
Verona, 14 Giugno 2019

# Colorectal Cancer: Poster Reviewer

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# Agenda

- Early-stage disease
- Hitting targets
- Immunotherapy
- Special Populations

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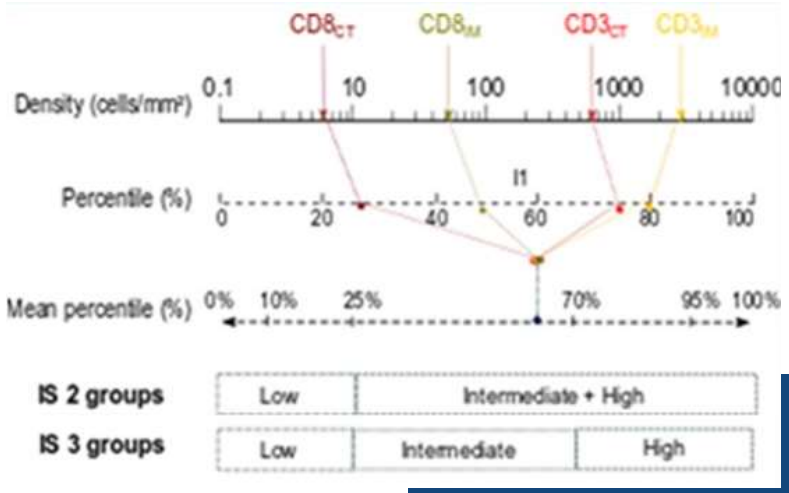
- Early-stage disease
  - #3513; #3519; #3518
- Hitting targets
- Immunotherapy
- Special Populations

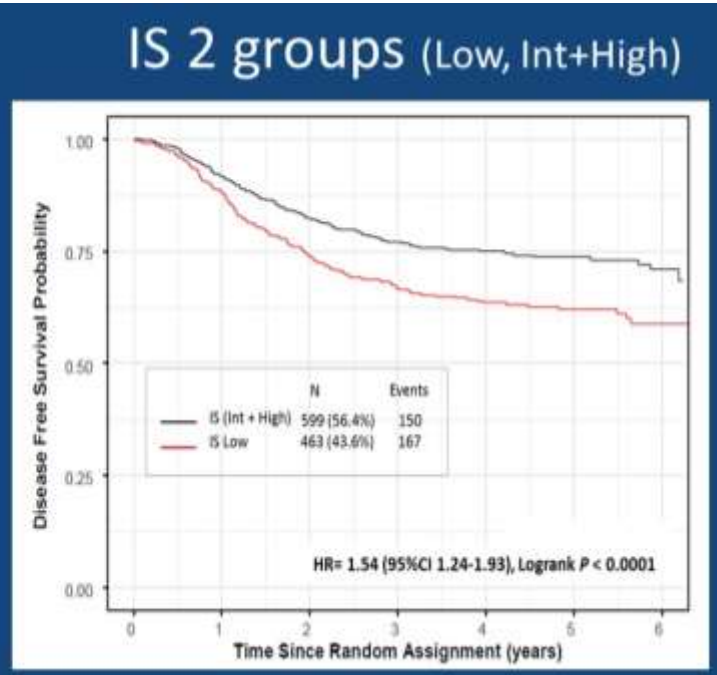
# #3513 IDEA France trial: Immunoscore®

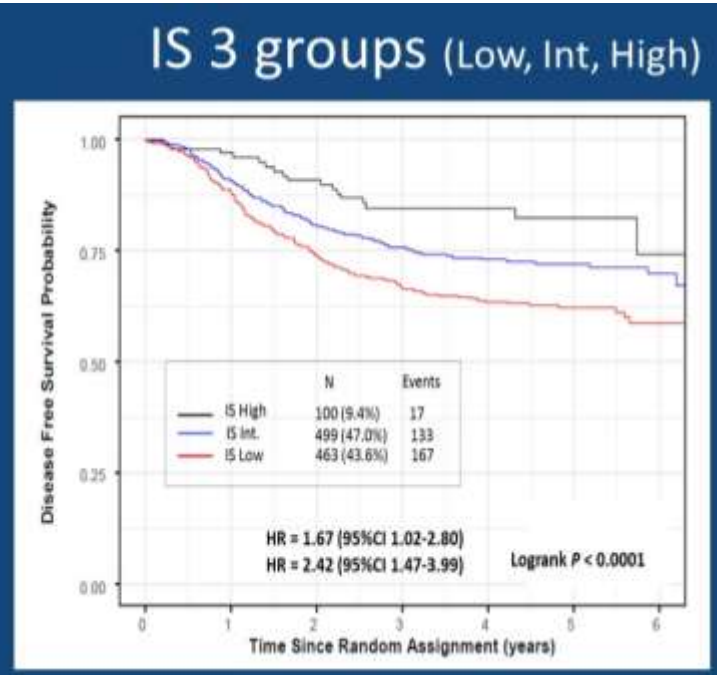



**1322 pts**

**DFS**

Primary objective




*Pages et al. #3513*

# #3513 IDEA France trial: Immunoscore®

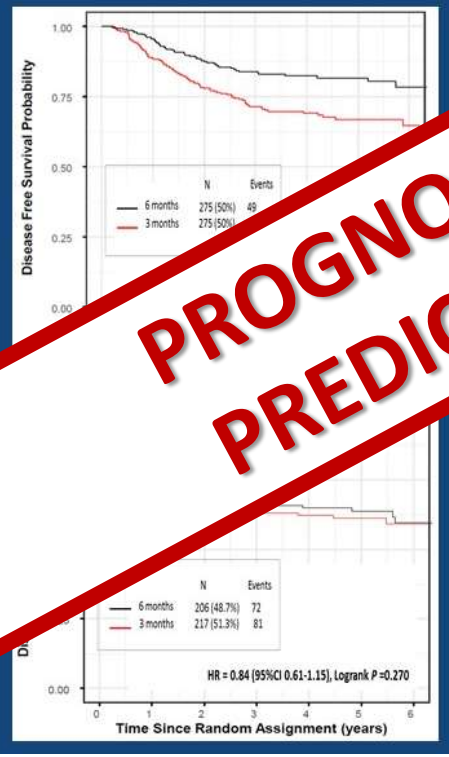
Patients with higher IS had a higher DFS with a longer duration of therapy, whereas the d n of therapy did not appear make a difference in the low IS group

6 months

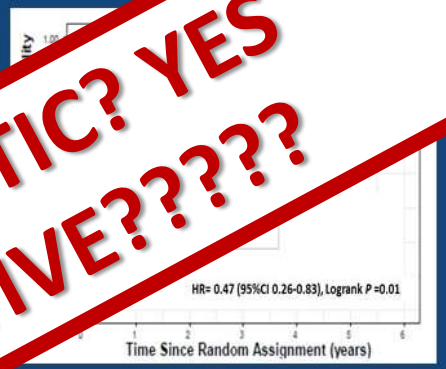
3 months

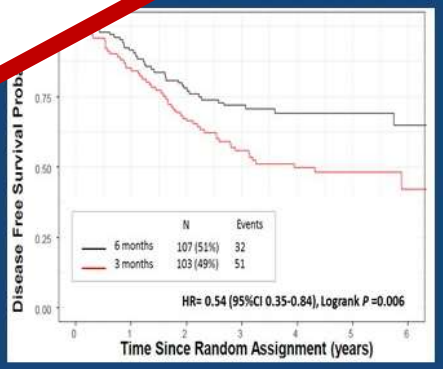
**IS** (Int + High)

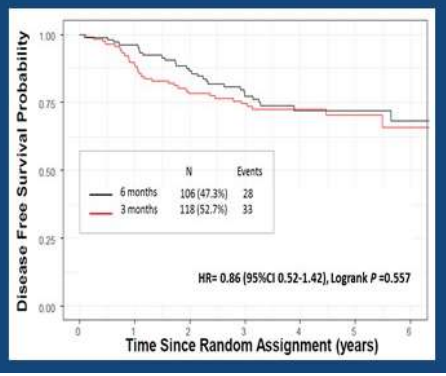
All patients

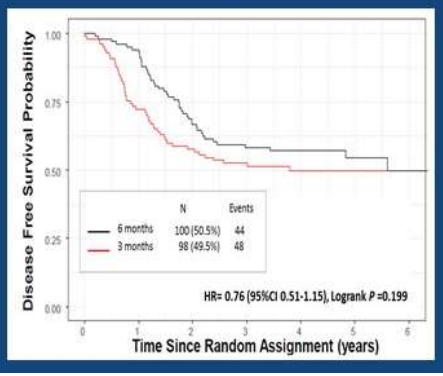



Low risk (T4 and/or N2)



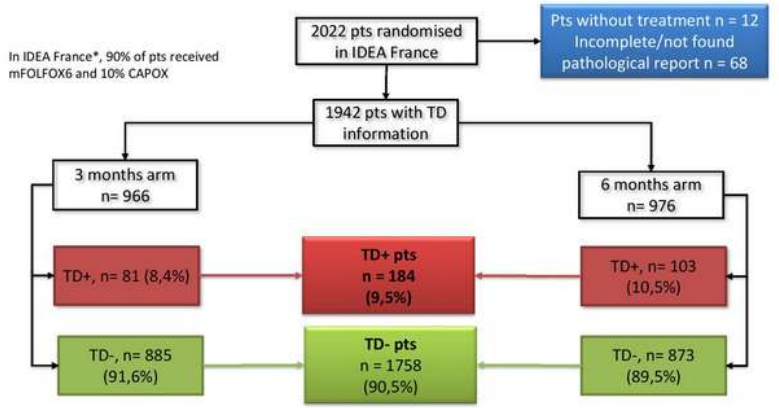




PROGNOSTIC? YES
PREDICTIVE????

*Pages et al. #3513*

# #3519 IDEA France trial: Tumor Deposits

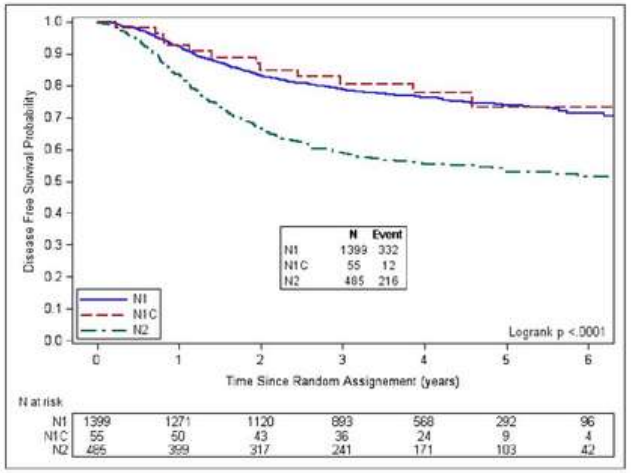
- **Tumor deposits (isolated tumor foci in the pericolic fat without residual lymph node tissue)**
  - occurs in approximately 20% of patients with colon cancer
  - are associated with poor outcome
- **In AJCC TNM 7 and 8 :**
  - **TD-positive tumors are classified N1c in the absence of lymph node metastases (LNM)**
  - **TD are not taken into account in the presence of a LNM**




***Delattre et al. #3519***

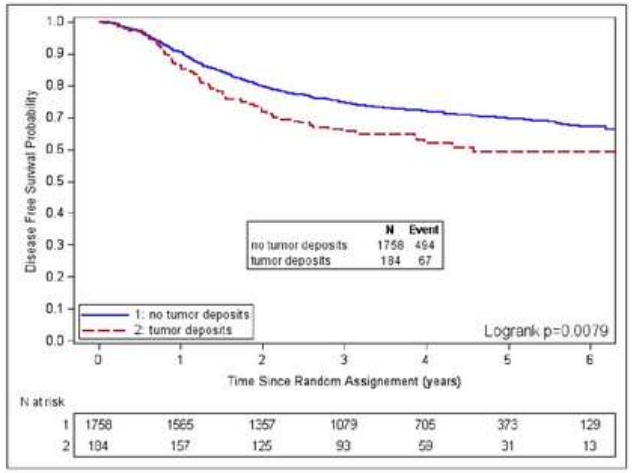
**TD+ CC patients had higher T stage, T/N stage and more frequently vascular or perineural invasion than TD- CC patients**

**N1c versus N1a/b vers N2 CC**



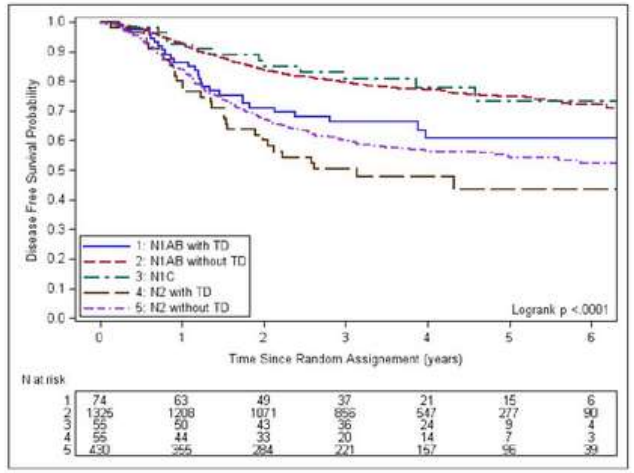

**No DFS difference between N1c and N1a/b CC patients**

**TD-positive *vs* TD-negative stage III CC**




**Significantly worse DFS in stage III patients with TD**

**Prognostic value of TDs according to pN stage**



# #3519 IDEA France trial: Tumor Deposits

## Restaging from low to high risk

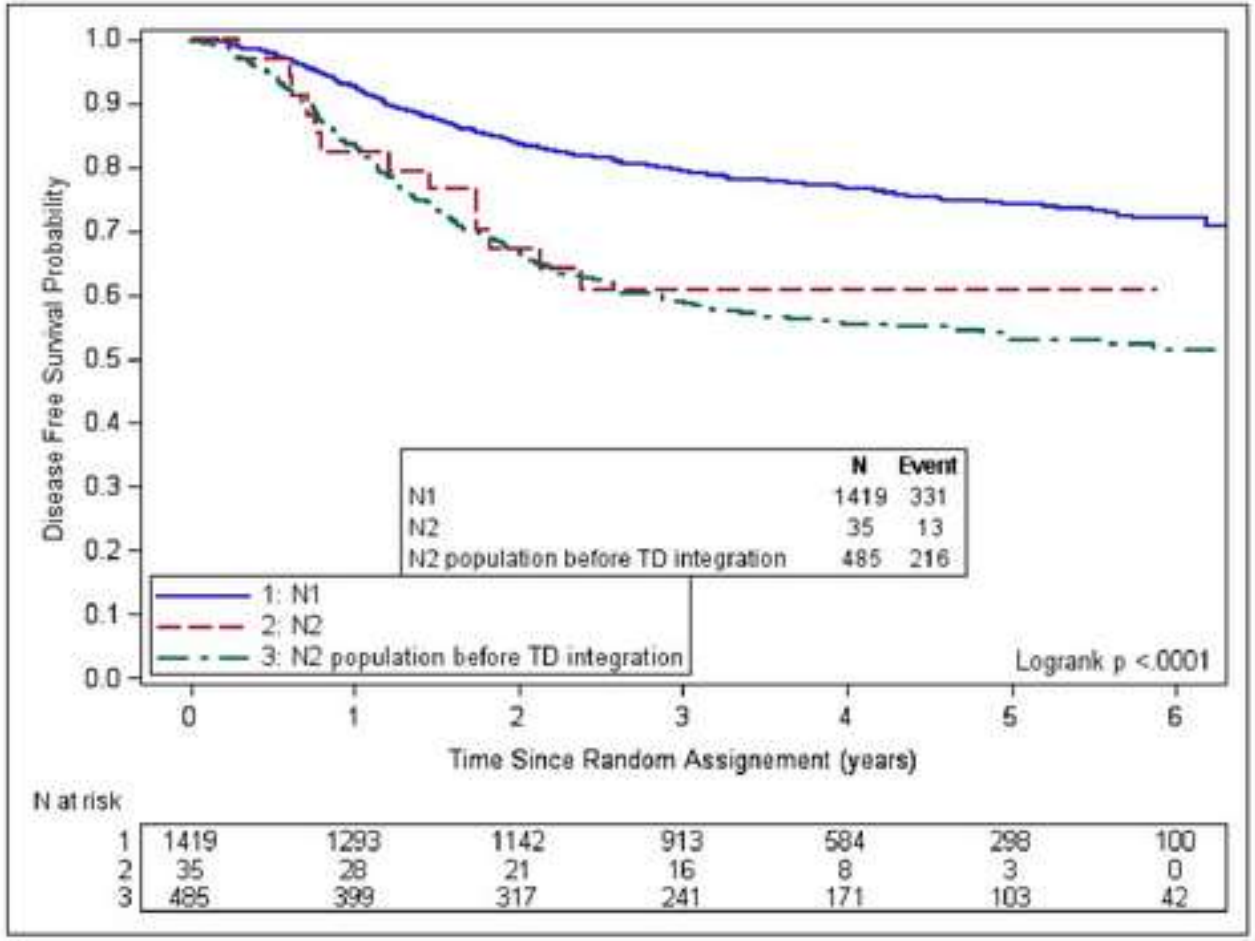
In TNM AJCC 7, the tumor is staged as N2 if LNM count ≥ 4.

Every TD was added to the LNM count in the N1 population.

**If the sum of LNM and TD* was equal or superior to 4, the patient was considered as « restaged N2 »**

*for the N1c population, CC with ≥ 4 TD were considered as "restaged N2"

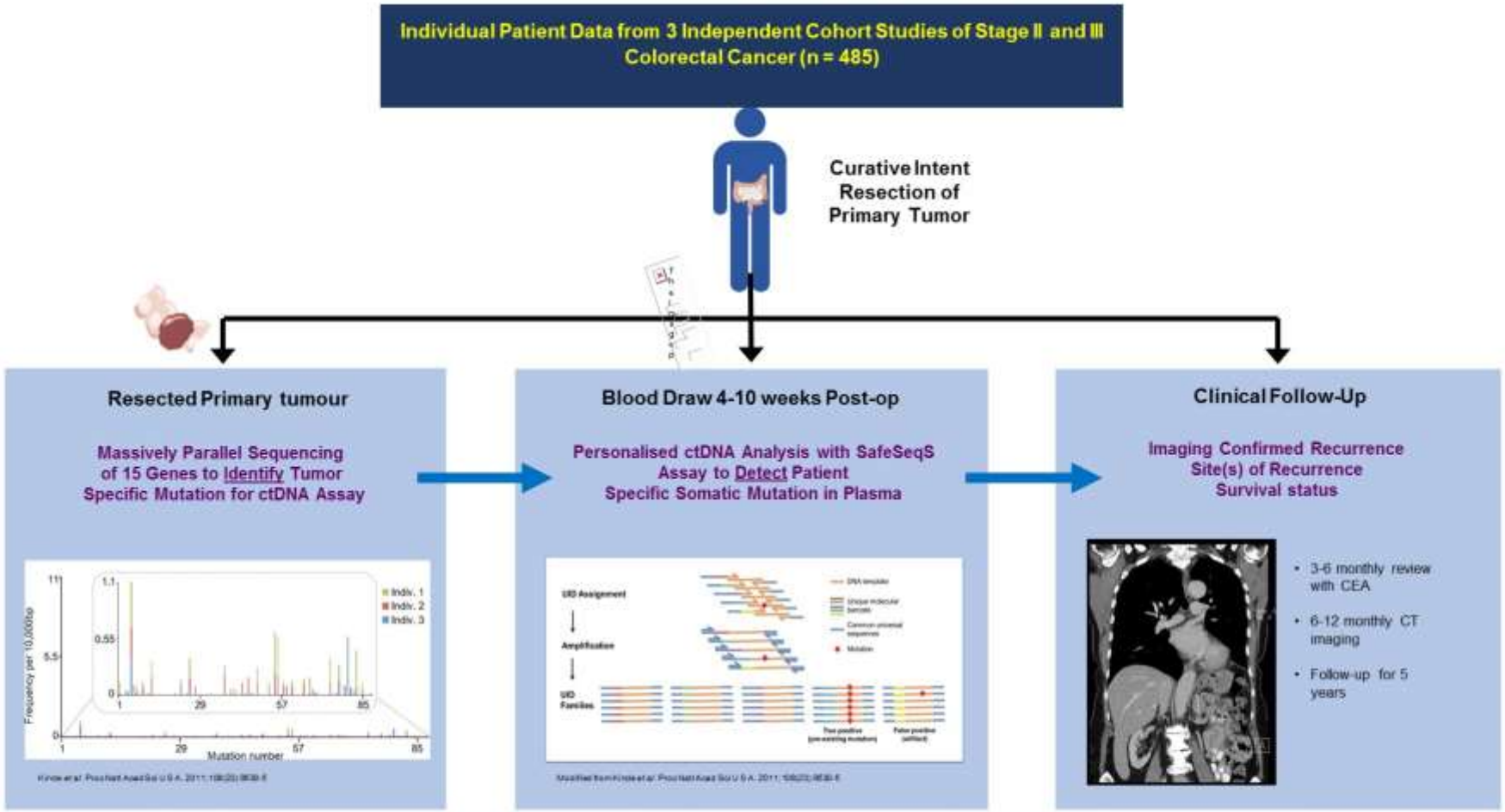
**A total of 35 pts (only 2.4% of the N1 population) were restaged from N1 to N2 by adding TDs to the LNM count**




- **TD are a major prognostic factor, both qualitatively and quantitatively.**
- TD should be considered in the evaluation of stage III colon cancer prognosis and **integrated to the LNM count** to help characterize high risk N1 patients.
- **Our results suggest that adding TD to the LNM count could reclassified some low risk CC as high risk, by restadifying them N2**, and therefore modify the optimal chemotherapy duration for those patients.
- **Further analysis in patients treated with CAPOX might be of great interest to address the issue of adjuvant treatment duration for TD-positive low-risk CC patients.**

*Delattre et al. #3519*

# #3518 ctDNA




**Combined analysis of 3 independent cohort studies to examine the prognostic significance of post-op ctDNA in stage II and III CRC**

*Tie et al. #3518*

# #3518 ctDNA: prognostic significance

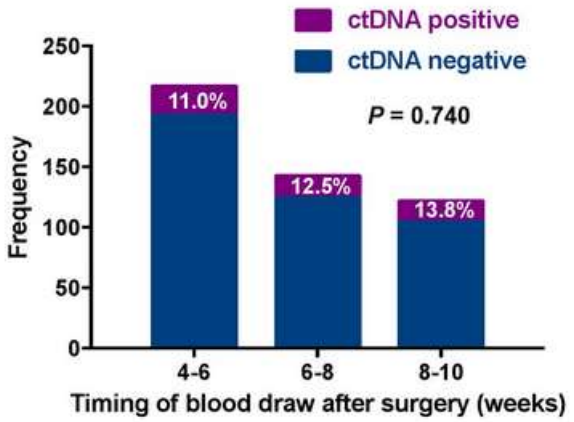



Figure 2. ctDNA detection rate (% positive test) according to the timing of blood draw after surgery. All blood draws were performed prior to any chemotherapy.

Median follow-up was 47.2 months; 249 (51%) patients received adjuvant chemotherapy

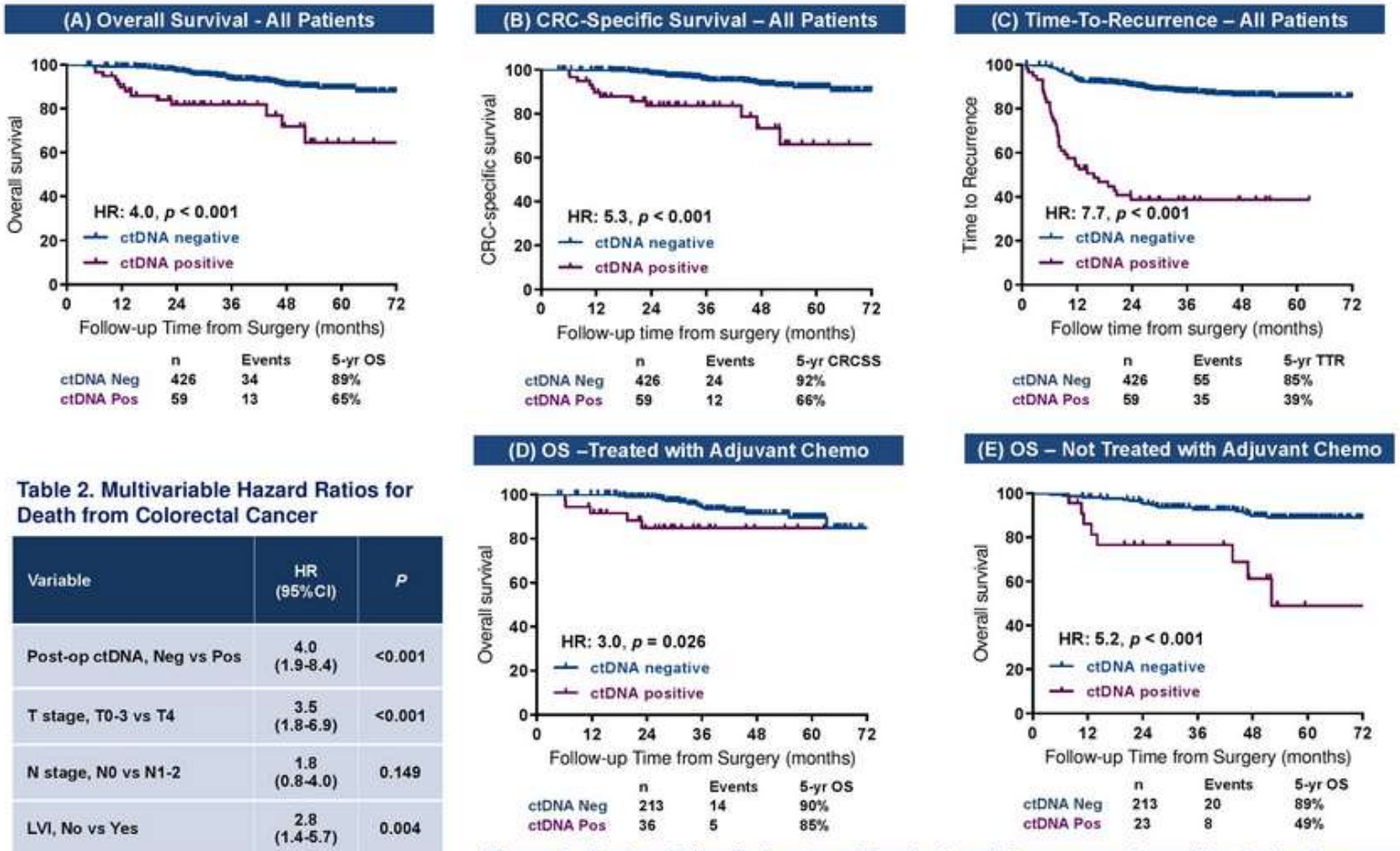



**Table 2. Multivariable Hazard Ratios for Death from Colorectal Cancer**

| Variable | HR (95%CI) | P |
|---|---|---|
| Post-op ctDNA, Neg vs Pos | 4.0 (1.9-8.4) | <0.001 |
| T stage, T0-3 vs T4 | 3.5 (1.8-6.9) | <0.001 |
| N stage, N0 vs N1-2 | 1.8 (0.8-4.0) | 0.149 |
| LVI, No vs Yes | 2.8 (1.4-5.7) | 0.004 |
| Age (continuous) | 1.04 (1.0-1.1) | 0.015 |

Figure 3. Kaplan–Meier Estimates of Survival and Recurrence According to the Presence or Absence of Post-Surgery ctDNA. (A) Overall Survival, (B) CRC-Specific Survival, (C) Time-to-Recurrence (TTR), (D) OS for patients treated with adjuvant chemotherapy, (E) OS for patients not treated with adjuvant chemotherapy

*Tie et al. #3518*

# #3518 ctDNA: role of MAF?

- Where samples for ctDNA analysis are collected 4 to 10 weeks post surgery, the timing of sample collection may not significantly impact detection rates. However, the numerical higher detection rate with a later blood draw needs to be considered when designing ctDNA-guided interventional clinical trials.
- Detection of ctDNA 4-10 weeks after surgery is associated with a significantly worse overall survival, CRC-specific survival and a shorter time to recurrence.
- While ctDNA status alone is a powerful prognostic factor, the prognostic significance of ctDNA detection may be further enhanced by analysis of the mutation allele frequency.
- There appears to be a clinical benefit from administering adjuvant chemotherapy regardless of mutation allele frequency.
- ctDNA analysis appears to be most sensitive for detecting minimal residual disease at distant sites.

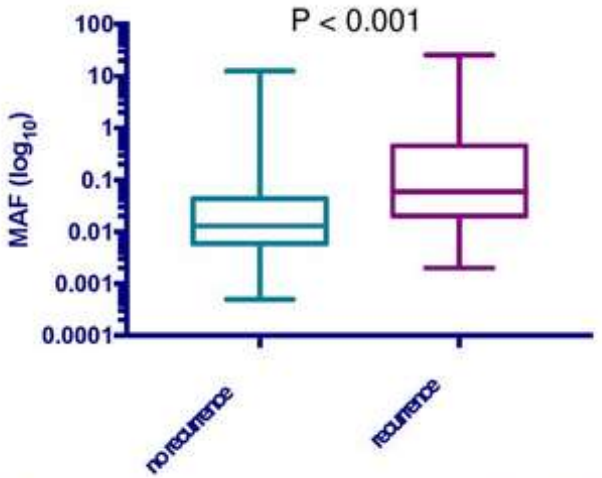



Figure 4. Box and whiskers plot of ctDNA MAF for ctDNA positive patients with or without recurrence. Groups are compared with Mann-Whitney test.

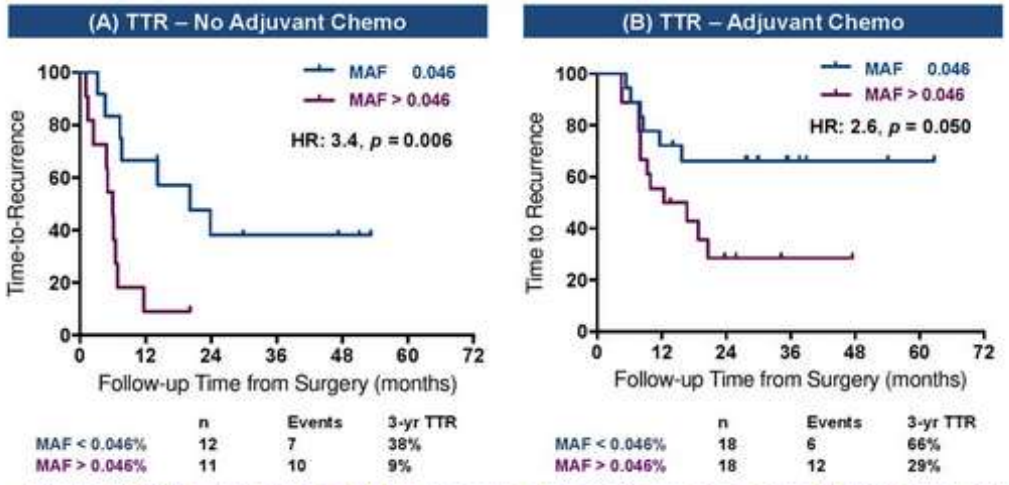



Figure 5. KM estimates of TTR according to post-surgery ctDNA MAF using the median MAF of 0.046% as cut-off in (A) patients not treated with adjuvant chemotherapy and (B) patients treated with adjuvant chemotherapy. Adjuvant chemotherapy administration appears to be associated with lower recurrence in both MAF sub-groups.

*Tie et al. #3518*

# Agenda

- Early-stage disease
- Hitting targets
  - #3509; #3511; #3526; #3527; #3580; #3538
- Immunotherapy
- Special Populations

# MGMT-deficiency

**Prevalence: ≈40%**

***MGMT***
**promoter hypermethylation/loss of IHC expression**

↓

**MGMT loss of expression**

↓

**Failure of repair of $O^6$-meG DNA adducts**

↓

**chemosensitivity to alkylating agents**

| Study | Schedule | N pts | ORR | PFS (months) |
|---|---|---|---|---|
| Amatu et al | DTIC 250 mg/m2/day d 1-4 q21d | 26 | 8% | 1.7 |
| Hochauser et al | TMZ 150 mg/m2/day d on/7 d off | 37 | 3% | / |
| Pietrantonio et al | TMZ 150 mg/m2/day d 1-5, q28d | 32 | 12% | 1.8 |
| Pietrantonio et al | TMZ 75 mg/m2/day d 1-21 q28d | 32 | 16% | 2.2 |
| Amatu et al | TMZ 200 mg/m2 d 1-5 q28 | 29 | 3% | 2.6 |
| Morano et al | TMZ 150 mg/m2 d 1-5 q28 IRINOTECAN 100 mg/m2 d 1, 15 q28 | 25 | 24% | 4.4 |

*Amatu et al, Clin Cancer Res 2013; Hochauser et al, Mol Can Ther 2013; Pietrantonio et al, Ann Oncol 2014; Pietrantonio et al, Target Oncol 2016;Amatu et al, Ann Oncol 2016; Morano et al, Ann Oncol 2018*

# #3509 CAPTEM trial

Figure 1. trial design

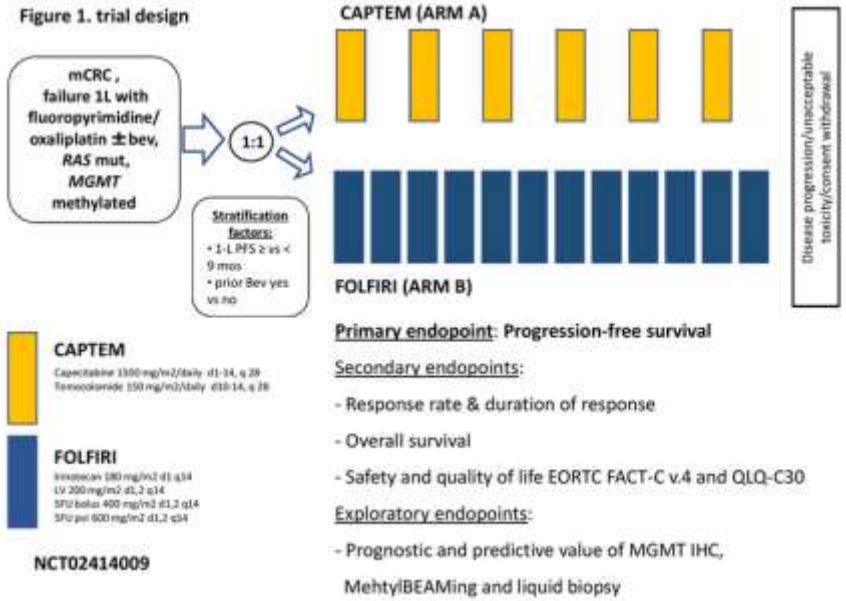
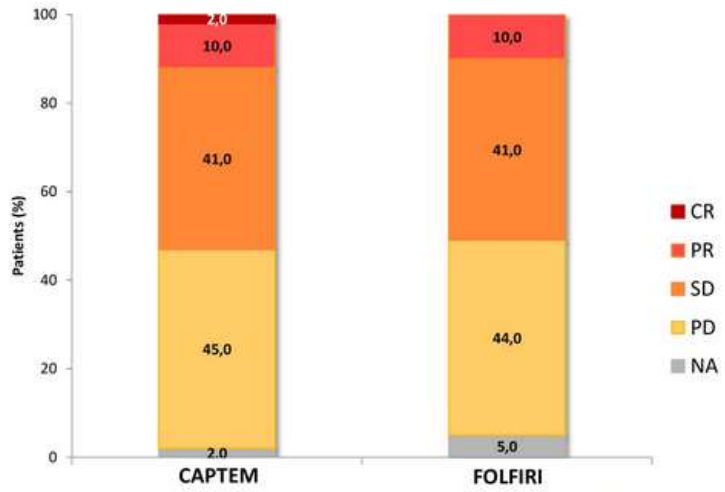



Fig 2. Best response according to RECIST v1.1 in ARM A vs ARM B




At a median follow up of 27.4 mos, 75 PFS/50 OS events were collected.
The median PFS in arm A vs B was 3.5 vs 3.7 mos (HR=1.23; 95%CI: 0.78-1.95; p=0.372; Fig. 3)
The median OS in arm A vs B was 14.8 vs 14.0 mos (HR=0.92; 95% CI: 0.52-1.63; p=0.782; Fig. 4).

Fig 3. Kaplan-Meier curves for PFS in ARM A vs ARM B

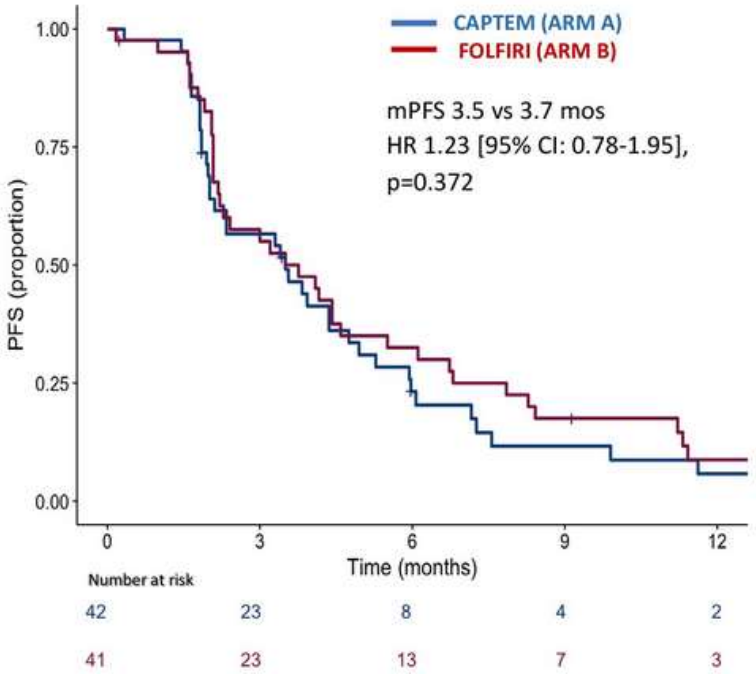
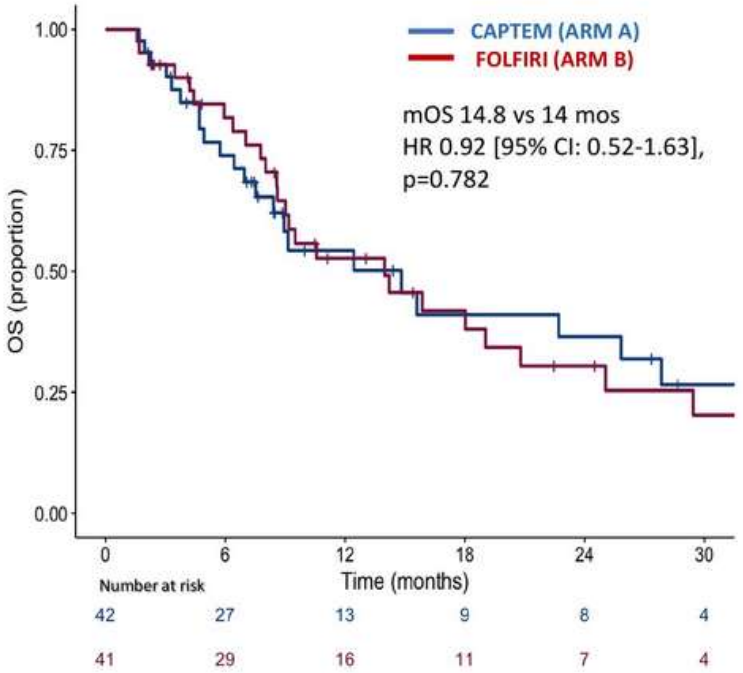



Fig 4. Kaplan- Meier curves for OS in ARM A vs ARM B




*Pietrantonio et al. #3509*

# #3509 CAPTEM trial: negative but..

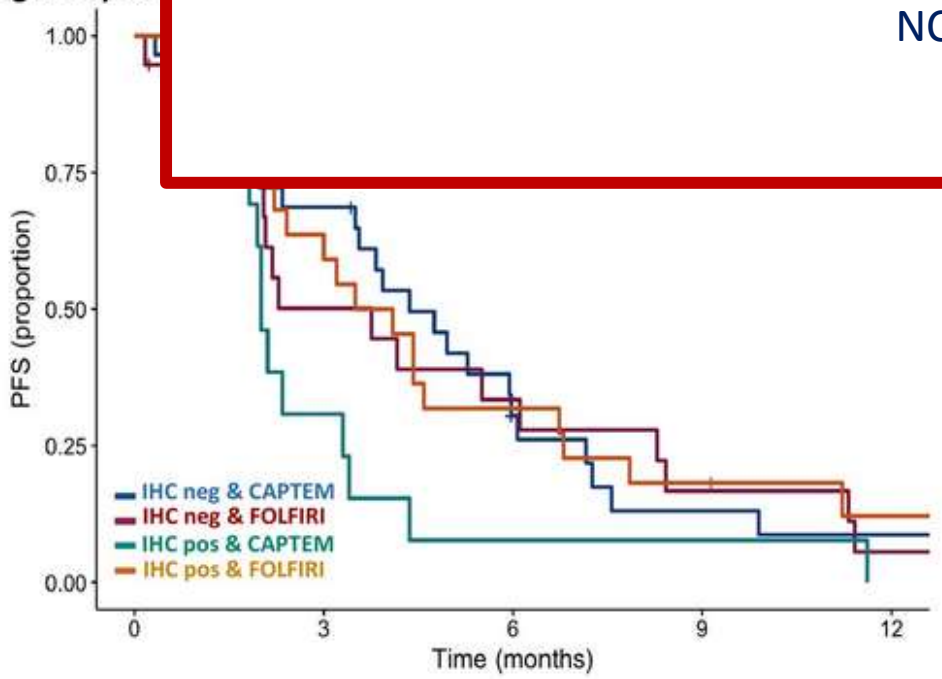
Overall, MGMT IHC status was not prognostic for PFS (p=0.532) and OS (p=0.436).
In the **MGMT IHC positive subgroup** (n = 49), mPFS in arm A vs arm B: 2.0 vs 3.8 mos; HR=2.22 [1.07-4.58], p=0.031), a
In the MG
1.86], p=0.
No signific

**TRIAL IN PROGRESS:**

**NIVOLUMAB Plus IPILIMUMAB and TEMOZOLOMIDE in Microsatellite Stable, MGMT Silenced Metastatic Colorectal Cancer (MAYA)**

NCT03832621

**Fig 5. Kaplan**

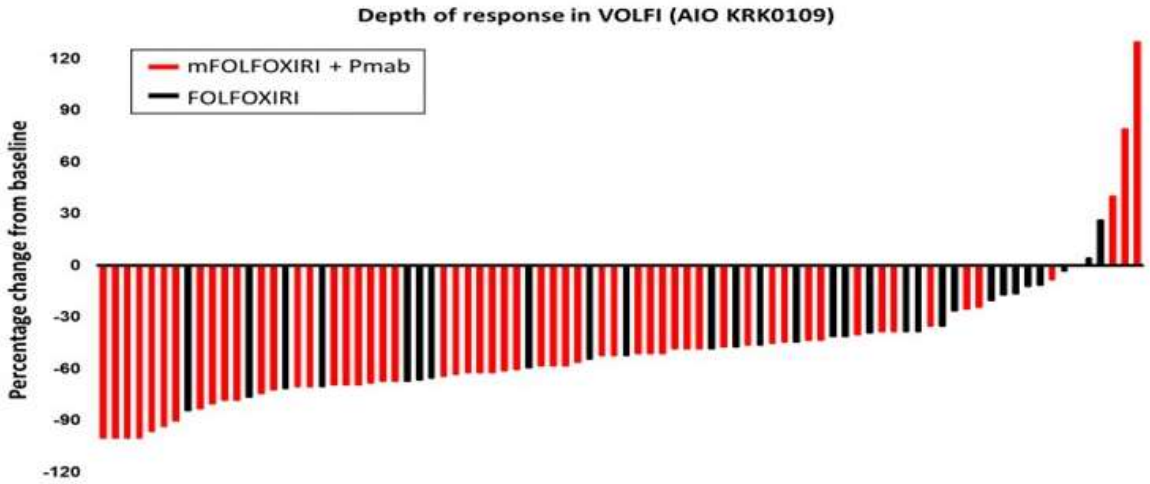



| Tab 3. mPFS according MGMT IHC | IHC positive | | IHC negative | |
|---|---|---|---|---|
| | CAPTEM | FOLFIRI | CAPTEM | FOLFIRI |
| Median PFS, mPFS | 2.0 | 3.8 | 4.4 | 3.8 |
| | HR 2.22 [1.07-4.58], *p*=0.031 | | HR 1.00 [0.53-1.86], *p*=0.99 | |

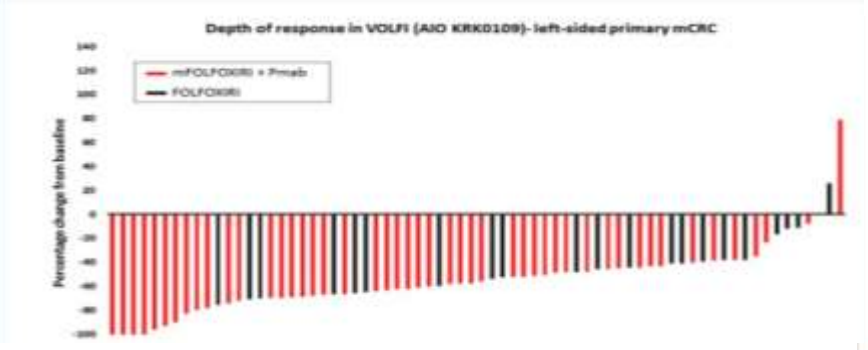
*Pietrantonio et al. #3509*

# #3511 VOLFI trial: final results

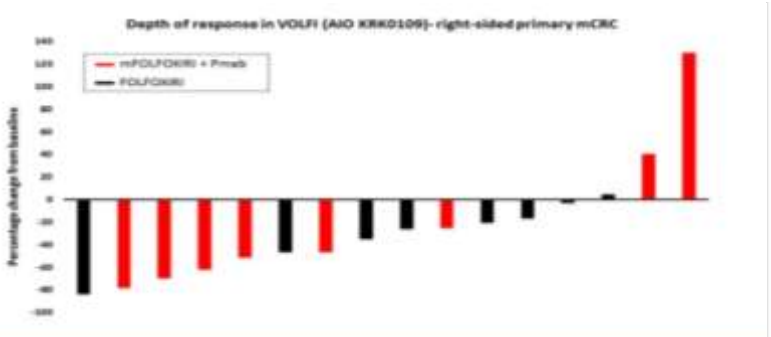

## All Patients



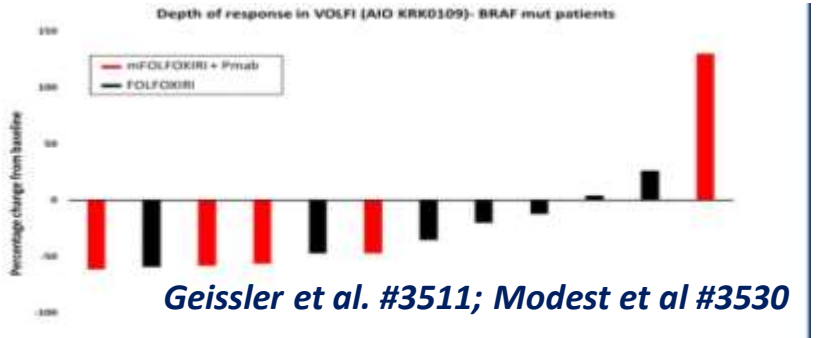

## Left sided




## Right sided



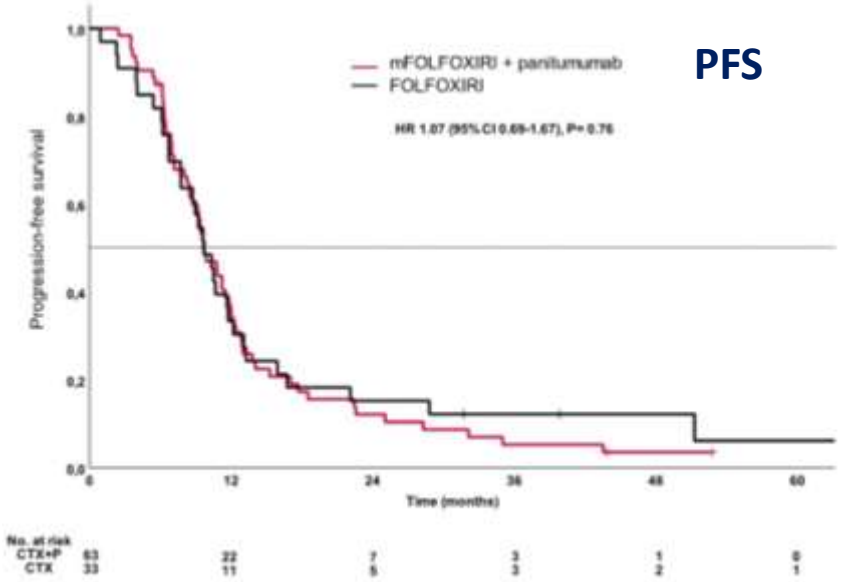

## BRAF mutants



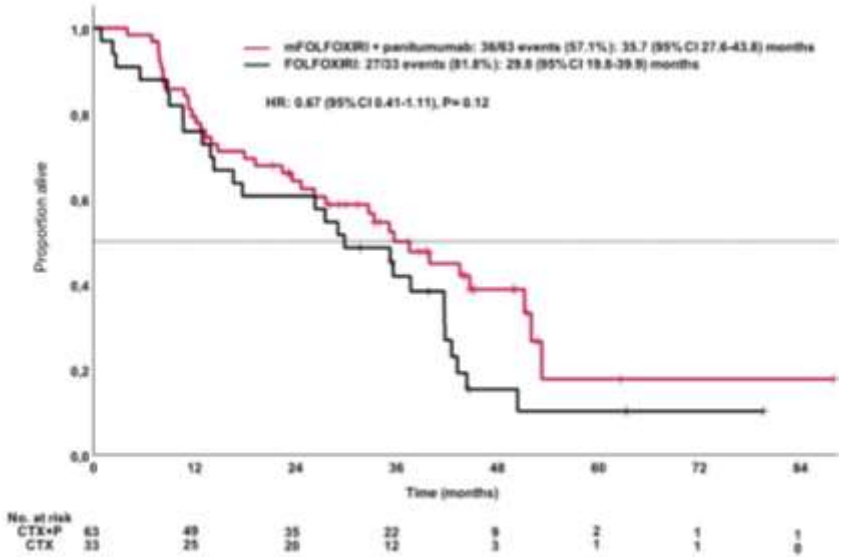

*Geissler et al. #3511; Modest et al #3530*

# #3511 VOLFI trial: final results

**PFS**




**OS**




- The trial met its primary endpoint, but failed its secondary endpoints of PFS and OS
- Impressive depth of response observed
- BRAF mutated?

*Geissler et al. #3511*

# #3580 EPIC trial:

**Figure 2. OS in the *RAS* wt population of EPIC**

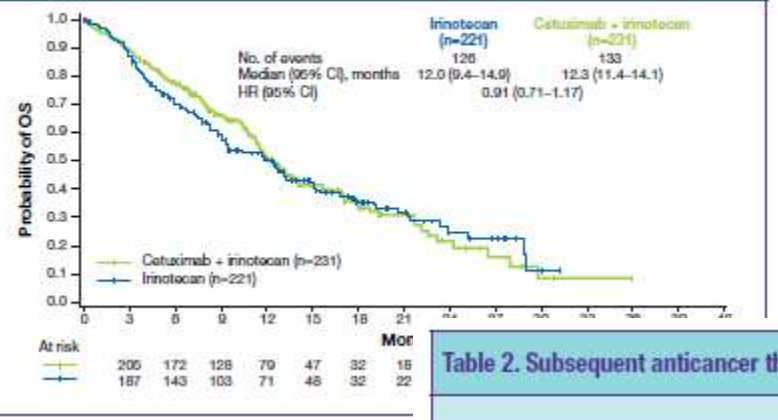
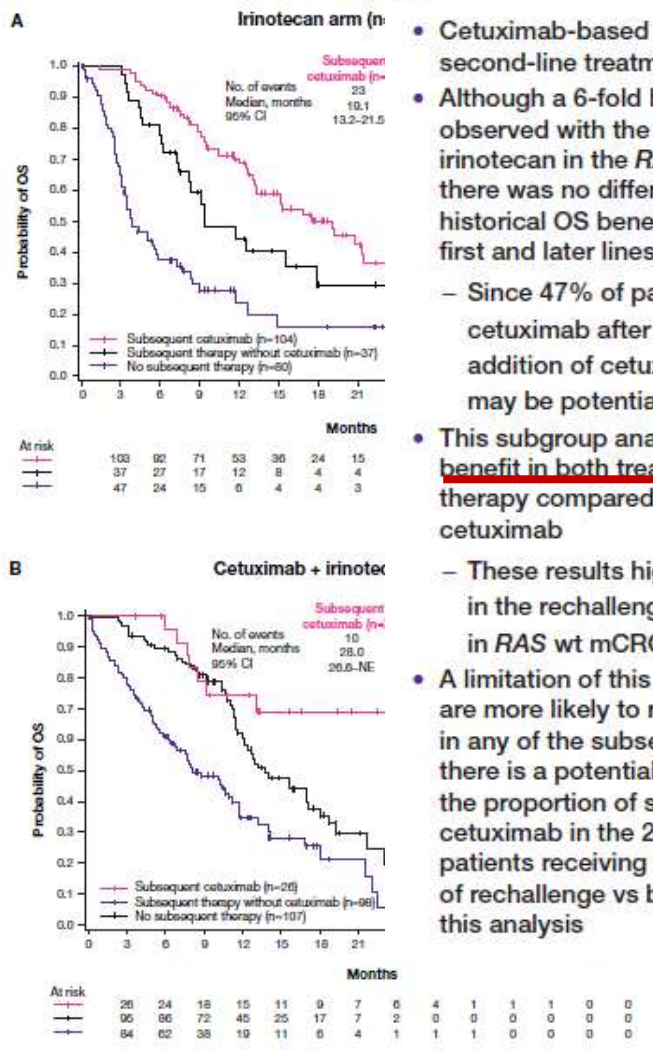



**Table 2. Subsequent anticancer therapies received**

| | Irinotecan n=221, n (%) | Cetuximab + irinotecan n=231, n (%) |
|---|---|---|
| **Subsequent systemic anticancer therapy** | | |
| Any therapy | 141 (63.8) | 124 (53.7) |
| No therapy | 80 (36.2) | 107 (46.3) |
| With cetuximab | 104 (47.1) | 26 (11.3) |
| Without cetuximab | 37 (16.7) | 98 (42.4) |
| *Most common anticancer drugs** | | |
| Irinotecan | 106 (48.0) | 36 (15.6) |
| Fluorouracil | 47 (21.3) | 49 (21.2) |
| Capecitabine | 35 (15.8) | 50 (21.6) |
| Folinic acid | 34 (15.4) | 37 (16.0) |
| Bevacizumab | 31 (14.0) | 36 (15.6) |
| Oxaliplatin | 23 (10.4) | 36 (15.6) |
| Mitomycin | 20 (9.0) | 28 (12.1) |
| **Reason for first subsequent anticancer regimen after EPIC** | | |
| Clinical deterioration without progression | 2 (0.9) | 1 (0.4) |
| Documented disease progression | 133 (60.2) | 112 (48.5) |
| Maintenance therapy without progression | 4 (1.8) | 11 (4.8) |
| Other | 2 (0.9) | 0 |

* Other than cetuximab; in ≥10% of patients in either arm.

**Figure 3. OS by subsequent therapy in the *RAS* wt population of EPIC**




- Cetuximab-based therapy is suitable as a standard, second-line treatment for patients with *RAS* wt mCRC
- Although a 6-fold higher ORR and 2-fold longer PFS were observed with the addition of cetuximab to second-line irinotecan in the *RAS* wt population of the EPIC study, there was no difference in OS, which is in contrast to the historical OS benefit afforded by cetuximab therapy in the first and later lines of therapy in *RAS* wt mCRC
  - Since 47% of patients in the control arm received cetuximab after the study, the lack of OS benefit of the addition of cetuximab to irinotecan in the EPIC study may be potentially attributed to post-study crossover
- This subgroup analysis suggests an increased survival benefit in both treatment arms with post-study cetuximab therapy compared with post-study therapy without cetuximab
  - These results highlight the potential value of cetuximab in the rechallenge setting as well as beyond progression in *RAS* wt mCRC
- A limitation of this analysis is that patients who live longer are more likely to receive cetuximab and other therapies in any of the subsequent treatment lines. Furthermore, there is a potential bias on OS due to the differences in the proportion of subsequent therapies with and without cetuximab in the 2 treatment arms. Finally, the ratio of patients receiving cetuximab-based therapy in the setting of rechallenge vs beyond progression was not captured in this analysis

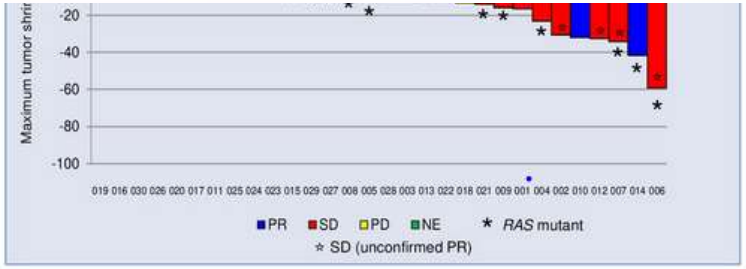
*Sobrero et al. #3580*

# #3538 Lenvatinib and #3527 Apatinib

Table 3. Tumor responses

| | Investigator review (N = 30) | Central review (N = 30) |
|---|---|---|
| CR | 0 | 0 |
| PR | 1 | 2 |
| SD | 20 | 19 |
| PD | 7 | 7 |
| NE | 2 | 2 |
| DCR (90% CI) | 70.0% (53.5-83.4) | 70.0% (53.5-83.4) |

- ✓ Lenvatinib showed promising antitumor activity with acceptable toxicity for heavily pretreated patients with mCRC after failure of standard chemotherapies.
- ✓ No unexpected safety signals were observed and toxicities were manageable with dose modification, interruptions, and supportive medications.




*Shoji et al. #3538*

**mCRC**
**2L→**
**ECOG 0-2**

**Apatinib 500 mg qd**

**q28 until PD**

- ✓ Apatinib monotherapy showed promising efficay and manageble toxicities.
- ✓ Phase III trial is warranted.

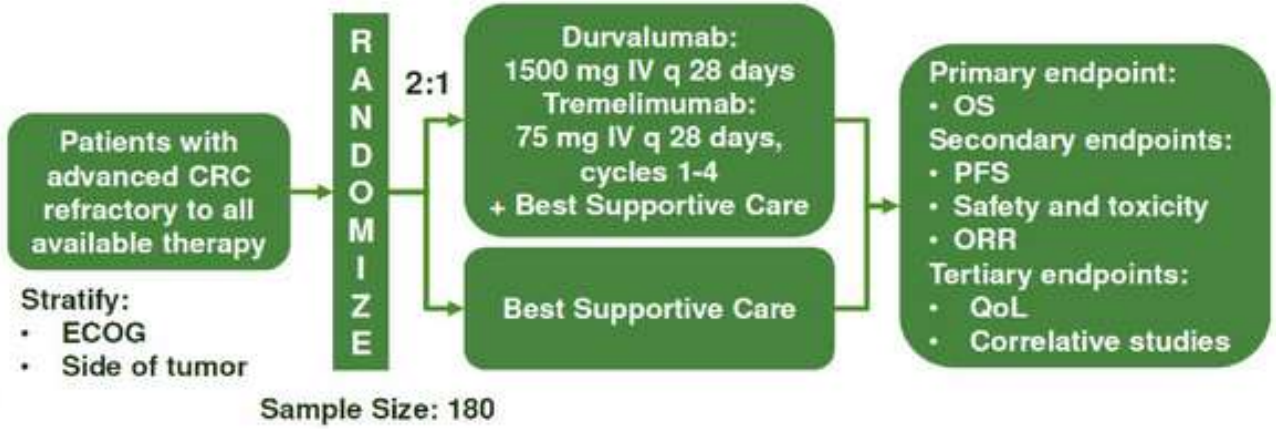
| | |
|---|---|
| DCR | 26 (60.4%) |
| mPFS | 4.7 mo (95% CI 3.7-5.9) |
| mOS | 9.7 mo (95% CI 5.9-13.6) |

*Wang et al. #3527*

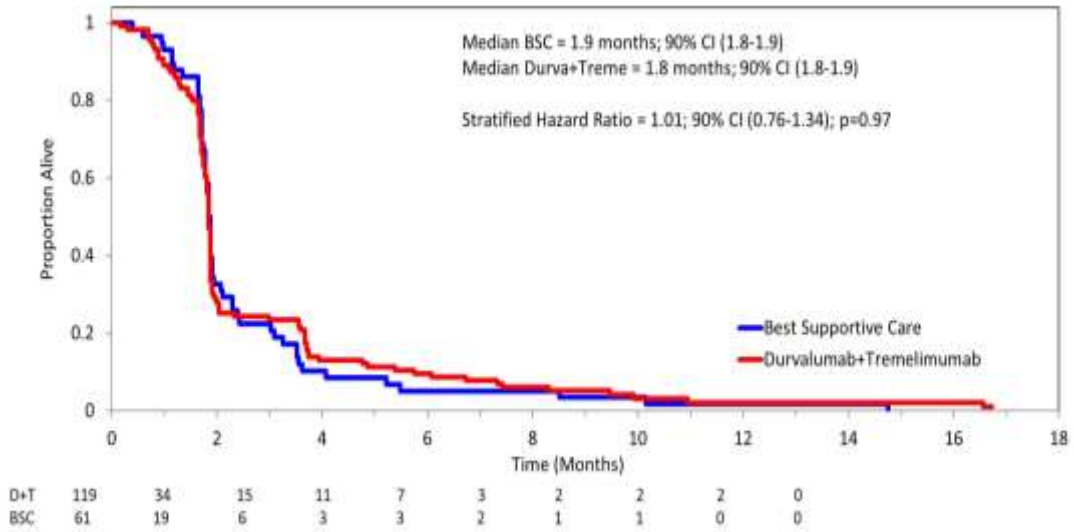
# Agenda

- Early-stage disease
- Hitting targets
- Immunotherapy
  - #3512; #3514; #2522; #3521
- Special Populations

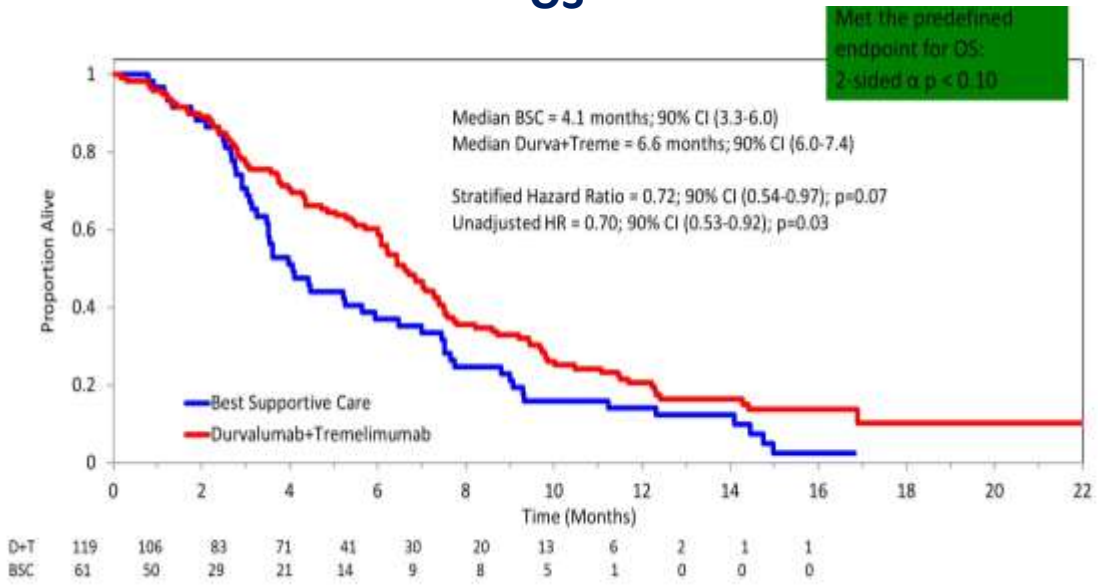
# #3512 CCTG CO.26 trial




## PFS



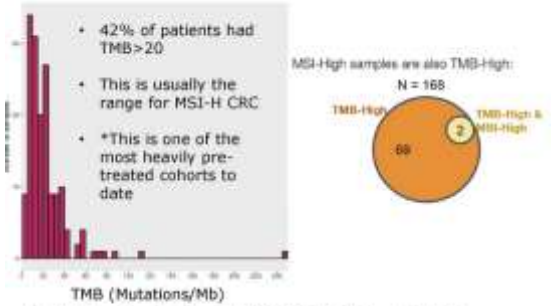

## OS




*Chen et al. #3512*

# #3512 CCTG CO.26 trial: TMB

**Figure 4. Tumor mutation burden (TMB)**




- Excluding 2 patients with MSI-H (247.1 and 74.4)
- TMB in MSS patients:
  - Mean: 20.4 ± 16.3 mts/Mb
  - Range: 0.96 – 114.0

**igure 5. Overall survival for pts in the BSC arm by TMB**

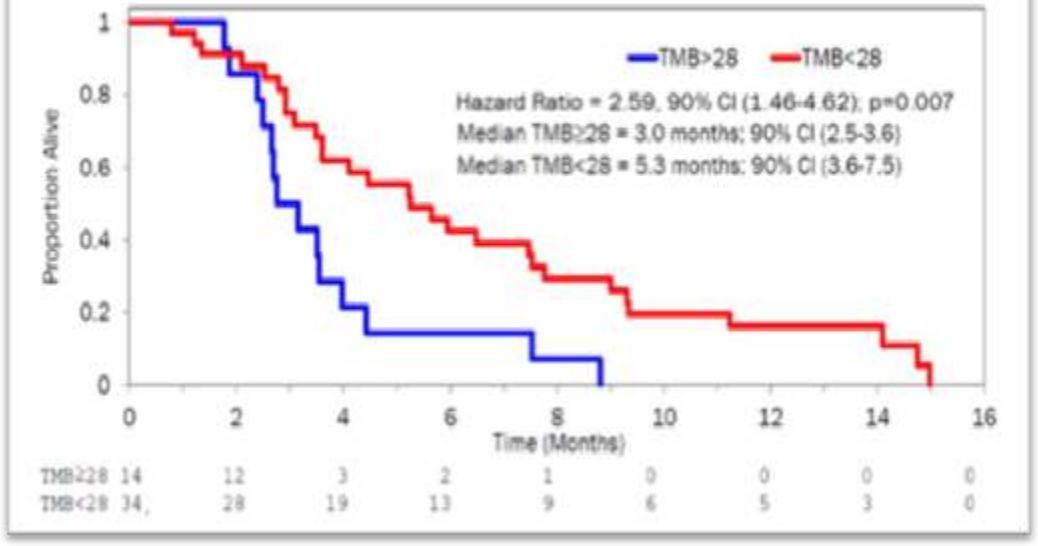



**Figure 6. Overall survival for pts with TMB ≥ 28**

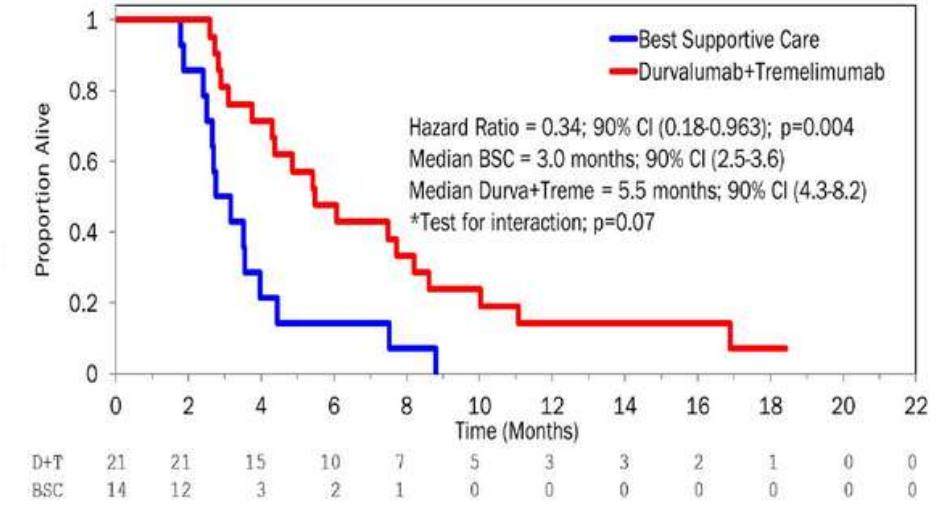
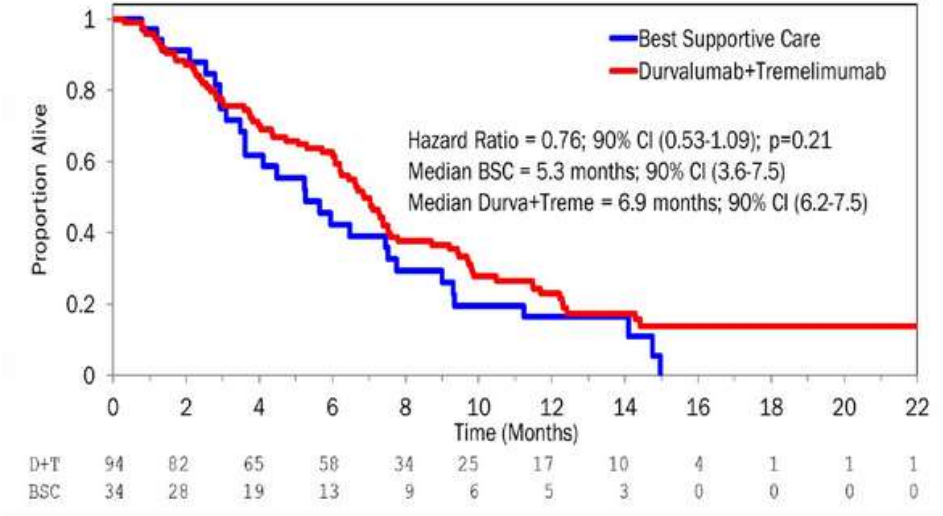


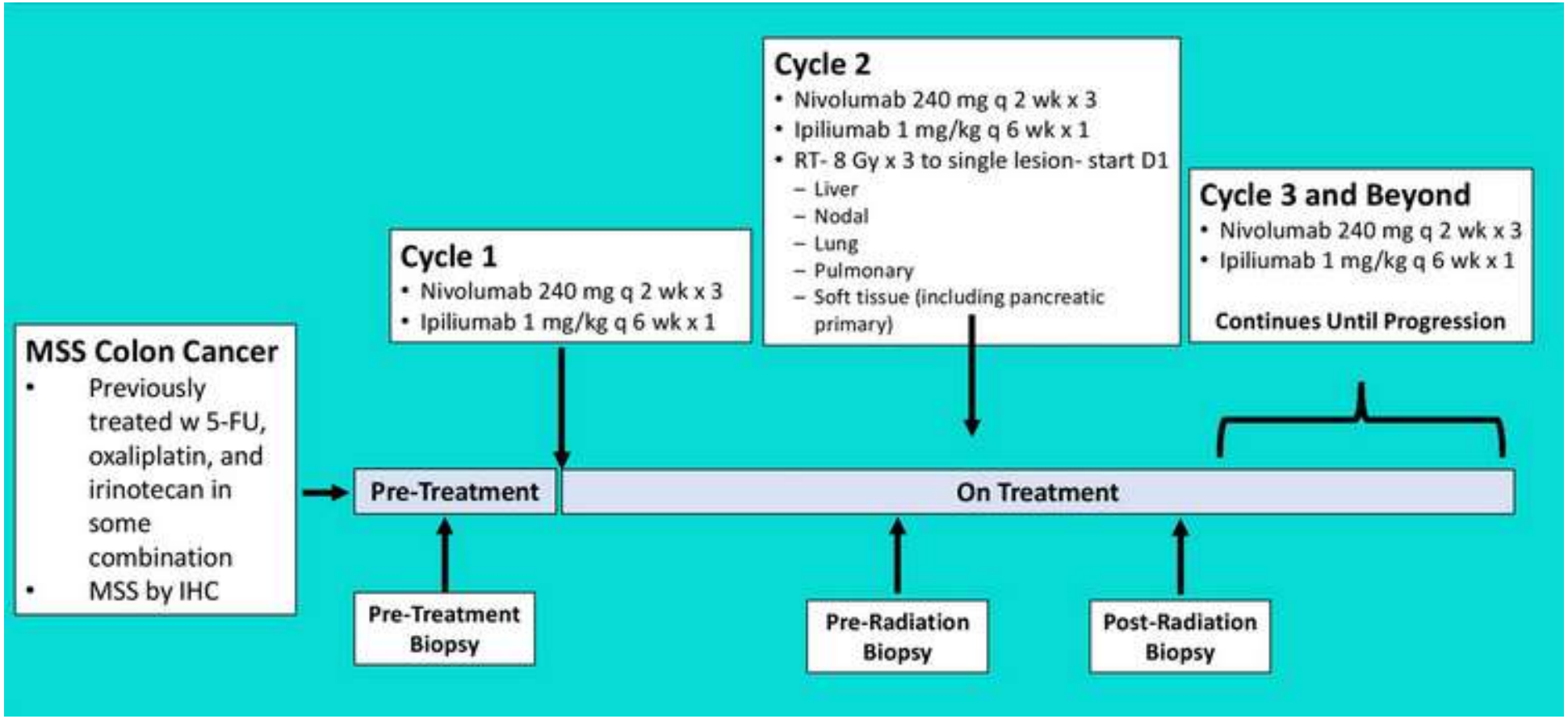

**Figure 7. Overall survival for pts with TMB < 28**




*Chen et al. #3512*

# #3514 Nivo+Ipi+RT

**40 pts**
**2L→**




Target lesions: not irradiated ones

*Parikh et al. #3514*

# #3514 Nivo+Ipi+RT: results

**Figure 1. % change in tumor dimension of comparable lesion(s) at Best Response for the mITT cohort**

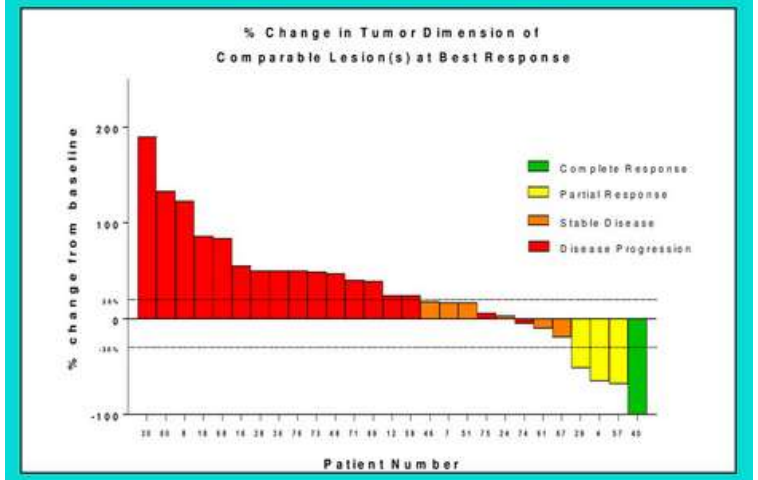



**Figure 2. Duration of Treatment for ITT cohort**

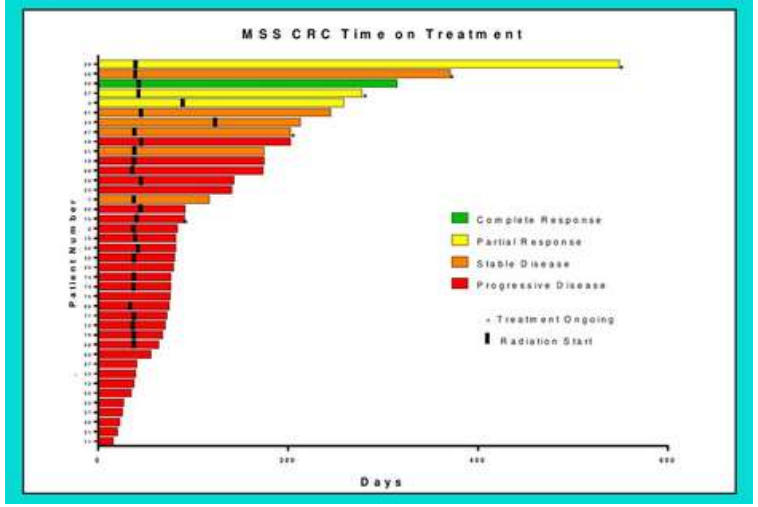



**Figure 3. Overall Survival in the ITT cohort; HR interpretation of time-varying model**

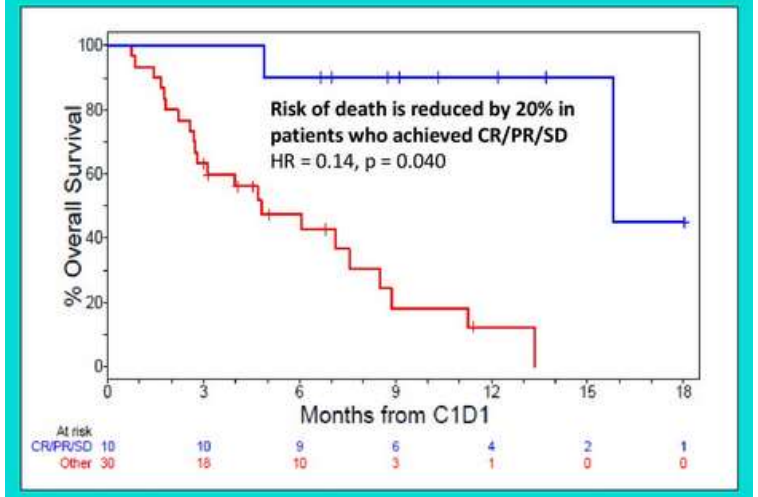



**Figure 4. Change in ctDNA (%) from baseline of a responding patient**

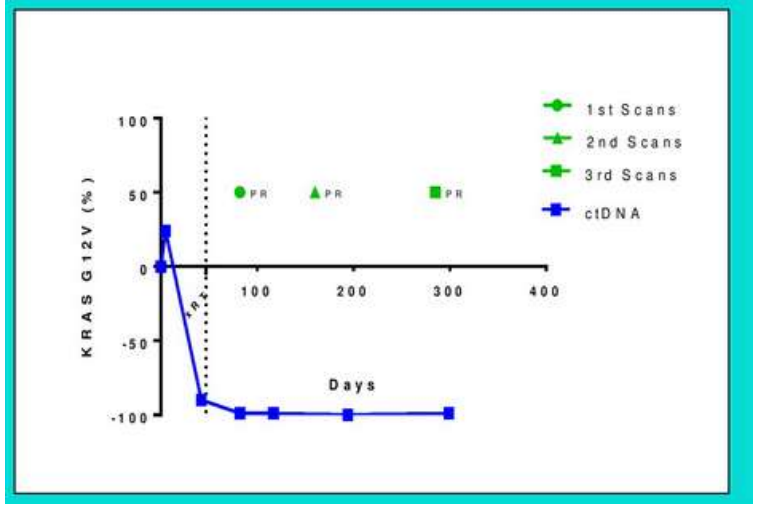



**Table 2. Efficacy Data**

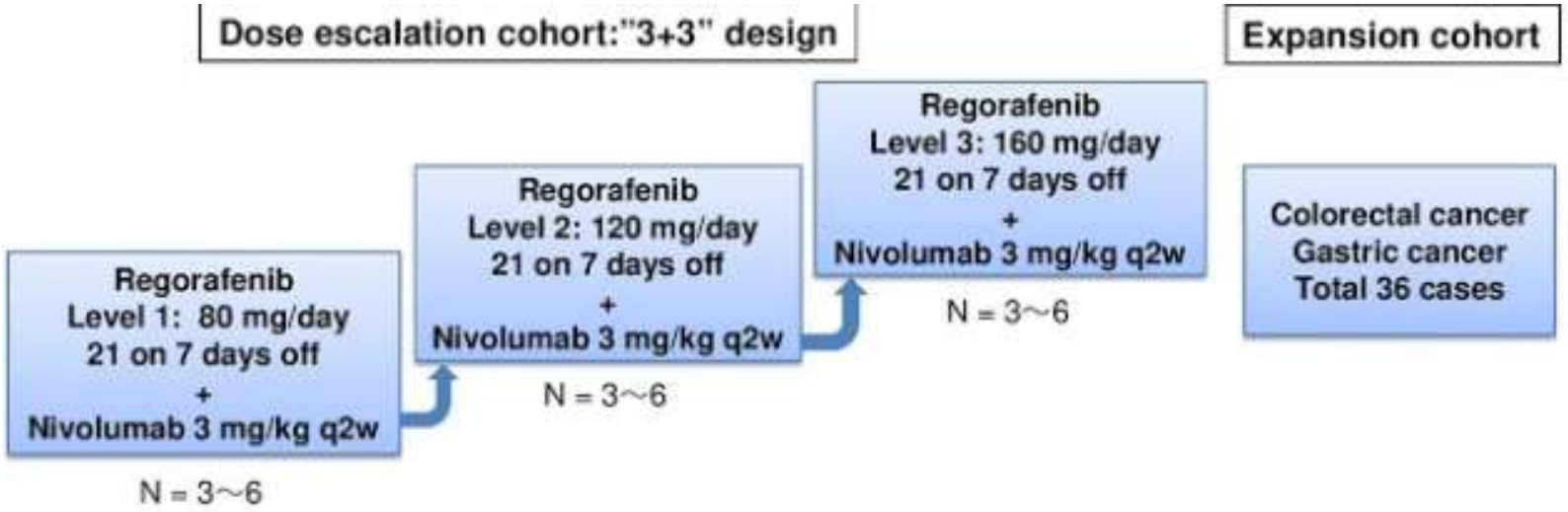
| | ITT (N=40) | Modified ITT (N=27) |
|---|---|---|
| ORR | 4 (10%) | 4 (15%) |
| DCR | 10 (25%) | 10 (37%) |
| Discontinued due to Toxicity | 4 (10%) | 1 (4%) |
| Duration of Disease Control (Months) | 2.4 | 2.5 |
| Patients with CR/PR/SD | 5.2 | 5.2 |
| Patients without CR/PR/SD | 2.0 | 2.4 |
| Overall Survival (median in Months) | 7.6 | 13.3 |
| Patients with CR/PR/SD | 15.8 | 15.8 |
| Patients without CR/PR/SD | 4.8 | 8.9 |

*16 patients alive with median follow-up of 6.9 months (range 3.0-18.0)
**Discontinuation prior to xRT: toxicity (3), progression (5), poor PS (4), withdrawn consent (1)

*Parikh et al. #3514*

# #2522 REGONIVO trial: design

- Immune suppressive cells such as regulatory T cells (Tregs) or tumor-associated macrophages (TAMs) may induce resistance to anti-PD-1/PD-L1 inhibitors.
- Regorafenib, a potent inhibitor of angiogenic and oncogenic kinases, reduced TAMs in murine models[1].
- The combination of regorafenib plus anti-PD1 monoclonal antibody (mAb) exhibited superior efficacy compared to each alone in murine models[1].




Primary objective: dose-limiting toxicity (DLT) during cycle one to investigate the maximum tolerated dose (MTD) and recommended dose (RD)

Secondary objective: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR)

*Fukuoka et al. #2522*

# #2522 REGONIVO trial

*Table 2. DLTs and MTD determination*

| Dose Schedule | Patients Enrolled | Number of Patients with DLTs | DLTs |
|---|---|---|---|
| Regorafenib 80 mg/day + Nivolumab 3 mg/kg | 4* | 0 | None |
| Regorafenib 120 mg/day + Nivolumab 3 mg/kg | 7* | 0 | None |
| Regorafenib 160 mg/day + Nivolumab 3 mg/kg | 3 | 3 | Grade 3 Rash, N = 1<br>Grade 3 Proteinuria, N = 1<br>Grade 3 Colonic perforation**, N = 1 |

- RD and MTD of regorafenib were determined as 120 mg
- Dose of regorafenib was decreased to 80 mg due to frequent grade 3 skin toxicities in expansion cohort (20% in 120 mg and 0% in 80 mg)

* One patient was excluded from DLT evaluation

*Table 3. Treatment-Related AE (≥ 10%)*

** Reconsider causal relationship at data cut-off

| Adverse event, N (%) | All N = 50 | | Regorafenib 80 mg N = 22 | | Regorafenib 120 mg N = 25 | | Regorafenib 160 N = 3 | |
|---|---|---|---|---|---|---|---|---|
| | All grades | Grade≥3 | All grades | Grade≥3 | All grades | Grade≥3 | All grades | Grade≥3 |
| All events | 50(100) | 20(40) | 22(100) | 6(27) | 25(100) | 11(44) | 3(100) | 3(100) |
| Palmar-plantar erythrodysesthesia | 35(70) | 5(10) | 13(59) | 0(0) | 20(80) | 5(20) | 2(67) | 0(0) |
| Hypertension | 24(48) | 2(4) | 10(46) | 2(9) | 14(56) | 0(0) | 0(0) | 0(0) |
| Fatigue | 23(46) | 0(0) | 10(46) | 0(0) | 12(48) | 0(0) | 1(33) | 0(0) |
| Rash | 21(42) | 6(12) | 8(36) | 0(0) | 11(44) | 5(20) | 2(66) | 1(33) |
| Fever | 20(40) | 0(0) | 8(36) | 0(0) | 11(44) | 0(0) | 1(33) | 0(0) |
| Proteinuria | 15(30) | 6(12) | 5(23) | 2(9) | 8(32) | 3(12) | 2(67) | 1(33) |
| Liver dysfunction | 14(28) | 3(6) | 5(23) | 2(9) | 8(32) | 1(4) | 1(33) | 0(0) |
| Oral mucositis | 11(22) | 0(0) | 3(14) | 0(0) | 6(24) | 0(0) | 2(67) | 0(0) |
| Diarrhea | 11(22) | 1(2) | 5(23) | 0(0) | 4(16) | 1(4) | 2(67) | 0(0) |
| Decreased appetite | 11(22) | 0(0) | 6(27) | 0(0) | 5(20) | 0(0) | 0(0) | 0(0) |
| Hyperthyroidism | 6(12) | 0(0) | 4(18) | 0(0) | 2(8) | 0(0) | 0(0) | 0(0) |
| Hyporthyroidism | 6(12) | 0(0) | 4(18) | 0(0) | 2(8) | 0(0) | 0(0) | 0(0) |
| Hoarseness | 5(10) | 0(0) | 4(18) | 0(0) | 1(4) | 0(0) | 0(0) | 0(0) |
| Platelet count decreased | 5(10) | 1(2) | 0(0) | 0(0) | 4(16) | 1(4) | 1(33) | 0(0) |

One treatment-related death was observed due to diabetic ketoacidosis

**CRC:**
**mPFS 6.3 mo**

*Figure 2. Waterfall plot of best tumor shrinkage*

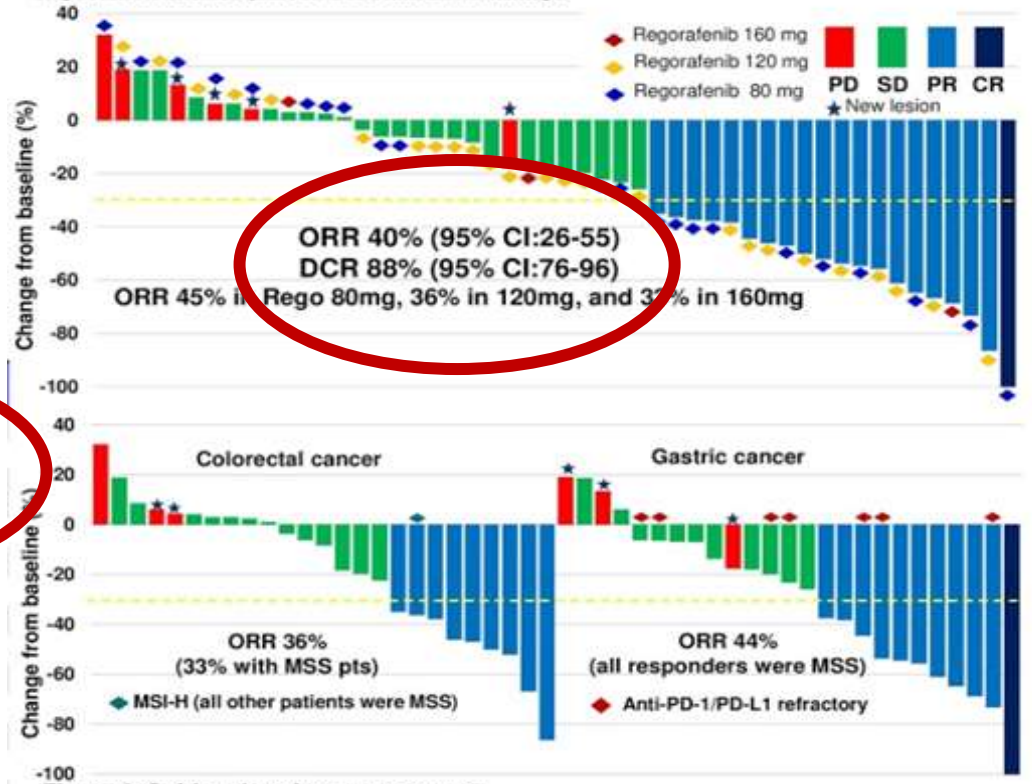
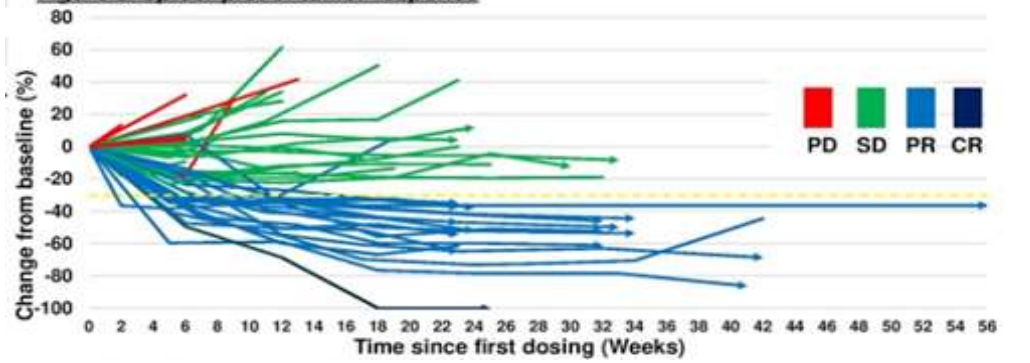


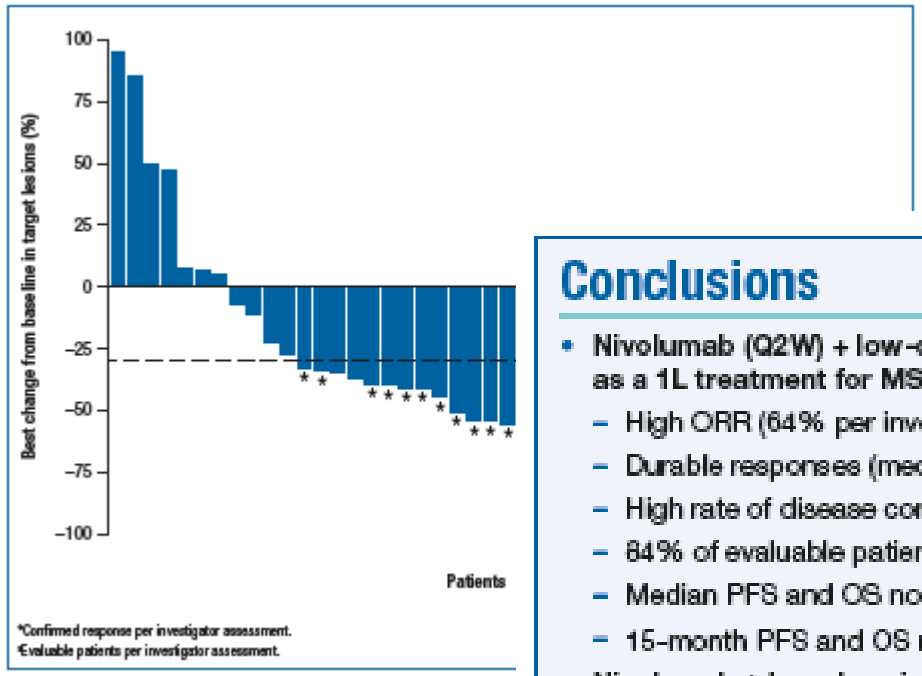

*Figure 3. Spider plot of tumor response*




*Fukuoka et al. #2522*

# #3521 CHECKMATE 142: update

**Figure 2.** Best change from baseline in target lesions[a]

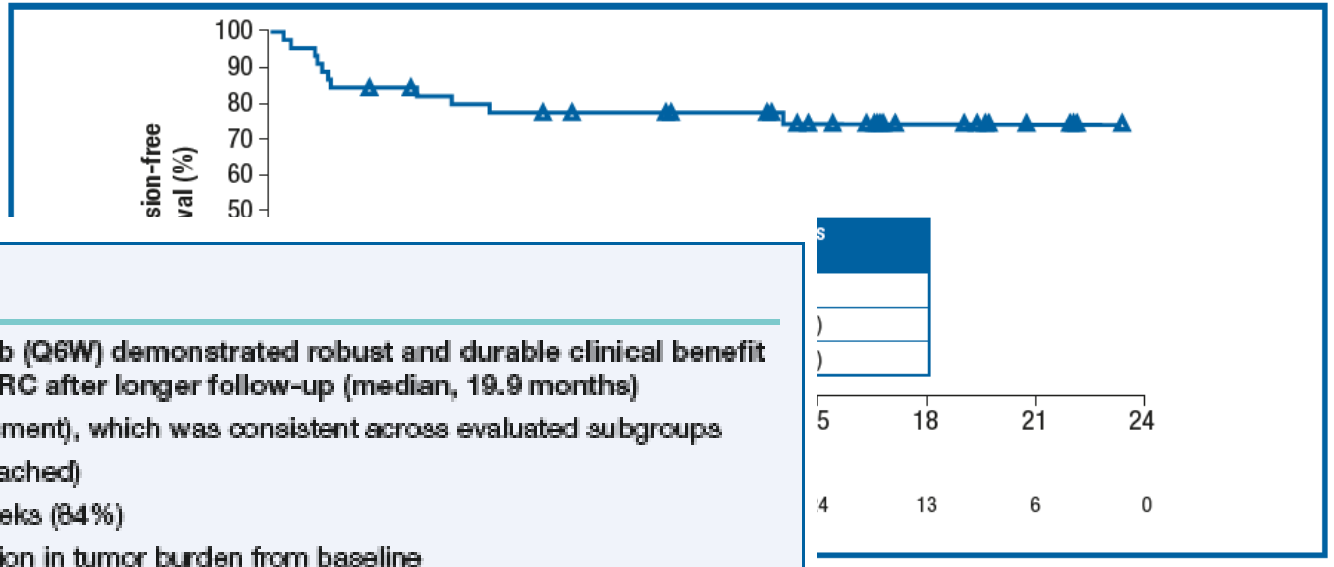


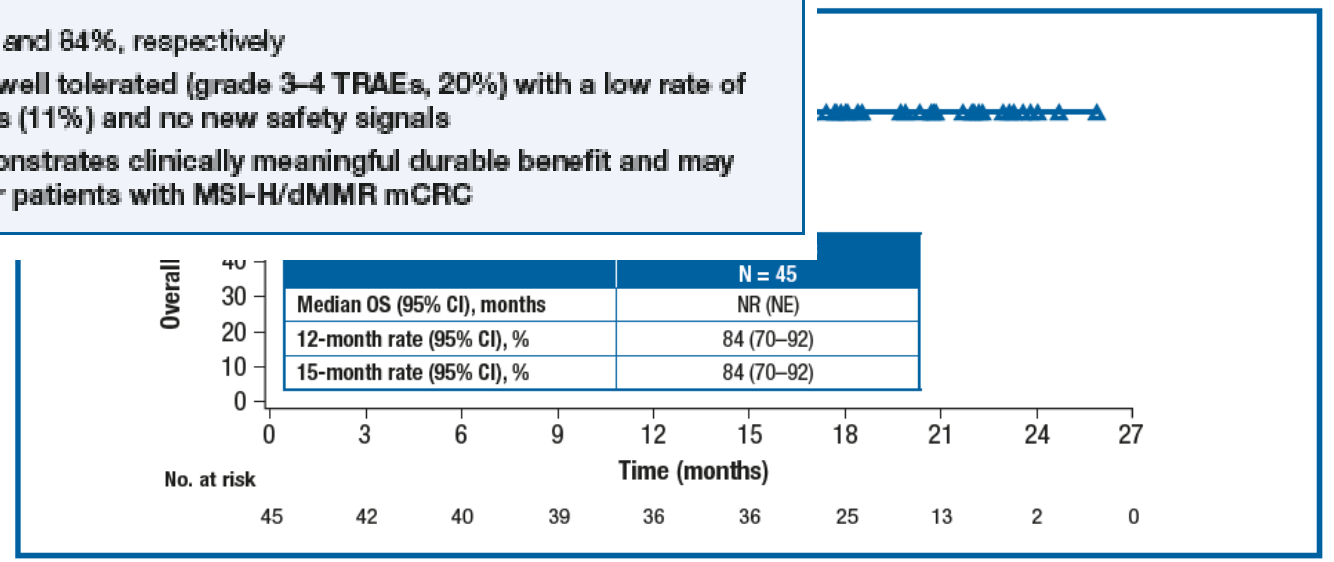

**ORR 60%**

## Conclusions

- Nivolumab (Q2W) + low-dose ipilimumab (Q6W) demonstrated robust and durable clinical benefit as a 1L treatment for MSI-H/dMMR mCRC after longer follow-up (median, 19.9 months)
  - High ORR (64% per investigator assessment), which was consistent across evaluated subgroups
  - Durable responses (median DOR not reached)
  - High rate of disease control for ≥ 12 weeks (84%)
  - 84% of evaluable patients had a reduction in tumor burden from baseline
  - Median PFS and OS not reached
  - 15-month PFS and OS rates were 75% and 84%, respectively
- Nivolumab + low-dose ipilimumab was well tolerated (grade 3–4 TRAEs, 20%) with a low rate of discontinuation due to any grade TRAEs (11%) and no new safety signals
- Nivolumab + low-dose ipilimumab demonstrates clinically meaningful durable benefit and may represent a new 1L treatment option for patients with MSI-H/dMMR mCRC

**Figure 4.** Progression-free survival[a]




| | N = 45 |
|---|---|
| Median OS (95% CI), months | NR (NE) |
| 12-month rate (95% CI), % | 84 (70–92) |
| 15-month rate (95% CI), % | 84 (70–92) |

*Lenz et al. #3521*

# Agenda

- Early-stage disease
- Hitting targets
- Immunotherapy
- Special Populations
  - #3534; #3536; #3541

# #3534 Pooled TRIBE and TRIBE2: impact of gender


✓ **Overall, women had a significantly higher risk of CT-related AEs, in particular gastrointestinal and hematologic AEs, asthenia and alopecia, independently of the treatment arm. No differences were shown in terms of bev-related AEs.**

| *Adverse events,* *% patients* | *Grade* | Males | Females | Univariate OR | Univariate p | Multivariate OR | Multivariate p |
|---|---|---|---|---|---|---|---|
| Nausea | | | | | | | |
| | *All* | 54 | 65 | 1.57 | <0.01 | 1.55 | <0.01 |
| | *≥ 3* | 3 | 6 | 2.08 | 0.01 | 1.98 | 0.02 |
| Vomiting | | | | | | | |
| | *All* | 29 | 41 | 1.73 | <0.01 | 1.72 | <0.01 |
| | *≥ 3* | 1 | 5 | 4.18 | <0.01 | 4.07 | <0.01 |
| Diarrhea | | | | | | | |
| | *All* | 61 | 65 | 1.16 | 0.24 | / | / |
| | *≥ 3* | 12 | 15 | 1.34 | 0.09 | / | / |
| Asthenia | | | | | | | |
| | *All* | 60 | 66 | 1.30 | 0.03 | 1.31 | 0.03 |
| | *≥ 3* | 8 | 12 | 1.62 | 0.02 | 1.65 | 0.01 |
| Alopecia | | | | | | | |
| | *All* | 10 | 14 | 1.55 | 0.02 | 1.56 | 0.02 |
| Anemia | | | | | | | |
| | *All* | 49 | 57 | 1.33 | 0.02 | 1.31 | 0.03 |
| | *≥ 3* | 1 | 3 | 2.62 | 0.04 | 2.55 | 0.05 |
| Neutropenia | | | | | | | |
| | *All* | 54 | 69 | 1.86 | <0.01 | 1.90 | <0.01 |
| | *≥ 3* | 30 | 44 | 1.86 | <0.01 | 1.90 | <0.01 |
| Febrile Neutropenia | | | | | | | |
| | *All* | 5 | 8 | 1.60 | 0.06 | / | / |

✓ **The risk of severe CT-related and bev-related AEs was increased with FOLFOXIRI/bev vs doublets/bev independently of gender.**

| *Adverse events,* *% patients* | *Grade* | Males Doublet/bev N=358 (30%) | Males Triplet/bev N=326 (28%) | Males OR | Females Doublet/bev N=232 (20%) | Females Triplet/bev N=260 (22%) | Females OR | *p* |
|---|---|---|---|---|---|---|---|---|
| CT-related AEs | | | | | | | | |
| | *≥ 3* | 31 | 60 | 3.26 | 47 | 70 | 2.57 | 0.33 |
| Bev-related AEs | | | | | | | | |
| | *≥ 3* | 19 | 17 | 0.92 | 17 | 17 | 1.00 | 0.78 |

✓ **Notably, among women treated with FOLFOXIRI/bev 50% and 68% experienced any grade of vomiting and nausea, respectively.**

**FOLFOXIRI/bev**

**Safety population N=586**

| *Adverse events,* *% patients* | *Grade* | Males N= 326 (56%) | Females N= 260 (44%) | OR | p |
|---|---|---|---|---|---|
| Vomiting | | | | | |
| | *All* | 34 | 50 | 1.90 | <0.01 |
| Nausea | | | | | |
| | *All* | 59 | 68 | 1.44 | 0.03 |

*Zucchelli et al. #3534*

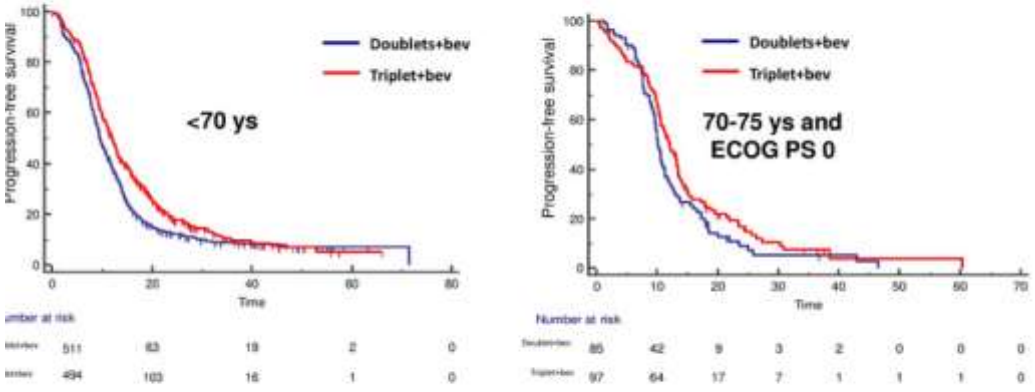
# #3536 Pooled TRIBE and TRIBE2: impact of age

**N=1187 ITT population**

- **N=1005 (85%) < 70 ys**
- **N=182 (15%) 70-75 ys and ECOG PS 0**

**The benefit provided by the intensification of the upfront chemotherapy was independent of the age subgroup in terms of both ORR and PFS.**

| | <70 ys | | 70-75 ys and ECOG PS 0 | | p for interaction |
|---|---|---|---|---|---|
| | Doublets + bev N=511 | Triplet + bev N=494 | Doublets + bev N=85 | Triplet + bev N=97 | |
| **ORR** | 52.8% | 63.6% | 47.0% | 61.9% | 0.554 |
| OR 95% CI | 1.53 [1.19-1.97] | | 1.75 [0.97-3.15] | | |
| **PFS, median** | 9.6 | 12.1 | 10.1 | 12.0 | 0.520 |
| HR 95% CI | 0.75 [0.66-0.86] | | 0.82 [0.60-1.11] | | |




**The risk of overall and chemo-related G3/4 AEs was increased with the triplet independently of age, while no difference in bevacizumab-related AEs was observed in both subgroups.**

**In the overall population, as compared to younger pts, those aged 70-75 were more susceptible to overall G3/4 AEs.**

| AE Grade ¾ | <70 ys | 70-75 ys and ECOG PS 0 | OR IC 95% | p |
|---|---|---|---|---|
| *Overall toxicity* | 60% | 73% | 2.04 | **0.0001** |
| *Chemo-related toxicity* | 52% | 68% | 2.04 | **0.0001** |
| *Bev-related toxicity* | 17% | 21% | 1.25 | 0.267 |

**In the FOLFOXIRI/bevacizumab subgroup a higher incidence of G3/4 diarrhea and febrile neutropenia and a lower incidence of all grade nausea and vomit were reported among elderly pts.**

| FOLFOXIRI/BEV subgroup AEs | | <70 ys N= 490 (84%) | 70-75 ys and ECOG PS 0 N= 96 (16%) | OR IC 95% | p |
|---|---|---|---|---|---|
| *Diarrhea* | | | | | |
| | All grades | 358 (73%) | 69 (72%) | 0.94 | 0.810 |
| | Grade 3-4 | 81 (17%) | 26 (27%) | 1.88 | **0.016** |
| *Febrile Neutropenia* | | | | | |
| | All grades | 31 (6%) | 15 (16%) | 2.74 | **0.001** |
| *Nausea* | All grades | 319 (65%) | 50 (51%) | 0.58 | **0.017** |
| *Vomiting* | All grades | 215 (44%) | 25 (26%) | 0.45 | **0.001** |

*Marmorino et al. #3536*

# #3541 FIRE-3: effect of patient age

| ≤ 65 years | N | ORR (%) | p | PFS (months) | p (HR) | OS (months) | P (HR) |
|---|---|---|---|---|---|---|---|
| FOLFIRI + Cet | 104 | 75.6 | 0.08 | 11.2 | 0.42 | 33.1 | **0.01** |
| FOLFIRI + Bev | 105 | 63.0 | | 10.2 | 1.10 | 24.8 | **0.68** |
| **≤ 70 years** | **N** | **ORR (%)** | **P** | **PFS (months)** | **P (HR)** | **OS (months)** | **P (HR)** |
| FOLFIRI + Cet | 136 | 79.1 | 0.02 | 10.7 | 0.52 | 33.3 | **0.02** |
| FOLFIRI + Bev | 150 | 65.2 | | 10.5 | 1.10 | 27.5 | **0.73** |
| **> 70 years** | **N** | **ORR (%)** | **p** | **PFS (months)** | **p (HR)** | **OS (months)** | **P (HR)** |
| FOLFIRI + Cet | 63 | 72.7 | 0.28 | 8.8 | 0.90 | 23.6 | 0.25 |
| FOLFIRI + Bev | 51 | 61.9 | | 10.4 | 0.98 | 23.8 | 0.67 |

*Heinemann et al. #3541*

# Take home messages

- Immunoscore confirms to be a prognostic factor
- Tumor deposits should be considered and implemented in nodes count→ potentially practice changing
- ctDNA is a strong predictor of minimal residual disease

- 2 new drugs in evaluation for mCRC

- TMB new biomarker?
- Regorafenib+nivolumab demonstrated impressive results

- Careful evaluation of toxicities for females and older patients is needed

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