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UPDATE ON FLEXIBLE DOSING OF ORAL THERAPY IN mCRC

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UPDATE ON FLEXIBLE DOSING OF ORAL THERAPY IN mCRC

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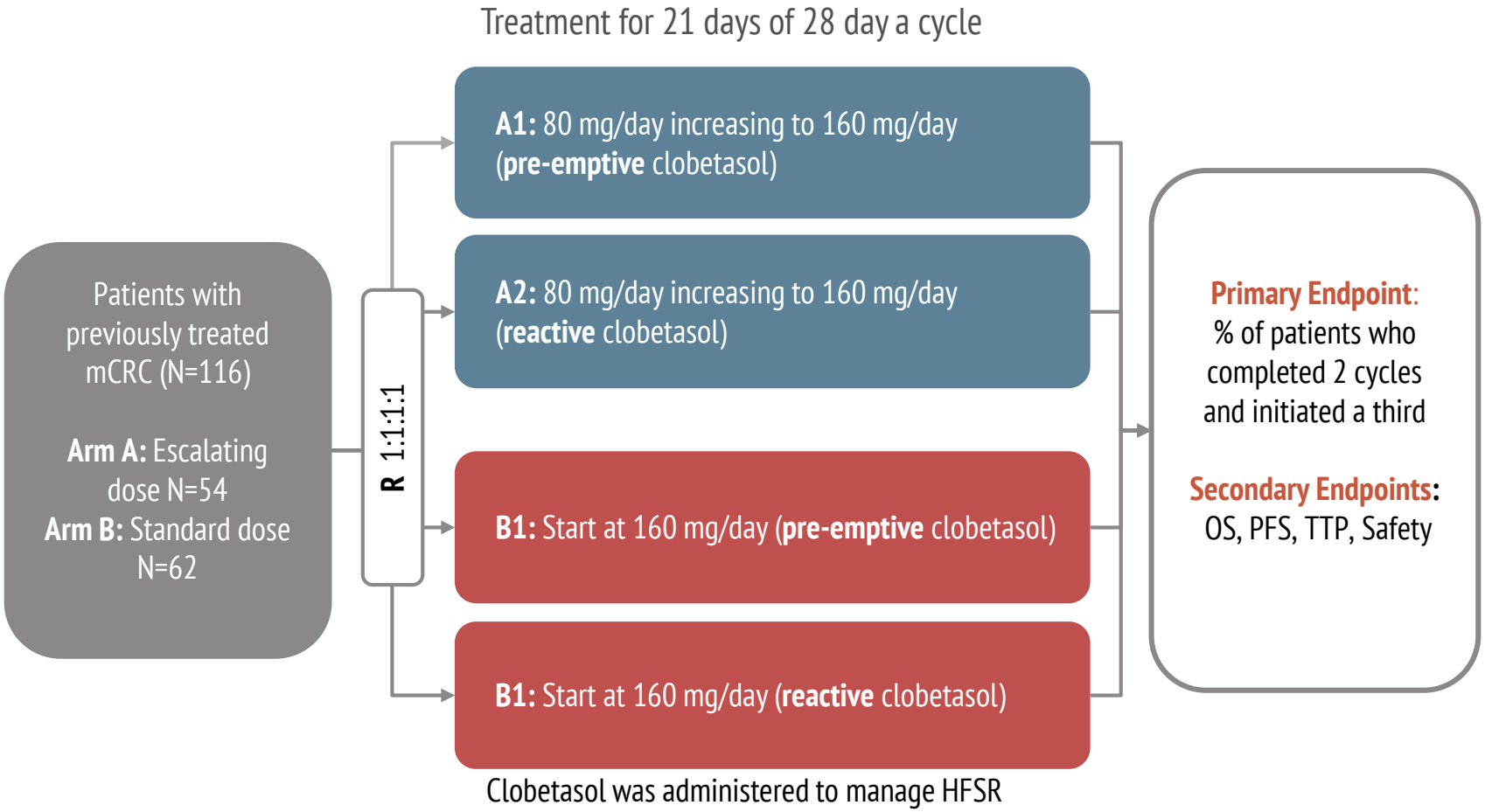
- Therapies covered in this update include
  - **Regorafenib**
  - **Capecitabine**
  - **Trifluridine/Tipiracil (TAS-102)**

REGORAFENIB DOSE OPTIMIZATION STUDY (ReDOS): RANDOMIZED PHASE II TRIAL TO EVALUATE DOSING STRATEGIES FOR REGORAFENIB IN REFRACTORY mCRC

Bekaii-Saab TS, et al. J Clin Oncol. 2018;36(4 suppl):611–611

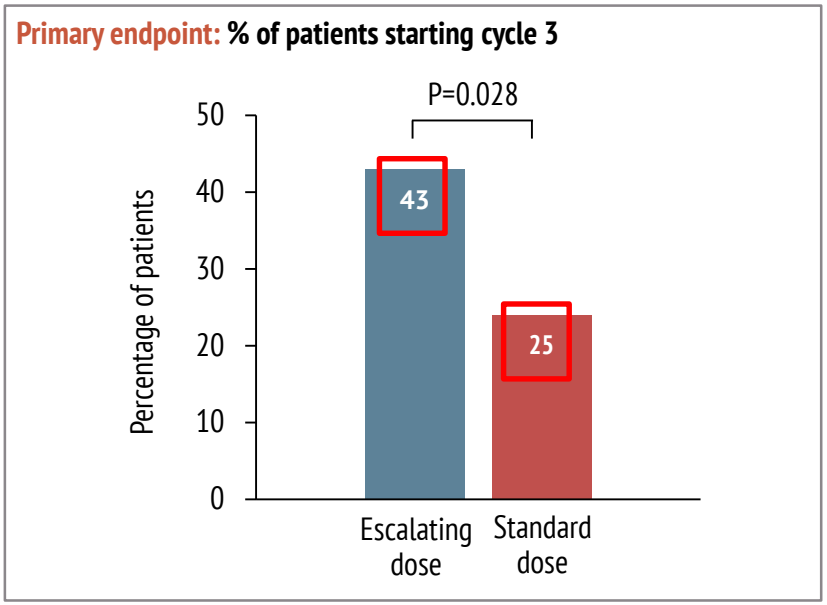
ReDOS
STUDY DESIGN



HFSR, hand-foot skin reaction; mCRC, metastatic colorectal cancer; N, number of patients; OS, overall survival; PFS, progression free survival; R, randomisation; ReDOS, regorafenib dose optimization study; TTP, time to progression

Bekaii-Saab TS, et al. J Clin Oncol 2018;36(4 suppl): 611–611; Bekaii-Saab TS, et al. ASCO GI 2018; Abstract 611 and poster

ReDOS
RESULTS: PRIMARY ENDPOINT AND AEs



Parameter	Escalating dose N=54	Standard dose N=62	HR (95% CI) P-value
Patients starting C3, %	43	25	P=0.028
HFSR, grade 3/4, %	15	16	–
Hypertension, grade 3/4, %	7	15	–
Fatigue, grade 3/4, %	13	18	–

- Lower rate of Grade 3 or 4 AEs with the escalating dose

AEs, adverse events; C3, cycle 3; HFSR, hand-foot skin reaction; N, number of patients; P, probability; ReDOS, Regorafenib dose optimization study

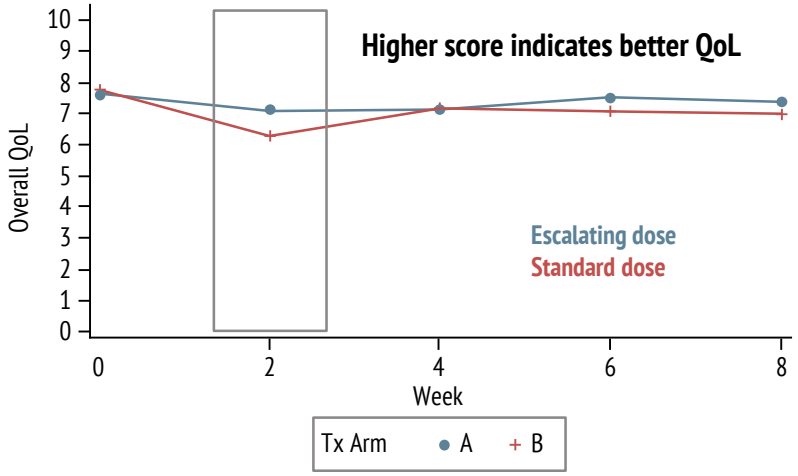
Bekaii-Saab TS, et al. J Clin Oncol 2018;36 (4 suppl): 611–611; Bekaii-Saab TS, et al. ASCO GI 2018; Abstract 611 and poster

ReDOS
RESULTS: OTHER ENDPOINTS AND QoL

Other endpoints

	Escalating dose (N=54)	Standard dose (N=62)
Median OS	9.0 months	5.9 months
	HR 0.65 (95% CI 0.39–1.08)	
Median PFS	2.5 months	2.0 months
	HR 0.89 (95% CI 0.59–1.33)	

Overall Quality Of Life (QoL)



CI, confidence interval; HR, hazard ratio; N, number of patients; OS, overall survival; PFS, progression-free survival; QoL, quality of life.; ReDOS, Regorafenib dose optimization study ; Tx, treatment

Bekaii-Saab TS, et al. J Clin Oncol 2018;36 (4 suppl): 611–611; Bekaii-Saab TS, et al. ASCO GI 2018; Abstract 611 and poster

EFFICACY AND SAFETY OF REGORAFENIB WITH 2/1 SCHEDULE FOR PATIENTS ⩾ 75 YEARS WITH mCRC AFTER FAILURE OF 2 LINES OF CHEMOTHERAPY

Petrioli R, et al. Chemotherapy Clin Colorectal Cancer 2018;17(4):307-312

FLEXIBLE DOSING OF REGORAFENIB IN ELDERLY PATIENTS

STUDY DESIGN

Prospective, single arm study

*Starting dose was reduced to 120 mg in patients considered vulnerable or with >1 comorbidity, and 80 mg in patients ⩾80 years old or with an ECOG PS of 2

DCR, disease-control rate; ECOG, Eastern Cooperative Oncology Group; FD, flexible dosing; mCRC, metastatic colorectal cancer; N, number of patients; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PS, performance status

Petrioli R, et al. Chemotherapy Clin Colorectal Cancer 2018;17(4):307-312

FLEXIBLE DOSING OF REGORAFENIB IN ELDERLY PATIENTS

RESULTS

- **DCR:** more than one-half (52.2%) of the patients obtained disease stabilisation, with no patients achieving a PR or CR
- Both median **OS** (8.9 months) and **PFS** (4.8 months) compared well with those observed in the CORRECT[1] study
- Most common Grade 3 AEs were HFSR (9%) and fatigue (9%). AEs led to dose reductions and discontinuation in 5 and 2 patients respectively
- A modified 2/1 schedule of regorafenib combined with an initially personalised starting dose might be safely proposed for selected non-frail patients aged ≥ 75 years with treatment refractory mCRC

AEs, adverse events; CR, complete response; DCR, disease-control rate; FD, flexible dosing; HFSR, hand-foot skin reaction; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; PR, partial response;

1. Grothey A et al. Lancet. 2013;381(9863):303-312; 2. Petrioli R, et al. Chemotherapy Clin Colorectal Cancer 2018; 17(4):307-312

FLEXIBLE DOSING OF REGORAFENIB
SUMMARY

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- In the CORRECT[1] and CONCUR[2], regorafenib was shown to prolong survival of patients with treatment-refractory mCRC. However, **regorafenib-related Aes led to treatment modification in the majority of patients (67%) and most Aes occurred during cycle 1-2[1]**
- In a **randomised phase II trial (ReDOS)[3], a strategy with weekly dose escalation of regorafenib from 80 mg to 160 mg/day** was found to be superior to a starting dose of 160 mg/day in terms of proportion of patients starting the 3rd cycle
  - A trend for improved OS was seen in the dose escalation arm
  - QoL parameters were improved in the dose escalation arm versus the standard dose arm at week 2 of the 1st cycle
- Other smaller studies, including a study in elderly individuals[4,5], reported **positive results with flexible dosing strategies**

FD, flexible dosing; mCRC, metastatic colorectal cancer; OS, overall survival; QOL, quality of life; ReDOS, Regorafenib dose optimization study

1. Grothey A et al. Lancet 2013;381(9863):303-312.; 2. Li J et al. Lancet Oncol 2015;16(6):619-29. 3. Bekaii-Saab TS, et al. J Clin Oncol 2018;36 (4 suppl):611–611; 4. Kudo T, et al. J Clin Oncol 2018;36(suppl 4S); abstr 821; 5. Petrioli R, et al. Clin Colorectal Cancer 2018; 17(4):307-312

FLEXIBLE DOSING OF REGORAFENIB
CONCLUSION

- Taken together, these results indicate that **a flexible dosing of regorafenib can be adopted without jeopardising treatment efficacy**, with the ReDOS dose escalation strategy potentially establishing a new standard for optimising regorafenib dosing

FD, flexible dosing; ReDOS, Regorafenib dose optimization study

TOLERABILITY OF CAPECITABINE MONOTHERAPY IN mCRC: A REAL-WORLD STUDY

Leicher LW et al. Drugs R D 2017; 17:117–124

TOLERABILITY OF CAPECITABINE MONOTHERAPY IN mCRC

OBJECTIVES AND METHODS

- Aim of this study was to provide real-world data on **AE rates, dose adjustments** and **discontinuations** associated with **capecitabine monotherapy** in patients with **mCRC**
- This was a **retrospective study** that analysed data from patients with mCRC scheduled to receive up to **8 planned cycles** of capecitabine monotherapy
- Data analysed included
  - **AEs** (HFS, GI, haematological and cardiac)
  - Relative dose intensities (**RDIs**)†
  - **Dose reductions and discontinuations**

† RDI was calculated for each patient to determine the dose received relative to the planned scheduled dose over 8 cycles. A patient receiving their starting dose over 8 cycles represented 100%. Reduced doses were based on their relative proportion of the starting dose

AE, adverse event; GI, gastrointestinal; HFS, hand-foot syndrome; mCRC, metastatic colorectal cancer; RDIs, relative dose intensities

Leicher LW et al. Drugs RD 2017; 17:117–124

TOLERABILITY OF CAPECITABINE MONOTHERAPY IN mCRC

RESULTS (1)

- Data from 86 patients analysed over 8 planned cycles of capecitabine monotherapy
- Most patients (77%) started at below the recommended dose
  - 750 mg/m^2 bid (N=12); 1000 mg/m^2 bid (N=54); 1250 mg/m^2 bid (N=20)
- Median RDIs (%) for each starting dose were:
  - 750 mg/m^2 (37.5%); 1000 mg/m^2 (67.2%); 1250 mg/m^2 (68.8%)
- 46.5% of patients experienced HFS
- 44.2% of patients experienced GI AEs
- **Dose reductions** and **treatment discontinuations** occurred in
  - **17–24% of patients** who experienced **HFS**
  - **15–25% of patients** who experienced **GI AEs**

AE, adverse event; bid, twice daily; GI, gastrointestinal; HFS, hand-foot syndrome; mCRC, metastatic colorectal cancer; RDIs, relative dose intensities

Leicher LW et al. Drugs RD 2017; 17:117–124

TOLERABILITY OF CAPECITABINE MONOTHERAPY IN mCRC

RESULTS (2)

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Number of AEs and dose reductions or discontinuations in patients reporting AEs over the course of 8 cycles

AEs	Number of AEs	Number of dose reductions	Number of discontinuations
HFS	88	21	15
GI	84	13	21
Haematological	6	2	3†
Cardiac	6	1	1

† one case where it was not explicitly stated that the discontinuation was due to anaemia

AE, adverse event; GI, gastrointestinal; HFS, hand-foot syndrome; mCRC, metastatic colorectal cancer
Leicher LW et al. Drugs RD 2017; 17:117–124

TOLERABILITY OF CAPECITABINE MONOTHERAPY IN mCRC

CONCLUSIONS

- **HFS and GI AEs were frequent** in patients treated with capecitabine monotherapy in a real world clinical setting
- Most patients **started treatment** at a dose **below the recommended dose**
- Patients who started at the lowest dose also had the lowest median RDIs, indicating interruption of the planned treatment regimen
- **Dose reductions** and **discontinuations occurred** in **15–25%** of patients who experienced HFS or GI AEs over the course of 8 cycles of therapy
- Limitations of the study include the retrospective design and small patient numbers

AEs, adverse events; GI, gastrointestinal; HFS, hand-foot syndrome; mCRC, metastatic colorectal cancer; RDIs, relative dose intensities

Leicher LW et al. Drugs RD 2017; 17:117–124

BI-WEEKLY ADMINISTRATION OF TAS-102 FOR NEUTROPENIA PREVENTION IN PATIENTS WITH CRC

Yoshida Y et al. Anticancer Res 2018; 38(7):4367-4373

BI-WEEKLY ADMINISTRATION OF TAS-102
BACKGROUND AND METHOD

- TAS-102 improves OS and PFS in previously treated patients with mCRC[1,2]
- Neutropenia is the most common AE that may negatively impact continuation of therapy[3]
- The aim of this retrospective study was to investigate factors associated with grade ≥3 neutropenia in TAS-102-treated patients with mCRC[4]
- Response rate, PFS, OS, and AEs were analysed
- Stratification factors included
  - KRAS mutation
  - Administration method
  - Concomitant drug administration
  - Neutrophil-to-lymphocyte ratio
  - Onodera's prognostic nutritional index

AEs, adverse events; KRAS, K-retrovirus associated sequence oncogene; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival

1. Mayer RJ et al. NEJM 2015;372:1909–19; 2. Xu J et al. J Clin Oncol 2018; 36:350–58; 3. LONSURF (trifluridine and tipiracil) US prescribing information; 4. Yoshida et al. Anticancer Res 2018; 38(7):4367-4373

BI-WEEKLY ADMINISTRATION OF TAS-102 RESULTS

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- Medical records of 41 patients were reviewed[1]
- **Biweekly administration was associated with significantly less neutropenia compared to recommended administration† (7.1% versus 44.4%, respectively)**
- No significant difference was observed in DCR and OS rates between the biweekly and recommended administration regimens
- Biweekly regimen was associated with significantly prolonged PFS versus recommended administration regimens

† Twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle[2]

DCR, duration of complete response; OS, overall survival; PFS, progression-free survival

1. Yoshida et al. Anticancer Res 2018; 38(7):4367-4373; 2. LONSURF (trifluridine and tipiracil) US prescribing information

BI-WEEKLY ADMINISTRATION OF TAS-102
CONCLUSIONS

- Biweekly administration of TAS-102 without a change in the drug dose intensity was associated with reduced neutropenia in patients with mCRC
- There was no evidence of reduced efficacy with biweekly administration versus recommended administration
- Limitations of the study include the retrospective design and small patient numbers

mCRC, metastatic colorectal

Yoshida et al. Anticancer Res 2018; 38(7):4367-4373

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