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Society for Immunotherapy of Cancer

Dr Nicola Annels
University of Surrey, UK
Presenter Disclosure Information

Dr Nicola Annels

No Relationships to Disclose

#SITC2016
Rationale

• NMIBC is highly prevalent cancer with lifelong risk of recurrence

• Managed with TURBT surgery, intravesical chemotherapy and/or immunotherapy. BCG has limited efficacy and significant toxicity

• Coxsackievirus A21 (CVA21), naturally occurring ‘common cold’ RNA virus that targets cell surface ICAM-1

• CAVATAK™ is a novel bio-selected oncolytic and immunotherapeutic strain of CVA21

• CVA21 capable of inducing rapid and complex cellular immune response when given i.t. and i.v.

• Intravesical route allows repeated exposure to CVA21 in a schedule already established in routine practice

• NMIBC expresses ICAM-1, enhanced by Mitomycin C, NMIBC perfect model.
CANON study design

VLA-012A (Monotherapy)
- 15 subjects with Non-muscle invasive Bladder cancer
  - Intravesicular instillation of CVA21 in 30 mL saline on Day 1 and/or Day 2
  - Transurethral resection (TUR) Day 8-11

VLA-012B (mitomycin-C combination)

Cohort A1
- Day 1
  - CVA21 (1x10^8 TCID_{so})
  - n=3

Cohort A2
- Day 1
  - CVA21 (3x10^8 TCID_{so})
  - n=3

Cohort A3
- Day 1 and 2
  - CVA21 (3x10^8 TCID_{so})
  - n=3

Cohort B1
- Day 1
  - CVA21 (3x10^8 TCID_{so})
  - Day 1
  - mitomycin C (10 mg)
  - n=3

Cohort B2
- Day 1 and 2
  - CVA21 (3x10^8 TCID_{so})
  - Day 1
  - mitomycin C (10 mg)
  - n=3

Study Endpoints

Primary
- Patient safety and tolerability
- Determination of MTD

Secondary
- Evidence of anti-tumor activity
- Virus-induced tumor cell infiltrates and immune response in TUR tissue
- Level of viral replication in TUR tissue
- Pharmacokinetics of serum viral load and anti-CVA21 antibodies
CVA21—well tolerated with no grade 2 or higher product-related adverse events

<table>
<thead>
<tr>
<th>AE terminology</th>
<th>grade 1</th>
<th>grade 2</th>
<th>grade 3</th>
<th>grade 4</th>
<th>grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal/discomfort</td>
<td>1(7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shivers/feeling cold</td>
<td>1(7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Haematuria</td>
<td>1(7%)</td>
<td>-</td>
<td>-</td>
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Levels of CVA21 viral RNA and live virus in patient urine following intravesicular CVA21 administration
Tumour Response: Pre and post treatment cystoscopy

Cohort 1: Pt 01-B001

Pre-treatment

Post-treatment Day 8

Surface hemorrhage and inflammation of the tumor

Cohort 3: Pt 01-B008

Complete clinical response (confirmed by histopathology)
Levels of CVA21 cytoplasmic replication and viral induced apoptosis in transurethral resection tissue

CVA21 viral protein staining, Red=viral protein, blue=nucleus. H&E stain, arrows indicate apoptotic bodies. Apoptotic cell staining, brown cells represent cleaved caspase 3 staining by IHC.
Increases in HMGB1 levels in the urine of CVA21-treated patients.
Urinary cytokine levels in CVA21-treated patients vs untreated NMIBC patients
(17-plex quantitative ELISA-based chemiluminescent assay, Quansys Biosciences)
Coxsackie A21 induces immune cell infiltration in the micro-environment of NMIBC tissue assessed by multi-spectral IHC analysis.

Untreated-NMIBC vs CVA21-treated NMIBC

R13-12579

R13-14281

Pt 01-B004

Pt 01-B008

PD-L1  CD3  CD8  FoxP3  CD163  CK  DAPI
Coxsackie A21 treatment up-regulates interferon-induced genes and immune checkpoint molecules within the microenvironment of NMIBC tissue (Nanostring analysis Pan cancer immune profiling)
Conclusions and Future directions

• Proof of concept viral targeting, replication and tumor cell death following a single or multiple intravesicular administrations of CVA21 was achieved in patients from monotherapy and mitomycin-C combination cohorts.

• Intravesicular administration of CVA21 as a single agent or in combination with mitomycin-C was generally well tolerated with no Grade 2,3 or 4 product-related AE’s.

• Clinical activity of CVA21 demonstrated by complete tumour response, viral mediated cell apoptosis, viral replication (infectious virus increases in urine and notable signs of viral-induced tumor inflammation).

• Single agent and CVA21-combination treatments facilitated notable changes within the NMIBC tissue by inducing increases in immune cell infiltrates (CD3+CD8+) and expression of PD-L1 compared to untreated NMIBC controls.

• CVA21 mediated increases in “immunological heat” within the tumor micro-environment with regards to immune-cell infiltrates and up-regulation of immune checkpoint molecules suggest possible increased anti-tumor activity when used in combination with immune checkpoint blockade strategies.

• The observed tumor targeting, viral replication is likely to provide a strong signal in generating both a strong local and systemic anti-tumor immune response.
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