Phase II trial of panitumumab (Pmab) plus FOLFOX4 or FOLFIRI in subjects with KRAS wild-type colorectal cancer (CRC) and liver-limited disease LLD): The PLANET study

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On behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

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PLANET randomized phase II trial
Objectives

- **Primary Endpoint:**
  - Objective response rate (ORR) over the entire Pmab + CT treatment period

- **Secondary Endpoints:**
  - Resection rate (R0+R1) of liver metastases
  - Time to resection
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Adverse Events (AEs) and peri-operative safety

- **Exploratory Endpoints:**
  - Response according to molecular biomarkers (RAS status)
ClinicalTrials.gov identifier: NCT00885885

**Sponsor:** Spanish Cooperative Group for Digestive Tumour Therapy (TTD)

**Principal investigators:** Dr. Albert Abad & Dr. Alfredo Carrato

**ClinicalTrials.gov identifier:** NCT00885885
PLANT study
Eligibility criteria: main inclusion criteria (I)

• >18 years of age
• WT KRAS CRC with at least one unidimensionally measurable lesion ≥20 mm with the conventional techniques (computed tomography (CT), magnetic resonance imaging) or >10 mm with spiral CT, according to the modified RECIST criteria (Version 1.1).
• Synchronous or metachronous liver-only metastases deemed resectable or unresectable, including those patients who had undergone complete resection (R0) of the primary tumor at least 4 weeks before randomization, fulfilling one of the following criteria:
  • ≥4 liver metastases
  • at least 1 metastasis >10 cm in diameter
  • Liver metastases technically not resectable (vascular compromise and/or location in which complete resection is impossible and/or 25-30% of healthy liver would not remain functional after resection)
## PLANET study

### Patient characteristics (WT KRAS population)

<table>
<thead>
<tr>
<th></th>
<th>Pmab-FOLFOX4 (N = 38)</th>
<th>Pmab-FOLFIRI (N = 39)</th>
<th>TOTAL (N = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>31 (81.6)</td>
<td>28 (71.8)</td>
<td>59 (76.6)</td>
</tr>
<tr>
<td>Median age, years (min, max)</td>
<td>65 (32, 79)</td>
<td>63 (37, 83)</td>
<td>64 (32, 83)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m² (SD)</td>
<td>27.4 (4.4)</td>
<td>25.9 (3.6)</td>
<td>26.7 (4.0)</td>
</tr>
<tr>
<td>Median time since CCR diagnosis, months (Q1, Q3)</td>
<td>3.4 (1.3, 22.7)</td>
<td>1.6 (0.6, 11.5)</td>
<td>1.9 (0.6, 22.2)</td>
</tr>
<tr>
<td>Technically resectable liver metastases, n (%)</td>
<td>12 (31.6)</td>
<td>12 (30.8)</td>
<td>24 (31.2)</td>
</tr>
<tr>
<td>Prior surgery for primary tumor, n (%)</td>
<td>26 (68.4)</td>
<td>22 (56.4)</td>
<td>48 (62.3)</td>
</tr>
<tr>
<td>Prior adjuvant/neoadjuvant CT and/or radiotherapy, n (%)</td>
<td>6 (15.8)</td>
<td>4 (10.3)</td>
<td>10 (13.0)</td>
</tr>
<tr>
<td>Prior FOLFOX, n (%)</td>
<td>3 (7.9)</td>
<td>3 (7.7)</td>
<td>6 (7.8)</td>
</tr>
</tbody>
</table>
PLANET study
Prevalence of RAS mutations (other than KRAS exon 2)

Any RAS mutation (n=64 patients, 83.1% ascertainment*)

*Ascertainment defined as percentage of patients with a known codon sequence result at all positions
## PLANET study
### Patient characteristics (WT RAS population)

<table>
<thead>
<tr>
<th></th>
<th>Pmab-FOLFOX4 (N = 27)</th>
<th>Pmab-FOLFIRI (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>23 (85.2)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td>Median age, years (min, max)</td>
<td>65 (32, 79)</td>
<td>60 (37, 78)</td>
</tr>
<tr>
<td>Median time since CCR diagnosis, months (Q1, Q3)</td>
<td>3.1 (1.5, 21.0)</td>
<td>1.6 (0.5, 27.0)</td>
</tr>
<tr>
<td>Technically resectable liver metastases</td>
<td>5 (18.5)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>Prior surgery for primary tumor, n (%)</td>
<td>19 (70.4)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Prior adjuvant/neoadjuvant CT and/or radiotherapy, n (%)</td>
<td>4 (14.8)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Prior FOLFOX, n (%)</td>
<td>2 (7.4)</td>
<td>3 (11.5)</td>
</tr>
</tbody>
</table>
In the RAS ascertainment subgroup, the **ORR was 75.5% in WT-RAS patients and 54.6% (25.1-84.0) in the Mutant (Mt)-RAS stratum.**

After preop tt, 52.8% of WT-RAS underwent **surgical resection** of liver mets. In the WT-RAS with non-resectable metastases group (n=39), surgical resection was possible in 53.8% of patients.

The **R0+R1 resection rate** in the WT-RAS subgroup was 39.6% (25.9% with P-FOLFOX4 and 53.8% with P-FOLFIRI). % of patients with R0 and R1 were 32.1% and 7.5%, respectively.

Longer **PFS and OS** were observed in WT-RAS versus Mutant-RAS patients in the overall population, although differences were not significant, probably due to small sample sizes.
### PLANET study

#### Response rate and resectability (WT RAS population)

<table>
<thead>
<tr>
<th></th>
<th>Pmab-FOLFOX4 (n=27)</th>
<th>Pmab-FOLFIRI (n=26)</th>
<th>TOTAL WT RAS (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>77.8% (62.1-93.5)</td>
<td>75.5% (63.9-87.1)</td>
<td>73.1% (56.0-90.1)</td>
</tr>
<tr>
<td></td>
<td>n=21</td>
<td>n=19</td>
<td>n=19</td>
</tr>
<tr>
<td><strong>Surgical resection</strong></td>
<td>37.0% (18.8-55.3)</td>
<td>52.8% (39.4-66.3)</td>
<td>40.0% (26.4-52.8)</td>
</tr>
<tr>
<td></td>
<td>n=10</td>
<td>n=28</td>
<td>n=21</td>
</tr>
<tr>
<td><strong>Resection rate (R0+R1)</strong></td>
<td>25.9% (9.4-42.4)</td>
<td>53.8% (34.6-73.0)</td>
<td>39.6% (26.4-52.8)</td>
</tr>
<tr>
<td></td>
<td>n=7</td>
<td>n=14</td>
<td>n=21</td>
</tr>
</tbody>
</table>

**ORR**: Objective response rate (not confirmed*); *patients resected before response confirmation
PLANET study
Progression-free survival according to treatment (WT KRAS & WT RAS populations)

WT-KRAS (exon 2)

Median (95% CI), months:
- Pmab-FOLFOX4: 12.6 (6.2-17.0)
- Pmab-FOLFIRI: 12.6 (7.1-16.3)

P log-rank = 0.943
P Wilcoxon = 0.966

WT-RAS (exons 2, 3, 4 of KRAS/NRAS)

Median (95% CI), months:
- Pmab-FOLFOX4: 12.8 (6.2-22.0)
- Pmab-FOLFIRI: 14.8 (7.1-18.7)

P log-rank = 0.621
P Wilcoxon = 0.675

CI: confidence interval
PLANET study
Overall survival according to treatment (WT KRAS & WT RAS populations)

WT-KRAS (exon 2)
Median (95% CI), months:
- Pmab-FOLFOX4: 32.5 (20.6-NA)
- Pmab-FOLFIRI: 42.4 (17.8-51.5)

P log-rank = 0.848
P Wilcoxon = 0.915

WT-RAS (exons 2, 3, 4 of KRAS/NRAS)
Median (95% CI), months:
- Pmab-FOLFOX4: 39.0 (26.4-NA)
- Pmab-FOLFIRI: 45.8 (32.8-51.5)

P log-rank = 0.935
P Wilcoxon = 0.634

CI: confidence interval; NA: not achieved
PLANET study
Progression-free survival
(WT RAS vs Mutant RAS)

Median (95% CI), months:
- Mutant RAS: 12.6 (3.7-24.9)
- WT-RAS: 13.4 (9.9-18.6)

P log-rank = 0.346
P Wilcoxon = 0.403
PLANET study
Overall survival
(WT RAS vs Mutant RAS)

CI: confidence interval; NA: not achieved
## PLANET study
### Summary of adverse events
(WT RAS population)

<table>
<thead>
<tr>
<th></th>
<th>Pmab-FOLFOX4 (N = 27)</th>
<th>Pmab-FOLFIRI (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4, n (%)</td>
<td>22 (81.5)</td>
<td>20 (76.9)</td>
</tr>
<tr>
<td>Treatment-related Grade 3-4, n (%)</td>
<td>18 (66.7)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Fatal AEs, n (%)</td>
<td>1 (3.7)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Treatment-related fatal AEs, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>6 (22.2)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Pmab and/or CT-related serious AE, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peri-operative AEs, n (%) (in patients with surgery)</td>
<td>1 (10.0)</td>
<td>5 (27.8)</td>
</tr>
</tbody>
</table>
PLANET study
Conclusions

• In this selected population with WT KRAS CRC and LLD, panitumumab plus CT offers the possibility of a high overall response and a potentially curative hepatic resection.

• Similar efficacy and safety results were obtained with either Pmab-FOLFOX4 or Pmab-FOLFIRI.

• Patients with RAS mutations (KRAS, NRAS) other than KRAS exon 2 showed a non-significant clear trend to worse efficacy outcomes than WT-RAS patients, without differences between Pmab-FOLFOX4 and Pmab-FOLFIRI.