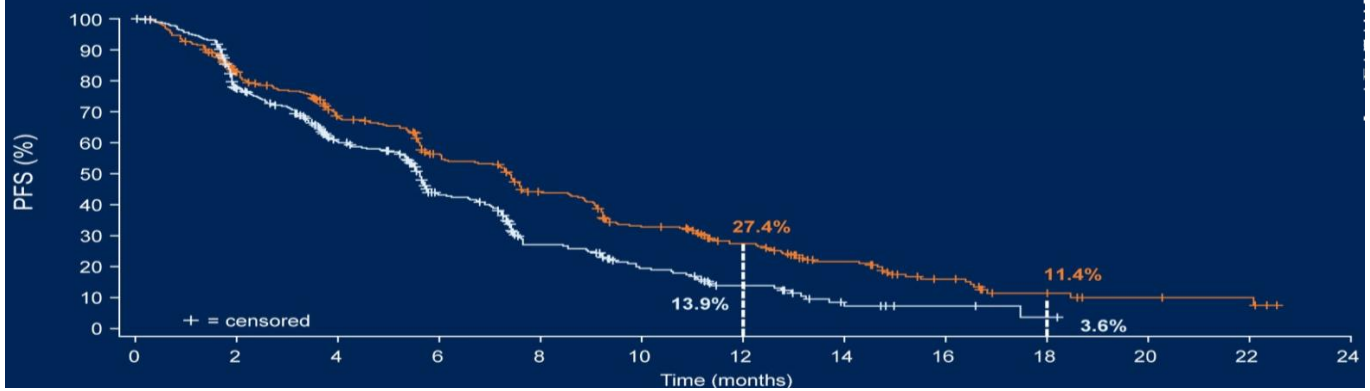
Secondary endpoints: PFS, ORR, Safety

J Clin Oncol 41, 2023 (suppl 16; abstr 4006)

Pancreatic Ductal Adenocarcinoma (PDAC): NAPOLI-3



	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
Objective response rate (95% CI), %	41.8 (36.8–46.9)	36.2 (31.4–41.2)
Best overall response, %		
Complete response	0.3	0.3
Partial response	41.5	35.9
Stable disease	25.8	26.1
Progressive disease	9.9	14.5
Not evaluable[b]	22.5	23.3
Disease control rate,[c] %	67.6	62.3
Duration of response, median (95% CI), months	7.3 (5.8–7.6)	5.0 (3.8–5.6)



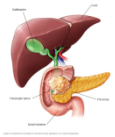
RESULTS:

- 12m-OS → NALIRIFOX 45.6% vs Gem-NabP 39.5%
- 18m-OS → NALIRIFOX 26.2% vs Gem-NabP 19.3%

- ORR→ NALIRIFOX 41.8% vs Gem-NabP 36.2%

- 12m-PFS→ NALIRIFOX 27.4% vs Gem-NabP 13.9%
- 18m-PFS→ NALIRIFOX 11.4% vs Gem-NabP 3.6%

J Clin Oncol 41, 2023 (suppl 16; abstr 4006)



Pancreatic Ductal Adenocarcinoma (PDAC): NAPOLI-3

NAPOLI-3: safety and conclusions

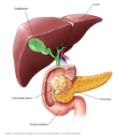
	NALIRIFOX (n = 370)		Gem+NabP (n = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	Any grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic				
Neutropenia[b] / febrile neutropenia	50.0 / 2.4	23.8 / 2.4	50.6 / 2.6	38.0 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia[c]	24.0	1.6	40.6	6.1
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy[d]	32.9	6.7	30.9	8.7
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

Median (range) duration of treatment was 24.3 (0.4-100.9) weeks with NALIRIFOX and 17.6 (0.7-81.7) weeks with Gem-NabP

Conclusions

- NALIRIFOX demonstrated statistically significant and clinically meaningful improvements in median OS and PFS compared to Gem-NabP
- 12- and 18-months OS and PFS also favoured NALIRIFOX over Gem-NabP
- The safety profile of NALIRIFOX was manageable and consistent with the profiles of the treatment components.

J Clin Oncol 41, 2023 (suppl 16; abstr 4006)

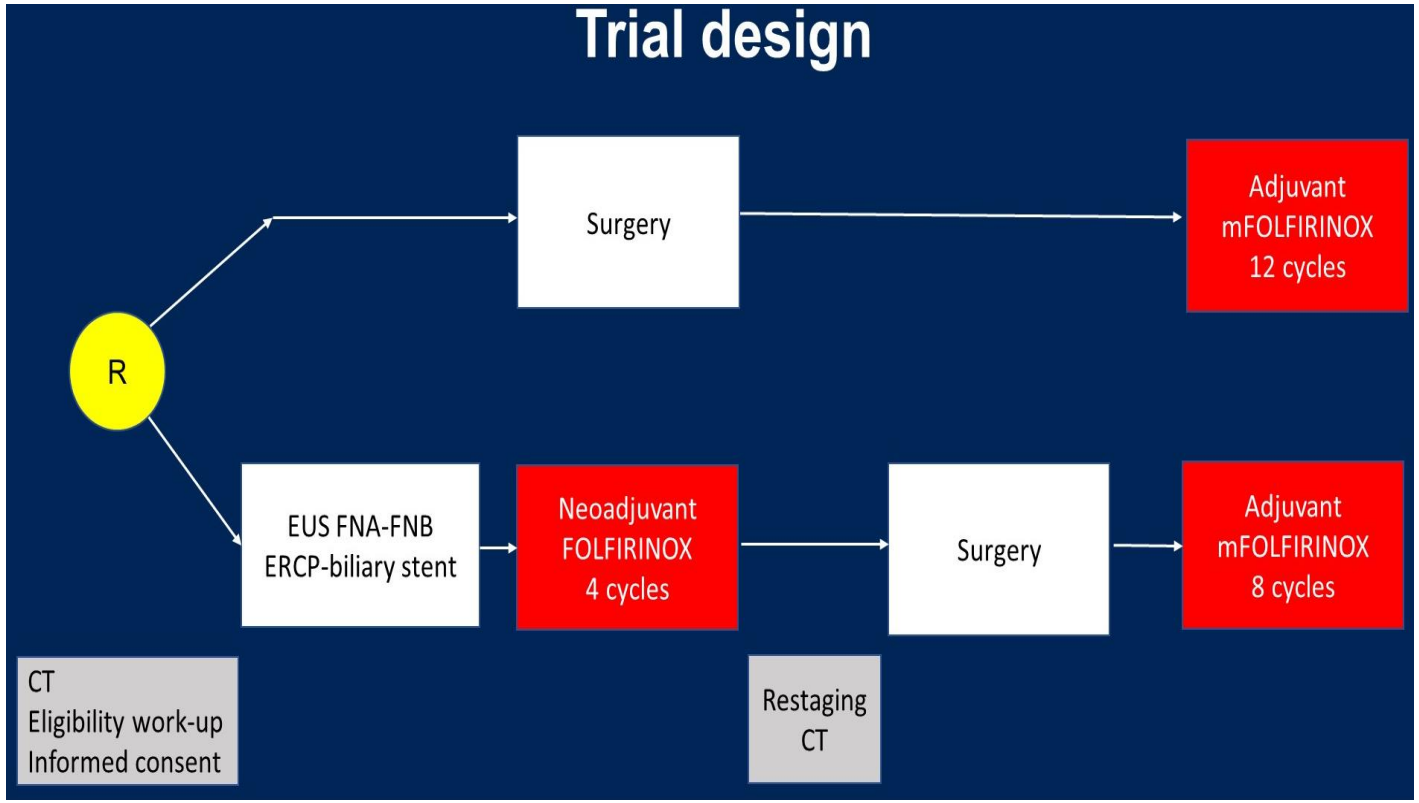


Pancreatic Ductal Adenocarcinoma (PDAC): NORPACT-1

Key eligibility criteria

- Radiologically (CT) resectable pancreatic head cancer (NCCN criteria)
  1. No arterial involvement (celiac, hepatic, superior mesenteric)
  2. <180° interface with portal/superior mesenteric vein, no contour irregolarity
  3. No distant metastasis

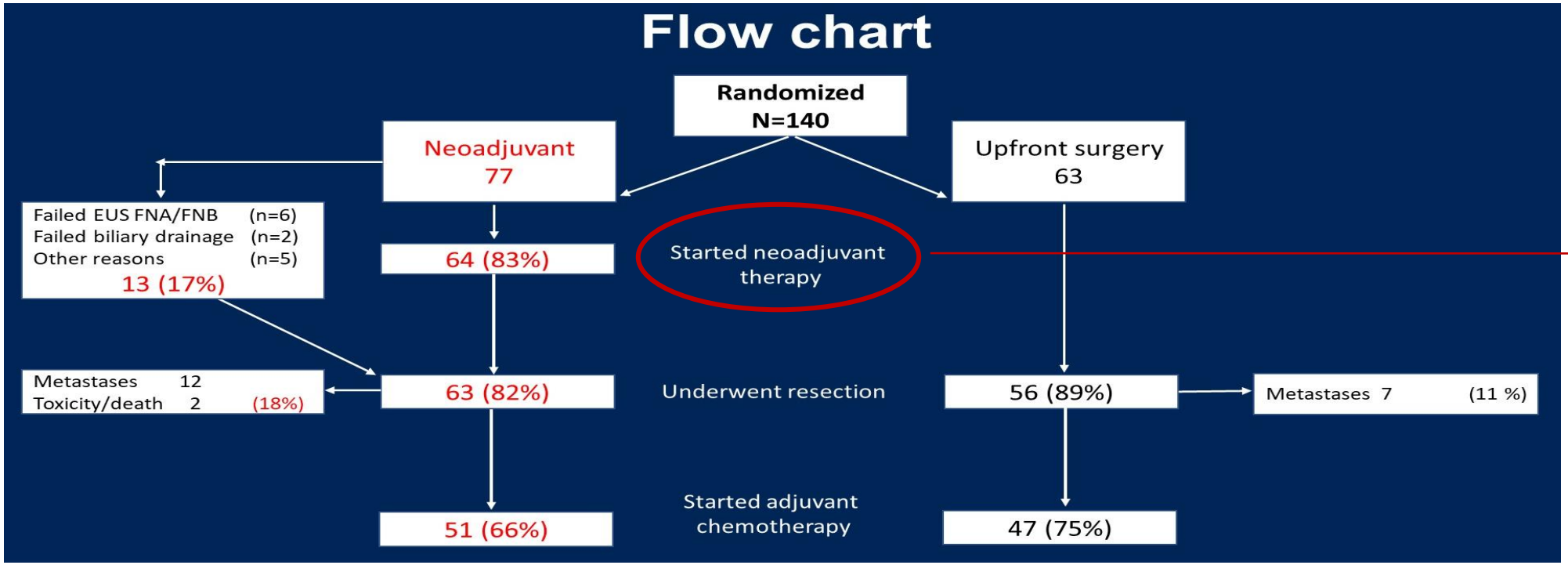
- Age > 18 year and considered fit for major surgery
- ECOG performance status 0 or 1
- Adequate bone marrow, hepatic and renal function



- Randomized, exploratory, unblinded phase-2 trial
- Primary endpoint: Overall survival
- Study designed to have 80 % power to detect an increase in survival rate at 18 months from 50% to 70 % with neoadjuvant therapy (significance level 0.15)

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

Pancreatic Ductal Adenocarcinoma (PDAC): NORPACT-1



	Neoadjuvant FOLFIRINOX ITT (N = 77)	Upfront surgery ITT (N = 63)	p-value
Went to resection	N = 63 (82%)	N = 56 (89%)	
R0	56%	39%	0.076
N0	29%	14%	0.060
Receipt of adjuvant rx	N = 51	N = 47	
	mFOLFIRINOX 25 % 5-FU 2% **Gem-based 73 %**	mFOLFIRINOX 40% 5-FU 2% **Gem-based 58%**	

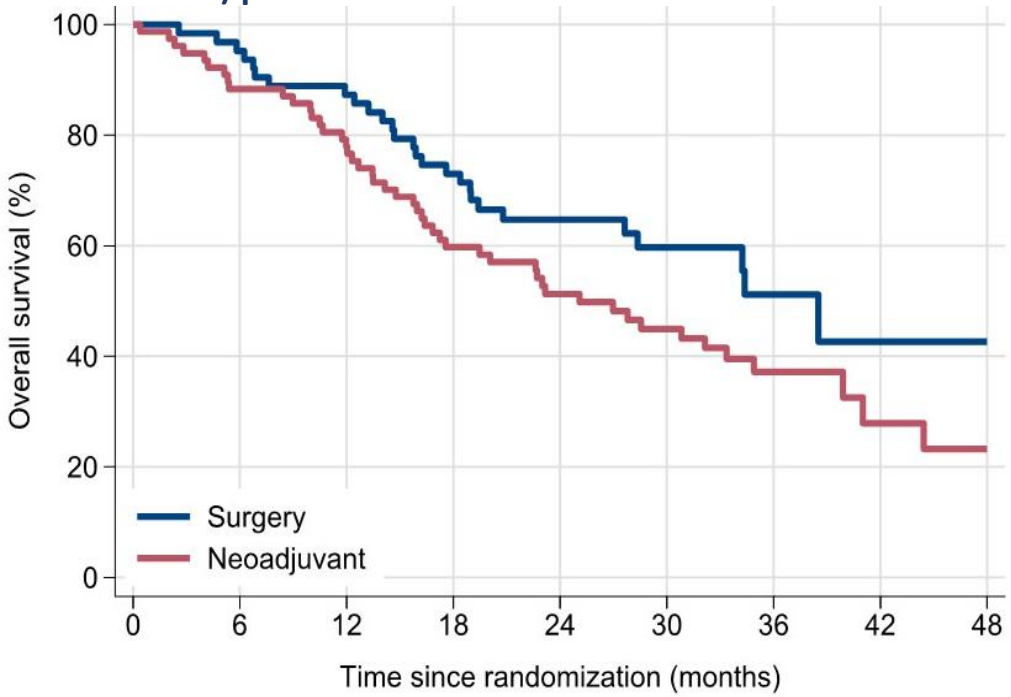
> 50% of patients in both arms didn't receive protocol adjuvant therapy

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

Pancreatic Ductal Adenocarcinoma (PDAC): NORPACT-1

NORPACT-1: results and conclusions

Median overall survival → **25.1 months (neoadjuvant) vs 38.5 months (upfront surgery) HR 1.52 (95% CI, 0.94-2.46) p= 0.096**



Despite more favorable surgical/pathological characteristics in neoadjuvant group, it didn't translate into best outcomes

	Neoadjuvant group (n=63)	Upfront surgery (n=56)	p-value
Intention-to-treat			
R0	56%	39%	0.076
N0	29%	14%	0.060
Per-protocol	(n=46)	(n=49)	
R0	59%	33%	0.011
N0	37%	10%	0.002

Conclusions:

- **Neoadjuvant FOLFIRINOX did not improve overall survival compared with upfront surgery**
- **Neoadjuvant FOLFIRINOX showed acceptable safety and resectability rates**
- **Additional follow-up may better elucidate the long-term effects of the improvement in R0 and N0 rates in neoadjuvant group**
- **The results do not support neoadjuvant FOLFIRINOX ad standard of care in resectable pancreatic cancer**

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4005)

Carcinoma epato cellulare

Studio IMBRAVE 050: adiuvante con atezolizumab + bevacizumab pazienti ECOG 0-1:
Endpoint primario RFS raggiunto con mantenimento della QoL e buon profilo di tossicità

Studio Himalaya sorafenib vs durvalumab vs Tremelimumab/Durvalumab: gli eventi avversi immuno correlati erano di basso grado e avvenivano nei primi tre mesi di trattamento, ciò non inficiava l'ottenimento della OS

Studio Morpheus: associare allo standard Atezo-Beva il Tiragolumab (anti TIGIT già usato in NSCLC). Buoni risultati In termini di RR e PFS ma sbilanciamento nei bracci di trattamento. Dati da verificare con
Ulteriori studi

Tumori delle vie biliari

KEYNOTE 966: anche la qualità di vita si mantiene con l'aggiunta del pembrolizumab
Al cisplatino-gemcitabina (PRIMA LINEA). Utile confronto con cis gem durvalumab

HERIZON-BTC-01 in HER2 Zanidatamab in seconda linea RR 41% e DCR 68 %, tempo mediano alla risposta 12.9 mesi .

SGNTUC-019 in HER2 Tucatinib (inibitore tirosin chinasi già utilizzato in breast) e Trastuzumab in seconda linea 47% ORR, 76% DCR con durata mediana risposta di 6 mesi.

GECCOR-GB Studio adiuvante stadi II-III Cis gem vs Cape RT (+++ R1 nel braccio RT cape, chemio ok, non comparative study)

Sintilimab (immuno checkpoint) e anlotinib (inibitore TK anti angio) associati a CDDP Gem in metastatic BTC

Driver Genes in colangiocarcinoma intraepatico (FGFR3 fusion, MET amplification, NTRK1 amplification)

CONCLUSIONI

Dati importanti nel trattamento del tumore del retto

Trattamento neoadj del tumore localmente avanzato del colon da verificare con altri studi

Nel colon adiuvante e metastatico importanza della selezione biomolecolare dei pazienti per programmare il migliore trattamento (ctDNA fondamentale)

Prima linea del pancreas pazienti fit (NALIRIFOX vs FOLFIRINOX)

Attendiamo altri studi per ct neoadiuvante per ca pancreas resecabile

Terapia adiuvante HCC atezo beva dati molto interessanti

Inibitori HER2 e Immunoterapia nei tumori delle vie biliari