Regorafenib Dose Optimization Study (ReDOS): A randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—An ACCRU Network study

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Background

- ReDOS is a randomized phase II study of a starting dose with planned dose escalation of regorafenib compared to the standard dose in patients with refractory mCRC
- ReDOS has been shown to improve overall survival (OS) in CORRECT® and CONCUR® trials for patients with mCRC
- Toxicities such as hand-foot skin reaction (HFSR), commonly occurring over the first 2 weeks and may lead to dose reductions
- There is a need to optimize the dose of Regorafenib in patients with refractory mCRC to allow maintenance of the observed anti-tumor benefits while improving the tolerability profile

Methods

A randomized phase II US-based study through the ACCRU (Academic and Community Cancer Research United) network of regorafenib dose-escalation (Arm A, 80 mg/day; weekly dose escalation if no significant drug-related toxicity, up to 160 mg/day) vs. standard dose (Arm B, 160 mg/day) in patients with mCRC for 21 days of a 28-day cycle. PIs were randomized 1:1:1:1:1:1:1:1:1 (pre-emptive close out for IFPES, AE and any other investigational treatment).

Primary endpoint: proportion of patients who complete 2 cycles of treatment and initiate Cycle 3

Assuming an 8-week planned continuation rate of 45% in the (Arm B) group, and achieving an improvement to ≥50% in the experimental (Arm A) group, a one-sided test with a p = 0.20 and power of 80% will require a sample size of 54 patients (27 per arm).

Analyses will be modified intent-to-treat (ITT) All PIs are evaluable for primary endpoint if eligible, consented, received any protocol treatment.

A Fisher’s Exact Test will be used to detect a difference in 8-week planned continuation rates between treatment strategies with 95% confidence intervals.

Study Design

Overall Survival

Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A (n=43)</th>
<th>Arm B (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 (25-88)</td>
<td>61 (26-88)</td>
<td>0.8670</td>
</tr>
<tr>
<td>Gender</td>
<td>16 (37.2%)</td>
<td>16 (37.2%)</td>
<td></td>
</tr>
<tr>
<td>Palmar-Erythrodysesthesia (n=110)</td>
<td>20 (25.4%)</td>
<td>25 (39.6%)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Median</td>
<td>2 (3.2%)</td>
<td>2 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5 (8.1%)</td>
<td>5 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Primary Tumor Status

Local recurrence: 47 (11%) 41 (10%) 0.5647
Distant: 27 (63%) 27 (63%) 0.2315
Unresected: 13 (24%) 14 (24%) 0.8015
Number of Metastatic Sites

6 (2%) 6 (2%) 0.0015
12 (22%) 11 (22%) 0.7717
3+ 20 (44%) 18 (34%) 0.2236

BRAF V600E

Mutated: 19 (44%) 22 (51%) 0.3114
Wild Type: 24 (56%) 21 (49%) 0.8785

KIRAS Results

Wild Type: 27 (63%) 24 (41%) 0.4856
Mutated: 21 (48%) 39 (69%) 0.0016

Overall Survival

Week 1

Percentage of planned dose received
Mean (SD): 98.3 (9.7) 98.3 (10.0) 0.0255
Mean (range): 100.0 (86.0, 160.0) 100.0 (87.0, 160.0) 0.0013

Week 2

Percentage of planned dose received
Mean (SD): 101.7 (8.7) 101.7 (8.7) 0.3391
Mean (range): 100.0 (86.0, 160.0) 100.0 (86.0, 160.0) 0.0004

Week 3

Percentage of planned dose received
Mean (SD): 100.0 (10.0) 100.0 (10.0) 0.0001
Mean (range): 100.0 (86.0, 160.0) 100.0 (86.0, 160.0) 0.0001

Overall Quality Of Life (QOL)

Conclusions

- 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.
- A trend for improved OS was seen in the dose escalation arm.
- At 2-weeks from initiation of therapy, the dose escalation strategy did not appear to compromise QOL unlike the standard dose administration.
- These results potentially establishing a new standard for optimizing regorafenib dosing through a dose escalation study.
- Further data on outcomes of preemptive or reactive clobetasol strategies and PK analysis will be presented at a later meeting.