UPDATE ON FLEXIBLE DOSING OF ORAL THERAPY IN mCRC

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DISCLAIMER

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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

ReDOS
STUDY DESIGN

Treatment for 21 days of 28 day a cycle

A1: 80 mg/day increasing to 160 mg/day (pre-emptive clobetasol)

A2: 80 mg/day increasing to 160 mg/day (reactive clobetasol)

B1: Start at 160 mg/day (pre-emptive clobetasol)

B1: Start at 160 mg/day (reactive clobetasol)

Primary Endpoint: % of patients who completed 2 cycles and initiated a third

Secondary Endpoints: OS, PFS, TTP, Safety

Clobetasol was administered to manage HFSR

Patients with previously treated mCRC (N=116)

Arm A: Escalating dose N=54
Arm B: Standard dose N=62

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
ReDOS
RESULTS: PRIMARY ENDPOINT AND AEs

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

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

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
RESULTS: OTHER ENDPOINTS AND QoL

<table>
<thead>
<tr>
<th>Other endpoints</th>
<th>Escalating dose (N=54)</th>
<th>Standard dose (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>9.0 months</td>
<td>5.9 months</td>
</tr>
<tr>
<td>HR</td>
<td>0.65 (95% CI 0.39–1.08)</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.5 months</td>
<td>2.0 months</td>
</tr>
<tr>
<td>HR</td>
<td>0.89 (95% CI 0.59–1.33)</td>
<td></td>
</tr>
</tbody>
</table>

Higher score indicates better QoL.

Overall Quality Of Life (QoL)

Higher score indicates better QoL.

Escalating dose

Standard dose

Tx Arm

A

B
EFFICACY AND SAFETY OF REGORAFENIB WITH 2/1 SCHEDULE FOR PATIENTS \( \geq 75 \) YEARS WITH mCRC AFTER FAILURE OF 2 LINES OF CHEMOTHERAPY

FLEXIBLE DOSING OF REGORAFENIB IN ELDERLY PATIENTS

STUDY DESIGN

Prospective, single arm study

**Patients**
nmCRC
> 75 years
previously progressed on 2 lines of chemotherapy
non-frail
N=23

**Modified treatment schedule (2/1)**

**Treatment:** Regorafenib* 160 mg/day, 2 weeks on treatment and 1 week off (2/1 schedule)

**Primary Endpoint:**
2-month DCR

**Secondary Endpoints:**
safety, PFS, OS, ORR

*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

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 \( \geq 75 \) 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;
FLEXIBLE DOSING OF REGORAFENIB

SUMMARY

- 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 3\(^{rd}\) 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 1\(^{st}\) 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

• 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.
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.
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/m² bid (N=12); 1000 mg/m² bid (N=54); 1250 mg/m² bid (N=20)
• Median RDIs (%) for each starting dose were:
  – 750 mg/m² (37.5%); 1000 mg/m² (67.2%); 1250 mg/m² (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
TOLERABILITY OF CAPECITABINE MONOTHERAPY IN mCRC

RESULTS (2)

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

<table>
<thead>
<tr>
<th>AEs</th>
<th>Number of AEs</th>
<th>Number of dose reductions</th>
<th>Number of discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFS</td>
<td>88</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>GI</td>
<td>84</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Haematological</td>
<td>6</td>
<td>2</td>
<td>3†</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

† 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

BI-WEEKLY ADMINISTRATION OF TAS-102

BACKGROUND AND METHOD

- TAS-102 improves OS and PFS in previously treated patients with mCRC\textsuperscript{1,2}
- Neutropenia is the most common AE that may negatively impact continuation of therapy\textsuperscript{3}
- The aim of this retrospective study was to investigate factors associated with grade ≥3 neutropenia in TAS-102-treated patients with mCRC\textsuperscript{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
\textsuperscript{1} Mayer RJ et al. NEJM 2015;372:1909–19; \textsuperscript{2} Xu J et al. J Clin Oncol 2018; 36:350–58; \textsuperscript{3} LONSURF (trifluridine and tipiracil) US prescribing information; \textsuperscript{4} Yoshida et al. Anticancer Res 2018; 38(7):4367-4373
BI-WEEKLY ADMINISTRATION OF TAS-102

RESULTS

• Medical records of 41 patients were reviewed¹
• 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 cycle²

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