IO-001 study, AACR abstract: First in human study with EOS100850, a novel potent A$_{2A}$ antagonist, shows excellent tolerance and clinical benefit in immune resistant advanced cancers.

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Author Disclosure Information

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IO-001 study: First in human study with EOS100850 (EOS-850), a novel potent A2A R antagonist, shows excellent tolerance and clinical benefit in immune resistant advanced cancers. AACR Abstract #: 10228

EOS-850 is a highly selective and potent A2A receptor antagonist that:
- **remains active** even at the high adenosine concentration found in tumors due to a long residence time
- **does not cross the blood-brain barrier**

**DRUG MECHANISM OF ACTION:**

Blocking the immunosuppressive Adenosine Pathway

**EOS-850 Monotherapy Dose Escalation**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Key inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>QD</td>
<td>- 3 + 3 design</td>
</tr>
<tr>
<td>40 mg</td>
<td>QD</td>
<td>- DLT 28 days = 1 cycle</td>
</tr>
<tr>
<td>40 mg</td>
<td>BID</td>
<td>- Pre- &amp; On-treatment biopsy for all</td>
</tr>
<tr>
<td>80 mg</td>
<td>BID</td>
<td>- Age ≥ 18 years</td>
</tr>
<tr>
<td>160 mg</td>
<td>BID</td>
<td>- Confirmed metastatic solid tumor</td>
</tr>
</tbody>
</table>

**Key exclusion criteria**

- Prior anti-cancer therapy within 4 weeks
- Known active CNS metastases, severe CV disease
- Prior significant toxicity with immunotherapy

**Primary Study Objectives**

- To define the MTD/RP2D of EOS-850
- Safety and tolerability of EOS-850

**Secondary Study Objectives**

- Pharmacokinetic & Pharmacodynamic assessment of EOS-850 monotherapy
- Antitumor activity of EOS-850

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>60 (39-75)</td>
</tr>
<tr>
<td>Male sex, n(%)</td>
<td>14 (66%)</td>
</tr>
<tr>
<td>Primary Diagnosis, n(%)</td>
<td></td>
</tr>
<tr>
<td>mCRPC</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>other n=1 each*</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>Prior immunotherapy, n (%)</td>
<td>4 (19%)</td>
</tr>
</tbody>
</table>

* Bladder, Breast, Endometrium, Lung, Melanoma, Ovarian, Pancreas, Prostate cancer (small cell), Sarcoma

mCRPC: metastatic castrate-resistant prostate cancer
EOS-850 was well tolerated across all doses tested

- 21 patients were enrolled at 5 dose levels and completed the DLT evaluation
- No DLTs observed and no grade 3/4 drug-related TEAE
- 5 patients remain on treatment; the remaining patients discontinued due to disease progression

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Events (n=21)</th>
<th>Drug-Related</th>
<th>Any Attribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>15 (71.4%)</td>
<td>21 (100.0%)</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>15 (71.4%)</td>
<td>21 (100.0%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0 (0.0%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>0 (0.0%)</td>
<td>2 (9.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Related TEAEs (Grade 1-2), n=21</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>4 (19.0%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (19.0%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Interstitial Pneumonitis</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (4.8%)</td>
</tr>
</tbody>
</table>
Good Pharmacokinetics and Prolonged Pharmacodynamics of EOS-850 Support Selection of 80mg BID as the RP2D

Inhibition of $A_2A$R signaling with EOS-850

**PK**

- **Plasma concentration**
  - Cycle 1
    - Day 1
  - Cycle 2
    - Day 1

**PD**

1°) **pCREB in CD8$^+$ cells**

- Baseline $A_2A$R-induced pCREB with CGS-21680§
- Full inhibition of pCREB

2°) **TNF$\alpha$ secretion**

- Full restoration of LPS-induced TNF$\alpha$
- Baseline $A_2A$R-inhibited TFN-$\alpha$ secretion with CGS-21680§

- Inhibition of $A_2A$R-induced pCREB is maintained at steady-state pre-dose

- Restoration of LPS-induced TNF$\alpha$ is maintained at steady state pre-dose

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- 20 mg QD, n=3
- 40 mg QD, n=3
- 40 mg BID, n=3
- 80 mg BID, n=6
- 160 mg BID, n=6

* Whole blood assays; § CGS-21680: $A_2A$R agonist
EOS-850 Demonstrates Monotherapy Clinical Benefit in heavily pretreated patients across multiple indications.

**Best Response**

<table>
<thead>
<tr>
<th></th>
<th>QD doses (n=6), n (%)</th>
<th>BID doses (n=15), n (%)</th>
<th>Total (n=21), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>0%</td>
<td>2 (13%)</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>1 (16.5%)</td>
<td>4 (27%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>4 (67%)</td>
<td>8 (53%)</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Not Assessed</td>
<td>1 (16.5%)</td>
<td>1 (7%)</td>
<td>2 (9.5%)</td>
</tr>
</tbody>
</table>

**Partial response in a 67-year-old Male with Castrate-Resistant Prostate Cancer**

- Documented Progression after all SOC hormonal therapy and 2 prior lines of chemotherapy
- Received EOS-850 80 mg BID
- Partial response at 16 weeks with 41% reduction in size of all target lesions per RECIST associated with decreased PSA.
- Therapy ongoing at 16 Weeks

**Partial response in a 67-year-old Male with BRAF Wild-Type Cutaneous Melanoma**

- 2 prior lines of immunotherapy, Pembrolizumab followed by Ipilimumab, with documented PD
- Received EOS-850 160 mg BID
- Grade 1 Pneumonitis at 8 weeks
- Partial response per RECIST at 16 weeks with 44% reduction in size of target lesion on the arm and reduced pain and lymphedema.
- Therapy ongoing at 19 Weeks

**Target Lesions**

- **T01 lymph node axillary right**
- **T02 lymph node para-aortic right**

**PSA (ng/mL)**

- Baseline (10/24/2019): 2.03
- Followup 1 (01/02/2020): 0.73
- Followup 2 (02/27/2020): 0.2

**Treatment**

- 20mg QD
- 40mg QD
- 40mg BID
- 90mg BID
- 160mg BID

**CRC**: Colorectal Cancer, **CRPC**: castrate-resistant prostate cancer, **SCPC**: prostate cancer with small cell histology, **TNBC**: triple-negative breast cancer, **Endom**: endometrial cancer, **NSCLC**: non-small cell lung cancer, **TCC**: transitional cell cancer of the bladder

**Partial Response**

- Complete Response: 0%
- Partial Response: 2 (13%)
- Stable Disease: 5 (24%)
- Progressive Disease: 12 (57%)
- Not Assessed: 2 (9.5%)

**Baseline**

**16 weeks on EOS-850**

**Baseline**

**Followup 1**

**Followup 2**

Do Not Post
EOS-850 Demonstrates Safe Profile with Good Target Coverage and Initial Clinical Benefit in Multiple Indications

80 mg BID selected as the Recommended Phase 2 Dose

- Safe and tolerated at all dose levels with no DLT observed
- Sustained inhibition of $A_{2A}R$ and prolonged pharmacodynamic (PD) activity with BID dosing
- PK: Good dose-proportionality through 80 mg BID
- Preliminary evidence of clinical benefit in 7 patients with ongoing partial responses in a checkpoint inhibitor-refractory melanoma patient and a patient with metastatic prostate cancer

Further evaluation is ongoing in selected indications:

- Monotherapy expansion
- Combination with pembrolizumab or chemotherapy

Presenter: Jean-Pascal Machiels (Coordinating Investigator)

Many Thanks to the Investigators: Laurence Buisseret, Sylvie Rottey, Johann De Bono, Manon Mossakowski, Brant Delafontaine, Thubeena Manickavasagar, Nuria Kotecki, Jean-Pascal Machiels, Study Staff and Patients

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