A Phase I dose escalation study of herpes simplex virus-1 mutant HSV1716 in paediatric/young adult patients with refractory non-central nervous system solid tumours

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Background

HSV1716 is a mutant herpes simplex virus type 1 deleted in both copies of the RL1 gene which encodes the protein ICP34.5, a specific determinant of virulence. Mutants lacking the RL1 gene are capable of replication in actively dividing cells but not in terminally differentiated cells – a phenotype exploited to selectively kill tumour cells. Studies in adult patients with high grade glioma, melanoma and squamous cell carcinoma report that HSV1716 is safe when administered by intratumoural injection. This is the first study of HSV1716 in paediatric/young adult patients and, following amendment to initial study design in Q1 2013, investigates both intratumoural and intravenous administration of HSV1716.

Objectives

The primary endpoint of the study is to assess safety of intratumoural and intravenous administration of HSV1716 in paediatric patients and to determine any dose-limiting toxicities at the doses given. Patients undergo long-term follow up in accordance with FDA guidelines for viral vectors. The secondary endpoints of the study are to measure: (i) antiviral immune response; (ii) systemic viraemia and viral shedding; and (iii) the antitumor activity of HSV1716 by radiological response.

Eligibility Criteria

Patients aged 7 to 30 with solid non-CNS tumours refractory to standard therapy are eligible for the study. Typically, patients will have been diagnosed with malignancies such as rhabdomyosarcoma, neuroblastoma, MPNST, osteosarcoma and Ewing sarcoma.

For subjects to be considered for intratumoural injection, they must have a localized lesion amenable to HSV1716 administration by needle (superficial lesions) or by needle and/or catheter (deep or pulmonary lesions), via interventional radiology without undue risk. To allow the tumour to absorb the injected fluid, the lesion to be injected must be at least 18mm in each of 3 dimensions as determined by CT or MRI scans or tumour volume >3mL per volumetric measurements.

For subjects to be considered for intravenous injection, they must have either metastatic disease or a localized lesion that is not suitable for direct intratumoural injection.

Methods

Eligible patients receive a single dose of HSV1716 either by intratumoural injection or intravenous infusion.

In the case of intratumoural injection, HSV1716 is administered directly to the target lesion via ultrasound or CT-guided imaging by an interventional radiologist. In the case of intravenous infusion, HSV1716 is diluted in ~250mL solution and administered over 1 hour.

Tumour response between baseline and day 28 is assessed by modified RECIST criteria and patients showing at least stable disease may receive up to an additional 3 doses of HSV1716.

Due to the temperature sensitive nature of oncolytic viruses, procedures are in place with pharmacy and the study team for the tracking of HSV1716 from dispensation to administration.

Methods (cont.)

Following administration, patients are seen and samples taken on days 4, 7, 14, 21 and 28 for assessment of any DLTs through to day 28. Thereafter, patients are seen on a monthly basis for the next 3 months with subsequent follow-up visits scheduled in line with FDA guidelines for viral vectors and the observation of any delayed adverse events.

A small panel of study-specific tests are conducted to assist in monitoring the safety and/or activity of HSV1716: (i) patient immune status is measured by IgG and IgM assay at baseline and day 28 (ii) blood samples are monitored for systemic viraemia (iii) urine samples and buccal swabs are taken to test for evidence of virus shedding.

We also established an independent Data Safety Monitoring Board to provide additional oversight and guidance to the study team.

Patient Numbers and Dosing

The study aims to recruit 4 cohorts of 3 patients. Observation of any DLT in any cohort will result in the expansion of each cohort to 6 patients in accordance with standard dose escalation rules.

<table>
<thead>
<tr>
<th>Dosing (pfu HSV1716)</th>
<th>ITu Dose</th>
<th>IV Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Dose Level</td>
<td>10^6</td>
<td>2x10^6</td>
</tr>
<tr>
<td>2nd Dose Level</td>
<td>2x10^6</td>
<td>10^7</td>
</tr>
</tbody>
</table>

Recruitment of the first cohort of 3 patients at the 1st dose level by intratumoural injection has been completed without DLT or procedure related serious adverse events (SAEs). Recruitment of the second cohort of patients for intratumoural injection has commenced and 2 patients have been treated without DLT or procedure related SAEs.

Following a recent amendment to the study design, the study is now open to enrol patients by both intratumoural injection and intravenous infusion.

Enrolment Status

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Gender</th>
<th>Age</th>
<th>Dose (pfu)</th>
<th>Tumour Type</th>
<th>Injection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV01</td>
<td>M</td>
<td>13</td>
<td>10^5</td>
<td>Rhabdomyosarcoma</td>
<td>Sinus/peri-orbital lesion</td>
</tr>
<tr>
<td>HSV02</td>
<td>M</td>
<td>21</td>
<td>10^6</td>
<td>Ewing sarcoma</td>
<td>Pulmonary lesion</td>
</tr>
<tr>
<td>HSV03</td>
<td>F</td>
<td>19</td>
<td>10^5</td>
<td>Peripheral nerve sheath tumour</td>
<td>Paraspinal lesion</td>
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<tr>
<td>HSV04</td>
<td>M</td>
<td>19</td>
<td>2x10^6</td>
<td>Osteosarcoma</td>
<td>Paraspinal lesion</td>
</tr>
<tr>
<td>HSV05</td>
<td>M</td>
<td>10</td>
<td>2x10^6</td>
<td>Clival chordoma</td>
<td>Peri-orbital lesion</td>
</tr>
</tbody>
</table>

Acknowledgments

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