#316: Safety and efficacy of combining genotype-guided irinotecan (Iri) with 5FU, leucovorin (LV), oxaliplatin (Qx), And docetaxel (Tax) (gFOLFOXIRITAX): The I-FLOAT phase 1 dose-escalation study for advanced upper GI cancers

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METHODS:

- Low risk (intermediate metabolizer)
  - UGT1A1 genotype (*1/*1 : *28/*28)
  - irinotecan doses were escalated in each UGT group by 15mg/m² increments and docetaxel to DL2 of 37.5mg/m² using a novel I3+3 design
- Intermediate risk (intermediate metabolizer)
  - UGT1A1 genotype (*1/*28, *28/*37, *37/*37, *4/*4 or *28/*80 with any of the above variants)
  - Oxaliplatin, leucovorin and 5FU were given as 85 mg/kg, 400 mg/kg and 2400 mg/kg (continuous infusion) guided irinotecan (Iri) with 5FU (Guardant Health). Pts were added if HER2 positive.
- High risk (poor metabolizer)
  - UGT1A1 genotype (*1/*36 or *1/*80 with any of the above variants)
  - Fatigue (Gr 3)
  - Thrombocytopenia
  - Elevated LFT
  - Hypocalcemia
  - Diarrhea
  - Anemia
  - Neutropenia
  - Sepsis

- Peripheral neuropathy

- Neutrophilic

- Total of 24 pts were enrolled in the study (6/30/2020 to 1/1/2022).

RESULTS:

- Of evaluable pts, best ctDNA response was seen in 12/13 (92%).
- In addition to safety/toxicity and MTD, we also evaluated ORR and ctDNA response by G360 (Guardant Health).
- Pts were currently enrolling pts.
- Of evaluable pts, best ctDNA response was seen in 12/13 (92%).
- Future investigation is warranted and ongoing.

CONCLUSIONS:

- gFOLFOXIRITAX has demonstrated tolerability at initial dose levels of irinotecan/docetaxel, with dose escalation continuing. Efficacy is promising and could be an aggressive approach in upper GI cancers that are advanced with high tumor burden/symptoms, and/or potentially peroperatively in those having high relapse risk.
- Further investigation is warranted and ongoing.

BACKGROUND:

- We hypothesized that a synergistic combination of the known effective agents 5-FU, platinum, irinotecan (Iri) and docetaxel (Tax) could improve outcomes in upper GI cancers.
- Toxicity of iri is UGT1A1 genotype dependent.
- An aggressive regimen could be applicable for highly symptomatic or oligometastatic stage IV pts, and ultimately borderline or locally advanced symptomatic or oligometastatic stage IV pts, irinotecan (iri) and docetaxel (tax) could improve outcomes in upper GI cancers.
- BACKGROUND:
  - irinotecan (Iri) with 5FU, leucovorin (LV), oxaliplatin (Qx), And docetaxel (Tax) (gFOLFOXIRITAX):
  - The University of Chicago Medical Center, Chicago, IL. 2. Department of Medicine, Division of Hematology/oncology, University of Illinois at Chicago 3. Northshore University Health System

METHODS:

- In addition to safety/toxicity and MTD, we also evaluated ORR and ctDNA response by G360 (Guardant Health). Pts were considered evaluable if they had a baseline & post-treatment blood draw.
- Oxaliplatin, leucovorin and 5FU were given as 85 mg/kg, 400 mg/kg and 2400 mg/kg (continuous IV over 46 hours) every 2 weeks with long-acting growth factor, respectively. Trastuzumab was added if HER2 positive.
- irinotecan and docetaxel dose levels (DL) were escalated as follows:

<table>
<thead>
<tr>
<th>UGT Risk Group</th>
<th>Low (e.g., *1/*1)</th>
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<td>DL1/DL1</td>
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<tr>
<td>DL2/DL2</td>
<td>155</td>
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<td>155</td>
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<tr>
<td>DL3/DL1</td>
<td>185</td>
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- Irinotecan doses were escalated in each UGT group by 15mg/m² increments and docetaxel to DL2 of 37.5mg/m² using a novel I3+3 design.
- Patients were evaluated at least every 4 cycles or every 8 weeks +/- 7 days either by CT scan of the chest/abdomen/pelvis or MRI.

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