First-in-human phase I study of the DNA repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma

Christophe Le Tourneau, 1,2 Brigitte Dreno, 3 Youlia Kirova, 4 Jean-Jacques Grosb, 5 Thomas Jouany, 6 Caroline Dutriaux, 7 Luc Thomas, 7 Celeste Lebbe, 8 Laurent Mortier, 9 Philippe Siajaj, 10 Marie-Françoise Avril, 11 Eve Maube, 11 Pierre Bey, 11 Jean-Marc Cossel, 4 Jean-Sheng Sun, 11 Bernard Asselain, 11 Flavien Devun, 14,16 Michel E. Marty, 14 Marie Duret15,17


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Background

- Melanoma is known to be resistant to palliative radiotherapy (RT).
- DNA damage repair is an important mechanism of resistance to RT.
- DT01 is a double stranded DNA oligonucleotide mimicking a "false" double strand break which lures and traps DNA repair proteins [1].
- DT01 displayed antitumor activity in combination with RT in several tumor types, including melanoma without additional toxicity in preclinical models [2].
- We evaluated in a first-in-human phase I trial the combination of intratumoral (IT) and peritumoral (PT) injections of DT01 with RT in patients with skin metastases of melanoma.

Patient and Methods

- Objectives
  1) Safety and tolerability of DT01
  2) Pharmacokinetics (PK)
  3) Preliminary antitumor activity
- Patient selection
  1) Patient with histologically confirmed skin metastases from melanoma not eligible for immediate surgery
  2) ECOG performance status of 0 or 1
  3) No prior RT
  4) Adequate organ and hematopoietic functions
- Study design
  Open label, non-randomized, multi-center, 3+3 dose escalation design
  Dose levels: 16, 32, 48, 64 and 96 mg total dose
  Expansion (96 mg): IT+PT versus PT only

Results

- Administration scheme
  All target lesions were irradiated (10x3 Gy over 2 weeks), including 2 lesions injected with DT01

- Patient characteristics
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>Male 11 (48%)</td>
</tr>
<tr>
<td></td>
<td>Female 12 (52%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>72</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 17 (74%)</td>
</tr>
<tr>
<td></td>
<td>1 6 (26%)</td>
</tr>
</tbody>
</table>

- Disease characteristics
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from diagnoses, years</td>
<td>Median 1.7</td>
</tr>
<tr>
<td></td>
<td>Range 0.3-16.4</td>
</tr>
<tr>
<td>Melanoma stage at inclusion, n (%)</td>
<td>III 16/70%</td>
</tr>
<tr>
<td></td>
<td>IV 7/30%</td>
</tr>
<tr>
<td>Site of metastases, n (%)</td>
<td>Leg 17/74%</td>
</tr>
<tr>
<td></td>
<td>Arm 14/4%</td>
</tr>
<tr>
<td></td>
<td>Chest 14/4%</td>
</tr>
<tr>
<td></td>
<td>Head 4/17%</td>
</tr>
<tr>
<td>No. of treated lesions, n</td>
<td>DT01-injected 45</td>
</tr>
<tr>
<td></td>
<td>DT01-non-injected 40</td>
</tr>
<tr>
<td></td>
<td>Total 85</td>
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</tbody>
</table>

- Safety
  Only reversible grade 1 or 2 local reactions were observed
  No DLTs were reported
  The MTD was not reached

Pharmacokinetics

- No dose-dependent exposure was observed
- AUC: 0.6 to 7.8 μg/mL (median: 2.6 μg/mL)
- Half-life: 5 hrs

Best overall response

- Patients (n=21)
  - Lesions (n=76)
    - All 25% 30% 55%
    - DT01-injected 49% 19% 68%
    - DT01-non-injected 6% 43% 34%

Pharmacokinetics

- Time (h)
  - 0 10 30 120 240

Conclusions

IT and PT DT01 in combination with RT is safe in patients with skin metastases of melanoma and provides antitumor activity. ORR correlated with AUC in DT01-non-injected lesions which can be possibly explained by a systemic distribution of the drug.

For further information: christophe.letourneau@curie.fr