SCENARIO - 1

Paziente metastatico MSI/dMMR

Workshop

Alessandro Pastorino
U.O. Oncologia Medica 1
IRCCS Ospedale Policlinico San Martino
Genova

Outline e snodi decisionali – MSI metastatico

Adenoca MSI/dMMR della flessura epatica con infiltrazione duodeno (cT4), sintomatico.

Anche se loc avanzato (inusuale per i ca colon e i dati di IT neoadj sono pochi anche se forti) in gioco cè la guaribilità

- **PRIMO SNODO**
  - chirurgia upfront (se paziente sintomatico non totalmente sbagliata)
  - attendo molecolare completo (soprattutto per BRAF e impatto su prognosi)
  - chemioterapia preoperatoria (sbagliata dato che è MSI)
  - Pembrolizumab ‘‘di conversione’’ o di prima linea (CORRETTA, se disponibile nel 2020)

Il paziente viene operato upfront (pT4 pN2 RAS/BRAF wt MSI) e fa XELOX per 8 cicli ‘adiuvanti’ DFS di 2 mesi e recidiva locoregionale (56 mm).

- **SECONDO SNODO**
  - 2 o 3+ Beva o 2 + aEGFR (SBAGLIATA)
  - RT (opzione possibile ma valutare il timing – Consulenza Dott.ssa Gambacorta)
  - re-chirurgia (SBAGLIATA)
  - Pembrolizumab (CORRETTA senza alcun dubbio)

Esegue Pembrolizumab per 3 mesi → lesione da 56 mm a 40 mm
Prosegue Pembrolizumab per altri 9 mesi → lesione da 56 a 21 mm.

- **TERZO SNODO**

- chirurgia (da discutere col chirurgo , costo/benefico e mettere clips e dopo PET)
- Pembrolizumab fino a 35 cicli complessivi (SCELTA maggiormente condivisa)
- RT (sì ma da ottimizzare il timing e dopo PET)

- DOMANDE e altri argomenti

Deve fare screening per Lynch (BRAF wt ! → ipermetilaz MLH1 → germinale)

NIVO + Ipi mi avrebbe dato di più? Lo avreste preferito a Pembro anche con il primitivo in sede?

SCENARIO – 2

Paziente con retto localmente avanzato MSI

Workshop

Alessandro Pastorino
U.O. Oncologia Medica 1
IRCCS Policlinico San Martino
Genova

Outline e snodi decisionali – retto MSI loc adv

62 aa, Adenocaricnoma del retto ultrabasso (3 cm r.a.) cT3 cN1 MSI
(infiltrazione sfintere int ed est)

- **PRIMO SNODO (tutte corrette ma soprattutto 2 e 4)**
  - CTRT
  - XELOX/FOLFOX → CTRT
  - mFOLFIRINOX → CTRT
  - CTRT o Short → consolidamento
  - Immunoterapia (se disponibile)

Il paziente viene avviato a XELOX di induzione per 4 cicli.
Alla RM di rivalutazione SD/minima PD locale.

- **SECONDO SNODO**
  - CTRT (ricordiamo che anche se MSI potrebbe beneficiare da CTRT)
  - TME immediata (attenzione alle recidive locali !!)
  - RT short-course e TME (Gambacorta no per sede e dati recenti su LR)
  - Immuno (se disponibile)

Scenario 2 - Trattamento

Marzo 2022 → Aprile 2022 CTRT long-course 50.4 Gy

RM pelvi (maggio 2022) → ……..

SPUNTI DI RIFLESSIONE

- 2 cambi di paradigma di trattamento → TNT e Immuno (anche se non disponibile)
- I retti dMMR hanno elevatissima probabilità di Lynch (50 – 80 %)
- La definizione di guarigione nei retti dMMR in cCR
- L'approccio ai pazienti in cCR dopo immunoterapia (NOM, LE, TME, RT..)

SCENARIO - 1

Paziente metastatico MSI/dMMR

Workshop

Alessandro Pastorino
U.O. Oncologia Medica 1
IRCCS Ospedale Policlinico San Martino
Genova

Scenario 1 - Diagnosi

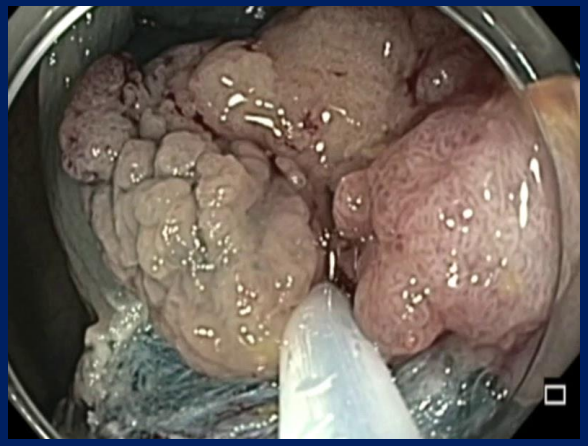
Uomo, 67 anni, no comorbidità

Gennaio 2020 dispepsia, epigastralgia e calo ponderale di 10 kg.

EGDS → bulging da sospetta compressione ab estrinseco della III porzione del duodeno. E.I: *adenocarcinoma*

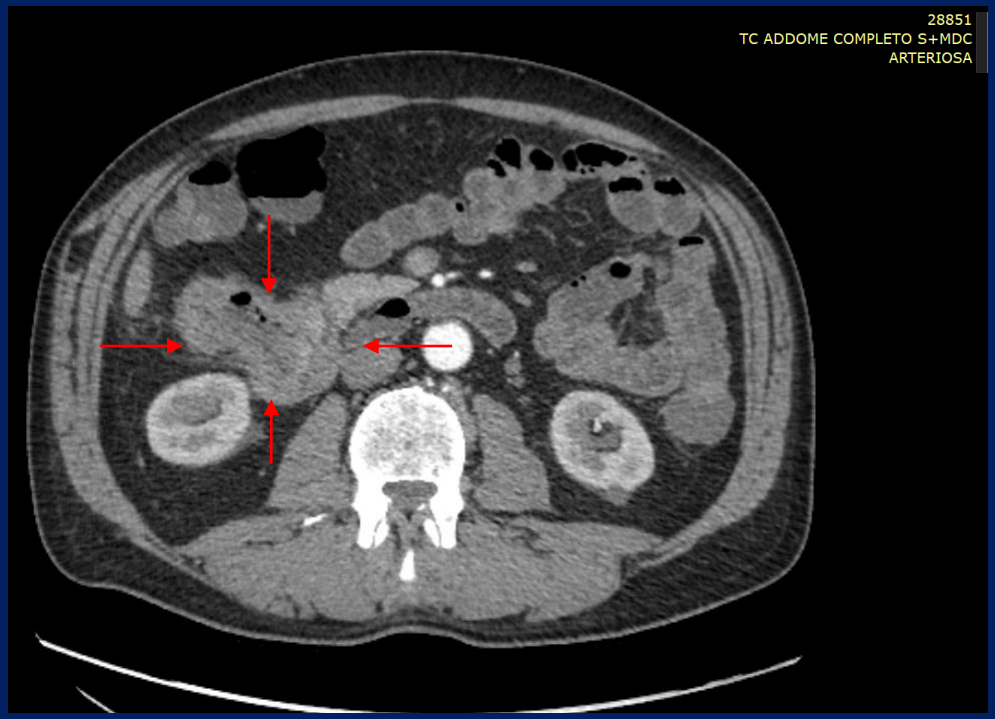
Colonscopia → voluminosa neoformazione della flessura epatica.
E.I: *adenocarcinoma, dMMR (perdita di MLH-1)*

CA 19.9 = 87 (+)



Scenario 1 - Diagnosi

TC torace-addome (maggio 2020): voluminosa neoformazione a carico della flessura epatica del colon senza sicuro clivaggio con la II-III porzione duodenale (cT4?).
Fegato e polmone NED.



PRIMO SNODO

- Adenocarcinoma colon dx
- cT4 (sospetto duodeno)
- dMMR

Chirurgia upfront

Chemioterapia ‘‘preoperatoria’’

Richiedo molecolare completo

Pembrolizumab

- Quale opzione sceglieresteste ?
- Ne vedete una totalmente errata ?

Cerchiamo di motivare o escludere ogni scelta sulla base dell’esperienza clinica e dei dati disponibili.

Scenario 1 - Trattamento

Maggio 2020

<u>Emicolectomia dx+ duodenocefalopancreasectomia</u>

pT4b [duodeno] G3 pN2[5/46] pV1, Stadio III ‘‘altissimo’’ rischio

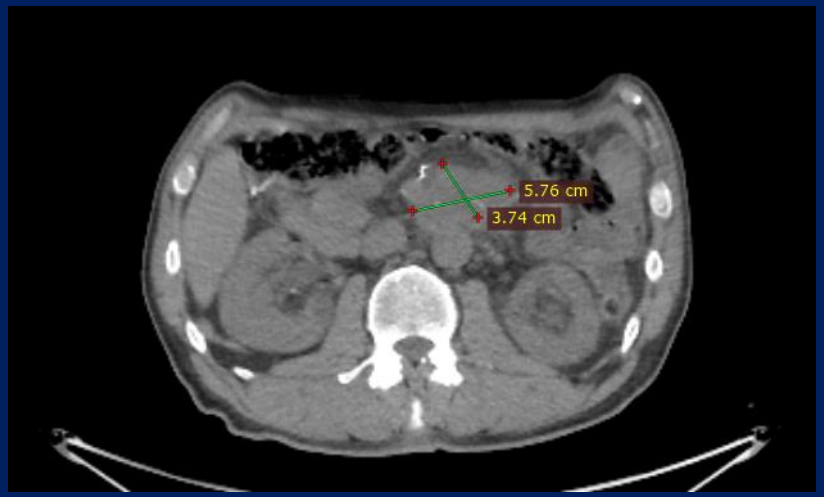
- *dMMR (perdita di MLH-1)*
- *RAS/BRAF wt*
- *HER2 neg*

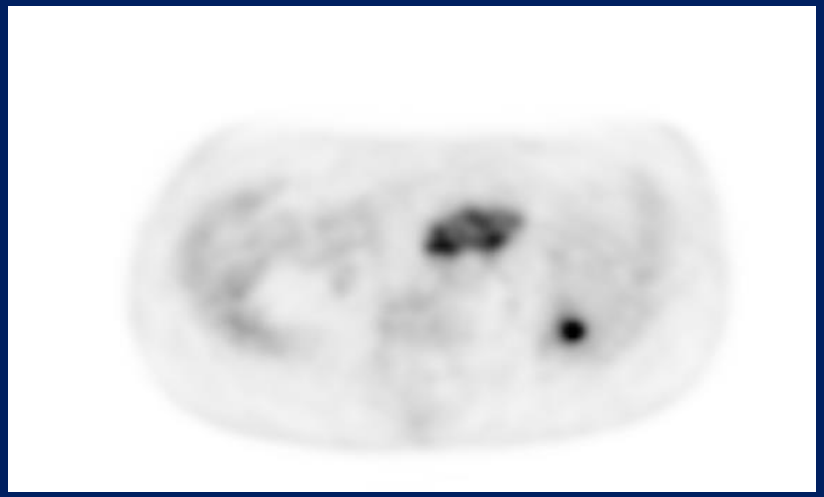
Luglio 2020 → dicembre 2020 XELOX adiuvante (8 cicli)

Scenario 1 – Recidiva

TC torace-addome (febbraio 2021) posteriormente al colon trasverso si apprezza una formazione di 56 x 38 mm con contorni non chiaramente definiti; non presenta piani di clivaggio con l'arteria mesenterica e posteriormente con l'aorta ed alcune diramazioni arteriose dell'arteria mesenterica superiore sembrano penetrare all'interno della formazione stessa.

PET (febbraio 2021): intenso ipermetabolismo glucidico nel contesto del mesocolon trasverso (SUV max 14.8) a livello di formazione di 57 x 36 mm.



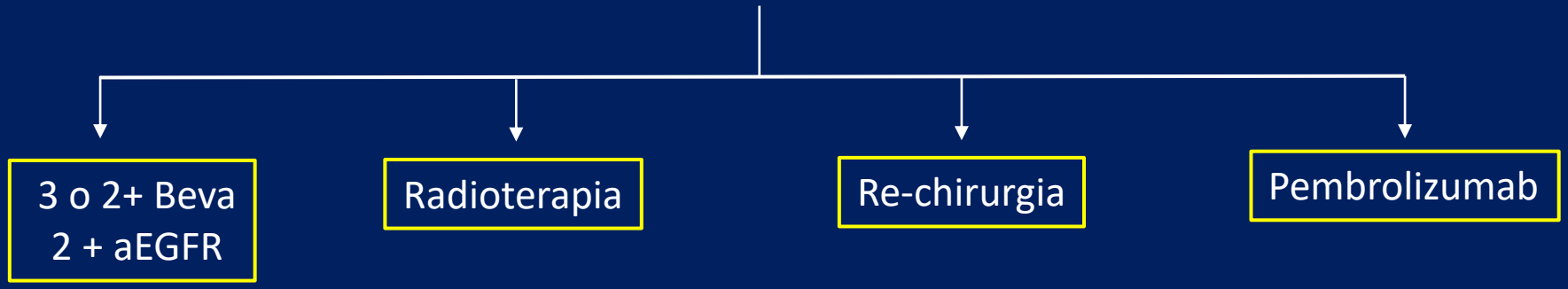


Clinica: dolore ‘‘a barra’’ e calo ponderale

CA 19.9 = 148 (++)

SECONDO SNODO

- Adenoca colon dx operato, recidiva locale
- dMMR, RAS/BRAF wt
- DFS post-chirurgia 8 mesi
- DFS post-adiuvante 2 mesi



- Quale opzione sceglieresti ?
- Ne vedete una totalmente errata ?

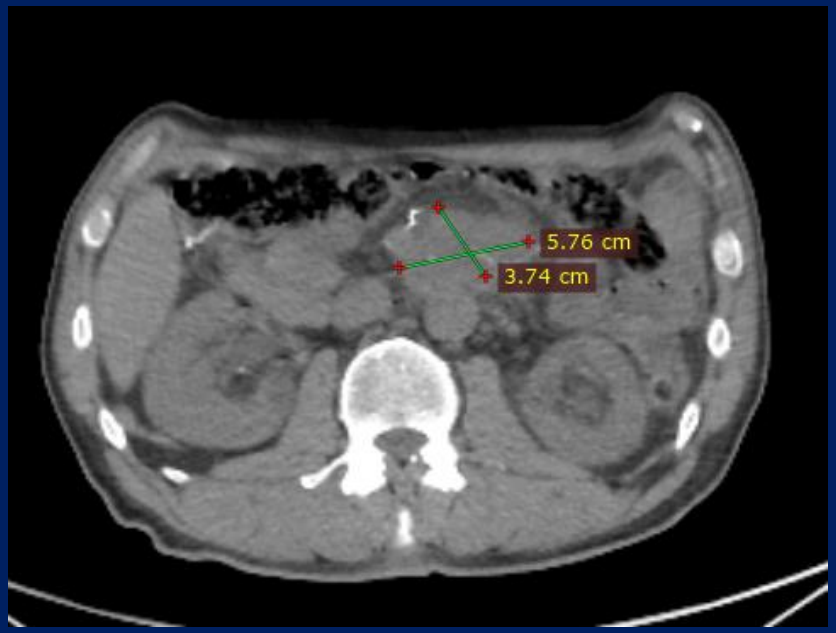
Cerchiamo di motivare o escludere ogni scelta sulla base dell'esperienza clinica e dei dati disponibili.

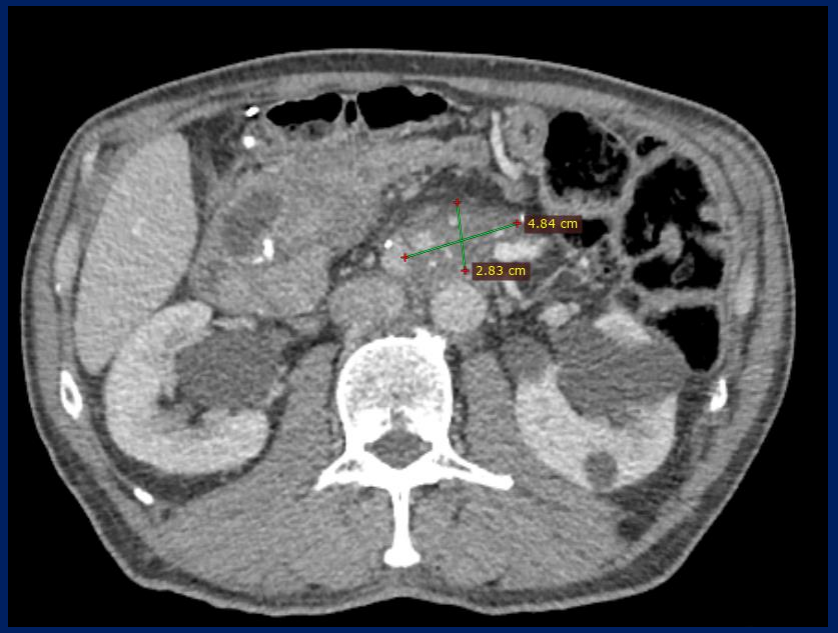
Scenario 1 - Trattamento

Marzo 2021 → Maggio 2021 Pembrolizumab (4 cicli).

TC torace-addome (giugno 2021): riduzione dimensionale nota massa mesenterica (48 x 27 mm vs 56 x 37 mm).

Clinica: regredito dolore. Ripresa attività fisica.
CA 19.9 nei limiti.



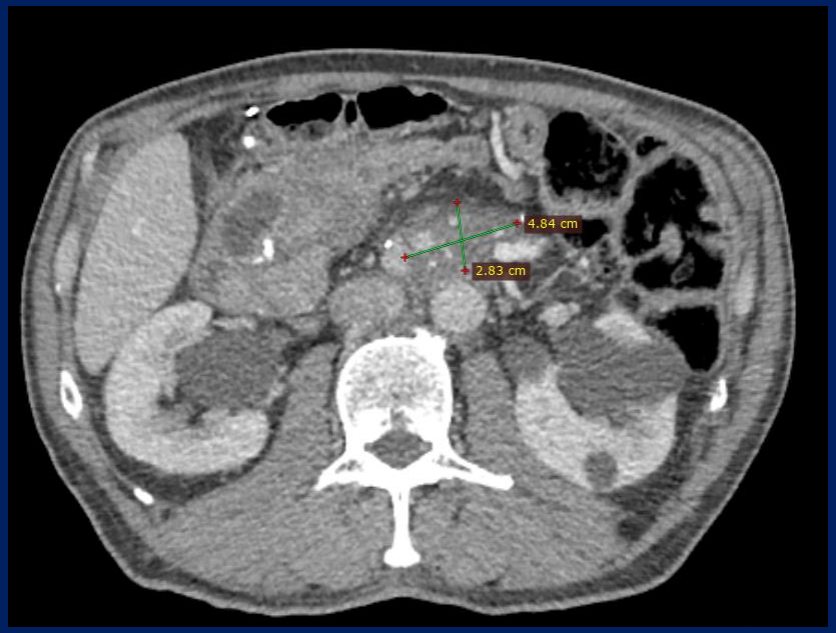


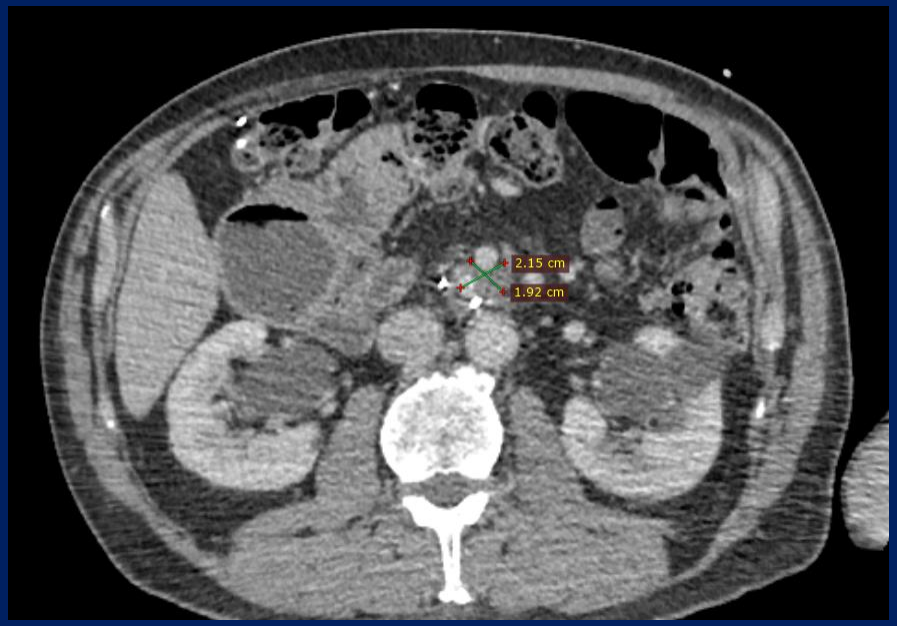
Scenario 1 - Trattamento

Giugno 2021 → Febbraio 2022 Pembrolizumab (13 cicli totali).

TC torace-addome (febbraio 2022): ulteriore riduzione dimensionale nota massa mesenterica (21 x 19 mm vs 48 x 27 mm).

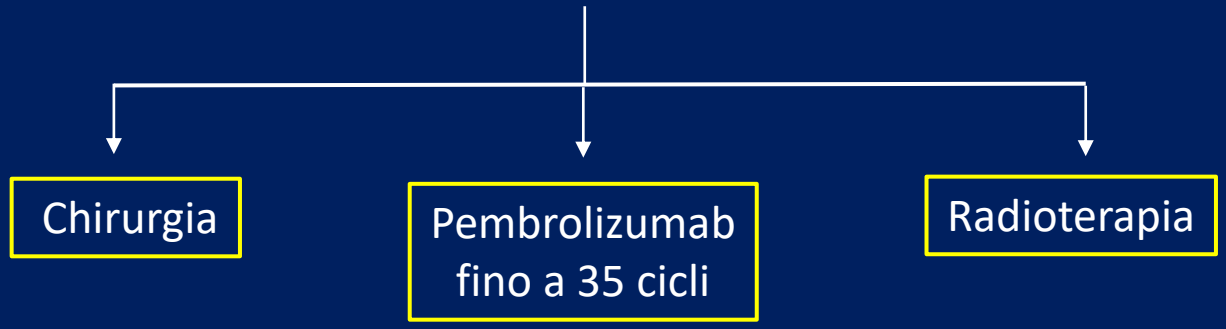
Clinica: ottima QoL. Asintomatico.
CA 19.9 nei limiti.





TERZO SNODO

- Adenoca colon dx operato, recidiva locale
- PFS 13 mesi con Pembrolizumab
- Major response su unica lesione ‘‘difficile’'



E dopo ?

- Quale opzione scegliereste ?
- Ne vedete una totalmente errata ?

Cerchiamo di motivare o escludere ogni scelta sulla base dell’esperienza clinica e dei dati disponibili.

KEYNOTE-177 Study Design (NCT02563002)

Key Eligibility Criteria
- MSI-H (PCR)/dMMR (IHC) Stage IV CRC
- Treatment naïve
- ECOG PS 0 or 1
- Measurable disease by RECIST v1.1

R (1:1)

N = 153: Pembrolizumab 200 mg Q3W for up to 35 cycles

N = 154: Investigator-Choice Chemotherapy[a]
mFOLFOX6 IV Q2W
OR mFOLFOX6 + Bevacizumab[b] IV Q2W
OR mFOLFOX6 + Cetuximab[c] IV Q2W
OR FOLFIRI IV Q2W
OR FOLFIRI + Bevacizumab IV Q2W
OR FOLFIRI + Cetuximab IV Q2W

Optional crossover to pembrolizumab 200 mg Q3W for up to 35 cycles for patients with centrally verified PD by RECIST v1.1, central review

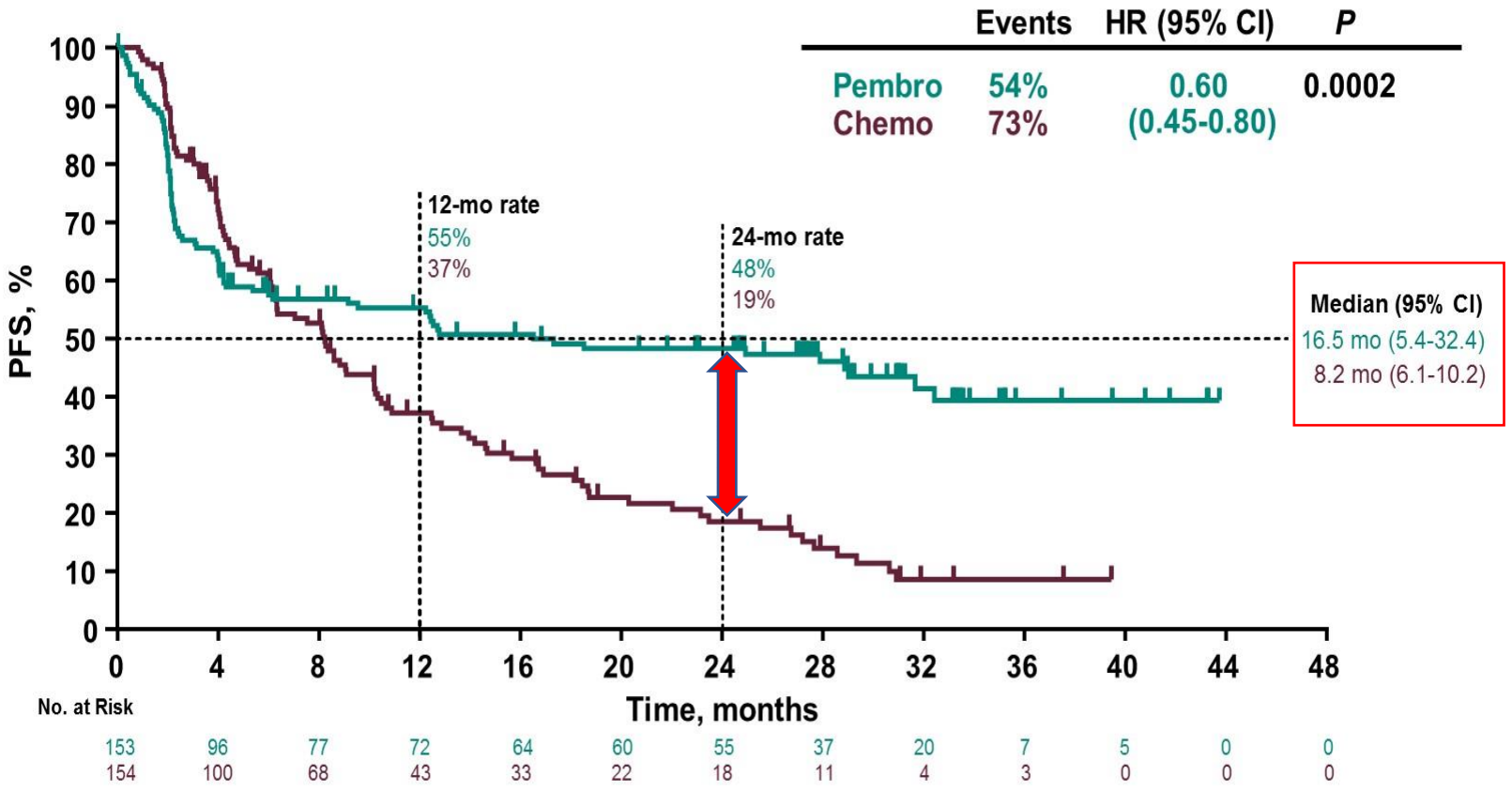
Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

Safety and survival follow-up

- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Progression-Free Survival



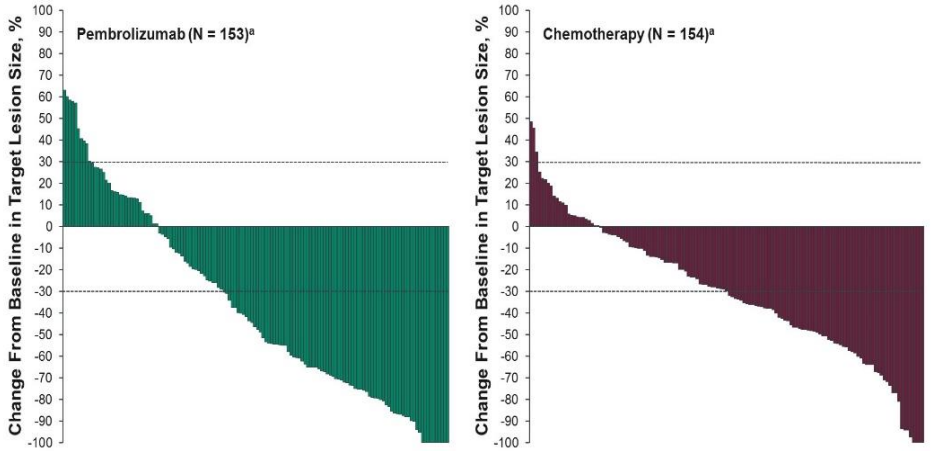
Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

Antitumor Response

	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**	**51 (33.1)**
Difference, estimate (95% CI)	10.7 (-0.2-21.3)	
P-value	0.0275	
Best Overall Response, n (%)		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)	2.1 (1.7-24.9)

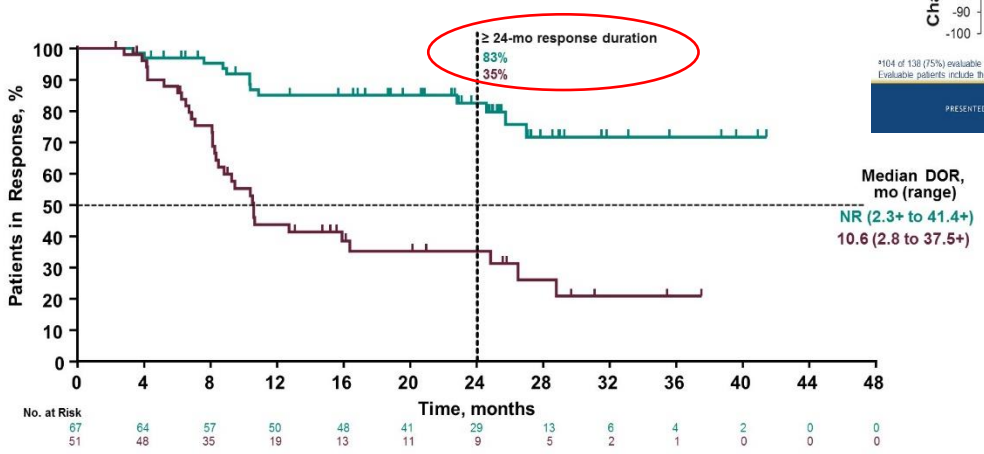
Data cut-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.

Radiographic Response in Target Lesions



[a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Duration of Response



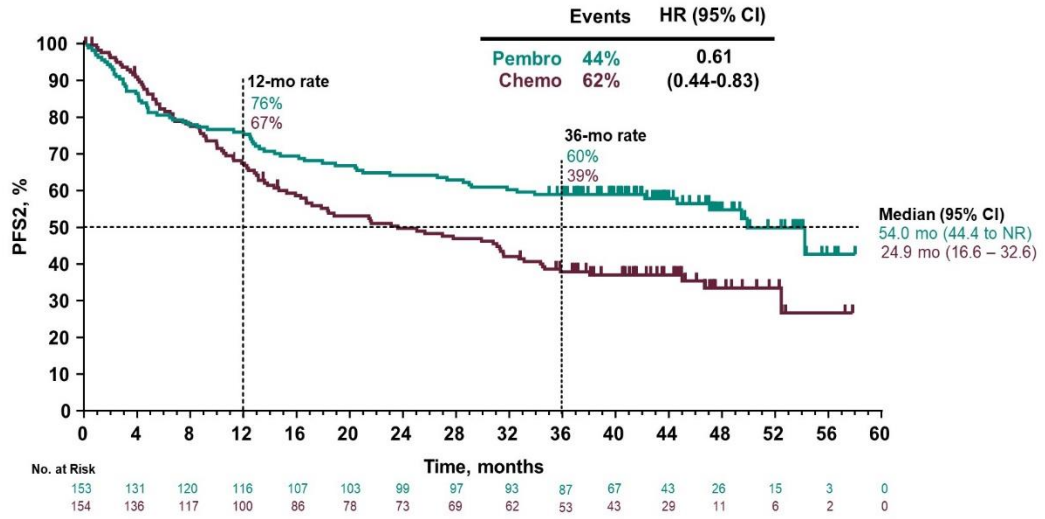
Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

André T, ASCO 2020

Andre KN177FA ASCO 2021

Progression-Free Survival 2

Time from randomization to progression on next line therapy or any cause death



Data cut-off: 19Feb2021.

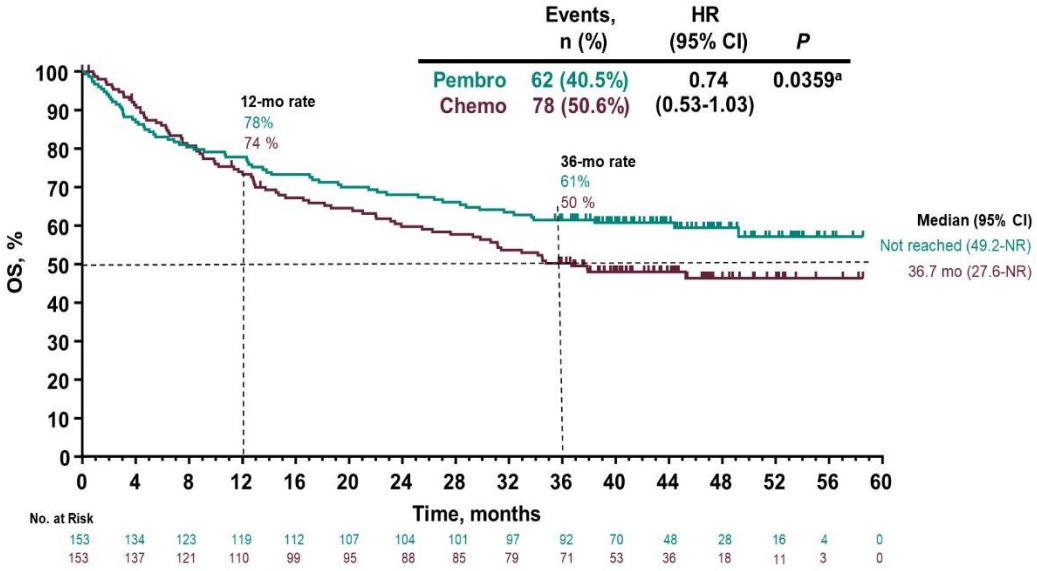
Vantaggio nel fare Pembro in prima linea e non "tenerlo per dopo " …

60 % crossover

Overman MJ, ASCO 2021

Andre KN177FA ASCO 2021

Overall Survival



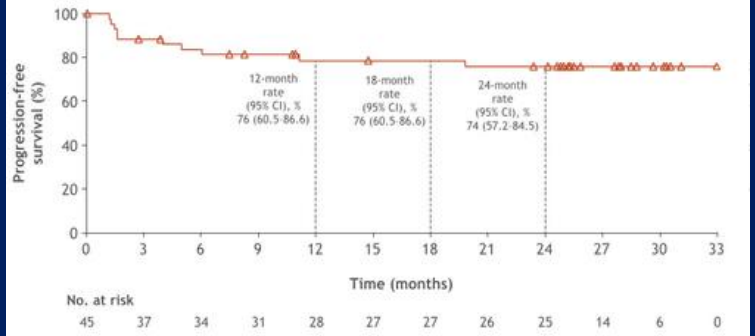
[a]Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

Presented at the American Society of Clinical Oncology (ASCO), May 29-31, 2020

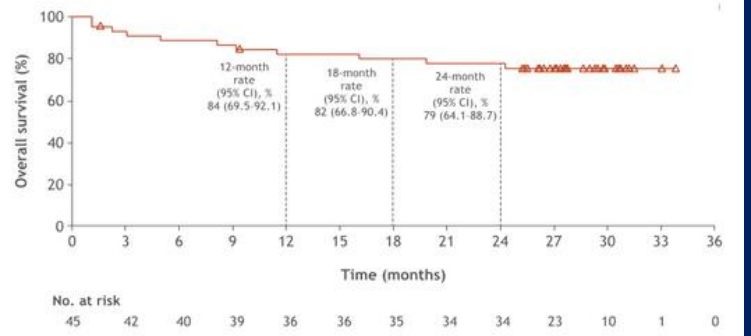
Nivolumab + low-dose ipilimumab as first-line therapy in microsatellite instability-high/ mismatch repair-deficient metastatic colorectal cancer: 2-year clinical update

Heinz-Josef Lenz,[1] Sara Lonardi,[2] Vittorina Zagonel,[3] Eric Van Cutsem,[4] Maria Luisa Limon,[4] Ka Yeung Mark Wong,[5] Alain Hendlisz,[6] Massimo Aglietta,[7] Pilar García-Alfonso,[8] Bart Neyns,[9] Fabio Gelsomino,[10] Dana B. Cardin,[11] Tomislav Dragovich,[12] Usman Shah,[13] Jing Yang,[14] Jean-Marie Ledeine,[14] Michael J. Overman[15]

	All patients n = 45
Median PFS (95% CI), months	NR (NE)
PFS rate (95% CI), %	
12 months	76 (60.5-86.6)
18 months	76 (60.5-86.6)
24 months	74 (57.2-84.5)



	All patients n = 45
Median OS (95% CI), months	NR (NE)
OS rate (95% CI), %	
12 months	84 (69.5-92.1)
18 months	82 (66.8-90.4)
24 months	79 (64.1-88.7)

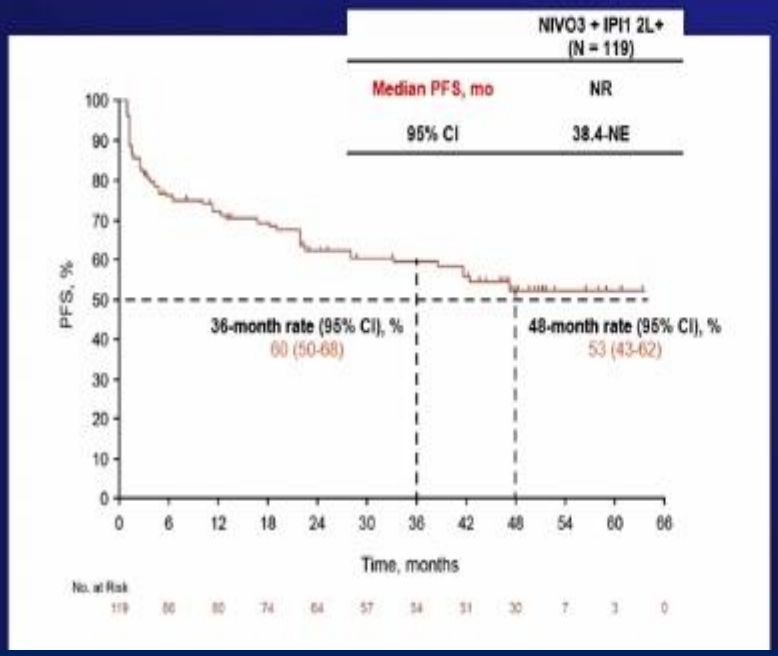


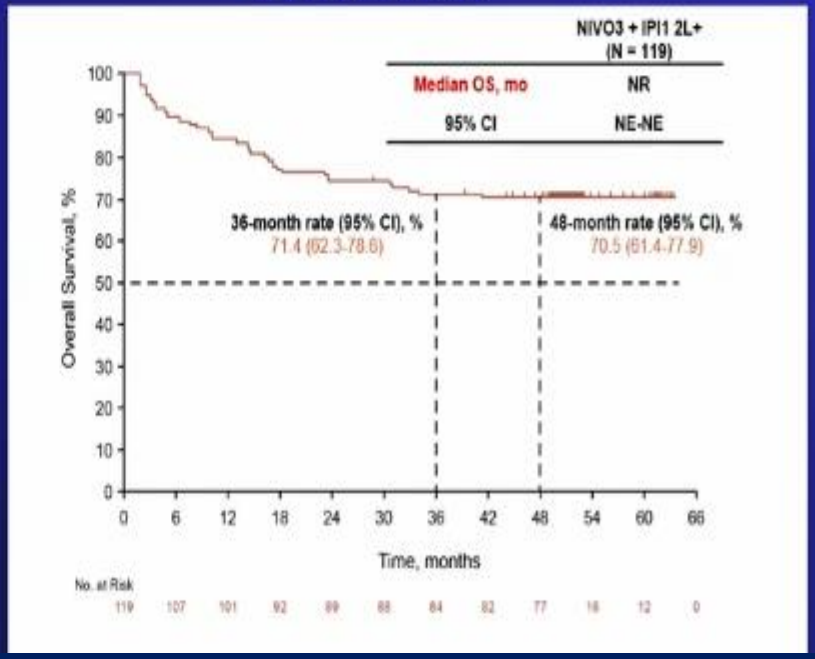
2-yr PFS: 74%

2-yr OS: 79 %

Lenz ASCO 2020, Lenz JCO 2021

CheckMate 142
Nivolumab + ipilimumab (≥2 linea) – follow-up a 4 anni





4-yr PFS: 53%

4-yr OS: 70.5 %

Andre' ESMO GI 2021

Immunoterapia: dati alla mano

	ORR	mPFS	2yr-PFS	mOS	2-yr OS	ePD
PRIMA LINEA						
Pembro (KN177)	44%	16	48%	NR	70%	29%
Nivo + Ipi (CM142)	69%	NR	74%	NR	79%	13%
≥2 LINEA						
Nivo (CM142)	31%	14	45%	NR	55%	35%
Nivo + Ipi (CM142)	55%	NR	65%	NR	75%	12%
Pembro (KN164)	33%	2-4	35%	31 - 47	60%	50%

- Solo 1 / 5 ha mOS matura
- Combo dimezza early PD (10-15 % vs 30-35%)
- Combo aumenta ORR (55-70% vs 30-45%)
- KN 177 dati solidi e vantaggi in mPFS e long term

Le PFS “storiche” in prima linea

	CM 142	KN177	CALGB	FIRE-3	PEAK	TRIBE	TRIBE2	CRYSTAL	PRIME
mPFS	NR	16	10	10	13	12	12	10	10
2-yr PFS	74%	48%	15%	10%	20%	25%	25%	20%	20%
Early PD	10%	29%	10%	10%	5%	5%	5%	5%	5%

mPFS: Pembro e Nivo + Ipi > chemio + biologico

2-yr PFS: Pembro e Nivo + Ipi > chemio + biologico

Early PD: Chemio + biologico e Nivo + Ipi > Pembro

SCENARIO – 2

Paziente con retto localmente avanzato MSI

Workshop

Alessandro Pastorino
U.O. Oncologia Medica 1
IRCCS Policlinico San Martino
Genova

Scenario 2 – Diagnosi e staging

Uomo, 71 anni, ipertensione arteriosa, IPB, ex fumatore da 30 anni (40 pack/yr)
Da luglio 2021 ematochezia e tenesmo.

Retto-Colonscopia → aumento della consistenza a livello del canale anale con presenza di lesione sulla parete posteriore con ulcerazione centrale.
E.I: *adenocarcinoma mucinoso, dMMR (perdita di MSH-2)*

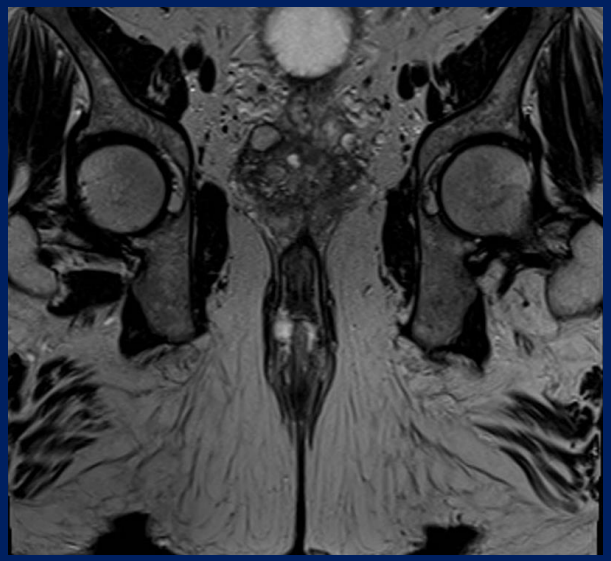
E.R: lesione a 1 cm dalla r.a. che si estende per circa 1-2 cm cranialmente a carico della parete posteriore del canale anale. La lesione presenta area centrale escavata e sembra parzialmente mobile sui piano profondi.

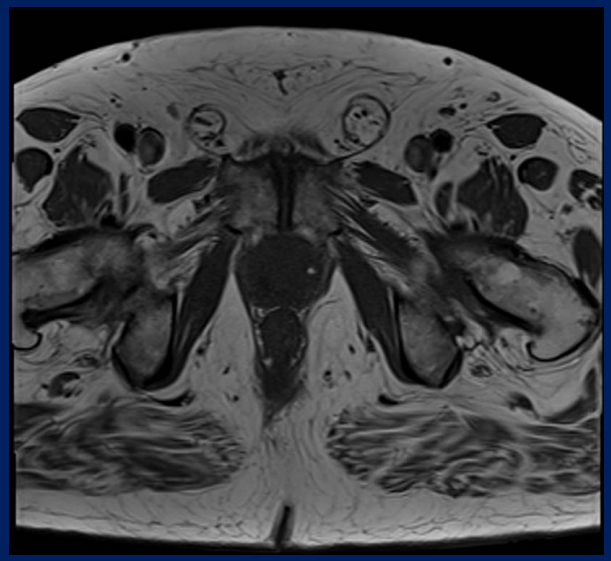
TC torace-addome (dicembre 2021) → negativa.

CEA e CA 19.9 nei limiti.

Scenario 2 – Diagnosi e staging

RM pelvi (dicembre 2021) → neoformazione a livello del canale anale di 44x35x20 mm a pochi mm dal margine anale a sviluppo extraluminale con infiltrazione degli sfinteri in assenza di sicuri piani di clivaggio con il muscolo elevatore. Plurimi linfonodi tondeggianti in sede perirettale (max 13 mm).





EUS rettale (dicembre 2021)→ neoplasia del retto distale con estensione al canale anale con interessamento degli sfinteri interno ed esterno compatibile con una stadiazione EUS di uT3;N0.

PRIMO SNODO

- Adenocarcinoma retto ultrabasso cT3 cN+
- Infiltrazione elevatore
- Infiltrazione sfinteri
- CRM +
- dMMR

- Quale opzione sceglierestе ?
- Ne vedete una totalmente errata ?

Cerchiamo di motivare o escludere ogni scelta sulla base dell'esperienza clinica e dei dati disponibili.

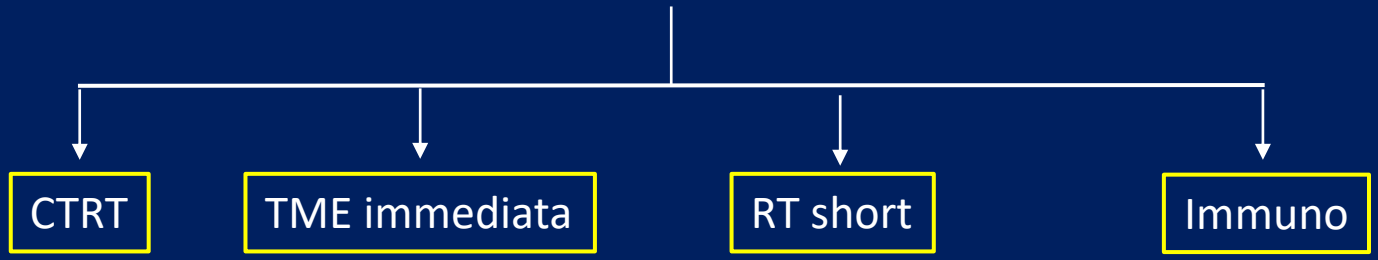
Scenario 2 - Trattamento

Dicembre 2021 → Marzo 2022 XELOX di induzione per 4 cicli

RM pelvi (marzo 2022) → sostanzialmente invariate le dimensioni (51x30x30mm) della nota lesione che dalla parete posteriore del canale anale si estende nello spazio intersfinterico attraverso una soluzione di continuità di circa 9 mm del muscolo sfintere interno (ore 06:00).

SECONDO SNODO

- Adenocarcinoma retto ultrabasso
- Infiltrazione elevatore
- Infiltrazione sfinteri
- CRM +
- dMMR/MSI
- SD dopo induzione con XELOX

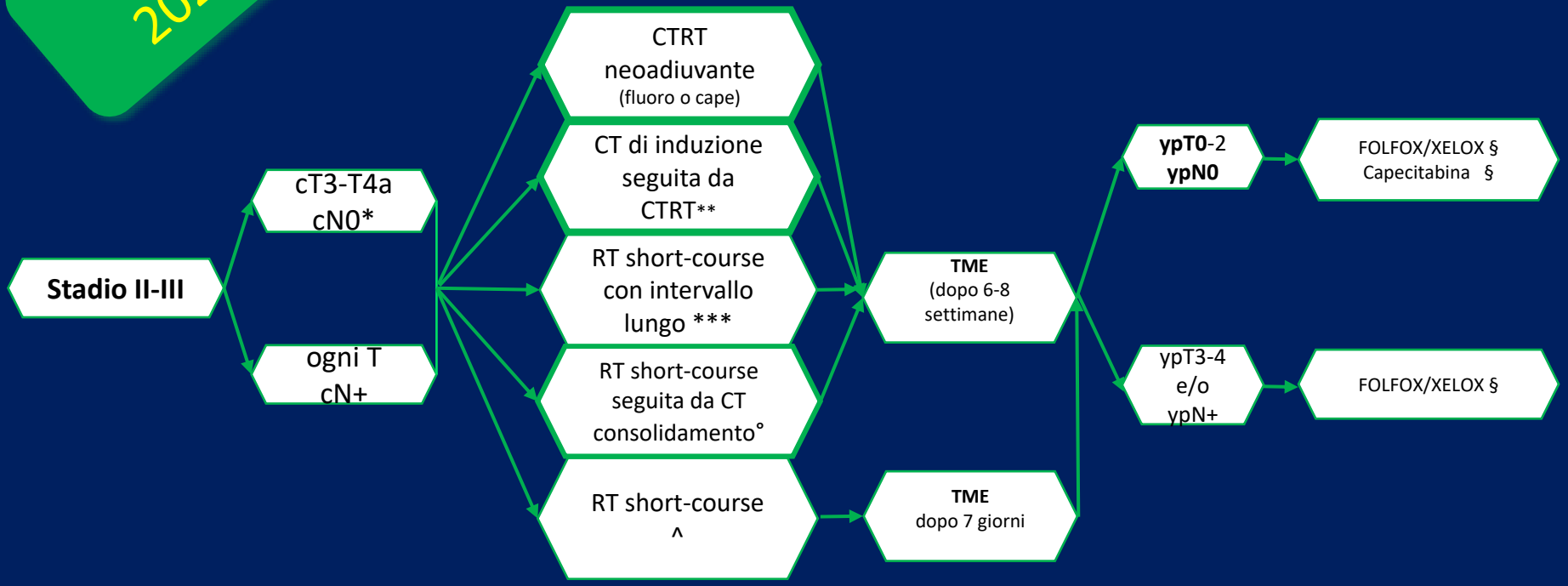


- Quale opzione sceglierestе ?
- Ne vedete una totalmente errata ?

Cerchiamo di motivare o escludere ogni scelta sulla base dell'esperienza clinica e dei dati disponibili.

Stadio II (cT3-cT4 e cN0)
Stadio III (any cT e cN+)

NEW 2021



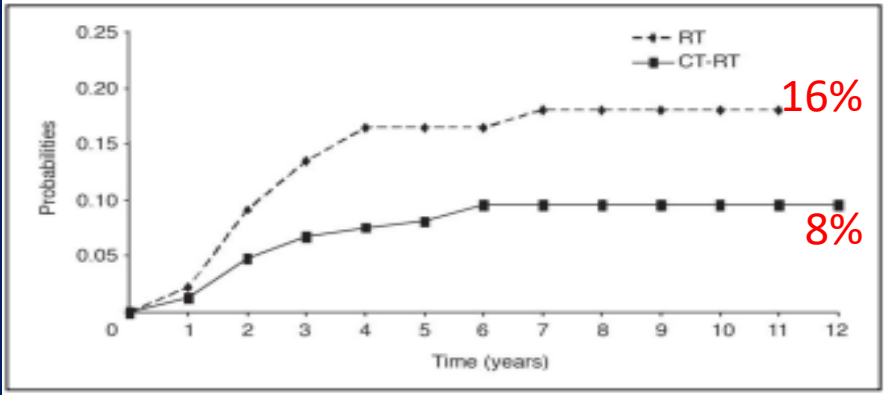
* se T3 del retto alto e T3 early (≤ 1 mm di infiltrazione adiposa perirettale) considerare TME upfront.
** può essere presa in considerazione se cT4a e/o sicuramente cN+ (per evitare overtreatment dei T3 e degli N0).
*** può essere presa in considerazione nei pazienti unfit per CTRT con TME ritardata (4-8 settimane) se necessario shrinkage tumorale
° può essere presa in considerazione nei pazienti cT4 o cCRM+ o EMVI+ o linfonodi laterali positivi seguita da XELOX/FOLFOX di consolidamento
^ può essere presa in considerazione se T3 del retto alto e T3 early con chirurgia dopo 7 giorni.
§ la durata del trattamento (pre e post operatorio) deve essere di 6 mesi complessivi.
+ In caso di pCR valutare attentamente l'età, le comorbidità, la logistica e l'orientamento del paziente prima di avviare il trattamento adiuvante

RT vs CTRT preoperatoria

VOLUME 24 · NUMBER 28 · OCTOBER 1 2006
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Preoperative Radiotherapy With or Without Concurrent Fluorouracil and Leucovorin in T3-4 Rectal Cancers: Results of FFCD 9203

Jean-Pierre Gérard, Thierry Conroy, Franck Bonnetain, Olivier Bouché, Olivier Chapet, Marie-Thérèse Closon-Dejardin, Michel Untereiner, Bernard Leduc, Éric Francois, Jean Maurel, Jean-François Seitz, Bruno Buecher, Rémy Mackiewicz, Michel Ducreux, and Laurent Bedenne



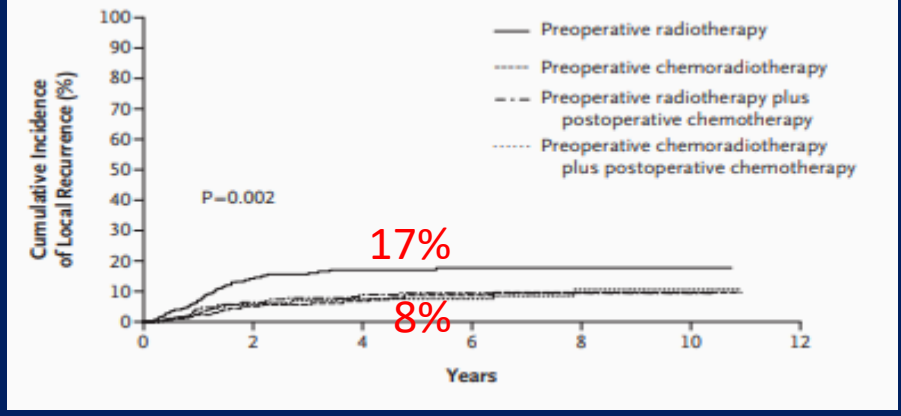
cT3 – cT4 resectable
Accessible to DRE

CT scan
EUS mandatory

ORIGINAL ARTICLE

Chemotherapy with Preoperative Radiotherapy in Rectal Cancer

Jean-François Bosset, M.D., Laurence Collette, Ph.D., Gilles Calais, M.D., Laurent Mineur, M.D., Philippe Maingon, M.D., Ljiljana Radosevic-Jelic, M.D., Alain Daban, M.D., Etienne Bardet, M.D., Alexander Beny, M.D., and Jean-Claude Ollier, M.D., for EORTC Radiotherapy Group Trial 22921*



cT3 – cT4 resectable
< 15 cm av

CT scan
Rigid sigmoidoscopy
EUS optional

CTRT preoperatoria vs CTRT postop

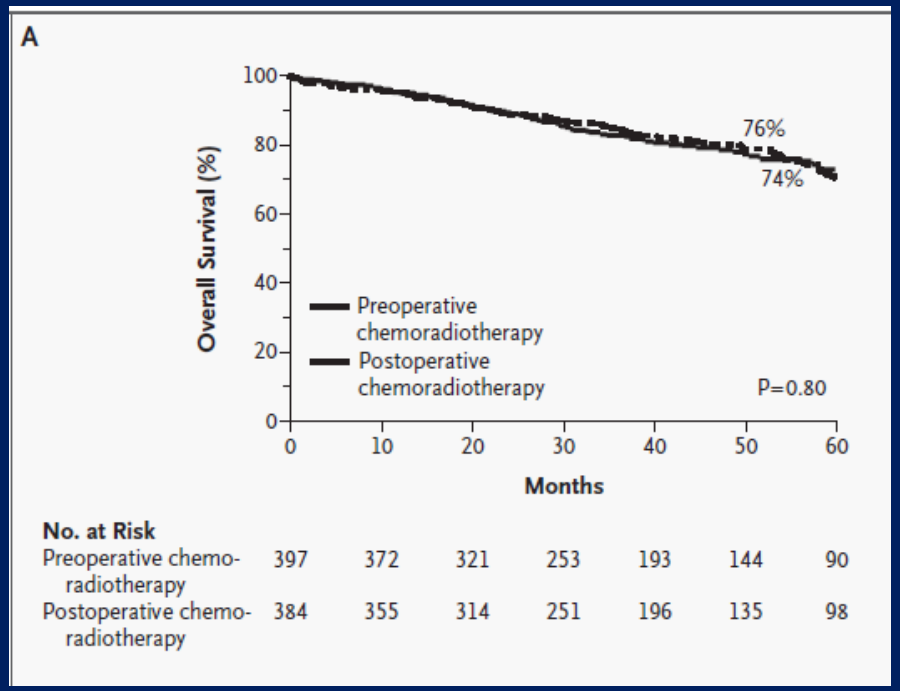
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

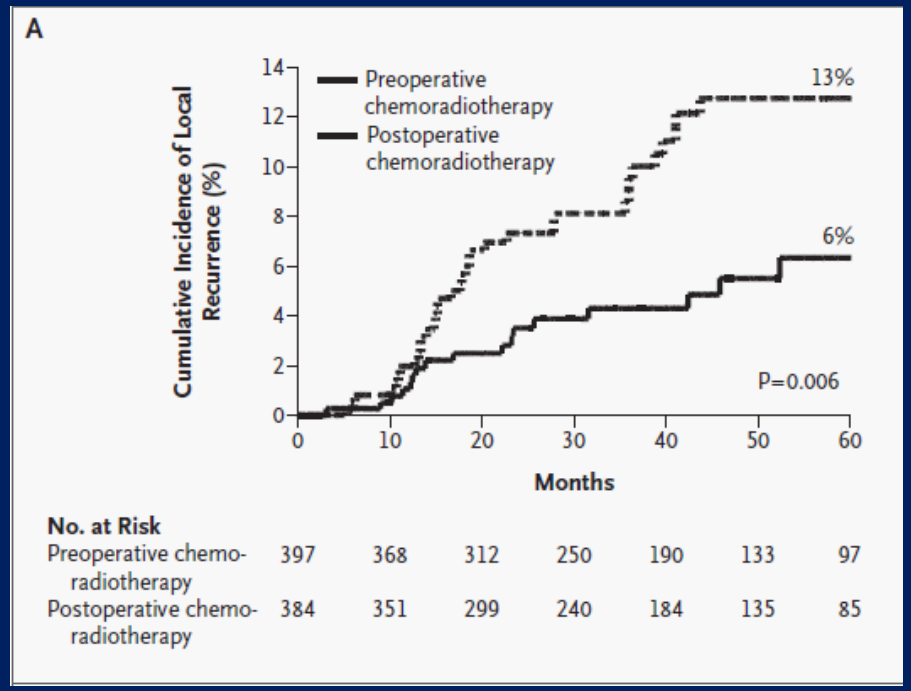
Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D.,

OS

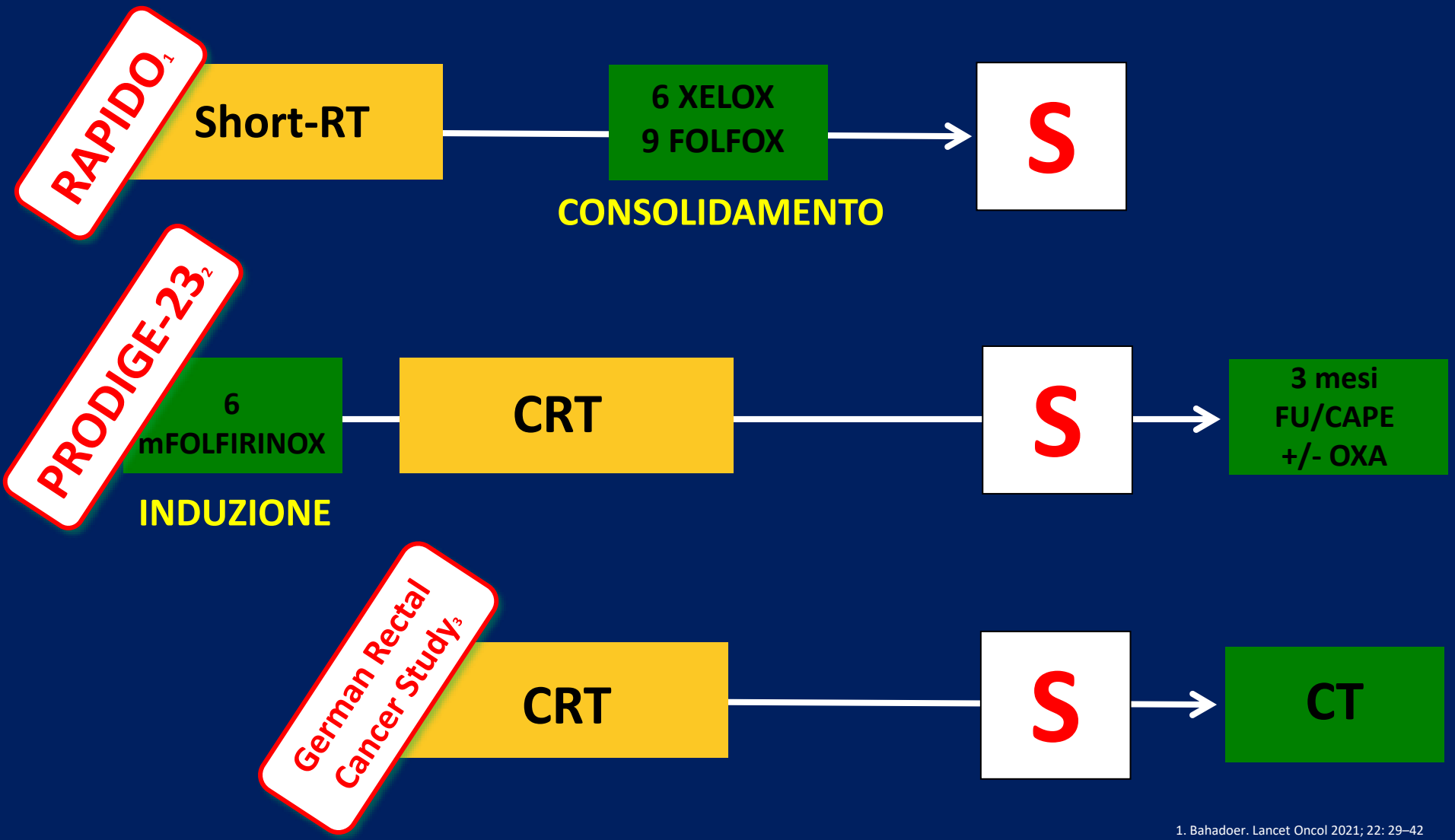


Local Recurrence



Sauer et al. NEJM 2004; 351: 1731-40.

TNT : NUOVI STANDARD..da implementare..

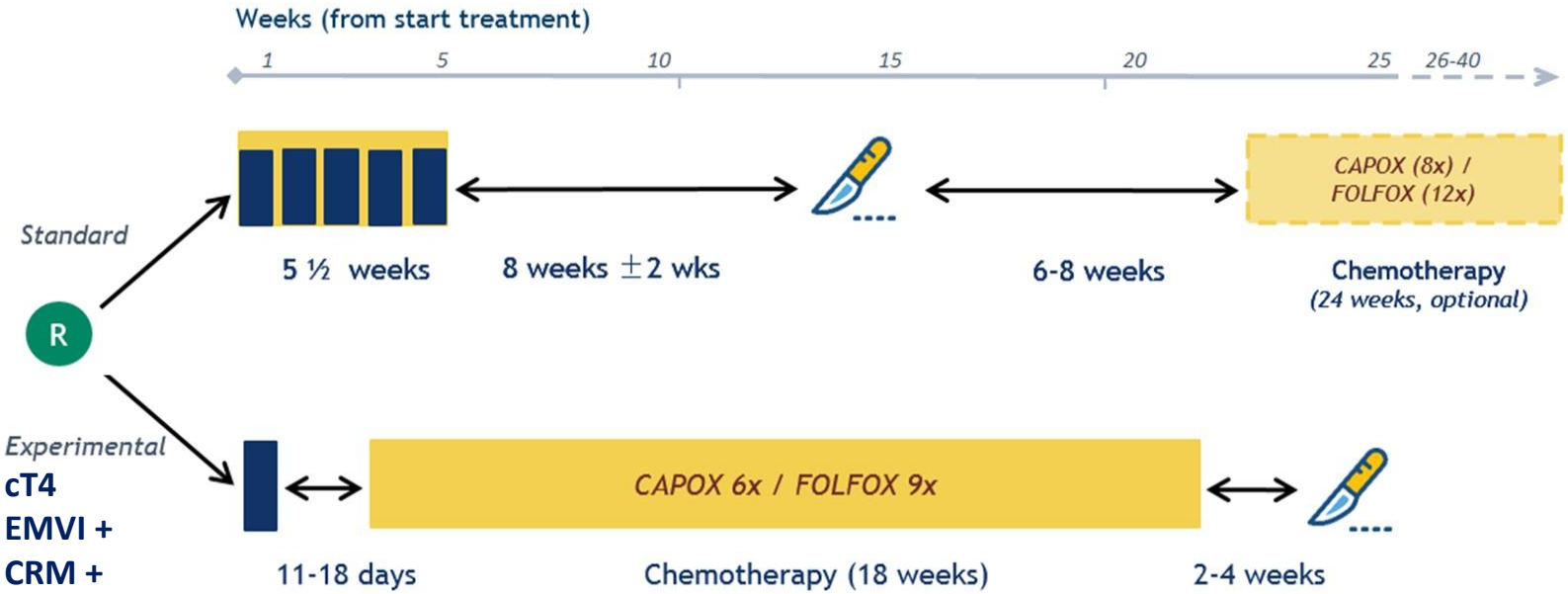


1. Bahadoer. Lancet Oncol 2021; 22: 29–42
2. Conroy. Lancet Oncol 2021; 22: 702–15
3. Sauer. N Engl J Med 2004;351:1731-40

Chemioterapia di consolidamento dopo RT short

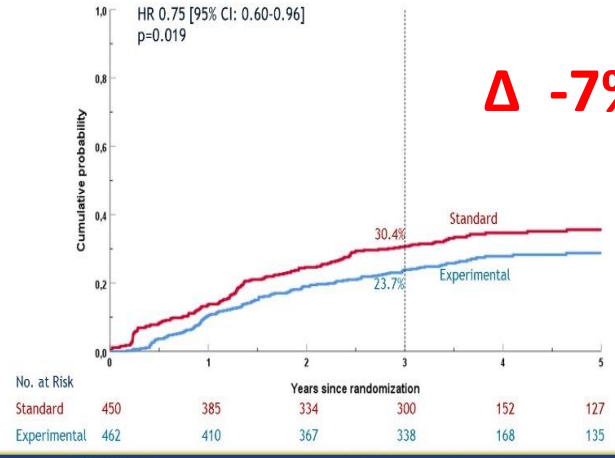
RAPIDO trial

Study design



Standard: week 1-6: 28x1.8 Gy or 25x2 Gy at working days combined with capecitabine b.i.d. 825 mg/m^2 (twice daily) day 1-33-38.
Experimental: week 1: 5x5 Gy, week 3-20: 6x CAPOX (capecitabine b.i.d.1000 mg/m^2 (twice daily) day 1-14 every 3 weeks orally, oxaliplatin 130 mg/m^2 day 1 every 3 weeks iv or alternatively 9x FOLFOX4 (folinic acid, fluorouracil and oxaliplatin all iv every 2 weeks)

Disease-related Treatment Failure

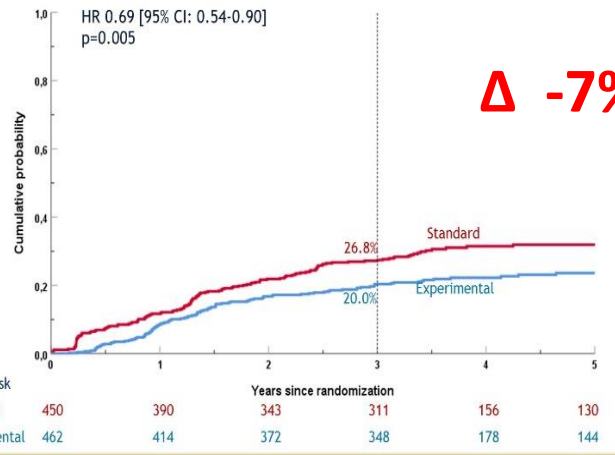


Δ -7%

No. at Risk

Standard	450	385	334	300	152	127
Experimental	462	410	367	338	168	135

Distant metastases



Δ -7%

No. at Risk

Standard	450	390	343	311	156	130
Experimental	462	414	372	348	178	144

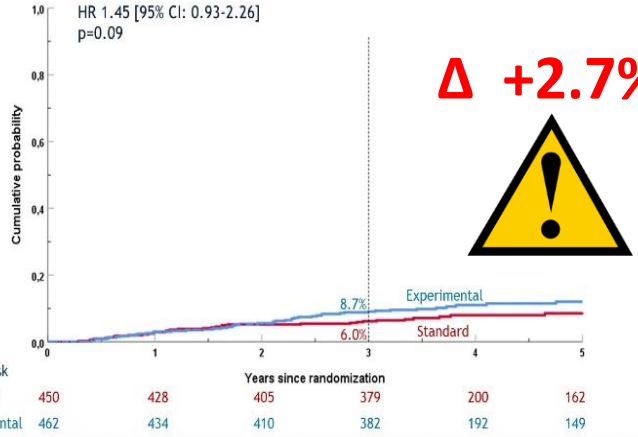
Pathology of resected rectal tumor

	Standard (n=398)		Experimental (n=423)		p-value
Residual tumor					0.62
R0 > 1 mm	360	(90.5)	383	(90.5)	
R1 ≤ 1 mm	37	(9.3)	37	(8.7)	
R2	1	(0.3)	3	(0.7)	
Pathological complete response					<0.001
Yes	57	(14.3)	120	(28.4)	
No	341	(85.7)	303	(71.6)	

Data is presented as n (%)

pCR 28% vs 14%

Locoregional Failure



Δ +2.7%

No. at Risk

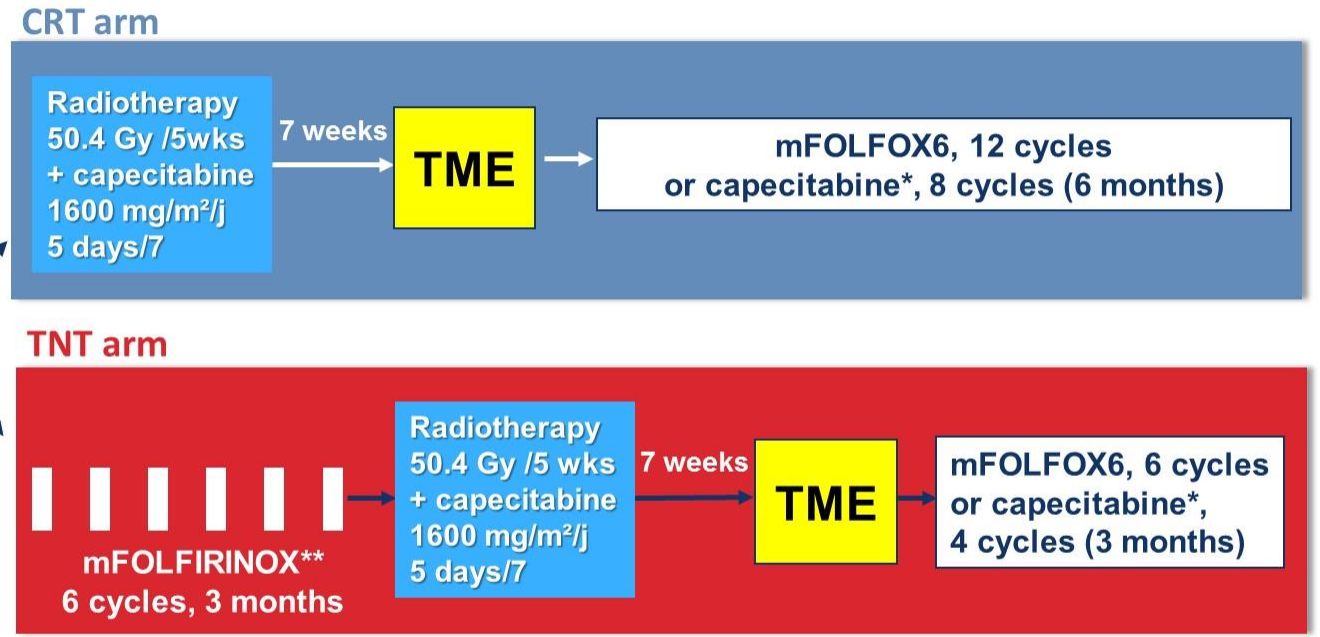
Standard	450	428	405	379	200	162
Experimental	462	434	410	382	192	149

PRODIGE 23 trial: study design

NCT 01804790; EudraCT 2011-004406-25

MRI staging
Randomisation: 1/1
Stratification:
- center
- cT3 vs cT4
- cN0 vs cN+
- extramural extension (≥5 vs. <5 mm)
- tumor location (cm from anal verge)

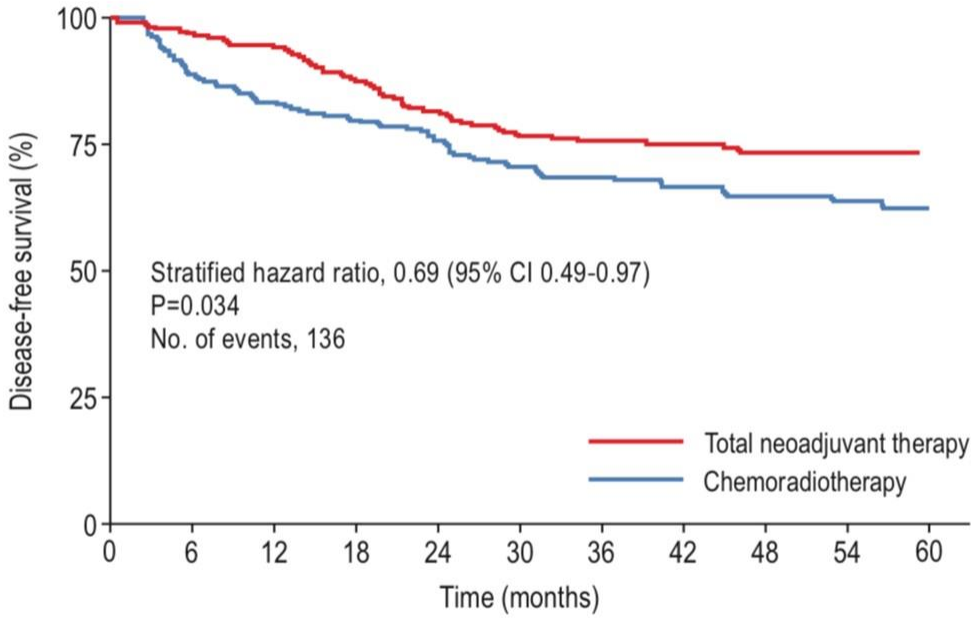
RANDOMIZE



**mFOLFIRINOX: At d1, Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²; Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours (no bolus Fluorouracil)

*according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.

Disease-Free Survival



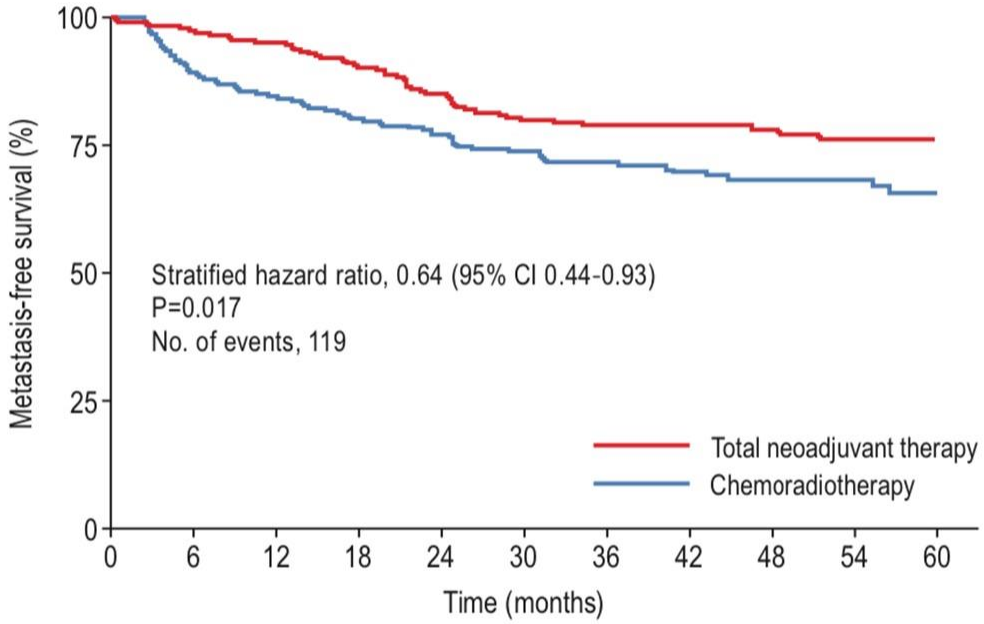
Number at risk											
Total neoadjuvant therapy	231	217	210	194	176	150	126	104	80	62	51
Chemoradiotherapy	230	201	188	177	167	146	117	91	65	55	40

3-yrs DFS rate:

- **75.7% [95%CI: 69.4-80.8] for the TNT group**
- **68.5% [95%CI: 61.9-74.2] for the CRT group**

HR: 0.69; p=0.034

Metastasis-free Survival



Number at risk											
Total neoadjuvant therapy	231	218	212	200	184	156	131	109	86	65	52
Chemoradiotherapy	230	202	191	178	170	153	123	96	70	60	43

3yr-MFS:

- **78.8%** [95%CI: 72.7-83.7] **for the TNT group**
- **71.7%** [95%CI: 65.3-77.2] **for the CRT group**

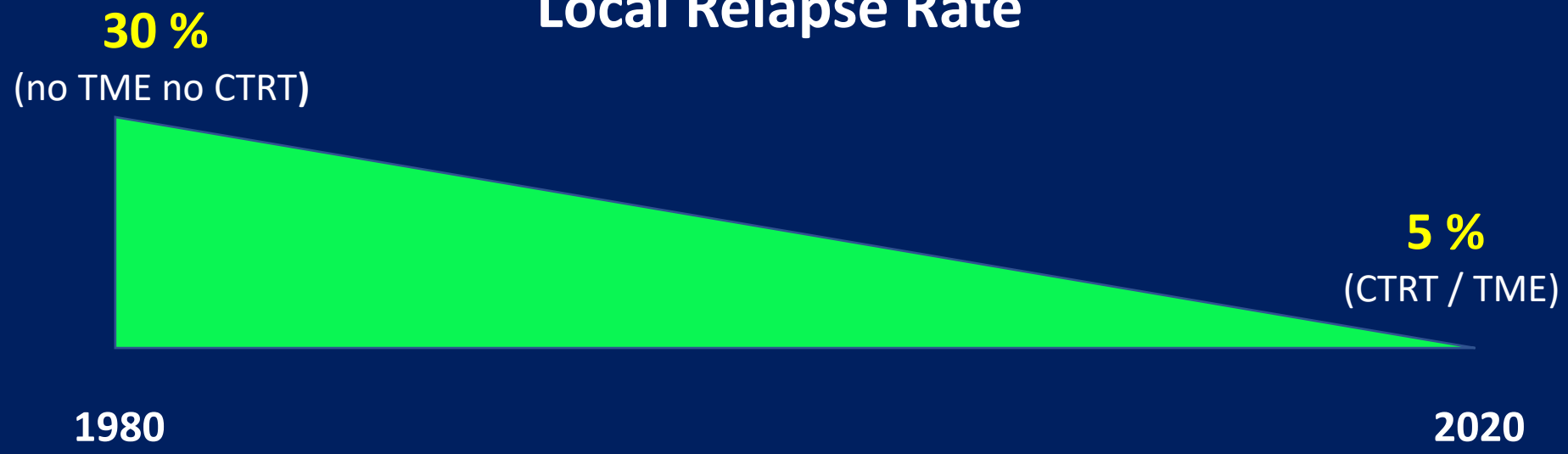
HR: 0.64; p=0.017

Notes:

- **54.2% of the patients with relapse were alive at time of the analysis**
- No difference in overall local relapse rates: 4.8% vs 7%

Stato dell'arte dal 2021 con TNT

Local Relapse Rate



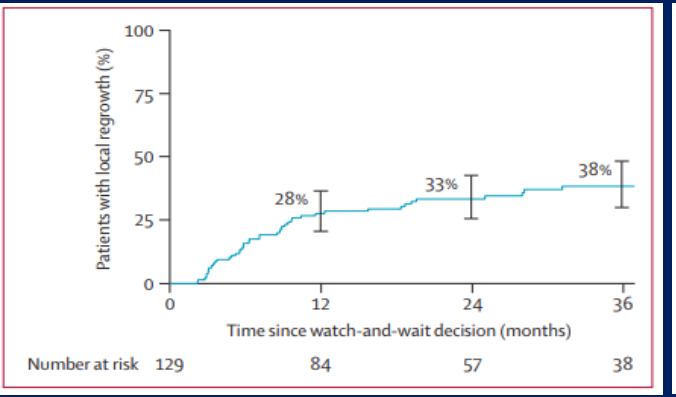
Distant Relapse Rate

NOM nelle cCR

NON STANDARD ..oggi..

Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis

Andrew G Renehan, Lee Malcomson, Richard Emsley, Simon Gollins, Andrew Maw, Arthur Sun Myint, Paul S Rooney, Shabbir Susnerwala, Anthony Blower, Mark P Saunders, Malcolm S Wilson, Nigel Scott, Sarah T O'Dwyer



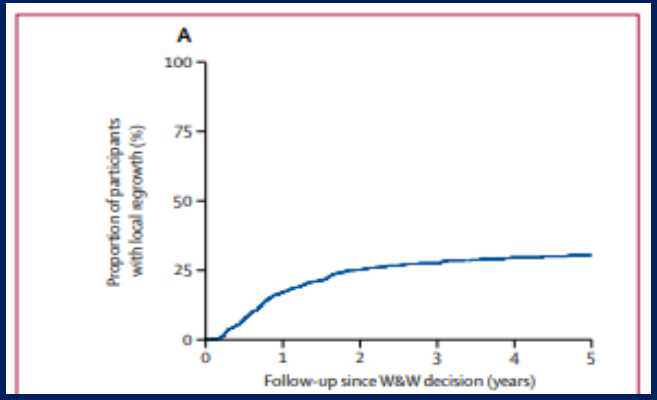
3-yr local regrowth: 34%

Salvage sx: 79%

R0: 97%

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium*



2-yr local regrowth: 25%

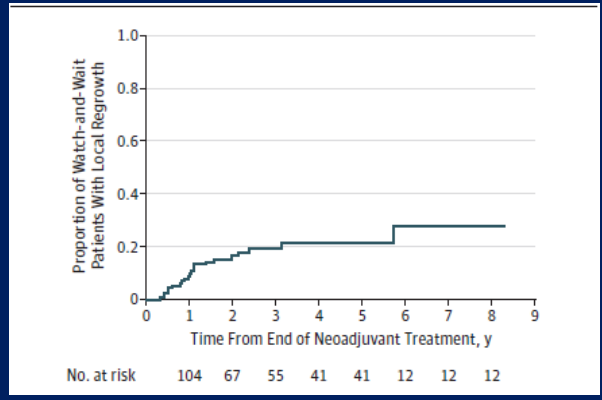
Salvage sx: 78%

R0: 88%

JAMA Oncology | Original Investigation

Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy

J. Joshua Smith, MD, PhD; Paul Strombom, MD; Oliver S. Chow, MD; Campbell S. Roxburgh, MD, PhD; Patricio Lynn, MD; Anne Eaton, MS; Maria Widmar, MD; Karuna Ganesh, MD, PhD; Rona Yaeger, MD; Andrea Cercek, MD; Martin R. Weiser, MD; Garrett M. Nash, MD, MPH; Jose G. Guillem, MD, MPH; Larissa K. F. Temple, MD, MSc; Sree B. Chalasani, MD; James L. Fuqua, MD; Iva Petkovska, MD; Abraham J. Wu, MD; Marsha Reyngold, MD, PhD; Efsevia Vakiani, MD, PhD; Jinru Shia, MD; Neil H. Segal, MD, PhD; James D. Smith, MD, PhD; Christopher Crane, MD; Marc J. Gollub, MD; Mithat Gonen, PhD; Leonard B. Saltz, MD; Julio Garcia-Aguilar, MD, PhD; Philip B. Paty, MD



2-yr local regrowth: 20%

Salvage sx: 100%

R0: 95%

1. Renehan. Lancet Oncol 2016; 17: 174–83
2. van der Valk. Lancet 2018; 391: 2537–45
3. Smith. JAMA Oncol 2019;5(8):1118-1123

Depotenziamento (no RT)

oggi CONTROINDICATO

FOWARC

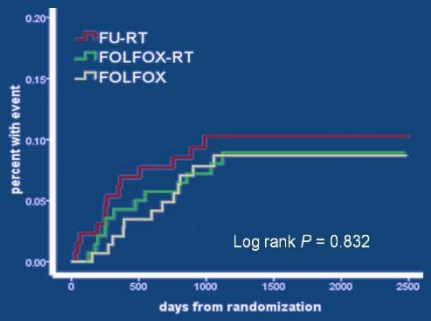
Study design

15 centers
NCT01211210

Radiation begin from day1 of cycle 2 chemotherapy
Radiation was conducted as long course in 23-25 fractions according to the principles of radiation therapy in NCCN guideline
De Gramont regimen constitutes of leucovorin 0.4/m² d1, followed by 5-FU 0.4/m² bolus iv, followed by 2.4/m² CIV 48 hours. With oxaliplatin 85mg/m² 2 hours IV infusion prior to leucovorin constitutes FOLFOX regimen.
Radiation is added to Arm C according to the physician's decision.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: LEI WANG

Local recurrence (LR)



Treatment	3y-LR (%)	HR (95% CI)
FU-RT	10.3±2.7	Ref
FOLFOX-RT	8.0±2.3	0.825 (0.377-1.809)
FOLFOX	8.7±2.4	0.800 (0.365-1.753)

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: LEI WANG

11

CONVERT

- Locally advanced rectal cancer
- Stage II/III & uninvolved MRF
- 5-12 cm (anal verge) before April 2019; <12 cm after April 2019
- Aged from 18-75 years
- ECOG ≤ 1

1:1 R

		SURGERY	FOLLOW-UP
nCT group	4 cycles of CapeOx * (capecitabine and oxaliplatin)		4 cycles of CapeOx * (capecitabine and oxaliplatin)
nCRT group	RT 50 Gy /5wks + Capecitabine 825mg/m² po bid 5 days/7 †		6 cycles of CapeOx * (capecitabine and oxaliplatin)

Staging: MRI

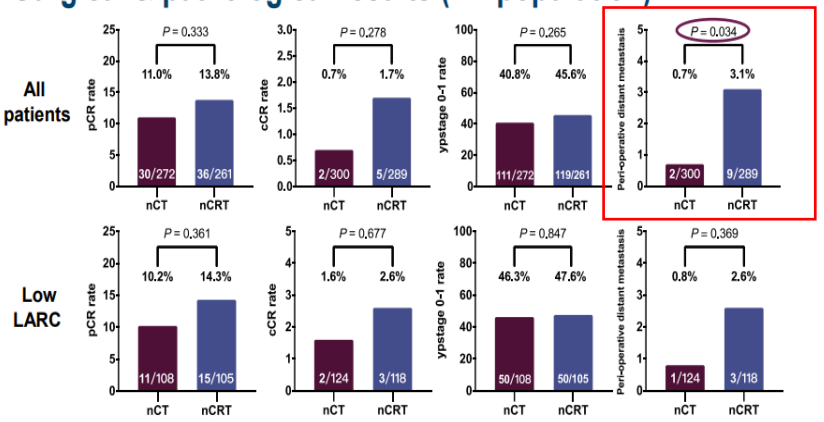
Primary endpoints: 3-year local regional failure free survival

Secondary endpoints: DFS, OS, pCR rate, TRG, R0 resection rate, safety, compliance, and preventive diverting ileostomy rate.

* Oxaliplatin 130 mg/m² iv drip over 2 hours on day 1, repeated every 21 days. Capecitabine 1000 mg/m² po twice daily on days 1- 14 repeated every 21 days.
† Capecitabine 825 mg/m² twice daily administered orally and concurrently with radiation therapy for 5 days per week. The total dosage of RT was 50 Gy in 25 fractions to the gross tumour volume (GTV) and 45 Gy in 25 fractions to the clinical target volume (CTV) delivered by IMRT.

2021 ESMO congress

Surgical & pathological results (PP population)



2021 ESMO congress

*Peri-operative metastasis: metastases identified before or during surgery

4) MSS/pMMR poco beneficio da CRT + IO

NRG-GI002 Ph II rand

mFOLFOX x 8 → CRT → TME

VS

mFOLFOX x 8 → CRT + Pembro → TME

NEGATIVE

	29.4%		13.6%		94%
pCR	p 0.75	cCR	p 0.95	R0	p 0.36
	31.9%		13.9%		89.4%

AVANA Ph II

CRT + Avelumab x 6 → TME → Adj

" POSITIVE "

pCR 27 %

VOLTAGE Ph II

CRT → Nivo x 5 → TME → Adj FFOX

" POSITIVE "

pCR 30%

AVERECTAL Ph II

Short RT → FFOX + Avelumab x 6 → TME

" POSITIVE "

pCR 37.5%

1. Rahma OE et al. JAMA Oncol. 2021;7(8):1225-1230 JAMA Oncol 2018.
2. Salvatore L et al. Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 3511-3511
3. Yuki S et al. Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 4100-4100.
4. Shamseddine A. Ann Oncol Vol. 32 Suppl S215 July 2021.

2) casistiche simili riportano dati simili

NICHE

41 pts (80% stage III colon cancers)

21 dMMR

20 pMMR

Ipi 1 d1 + Nivo 3 d1,15

Surgery within 6 wks

20/20 Path Resp
19/20 MPR
12/20 (60%) pCR

4/15 Path Resp
3/15 MPR*
0/15 pCR

* CD8 PD1 TCI

Chalabi, Nature Med 2020

NCT04082572

10 colon + 2 rectal dMMR (Stage II-III)

Pembro 8 cycles (6 mos)

Surgery

9/10 (90%) pCR in colon
1/2 (50%) pCR in rectal

Ludford, ESMO 2021

3) MSI/dMMR resistenti a CT di induzione

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Mismatch Repair–Deficient Rectal Cancer and Resistance to Neoadjuvant Chemotherapy

Andrea Cercek[1], Gustavo Dos Santos Fernandes[2], Campbell S. Roxburgh[3], Karuna Ganesh[1], Shu Ng[4], Francisco Sanchez-Vega[5], Rona Yaeger[1], Neil H. Segal[1], Diane L. Reidy-Lagunes[1], Anna M. Varghese[1], Arnold Markowitz[1], Chao Wu[6], Bryan Szeglin[6], Charles-Etienne Gabriel Sauvé[6], Erin Salo-Mullen[1], Christina Tran[1], Zalak Patel[1], Asha Krishnan[1], Kaitlyn Tkachuk[1], Garrett M. Nash[6], Jose Guillem[6], Philip B. Paty[6], Jinru Shia[7], Nikolaus Schultz[5], Julio Garcia-Aguilar[6], Luis A. Diaz[1], Karyn Goodman[8], Leonard B. Saltz[1], Martin R. Weiser[6], J. Joshua Smith[6,9], and Zsofia K. Stadler[1]

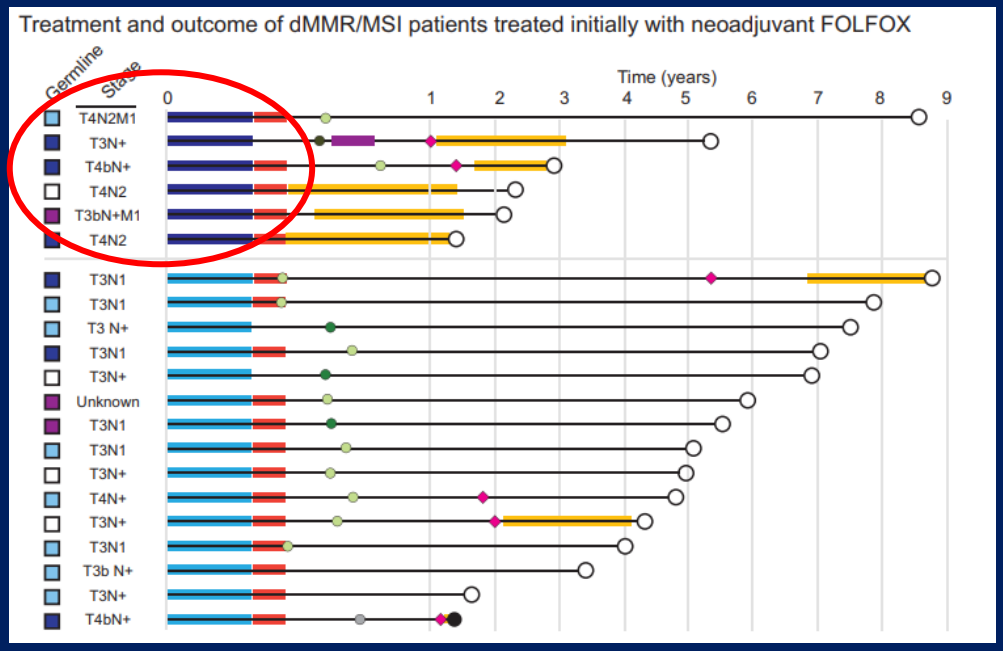


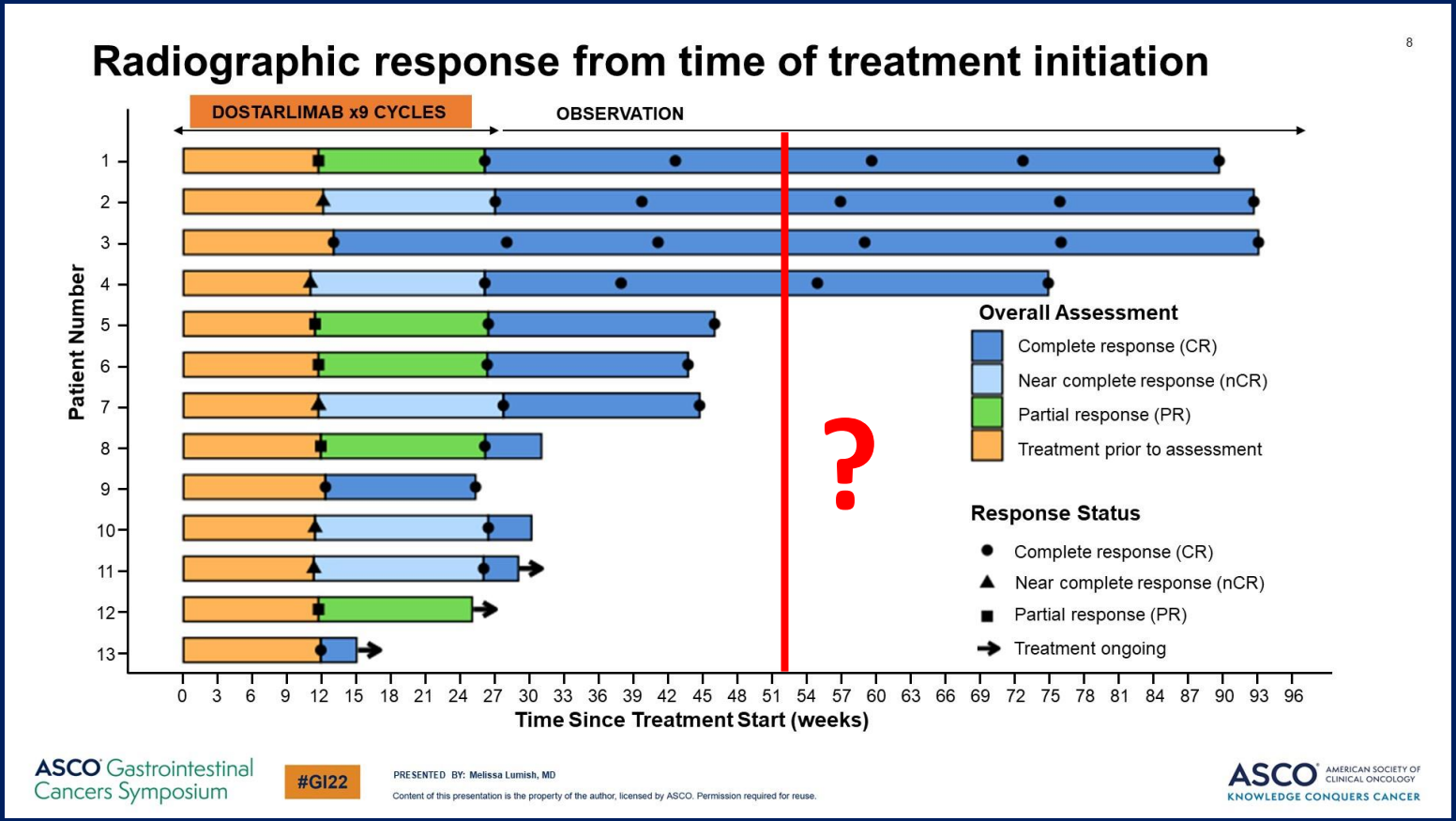
Table 2. Outcomes in patients with rectal cancer with dMMR or pMMR.

Outcome	No. of patients (%) dMMR	pMMR
FOLFOX as initial treatment	*n* = 21	*n* = 63
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	*n* = 16	*n* = 48
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

pCR 24 % con CRT di "salvataggio"

Clin Cancer Res 2020;26:3271–9

3) 6 mesi di aPD-1 possono guarire un LARC?



Serve follow-up più lungo (e appropriato)

JAMA Surgery | Original Investigation

Association of Delayed Surgery With Oncologic Long-term Outcomes in Patients With Locally Advanced Rectal Cancer Not Responding to Preoperative Chemoradiation

Simona Deidda, MD; Ugo Elmore, MD; Riccardo Rosati, MD; Paola De Nardi, MD; Andrea Vignali, MD; Francesco Puccetti, MD; Gaya Spolverato, MD; Giulia Capelli, MD; Matteo Zuin, MD; Andrea Muratore, MD; Riccardo Danna, MD; Marcello Calabrò, MD; Mario Guerrieri, MD; Monica Ortenzi, MD; Roberto Ghiselli, MD; Stefano Scabini, MD; Alessandra Aprile, MD; Davide Pertile, MD; Giuseppe Sammarco, MD; Gaetano Gallo, MD; Giuseppe Sena, MD; Claudio Coco, MD; Gianluca Rizzo, MD; Donato Paolo Pafundi, MD; Claudio Belluco, MD; Roberto Innocente, MD; Maurizio Degiuli, MD; Rossella Reddavid, MD; Lucia Puca, MD; Paolo Delrio, MD; Daniela Rega, MD; Pietro Conti, MD; Alessandro Pastorino, MD; Luigi Zorcolo, MD; Salvatore Pucciarelli, MD; Carlo Aschele, MD; Angelo Restivo, MD

ypT2-T3 e/o ypN+

Figure 1. Mean Wait Period Between Chemoradiotherapy and Surgical Resection Between 2000 and 2014 Among Patients With Nonresponsive Locally Advanced Rectal Cancer

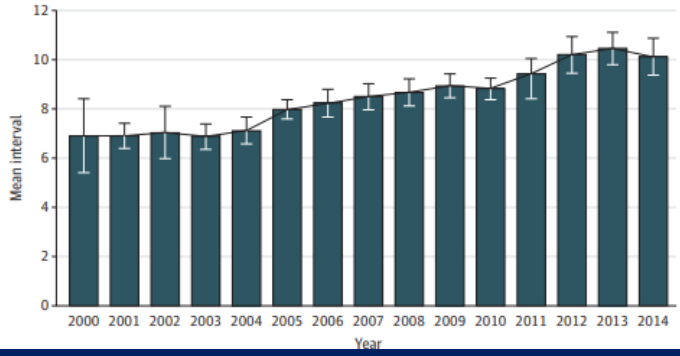


Figure 2. Survival and Recurrence Among Patients With Nonresponsive Locally Advanced Rectal Cancer

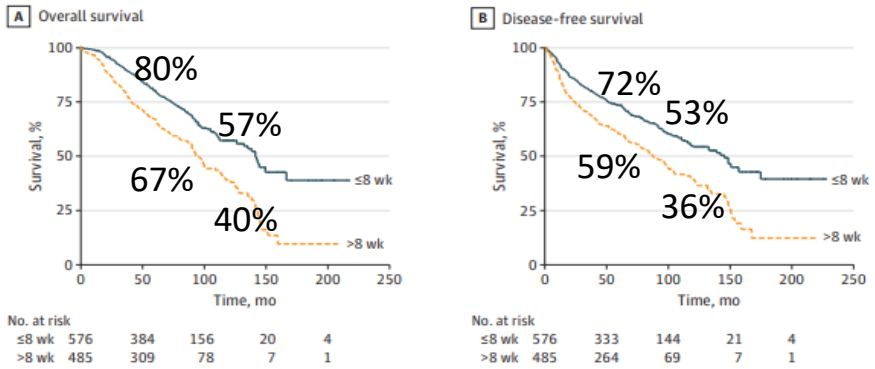
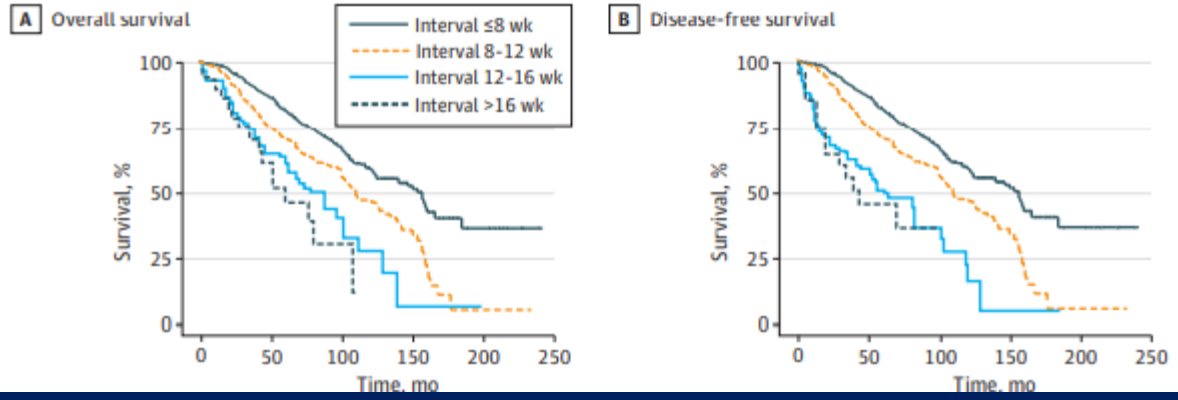


Figure 3. Survival Curve of Patients Stratified for Every Additional Month of Waiting After 8 Weeks



JAMA Surg. 2021;156(12):1141-1149. doi:10.1001/jamasurg.2021.4566
Published online September 29, 2021.