After 4 cycles of treatment, 20 1st grade 5. There were 2 deaths in the study, both related to progressive colorectal cancer.

serious adverse events

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>(quantity)</th>
<th>related to arfolitixorin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (2)</td>
<td>Infected</td>
<td></td>
</tr>
<tr>
<td>Mucositis (3)</td>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Neutropenia (3)</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea (3)</td>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td>UTI (4)</td>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Mucositis (4)</td>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Fatigue (5)</td>
<td>Increased CRI</td>
<td></td>
</tr>
</tbody>
</table>

Most frequent Adverse Events (AES)

<table>
<thead>
<tr>
<th>Most frequent Adverse Events (AES)</th>
<th>quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>46</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>32</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
</tr>
</tbody>
</table>

CONCLUSIONS

The use of MTHF for metabolic activation increases arfolitixorin a better candidate than LV/LV for improved outcome of 5-FU-based chemotherapy regimens in mCRC.

The ISO-CC-005 study evaluates arfolitixorin combination with 5-FU, irinotecan, oxaliplatin ± bevacizumab in mCRC patients in 4 countries in Europe.

The results, so far, in patients treated with different doses of arfolitixorin and in different treatment combinations seem promising for both safety and efficacy.

A multicenter study compares efficacy of arfolitixorin and LV in a standard chemotherapy/fluoropyrimidine combination in 1st line metastatic CRC: MCRIP is planned.

More information about the study is available at www.esmoaltt.com

REFERENCES

1. Desouza et al. ESMO 2018 Congress. Poster no.569P

Table 1. Serious adverse events (SAEs)

Table 2. Most frequent Adverse Events (AES)

Figure 1. ETS and ORR in first line patients in the ISO-CC-005 study after 4 cycles (8 weeks) of treatment

% Change of tumour size from baseline - 1st line mCRC patients treated with different dosages of Arfolitixorin and various combination treatments

Among 20 first line patients in ISO-CC-005:

- 10 patients with ETS (x=25%)
- Objective Response Rate*: 8 patients with partial response, PR (x=50%)
- 11 patients with stable disease, SD (x<20% to >50%)
- 1 patient with progressed disease, PD (x>20%)

* According to RECIST 1.1

CONCLUSIONS


Figure 1. Mechanism of action of arfolitixorin

ISO-CC-005 study of arfolitixorin ([6R]-5,10-MTHF) in combination with 5-fluorouracil (5-FU), irinotecan and oxaliplatin ± bevacizumab in patients with metastasizing colorectal cancer

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INTRODUCTION

Chemotherapy treatment of colorectal cancer, often includes 5-FU. 5-FU inhibits thymidylate synthase (TS), stopping the supply of thymidine for DNA synthesis. 5-FU is always combined with a folate, which enhances the 5-FU effect. Marked folates such as LV/LV are preferred because of their intrinsic activity (Figure 1).

Arfolitixorin (formerly called Modufolin®) is the natural, biologically active form of the folates and is expected to be efficacious in a larger proportion of patients with less inter- and intra-individual variability.

METHODS

ISO-CC-005 is a multi-center, phase I clinical trial of mCRC patients eligible for 5-FU/leucovorin therapy alone or in combination with irinotecan or oxaliplatin ± bevacizumab.

The study investigates safety and tolerability of 4 dose levels by analysing the number and severity of AEs, SAEs and DLTs. All receives arfolitixorin twice every two weeks during at least 4 cycles of chemotherapy. Safety is evaluated after every cycle and efficacy is evaluated after 4 cycles of chemotherapy. Gene expression, deoxyuridine levels as an indirect marker of TS inhibition and time to death is also investigated.

RESULTS

To date, 61 patients with mCRC have been enrolled (of which 75 have initiated treatment). 26 patients showed clinical benefit of the therapy, i.e. partial response (PR) or stable disease (SD). 1 patient with progressed disease (PD) was observed after 2 cycles of treatment. 21 patients were evaluable for efficacy after 4 cycles of treatment.

The results, so far, in patients treated with different doses of arfolitixorin and in different treatment combinations seem promising for both safety and efficacy.

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