Optimizing the tolerability of intravenous oncolytic viral immunotherapy administration: a sub-analysis of tolerability and cytokine data from the EVOLVE study of enadenotucirev (EnAd), an oncolytic adenovirus.

Abstract #203

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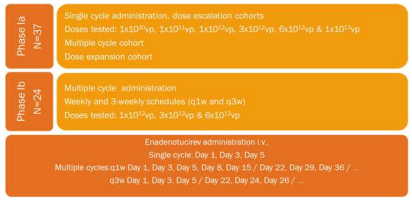
1. BACKGROUND

- Enadenotucirev is a tumor-selective chimeric Ad11/Ad3 group B oncolytic adenovirus developed using a process of directed evolution [Khun, 2008], which shows a high level of selective replication and cell killing for a broad range of carcinoma cell lines with little replication in normal and non-carcinoma cells
- Following intravenous (IV) dosing in clinical studies, uptake and replication of enadenotucirev, associated with CD8+ cell infiltration, has been shown in various carcinomas [Boni, 2014].
- EVOLVE was a first time in human study to primarily explore the safety and tolerability of enadenotucirev following IV administration of doses from $1x10^{10}$ to $1x10^{13}$ viral particles. Treatment cycles comprised IV infusions on Days (D) 1, 3 and 5, repeated every 3 weeks in Phase 1a. Phase 1b explored a weekly schedule vs the 3-weekly schedule.
- The primary objectives for the Phase Ia part of the study were to evaluate the safety and tolerability of enadenotucirev administered IV to subjects with advanced or metastatic epithelial solid tumours, and to recommend a maximally-tolerated dose for further studies. The primary objectives for the Phase Ib were to select a suitable schedule and dose for repeat cycle IV infusion of enadenotucirev in subjects with metastatic colorectal cancer (mCRC) or urothelial cell carcinoma (UCC).
- Preliminary data have been reported [Calvo, 2014] concluding that enadenotucirev can be safely administered to cancer patients. Adverse events (AEs) seen in ≥ 10% patients included pyrexia, chills, flu like illness, nausea, vomiting, diarrhoea, anorexia, asthenia, fatigue, musculoskeletal pain, thrombocytopenia and increased transaminase and fibrin d-dimer. All patients received standardised prophylactic treatment of paracetamol and ibuprofen pre- and post-dose.
- Here we present an analysis of the incidence and timing of adverse events (AEs) alongside the cytokine response data.

2. STUDY DESIGN

- Evolve was a phase 1 dose escalation study comprised of two phases:
  - Phase 1a was designed to determine the MTD of enadenotucirev, given in one only cycle
  - Phase 1b was then initiated to select a suitable schedule and dose for repeat cycle IV infusion of enadenotucirev in patients with mCRC or UCC



3. TOLERABILITY RESULTS

- Treatment–related adverse events within 24 hours of Cycle 1 Day 1 dosing were analysed.
- During dose escalation, DLTs of acute lung injury, dyspnoea and hypoxia were reported at the highest dose tested ($1x10^{13}$vp), occurring on Cycle 1 Day 1 (C1D1).

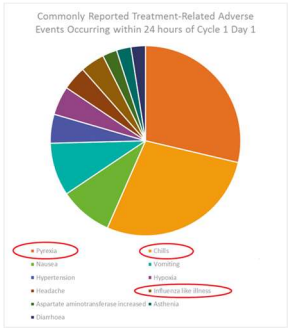
Preferred Term (MedDRA version 19.1)	<1x10¹² vp (N=6)	1 to 3x10¹² vp (N=26)	>3x10¹² vp (N=29)	All dosing groups (N=61)
Pyrexia	0	13	22	35
Chills	0	14	20	34
Nausea	0	3	8	11
Vomiting	0	5	6	11
Hypertension	0	3	3	6
Hypoxia	0	1	5	6
Headache	0	2	3	5
Influenza like illness	0	1	4	5
Aspartate aminotransferase increased	0	0	3	3
Asthenia	0	0	3	3
Diarrhoea	0	0	3	3

*>2 events reported per treatment group; TEAE = treatment emergent adverse event; vp = viral particles

Table of commonly reported TEAEs* occurring within 24 hours in Phase Ia and Ib combined (Safety Population)

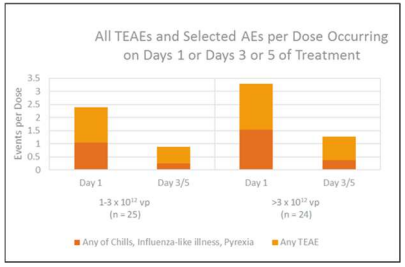
4. TOLERABILITY- CYCLE 1 DAY1 OVERALL PROFILE

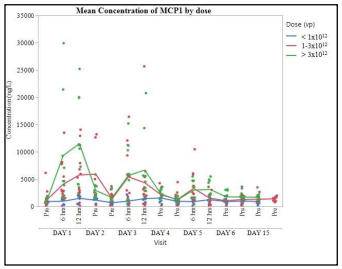
- The most commonly reported treatment-emergent adverse events with onset within 24 hours of C1D1 dosing are:
  - Pyrexia, chills and influenza-like illness



5. TOLERABILITY – DAY 1 vs DAY 3/DAY 5

- An increased number of events (both TEAEs and selected AEs) were reported following enadenotucirev administration IV on Day 1 in comparison to Day 3 and Day 5.
- Similarly, the cytokine response is most pronounced at Cycle 1 Day 1 and attenuates thereafter (MCP-1 is shown here, but IL-6 and IFN-γ show a similar pattern).
- The cytokine response at Day 1 is consistent with the hypothesis of initial activation of, and removal of virus by, Kuppfer cells in the liver.

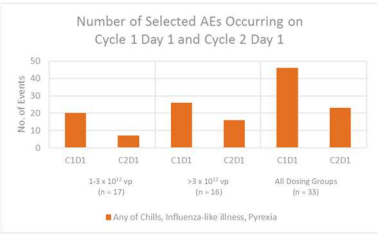




Analysis conducted on all patients from both Phase 1a and Phase 1b

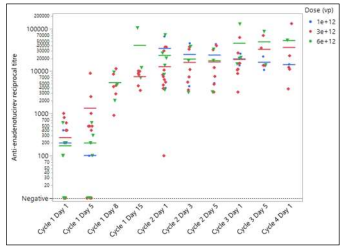
6. TOLERABILITY – CYCLE 1 vs CYCLE 2

- The occurrence of selected events (chills, influenza-like illness and pyrexia) was analysed in patients in Phase 1a and 1b receiving at least 2 cycles of enadenotucirev.
- Day 1 of Cycle 1 was less well tolerated than Day 1 of Cycle 2, regardless of dose level tested.



7. ANTIBODY RESPONSE

- Before dosing, most patients had no or very low levels of detectable anti-enadenotucirev antibodies.
- Following enadenotucirev infusion, all patients showed an increase in antibody titer which plateaued by Day 20.
- This anti-enadenotucirev antibody response appears to be unrelated to the tolerability profile shown above.



Graph shows the anti-EnAd antibody response in patients from Phase 1b receiving the weekly or 3-weekly schedule

8. CONCLUSIONS

- Tolerability of EnAd is primarily determined by C1D1, correlating with the cytokine response across the patient cohort.
- This supports the hypothesis that tolerability of the C1D1 dose of EnAd is limited by the particle-mediated activation of innate immune cells (for example, Kuppfer cells in the liver) with associated cytokine release.
- The MTD of EnAd has been determined primarily based on AEs occurring on C1D1, however higher subsequent doses may be tolerable.
- Manipulation of dosing regimens may allow administration of higher doses of EnAd on D3 & D5, and/or more doses per cycle, to increase EnAd delivery to tumour and optimize its immunotherapeutic potential.

9. REFERENCES

Boni (2014) Ann Oncol; 25 (suppl 4): iv368.
Calvo (2014) Annals of Oncology, Volume 25, Supplement 4, 2014 (1064P)
Kuhn (2008) *Directed evolution generates a novel oncolytic virus for the treatment of colon cancer.* PLoS One 3, e2409.