Oral Tyrosine Kinase Inhibitor Masitinib in Combination with Gemcitabine in Patients with Advanced Pancreatic Cancer: a Multicenter Phase 2 Study

Masitinib

- A novel tyrosine-kinase inhibitor
- Targets c-kit, PDGFR and CSF-1R
- Blocks FAK pathway (cell proliferation, invasion, resistance to conventional therapy by inhibiting FAK kinase activity)
- Resensitizes gemcitabine-resistant pancreatic cancer cells to gemcitabine

Multicentric, one-arm, open-label phase 2 trial evaluating the efficacy and safety of masitinib combined with gemcitabine in the treatment of patients with advanced pancreatic cancer.

Procedures

- Oral masitinib 9 mg/kg/day in two intakes.
- Gemcitabine 1,000mg/m² weekly 30 minutes IV for three weeks per 4 weeks period.
- Tumor response was measured according to RECIST criteria at week 4, week 8 and week 12, then every 8 weeks.
- The primary endpoint for efficacy was Time-To-Progression (TTP). Hypothesis in that TTP is over 2.1 months.
- Secondary endpoints were Overall Survival (OS), tumor response and clinical benefit.
- Safety of masitinib was assessed according to NCIC CTCAE v3.0.

Safety

- All 22 patients were evaluated for safety.
- Mean-masitinib duration was 12.5 ± 1.47 days.
- Mean-dose of masitinib received was 8.8 ± 0.8 mg/kg/day.
- All patients experienced at least one AE, 96% of patients had at least one AE suspected to be related to masitinib (or not assessable).
- One patient reported suspected adverse events leading to dose reduction.
- No masitinib-related death occurred during the study.

Demographics and Clinical Characteristics of the 22 Patients Enrolled

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=22)</th>
<th>Metastatic (n=13)</th>
<th>Locally advanced (n=9)</th>
<th>KPS [80-100] (n=18)</th>
<th>[70] (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>64</td>
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</tr>
<tr>
<td>Sex (male)</td>
<td>12</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Patients</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Mean time from diagnosis to treatment (months)</td>
<td>6.0 ± 3.8</td>
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Most Frequent Adverse Events in patients undergoing combination therapy with gemcitabine and masitinib.

<table>
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<tr>
<th>AE description</th>
<th>All patients (n=22)</th>
<th>Metastatic (n=13)</th>
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<tr>
<td>Edema (peripheral)</td>
<td>9 (40.9%)</td>
<td>6 (27.3%)</td>
<td>2 (9.1%)</td>
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<td>1 (4.5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (50.0%)</td>
<td>8 (36.4%)</td>
<td>3 (13.6%)</td>
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<td>Pyrexia</td>
<td>13 (59.1%)</td>
<td>1 (4.5%)</td>
<td>5 (22.7%)</td>
<td>6 (27.3%)</td>
<td>11 (50.0%)</td>
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<td>Diarrhea</td>
<td>15 (68.2%)</td>
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<td>4 (18.2%)</td>
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<td>9 (40.9%)</td>
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<td>6 (27.3%)</td>
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Efficacy

- TTP and patients without progression at 6 months and 1 year.
- The combination masitinib + gemcitabine increases median TTP above our defined limit for efficacy of 2.1 months.

Conclusions

- The addition of masitinib to gemcitabine seems to:
  - Delays progression
  - Provides a clinical benefit (pain reduction)
  - Improves the patient's general status following the treatment
  - Disruption of metastatic dissemination and prevention of new metastases
  - Reduction of interstitial pressure within the tumor, enhancing chemotherapy uptake
  - Inhibition of FAK pathway
  - Prevention of the angiogenic process
  - Resensitization of gemcitabine-resistant pancreatic tumor cells

Overall Survival and survival rates

- Patients with a PD (73%) succumbed within one year.

- At 18 months:
  - Locally advanced and metastatic cancer patients had similar survival rates.

- MPS (95-103) patients had a survival rate of 28%

- Observed survival rate

  - 6 months: 56% 56% 68% 67% 56%
  - 12 months: 32% 44% 25% 38% 9%
  - 18 months: 22% 22% 22% 22% 10%

- KPS [80-100] patients had a survival rate of 28%

- TTP and patients without progression at 6 months and 1 year.
- The combination masitinib + gemcitabine increases median TTP above our defined limit for efficacy of 2.1 months.

- The addition of masitinib to gemcitabine seems to:
  - Delays progression
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This study, performed on a limited number of patients, provided encouraging results regarding the efficacy and safety of the combination of masitinib plus gemcitabine in patients with locally advanced or metastatic pancreatic cancer, and supports the initiation of a confirmatory phase 3 clinical trial.

The study was supported by funding from AB Science.