COLORECTAL CANCER

PROGRESS and NEWS IN 2018

J Collignon
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Medical Oncology DpTh
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OUTLINE

1) **DURATION OF ADJUVANT CHEMOTHERAPY**

2) **IMMUNOTHERAPY AND mCRC**

3) **QUICK NEWS**

BACKGROUND

ADJUVANT OXALIPLATINE CLEAR BENEFIT IN STAGE III

		XELOX	FOLFOX
	NSABP C-07 STAGE III	N016968 (ALL STAGE III)	MOSAIC STAGE III
ABSOLUTE IMPROVEMENT DFS 5Y	**6,6 %**	**6,3 %**	**8,4 % (10 Y)**
RELATIVE IMPROVEMENT DFS	**18 %**	**20 %**	**22 %**
ABSOLUTE IMPROVEMENT OS	2,7 % (5Y) NS	**6 %(7Y)**	**8,1 % (10 Y)**
RELATIVE IMPROVEMENT OS	12 % NS	**17 %**	**20 %**

THREE pivotal studies confirmed increased DFS in stage III and for 2 studies OS was also clearly increased

BACKGROUND

ADJUVANT OXALIPLATINE FOLFOX

WHEN TAKING DECISION FOR ADJUVANT TREATMENT,DON'T FORGET TOXICITY!

PNP EVALUATION IN MOSAIC TRIAL

N=976 evaluable at 48 months	
Grade 0	**85,5 %**
Grade 1	**12 %**
Grade 2	**2,8 %**
Grade 3	**0,7 %**

PNP at 4 year!!!
Still 12 % grade 1

Neurotoxicity may peak after stopping oxaliplatin,may be severe and persist long after and affect QoL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 29, 2018 VOL. 378 NO. 13

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

A. Grothey, A.F. Sobrero, A.F. Shields, T. Yoshino, J. Paul, J. Taieb, J. Souglakos, Q. Shi, R. Kerr, R. Labianca, J.A. Meyerhardt, D. Vernerey, T. Yamanaka, I. Boukovinas, J.P. Meyers, L.A. Renfro, D. Niedzwiecki, T. Watanabe,* V. Torri, M. Saunders, D.J. Sargent,* T. Andre, and T. Iveson

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

A New IDEA in Adjuvant Chemotherapy for Colon Cancer

Richard L. Schilsky, M.D.

ADJUVANT NEWS IN 2018

ASCO 2017
ESMO 2017

As oxaliplatin mediated neurotoxicity is cumulative, the idea is to see if shorter adjuvant treatment maintain its efficacy

IDEA COLLABORATIVE TRIAL
6 trials in different countries
N=12.834 stage III patients

ADJUVANT NEWS IN 2018

Basic Schema for IDEA

Stage III colon cancer patients who underwent surgery

R

1:1

- 3 months
- Investigator's choice FOLFOX or CAPOX
- 6 months

NOTE: Objective was to focus on the duration of therapy with an oxaliplatin-based regimen but not to directly compare FOLFOX vs. CAPOX

Primary endpoint=DFS
Pre planned subgroup analyses by regimen and T/N

Shi et al ASCO 2017

Rationale for non inferiority margin

ADJUVANT NEWS IN 2018

IDEA consensus

Non inferiority margin (DFS HR) choosen is 1,12
= worsening of 2.7 percentage points in the 3-year rate of disease-free survival (from 72% to 69.3%) with the aim to also reduce toxicity

IDEA COLLABORATIVE TRIAL

ADJUVANT NEWS IN 2018

Table 1. Characteristics of the Study Patients (Modified Intention-to-Treat Population).*

Characteristic	TOSCA (N=2402)	SCOT (N=3983)	IDEA France (N=2010)	CALGB/SWOG 80702 (N=2440)	HORG (N=708)	ACHIEVE (N=1291)	All Patients (N=12,834)
Countries	Italy	U.K., Denmark, Spain, Australia, Sweden, New Zealand	France	U.S., Canada	Greece	Japan	
Median age (range) — yr	64 (20–83)	65 (20–84)	64 (18–85)	61 (19–88)	67 (20–75)	66 (28–85)	64 (18–88)
Male sex — no. (%)	1348 (56.1)	2356 (59.2)	1144 (56.9)	1348 (55.3)	398 (56.2)	649 (50.3)	7,243 (56.4)
ECOG performance status — no. (%)							
0	2268 (94.4)	2827 (71.0)	1479 (73.6)	1734 (71.1)	579 (81.8)	1245 (96.4)	10,132 (79.0)
1	130 (5.4)	1156 (29.0)	502 (25.0)	680 (27.9)	128 (18.1)	46 (3.6)	2,642 (20.6)
2	1 (<0.1)	0	29 (1.4)	26 (1.1)	1 (0.1)	0	57 (0.4)
Missing data	3 (0.1)	0	0	0	0	0	3 (<0.1)
Tumor stage — no. (%)							
T1	76 (3.2)	128 (3.2)	78 (3.9)	135 (5.5)	1 (0.1)	75 (5.8)	493 (3.8)
T2	236 (9.8)	333 (8.4)	161 (8.0)	288 (11.8)	60 (8.5)	119 (9.2)	1,197 (9.3)
T3	1773 (73.8)	2347 (58.9)	1399 (69.6)	1598 (65.5)	549 (77.5)	734 (56.9)	8,400 (65.5)
T4	12 %	29 %	13 %	15 %	14 %	28 %	
N1	1748 (72.8)	2749 (69.0)	1501 (74.7)	1739 (71.3)	472 (66.7)	959 (74.3)	9,168 (71.4)
N2	26,5%	31 %	25,2 %	25,8 %	32,5%	27,8 %	
Risk group — no. (%)							
T1, T2, or T3 N1	1553 (65.5)	2032 (51.0)	1245 (62.0)	1507 (63.6)	416 (59.1)	718 (55.6)	7,471 (58.7)
T4, N2, or both	817 (34.5)	1950 (49.0)	764 (38.0)	864 (36.4)	288 (40.9)	573 (44.4)	5,256 (41.3)
Median no. of lymph nodes examined (range)	18 (0–85)	Not recorded	20 (1–99)	20 (1–132)	18 (10–85)	21 (1–123)	19 (0–132)
Chemotherapy regimen — no. (%)							
CAPOX	840 (35.0)	2649 (66.5)	201 (10.0)	0	412 (58.2)	969 (75.1)	5,071 (39.5)
CAPOX	35 %	67 %	10%	0%	58 %	75%	

Overall 40% CAPOX/60 % FOLFOX

ASCO17 Q. Shi ; NEJM 2018 A. Grothey

IDEA COLLABORATIVE TRIAL

ADJUVANT NEWS IN 2018

TREATMENT COMPLIANCE

Treatment Compliance	FOLFOX		CAPOX	
	3m Arm	6m Arm	3m Arm	6m Arm
Total no. weeks received treatment Median (Q1-Q3)	12 (12-12)	24 (20-24)	12 (12-12)	24 (18-24)
Reached the planned last cycle[1]	90%	71%	86%	65%
% of dose actually delivered, Mean (Standard Deviation)				
5FU[2]	92.4 (22.7)	81.6 (26.6)	---	---
Capecitabine	---	---	91.2 (23.5)	78.0 (29.4)
Oxaliplatin	91.4 (19.9)	72.8 (25.6)	89.8 (21.7)	69.3 (28.3)

COMPLIANCE LOWER IN 6 MONTHS ARM

ASCO17 Q. Shi ; NEJM 2018 A. Grothey

IDEA COLLABORATIVE TRIAL

ADJUVANT NEWS IN 2018

ADVERSE EVENTS

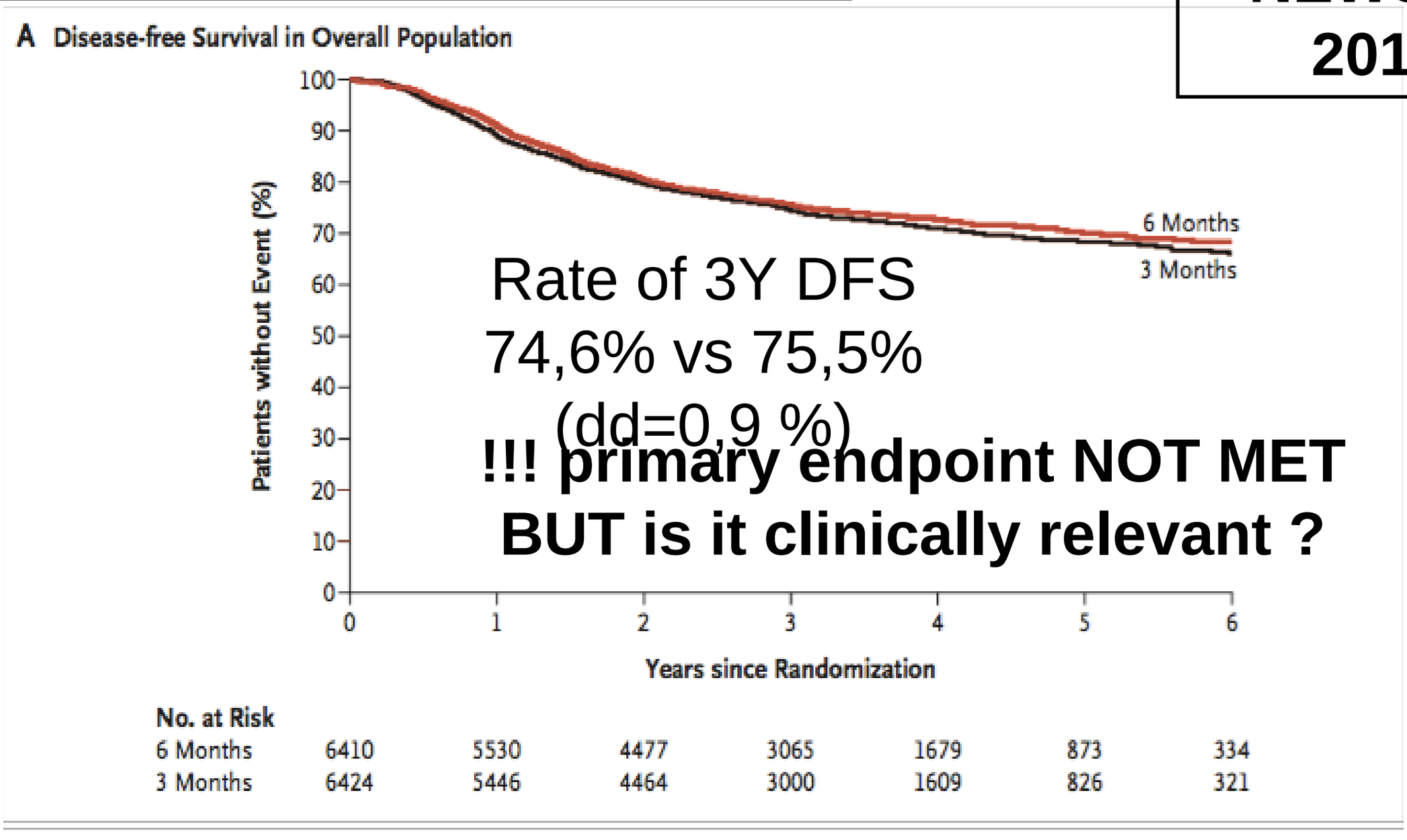
Adverse Events	FOLFOX 3m Arm	FOLFOX 6m Arm	FOLFOX p-value[1]	CAPOX 3m Arm	CAPOX 6m Arm	CAPOX p-value[1]
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

[1] 1% of patients assigned to 3m treatment (both FOLFOX and CAPOX) received > 3m of treatment; [2] combining infusion and bolus

ASCO17 Q. Shi ; NEJM 2018 A. Grothey

IDEA COLLABORATIVE TRIAL

ADJUVANT NEWS IN 2018



Rate of 3Y DFS
74,6% vs 75,5%
(dd=0,9 %)

!!! primary endpoint NOT MET
BUT is it clinically relevant ?

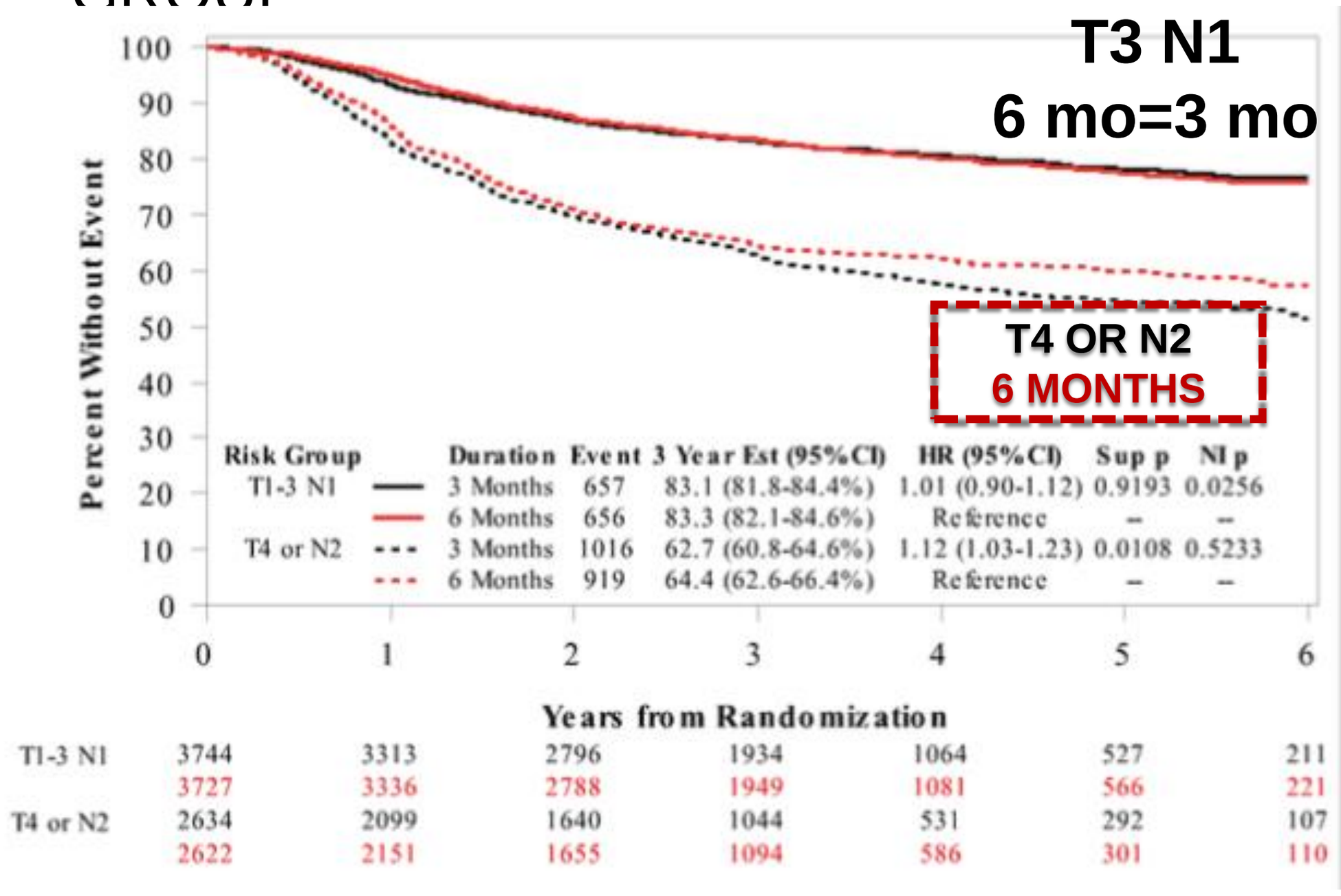
NON INFERIORITY OF 3 MONTHS VS 6 MONTHS WAS NOT CONFIRMED

ASCO17 Q. Shi ; NEJM 2018 A. Grothey

IDEA COLLABORATIVE TRIAL

ADJUVANT NEWS IN 2018

BY RISK GROUP



ASCO17 Q. Shi ; NEJM 2018 A. Grothey

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

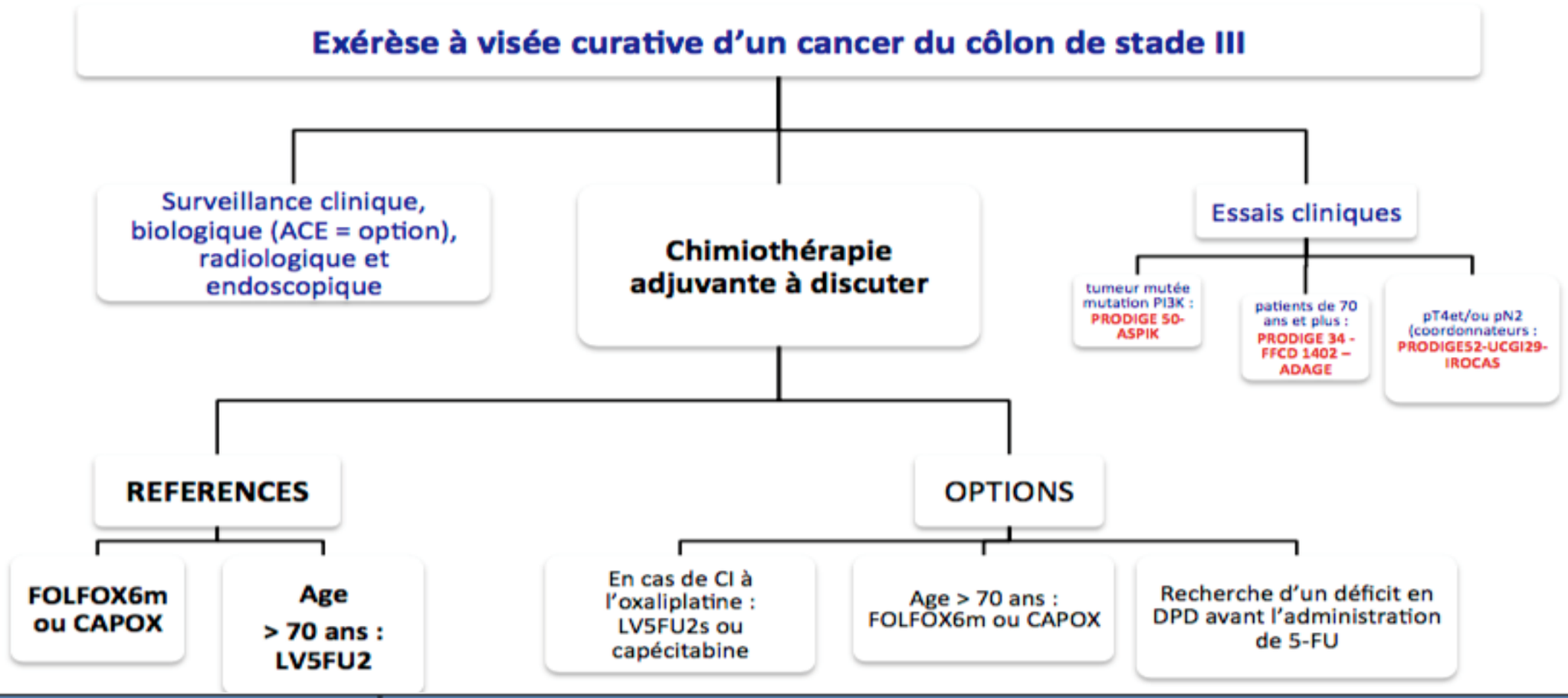
Colon Cancer

Version 4.2018 — October 19, 2018

T1-3,N1 **Low risk stage III**	**<u>Preferred</u>** • **CAPEOX (3 mo)** • **FOLFOX(3-6 mo) (<u>CATEGORY 1 for 6 months)</u>** • Or other options include capecitabine (6 mo) or 5-FU (6 mo)
T4,N1-2;T any,N2 **High risk stage III**	**<u>Preferred</u>** • **CAPEOX (3 - 6mo) (<u>CATEGORY 1 for 6 months</u>** • **FOLFOX(6 mo) (<u>CATEGORY 1)</u>** • Or other options include capecitabine (6 mo) or 5-FU (6 mo)

TNCD

THESAURUS NATIONAL DE CANCEROLOGIE DIGESTIVE (TNCD) ©



STADE III	Schéma	
	XELOX	FOLFOX
Faible risque (T1-3,N1)	3 mois	6 mois (alternative : 3 mois)
Haut risque (T4 et/ou N2)	6 mois (alternative : 3 mois)	6 mois

OUTLINE

1) DURATION OF ADJUVANT CHEMOTHERAPY

2) **IMMUNOTHERAPY and MSI-H mCRC**

3) QUICK NEWS

IMMUNOTHERAPY AND CRC
MSI-H tumor

	STAGE II	STAGE III	STAGE IV
MSI-H	22 %	12 %	3,5 %

D.T.LE
ASCO
2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

Study Design

Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=25)

Cohort B
Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

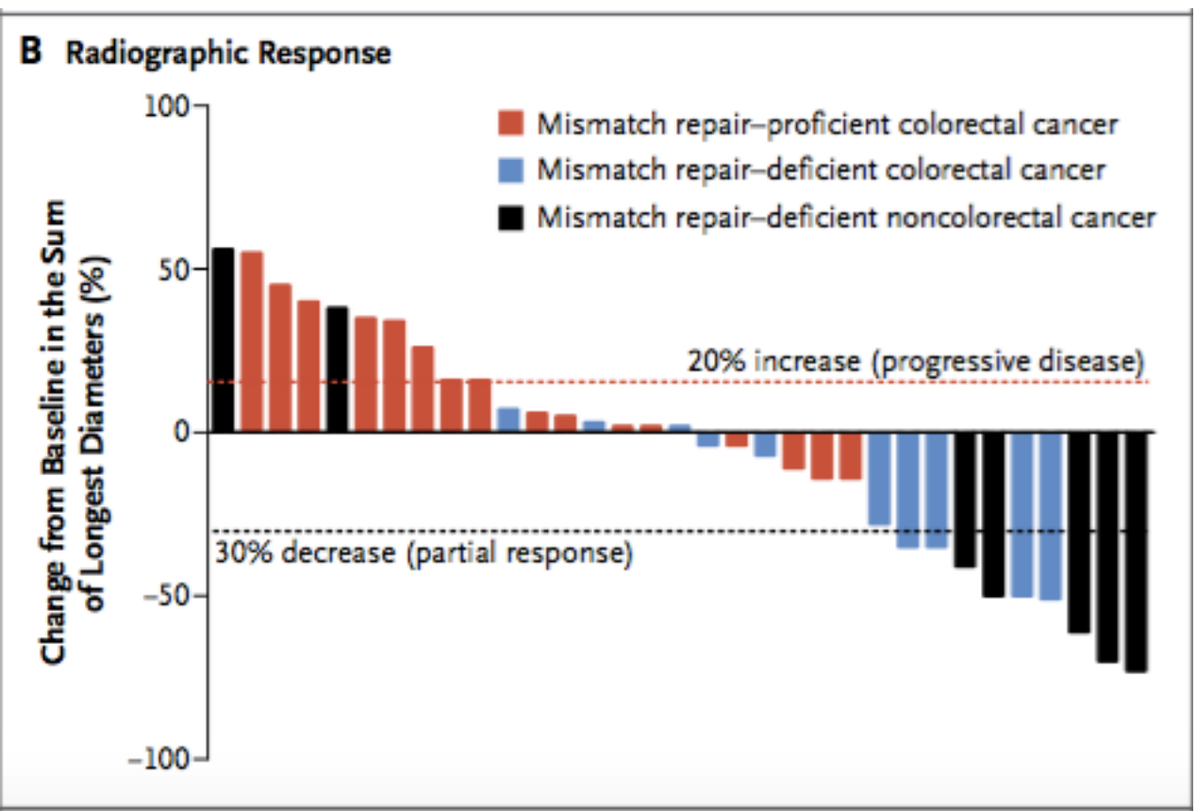
Cohort C
Deficient in Mismatch Repair (n=21)

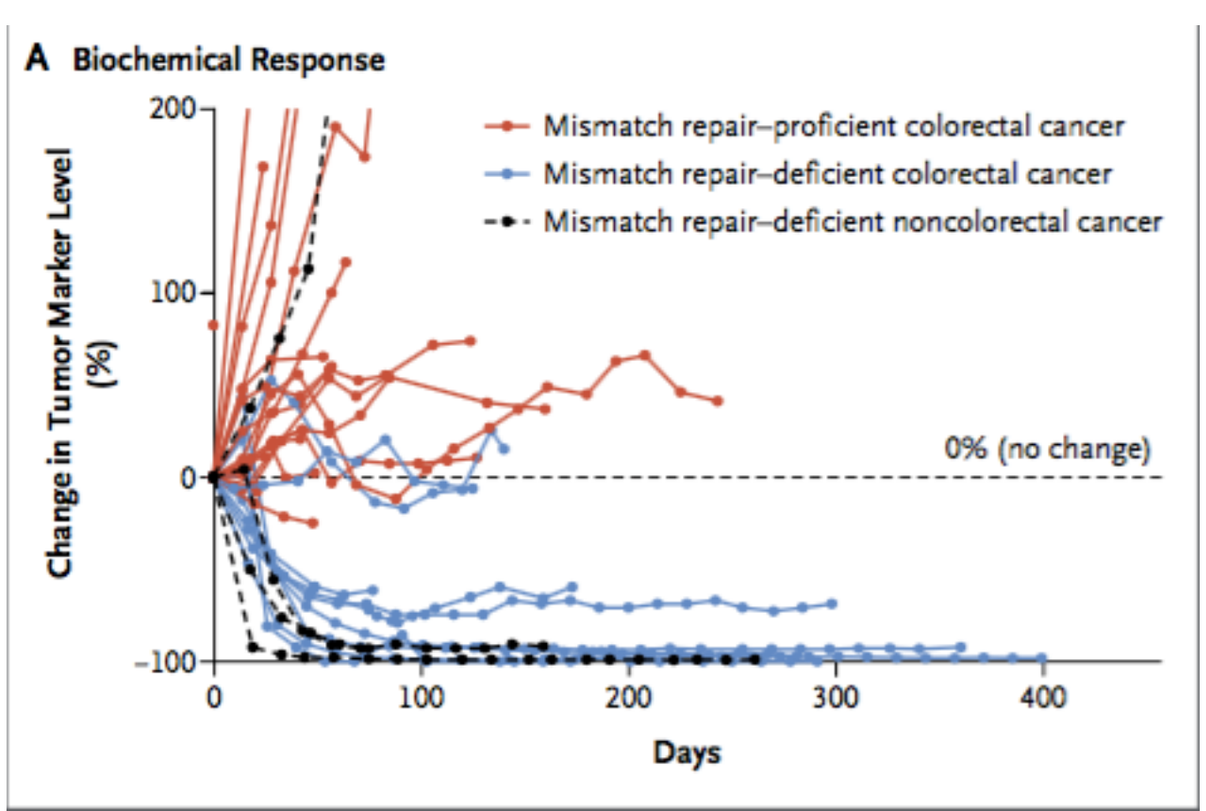
Pembrolizumab dose of 10 mg per kilogram of body weight every 14 days

The coprimary end points were

the immune-related objective response rate: 40%vs 0 % for MMR deficient CRC

the 20-week immune-related progression-free survival rate: 78 % vs 11 %





U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release May 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

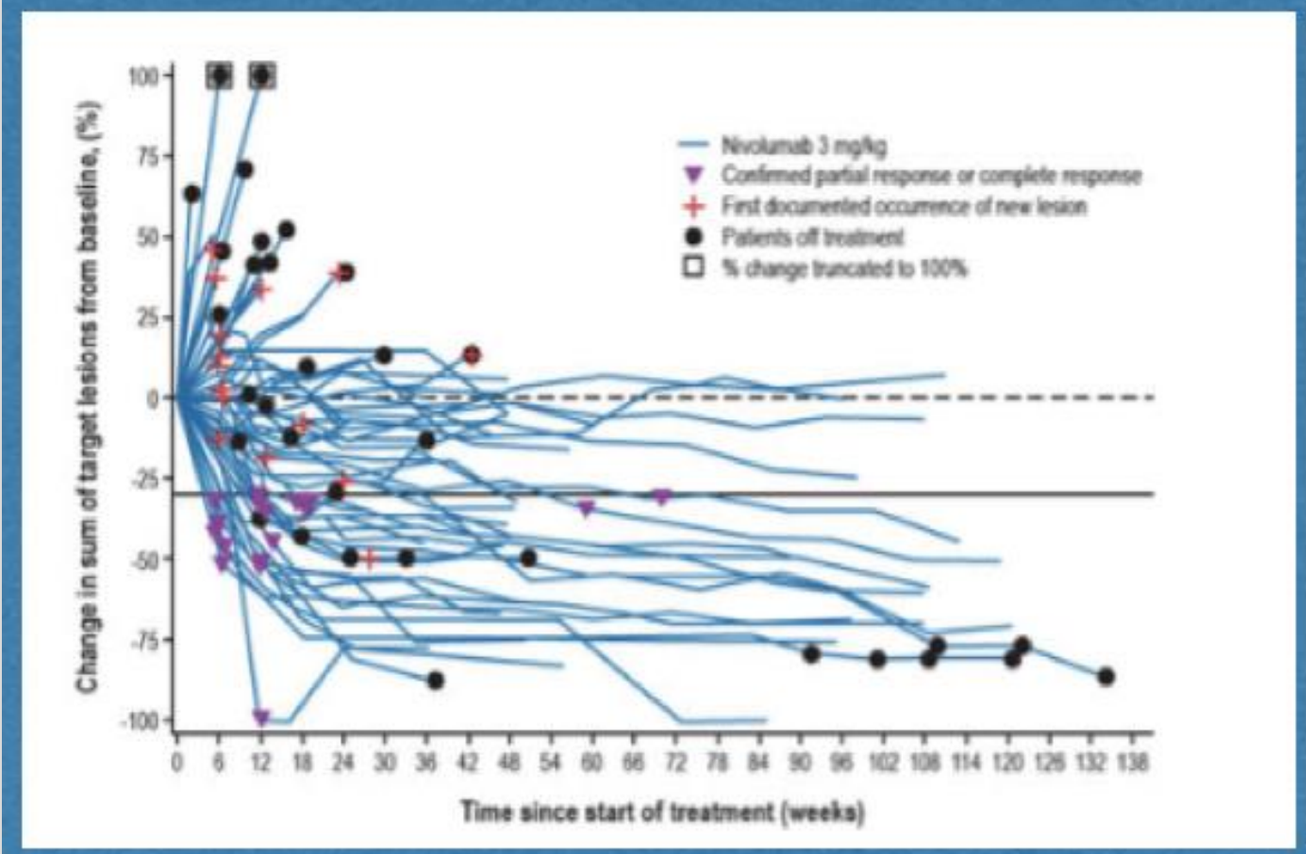
Biomarker for Pembrolizumab= MMR-D or MSI-H ALL TUMORS

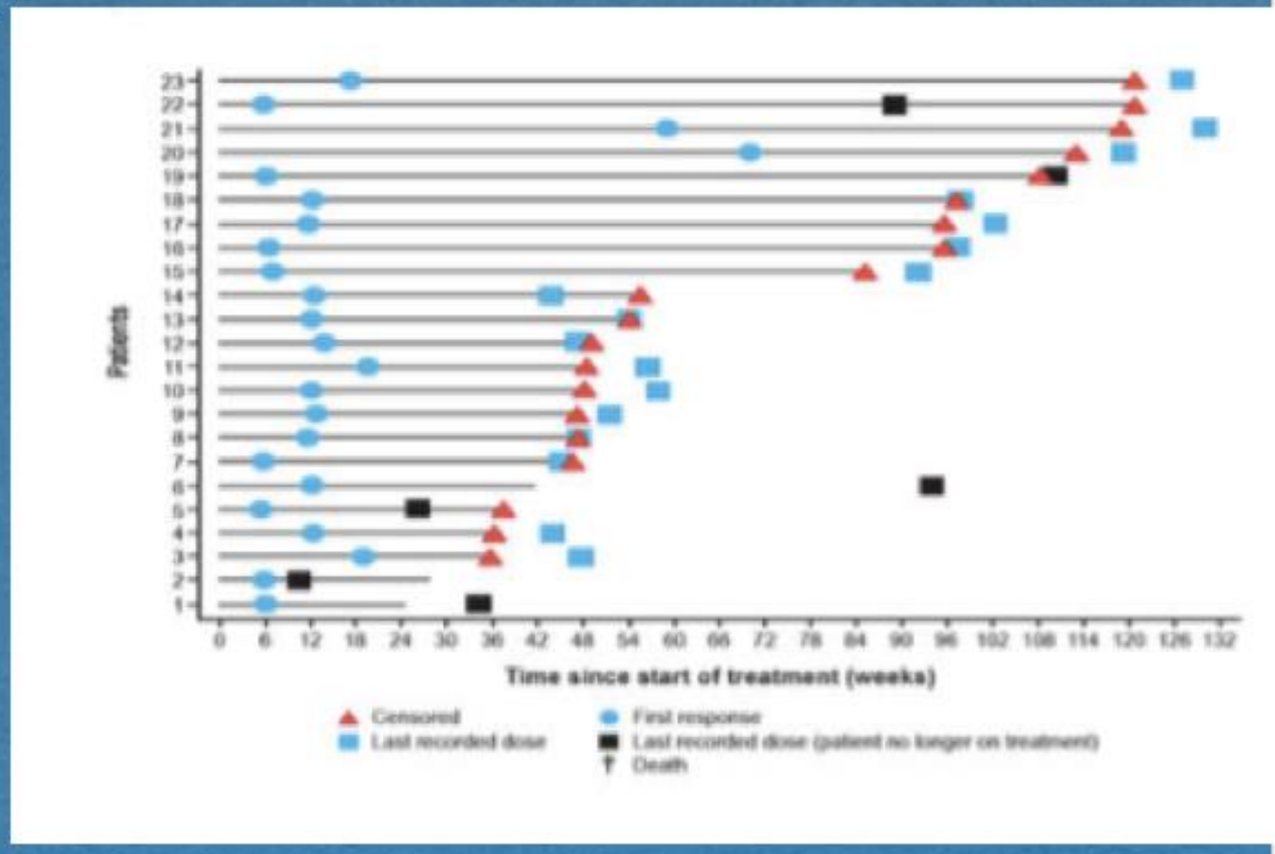
NCCN recommendations in CRC: MSI or MMR testing in all patient with personal history of colon or rectal cancer

COHORT A NIVO ALONE PREVIOUSLY TREATED
MSI-H mCRC
3 mg/KG every 3 weeks

Lancet Oncology` Sep 2017

ORR 31,1 %
disease contrôle for ≧ 3 months: 68,9 %





COHORT A NIVO 3mg/kg alone
PREVIOUSLY TREATED MSI-H mCRC

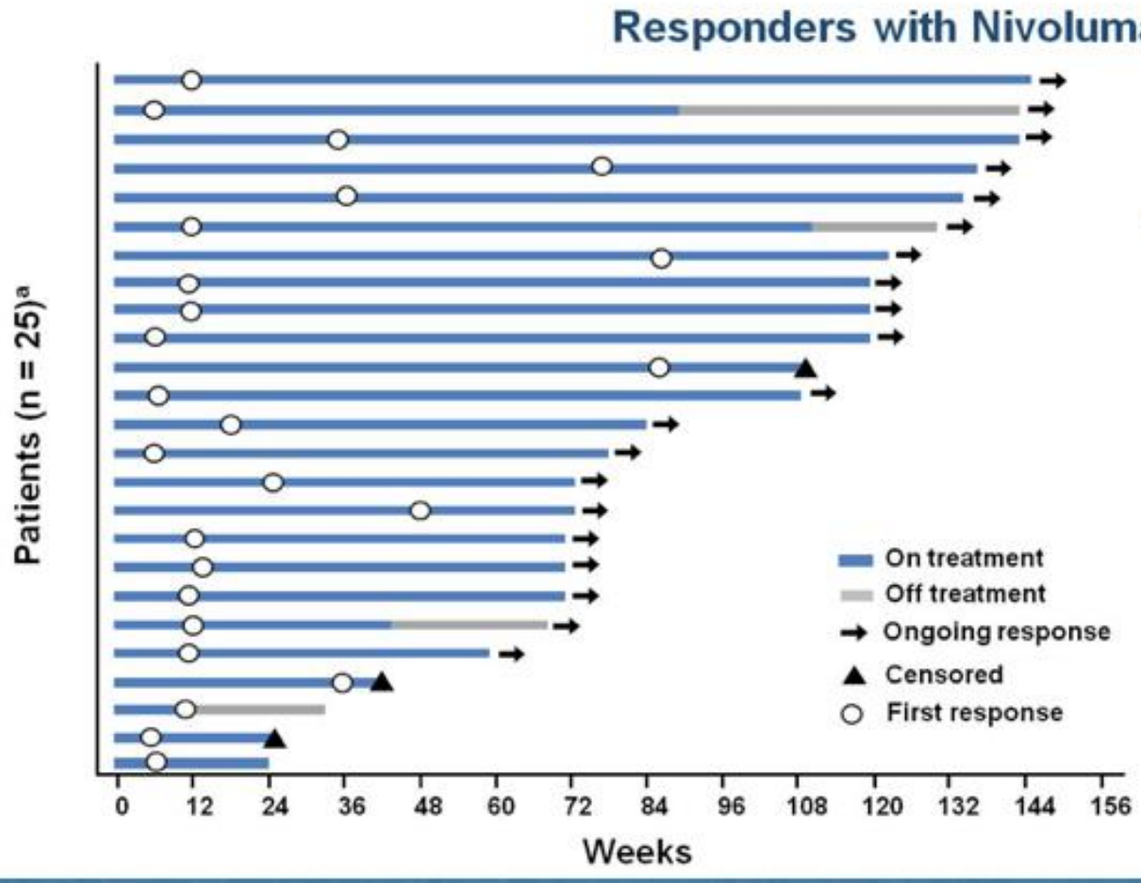
LONGER MEDIAN FU: 21 MONTHS

INCREASED CR = 9% (3%)

Overman
ASCO GI 2018

SAME DISEASE CONTROL RATE=62%
MEDIAN DOR AND OS NOT YET REACHED

Characterization of Response: All Patients



- Nivolumab continued to provide clinically meaningful and durable responses
  - 80% of responders had ongoing responses at data cutoff
  - 64% had responses lasting ≥ 12 months

COHORT B NIVO 3mg/kg + IPILIMUMAB 1 mg/kg /3W(4 doses)-then NIVO alone PREVIOUSLY TREATED MSI-H mCRC

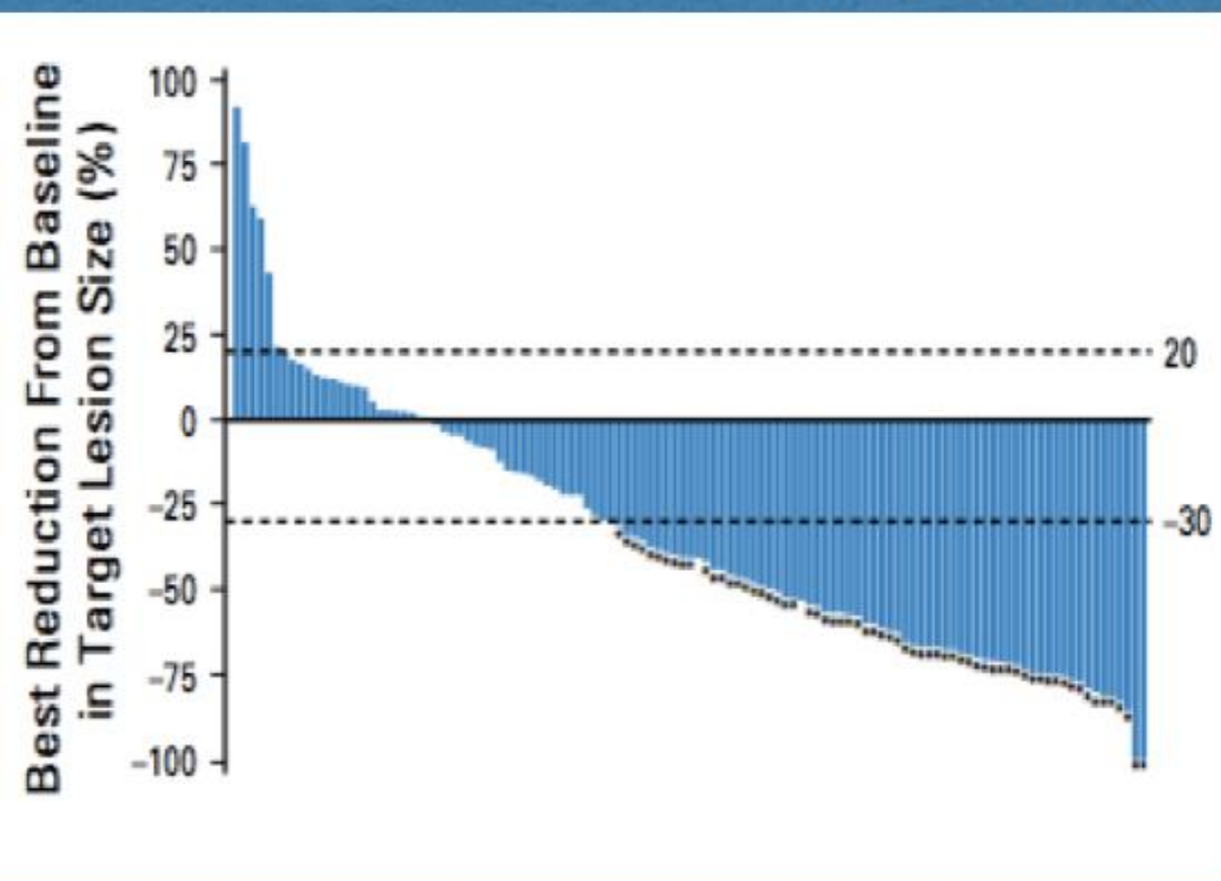
Andre
ASCO GI 2018
Overman
JCO 2018

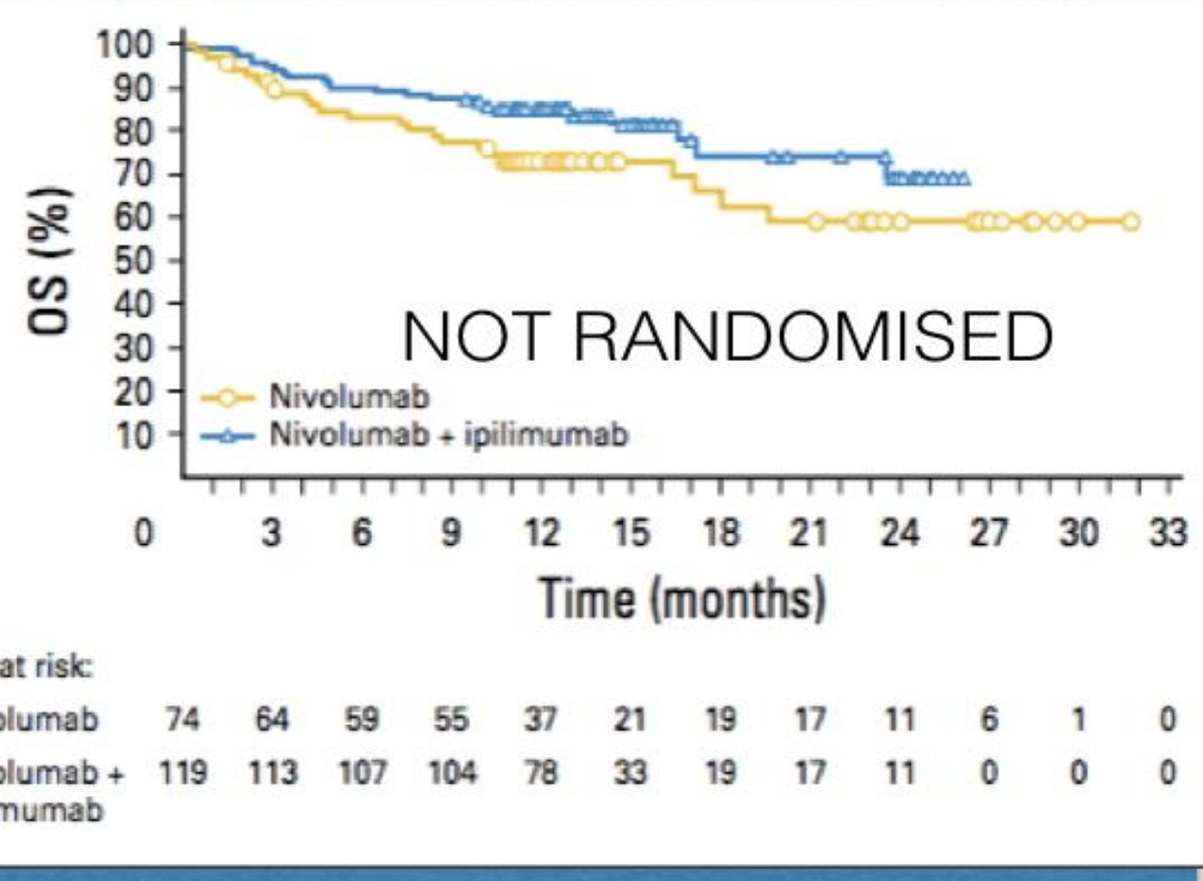
76 % more than 2 lines

ORR 55 %

disease control for ≧ 3 months= 80 %

Median FU:13,4 mo





COHORT C

NIVO 3mg/kg / 3 W + IPILIMUMAB 1 mg/kg/ 6 W in First line MSI-H mCRC

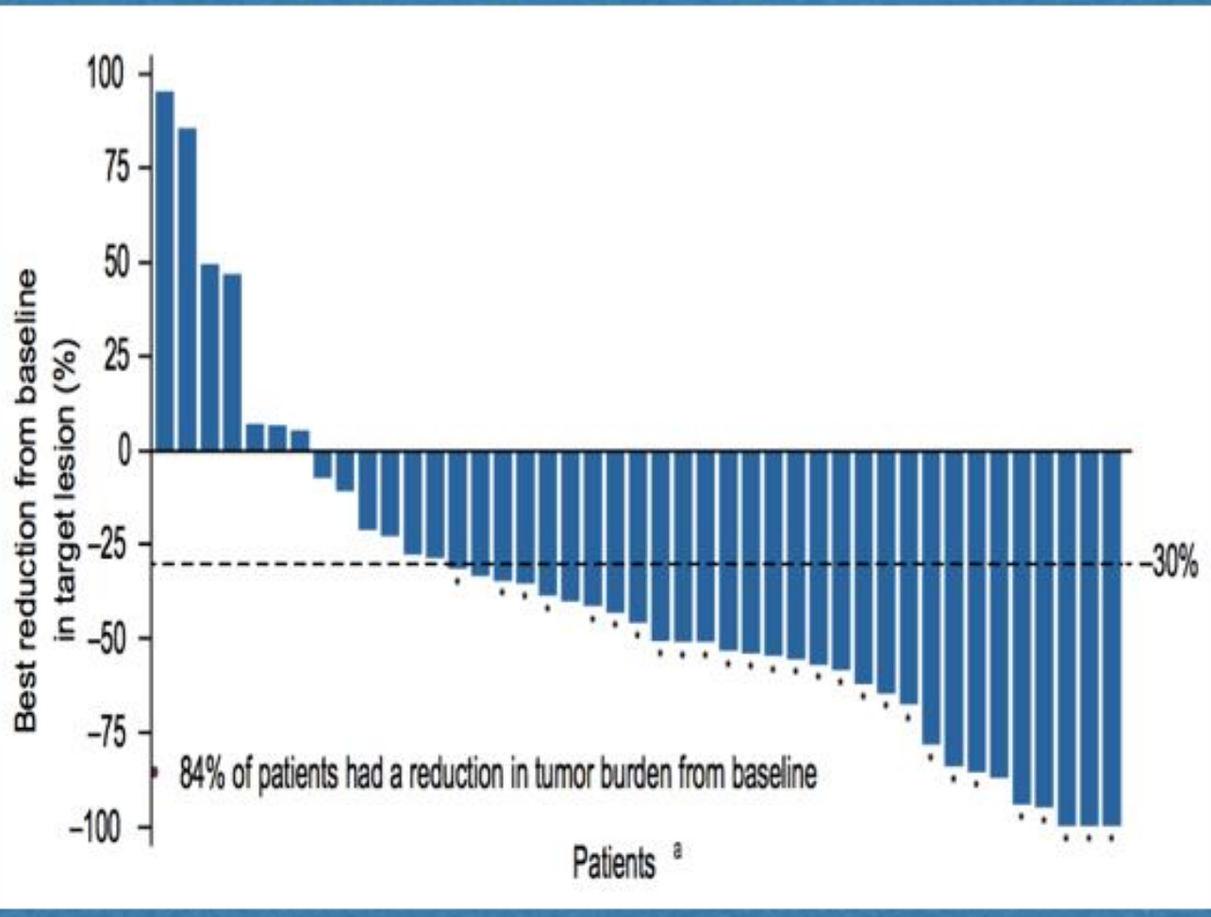
Lenz
ESMO 2018

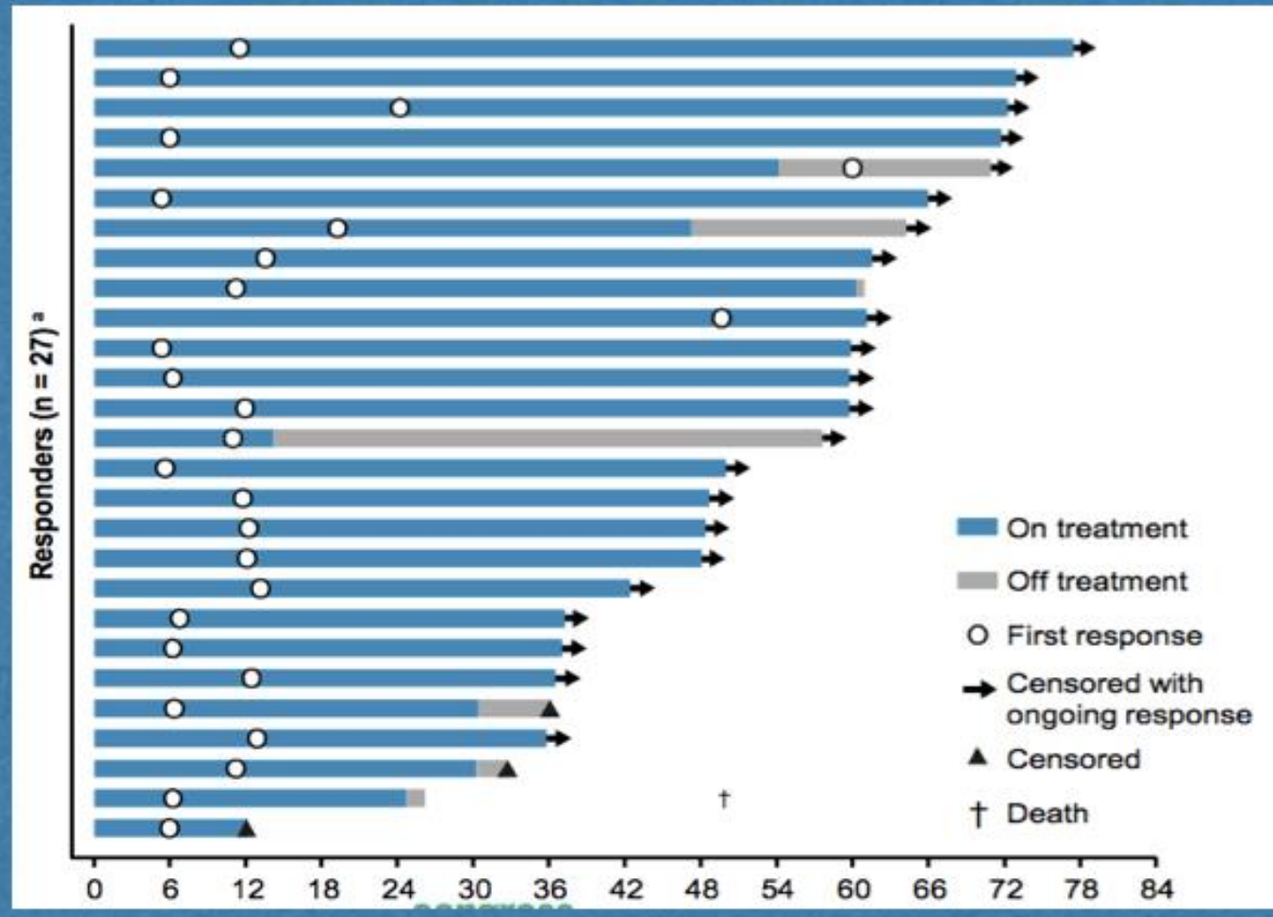
HIGH ORR: 60 % WITH 7 % CR

Median DOR not reached

HIGH RATE OF DISEASE CONTROL≧ 3 mo: 84 %

Most patients with reduction in tumor burden: 84 %





IMMUNOTHERAPY AND MSI-H mCRC

- **NCCN**

- **Recommends NIVO +/- IPI or PEMBRO as treatment options in patients with metastatic dMMR CRC in second or third line or for patients unfit for intensive therapy**

- **FIT FIRST LINE: AWAIT KEYNOTE 177 PHASE III RANDOMISED FOLFO+ bevacizumab VS PEMBRO**

IN BELGIUM ONLY MNP
TO BE DISCUSSED CASE BY CASE

OUTLINE

1) DURATION OF ADJUVANT CHEMOTHERAPY

2) IMMUNOTHERAPY AND mCRC

3) QUICK NEWS

A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7

ASCO 2018

Unicancer Prodige 7 trial design

Peritoneal carcinomatosis of colorectal origin

Surgery: complete surgical resection ≤ 1 mm

RANDOMIZE

1:1

- **with HIPEC**
- without HIPEC

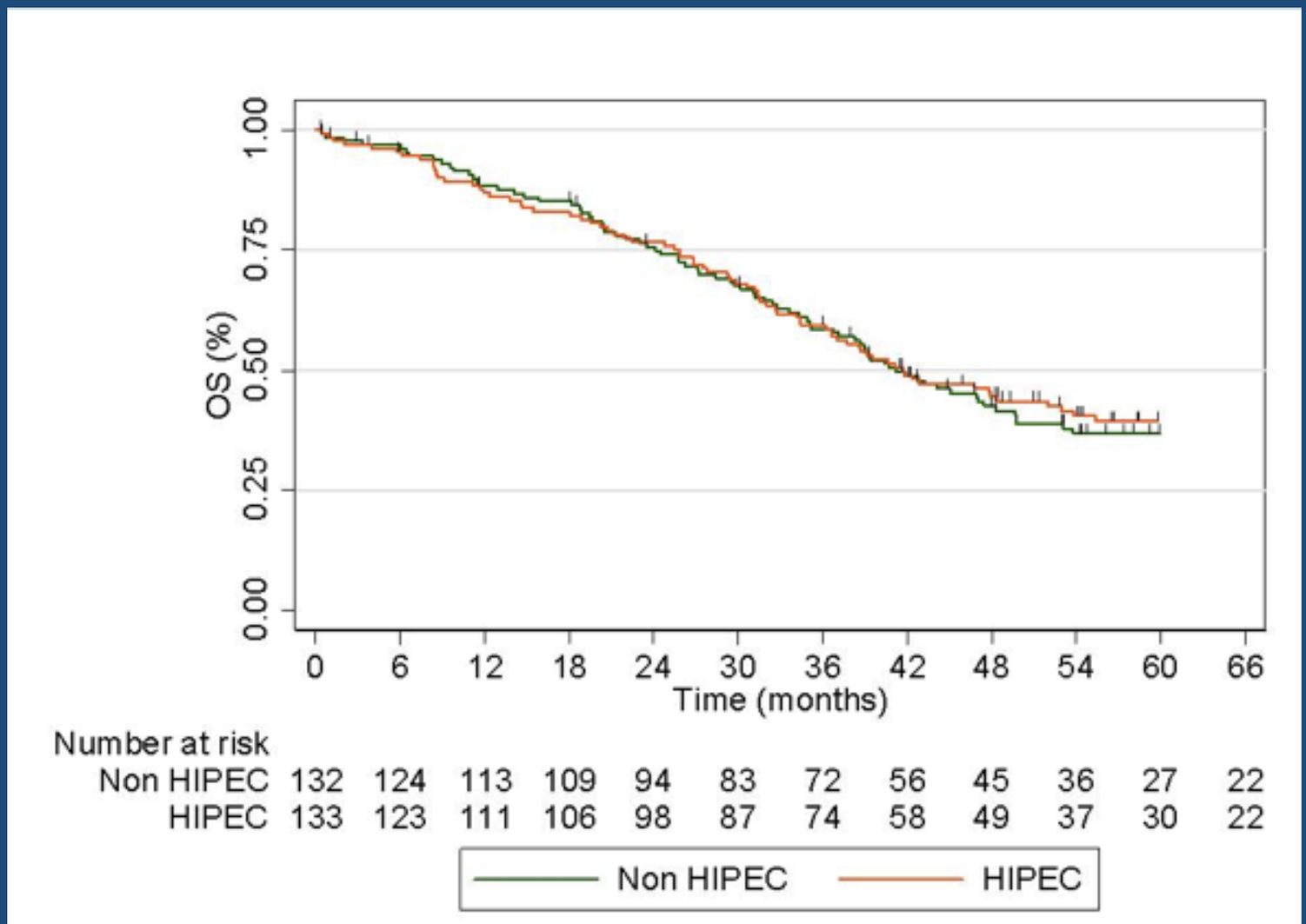
For both arms:

Patients received systemic chemotherapy for 6 months, either pre-operative, post-operative, or both

Stratification :

- Centre
- Residual tumor status (R0/R1 vs R2 ≤ 1 mm)
- Prior regimens of systemic chemotherapy
- Neoadjuvant Chemotherapy

ASCO 2018



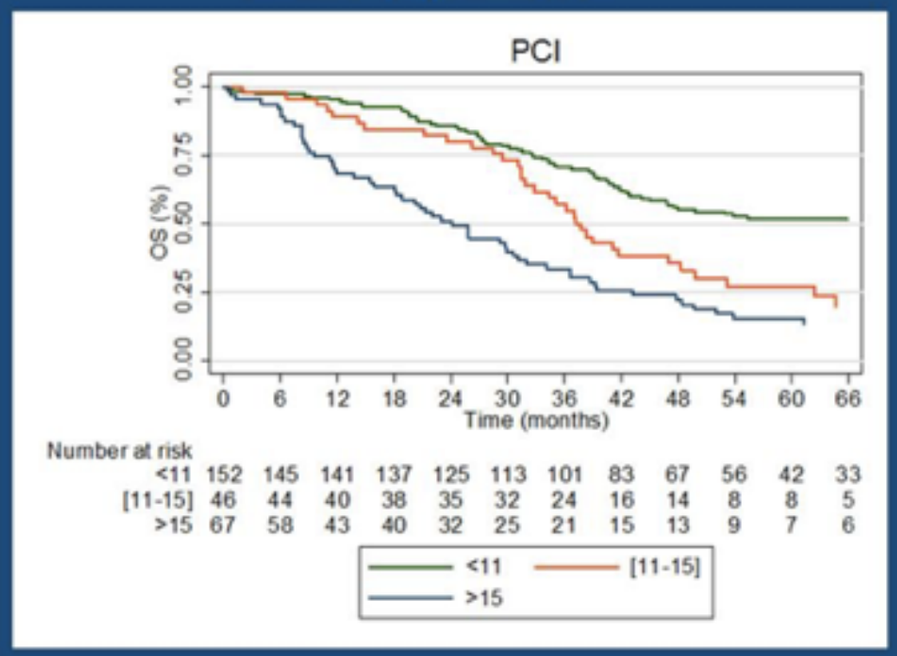
Median OS
HIPEC: 41,7 Mo
Non HIPEC 41,2 MO

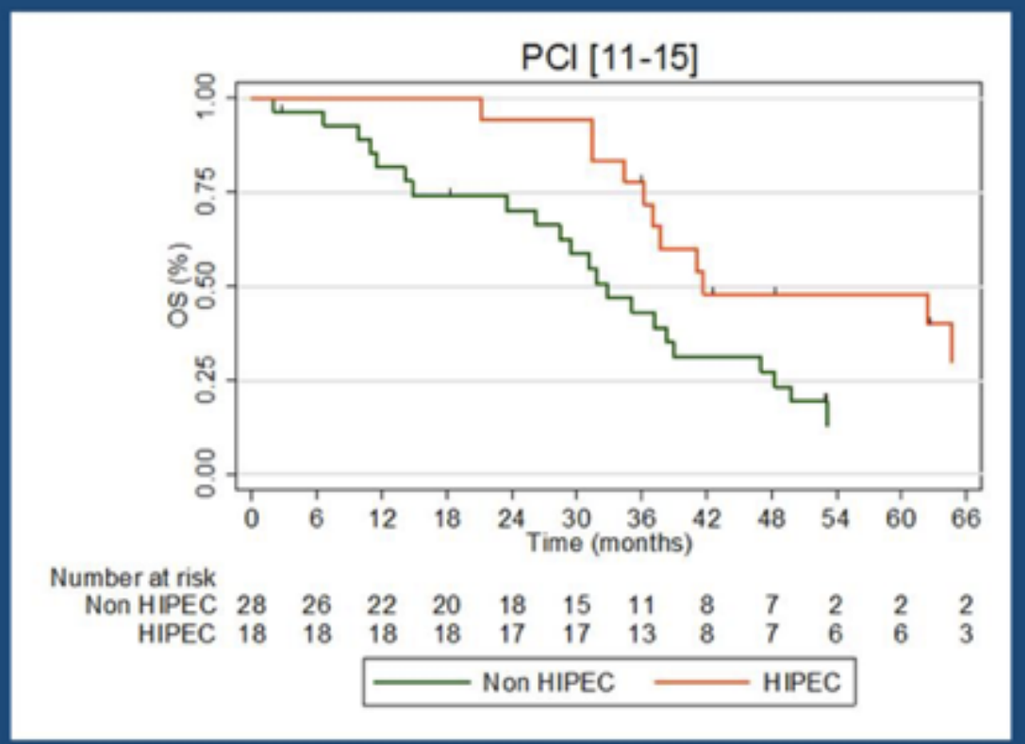
NCCN OCT 2018
HIPEC REMAINS VERY CONTROVERSIAL

ASCO 2018

Overall survival and PCI

Entire population





<11 HR= 1
[11-15] HR= 1.88 95%CI [1.25-2.88] p=0.003
16-24 HR= 3.57 95%CI [2.43-5.23] p<0.001

OS PCI [11-15]	HIPEC	Non-HIPEC	HR	P-value
Median Survival (months) [95% CI]	41.6 [36.1-nor reach]	32.7 [23.5-38.9]	0.437 [23.5-38.9]	0.0209

NO MORE HIPEC IN CRC
PERHAPS ONLY IF INTERMEDIATE PCI

ESMO 2018

DPYD genotype-guided dose individualization of fluoropyrimidine therapy:
A prospective safety and cost-analysis on *DPYD* variants *DPYD**2A, c.2846A>T, c.1679T>G and c.1236G>A

DPD deficiency is rare:3-15 % heterozygote and < 0,1 % homozygote

DPD deficiency is caused by genetic variants in gene encoding DPD (DPYD) but patients with deficiency may suffer from high toxicity even death

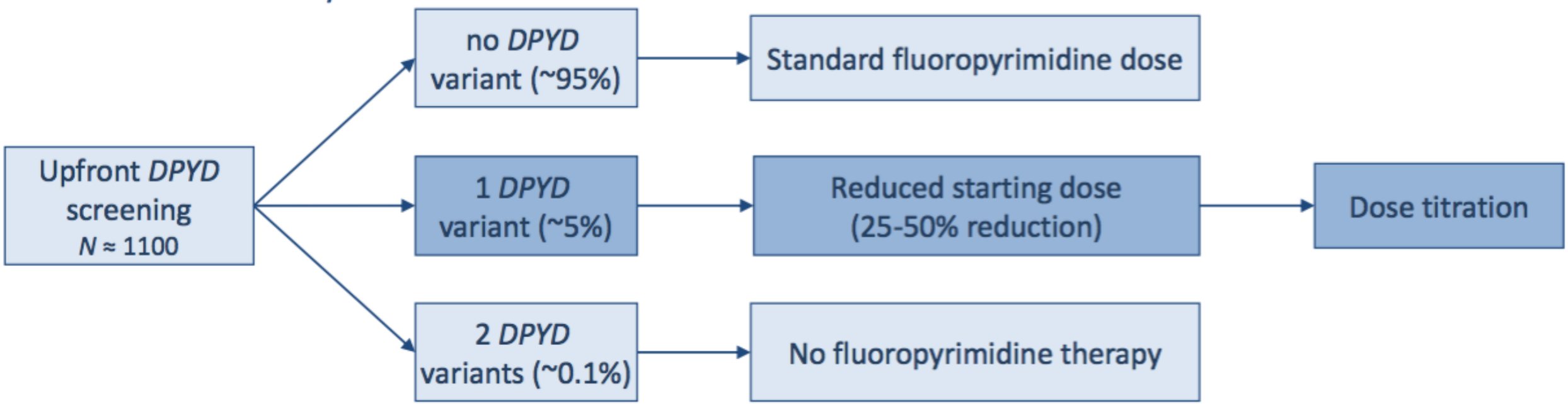
Genotyping of the 4 allenic variants of DPYD gene associated with reduction or complete loss of enzymatic function

Study overview

ESMO 2018

- Primary objective:
  - Determine if the risk of severe (grade ≥3) fluoropyrimidine-related toxicity is decreased by upfront *DPYD* genotyping and dose individualization of fluoropyrimidine treatment

- Secondary objectives:
  - Pharmacokinetic analysis
  - Cost-analysis



DPYD variants	AMOUNT OF DOSE REDUCTION
DPYD*2A	50 %
c.1679T>G	50 %
c.2846A>T	25 %
c.1236G>A	25 %

N=1103 included; 85 DPYD variants carriers
Dosage adapted and toxicity compared between wt and allenic variants

PRACTICE CHANGING ?
French TNCD,PAMM-EORTC group recommendation

ESMO 2018

Upfront *DPYD* genotyping improves patient safety with FLUOROPYRIMIDINE therapy

This strategy is feasible in routine clinical practice and cost saving

- **– For *DPYD**2A and c.1679T>G carriers, a 50% initial dose reduction is adequate**
- **– For c.1236G>A and c.2846A>T carriers, a larger dose reduction (instead of 25%) is advised**

THE LANCET Oncology

DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis

Advanced anal cancer
A RARE DISEASE WITH A NEW STANDARD

ESMO 2018

InterAACT Study Design

International multi-centre randomised phase II study

Stratified
PS- ECOG 0,1:2
HIV status +:-
Extent of disease LA:Met
Region UK:Aus:US:Europe

Advanced anal cancer

R

Carboplatin AUC5 D1
Paclitaxel 80mg/m²
D1,8,15
q=21 days

Cisplatin 60mg/m² D1
5FU 1000mg/m²D1-4
q=28 days

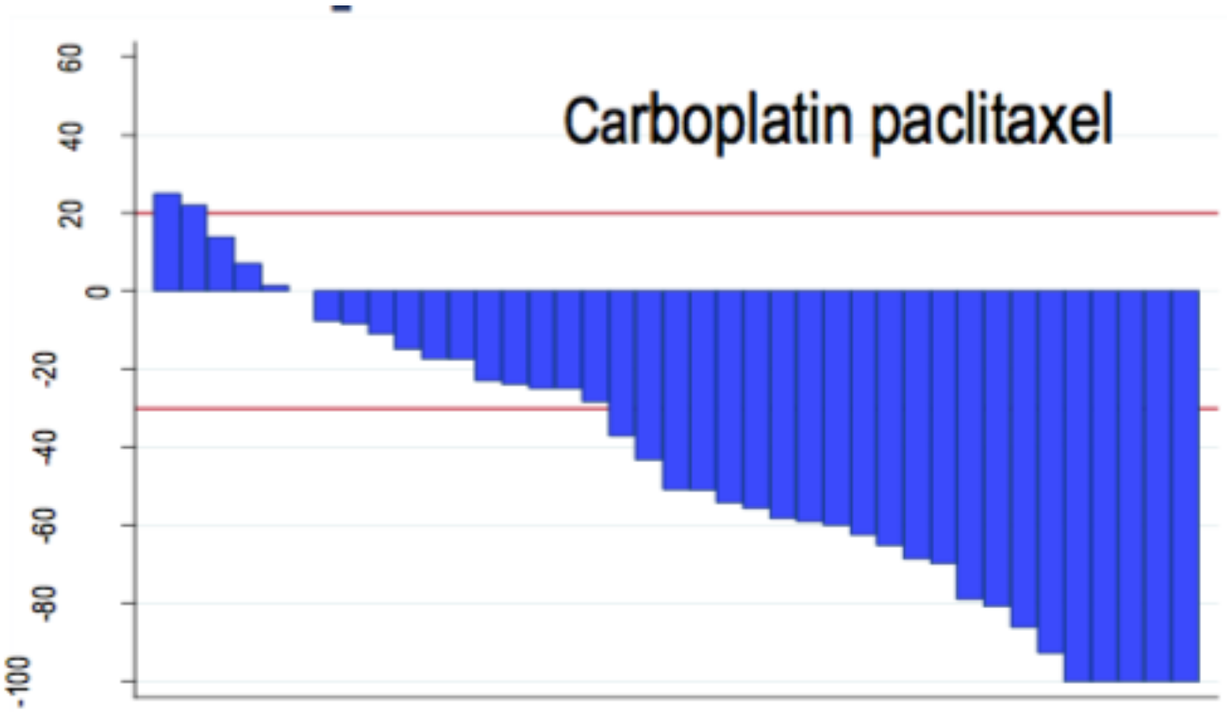
Planned N=90 R1:1

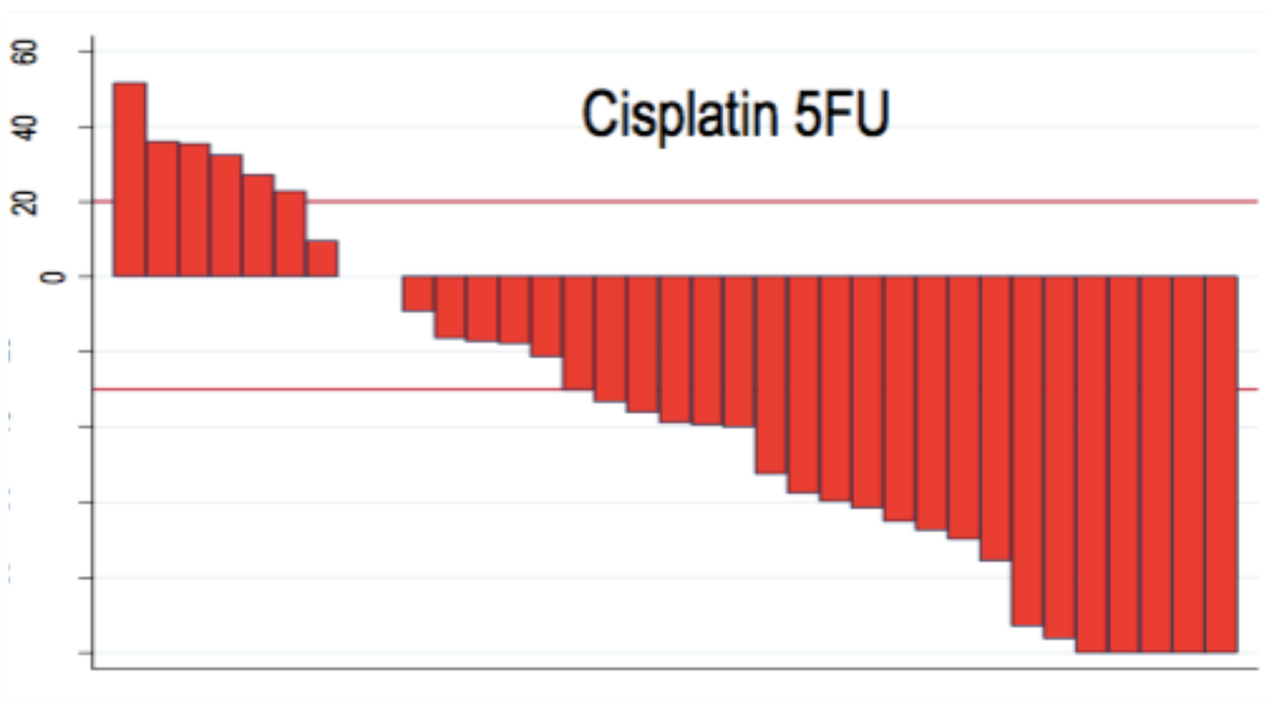
1 End Point ORR
2 End Point
- Feasibility of international study
- Toxicity, PFS, OS, DCR, QOL
- Exploratory biomarker analysis

RAO,ESMO 2018

PRIMARY: SAME ORR

ESMO 2018





LESS TOXICITY

TOXICITY GRADE≧ 3	CARBO/PACLITAXEL %	CISPLATINE/5FU %
MUCOSITIS	0	26
NAUSEA	2	17
SAES	36	62

SECONDARY: IMPROVED OS

ESMO 2018

PRACTICE CHANGING

MAY BE CONSIDERED AS NEW STANDARD FOR TREATMENT NAIVE ADVANCED ANAL CANCER

RAO,ESMO 2018

CONCLUSIONS: CRC SOME NEWS

- **DURATION OF ADJUVANT CHEMOTHERAPY with 3 MONTHS CAPOX IN LOW-RISK STAGE III COLON CANCER**

- **HIGH ORR (even CR) WITH IMMUNOTHERAPY IN MSI-H mCRC and duration of response ≧ 3 months in high number patients in all lines even first line**

- **HIPEC after surgical resection of peritoneal carcinomatosis remains controversial**

- **Advanced ANAL CANCER:PRACTICE CHANGING in favor of CARBO/PACLITAXEL**

- **MORE EVIDENCE FOR IMPLEMANTATION OF DPYD GENOTYPING when starting treatment with FLUOROPYRIMIDINE THERAPY**

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IDEA COLLABORATIVE TRIAL

ADJUVANT NEWS IN 2018

DFS = disease-free survival, HR = hazard ratio, CI = confidence interval

3 yr DFS rate (%) and HR by regimen and risk group		Regimen								
		CAPOX			FOLFOX			CAPOX/FOLFOX combined		
		3 yr DFS, % (95% CI)		*HR (95% CI)*	3 yr DFS, % (95% CI)		*HR (95% CI)*	3 yr DFS, % (95% CI)		*HR (95% CI)*
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	*0.85 (0.71-1.01)*	81.9 (80.2-83.6)	83.5 (81.9-85.1)	*1.10 (0.96-1.26)*	83.1 (81.8-84.4)	83.3 (82.1-84.6)	*1.01 (0.90-1.12)*
	High-risk (T4 and / or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	*1.02 (0.89-1.17)*	61.5 (58.9-64.1)	64.7 (62.2-67.3)	*1.20 (1.07-1.35)*	62.7 (60.8-64.4)	64.4 (62.6-66.4)	*1.12 (1.03-1.23)*
	Risk groups combined	75.9 (74.2-77.6)	74.8 (73.1-76.6)	*0.95 (0.85-1.06)*	73.6 (72.2-75.1)	76.0 (74.6-77.5)	*1.16 (1.06-1.26)*	P-value interaction test: Regimen: 0.0061 Risk group: 0.11		

Non-inferior | Not proven | Inferior

ASCO17 Q. Shi ; NEJM 2018 A. Grothey