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Synergistic anti-tumor effect of Allocetra-OTS in combination with immune checkpoint inhibitors (ICI)/chemotherapy/CAR-T, through in-vivo reprogramming of macrophages

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Background & Aim

ICI revolutionized solid tumor treatment, however, in many tumors only partial response is achieved. Here we investigated the potential anti-cancer activity of Allocetra-OTS, a novel macrophages reprogramming cell therapy (Enlivex Therapeutics Ltd), on solid tumor progression as a monotherapy and in combination with various ant-cancer agents.

Methods

Allocetra-OTS is manufactured from enriched mononuclear fractions and induced to undergo stable early apoptosis.

In an immunocompetent model, Balb/c mice were inoculated in the peritoneal cavity with AB12 (mesothelioma) stably transduced with pLenti-PGK-V5-Luc-Neo for IVIS visualization and treated with anti-CTLA4, anti-PD1, or cisplatin, with or without Allocetra-OTS. Allocetra-OTS was also administered as monotherapy. Kaplan-Meier log rank test was done for survival. CAR-T model was induced in immune-deficient SCID-Bg mice that were inoculated intraperitoneally with human HeLa-CD19 or HeLa-CD19-luciferase cells, followed by treatment with 10×10^9 cells of Allocetra-OTS or vehicle, and 1×10^7 CD19-CAR-T cells or mock T cells.

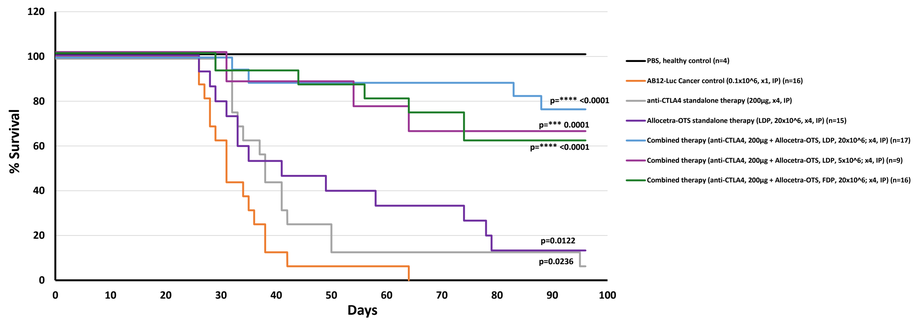
Results

Anti-CTLA4 standalone therapy significantly improved survival from **mean 34±9** to **44.9 ±20 days (p<0.05).** Allocetra-OTS standalone therapy improved survival to **52.3 ±20 days (p<0.02)** and combinational therapy; anti-CTLA4 + Allocetra-OTS improved survival to **86.7±20 days (p<0.0001)** with complete cancer remission in 60-100% of mice (Fig. 1 A+B). Similar anti-tumoral effects of Allocetra-OTS were seen in combination therapy with cisplatin (Figure 2) or anti-PD1 (Figure 3).

In the CAR-T model, SCID-Bg mice survived **30±5 days (range 27–37)** and were sacrificed or died from tumor progression. Results were verified using IVIS of intraperitoneal HeLaCD19-Luc cells. CAR-T cell therapy significantly ameliorated survival to **55±11 days (p<0.05 vs MOCK)**. However, when mice received co-administration of Allocetra-OTS and CAR T cells, a further significant increase in survival was seen, with a survival of **70±20 days (range 48-90, P<0.05 vs CAR-T alone).**

During the progression of intraperitoneal tumor, Allocetra-OTS as standalone therapy was effective and in combinational therapy with either anti-CTLA4, anti-PD-1, cisplatin or CAR-T, significantly reduced tumor size and enabled complete remission in up to 100% of treated mice.

A



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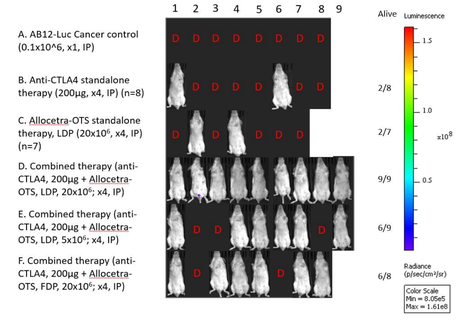

Figure 1. A. BALB/c mice (female, 7 weeks) were IP inoculated with $0.1x10^6$ luciferase- expressing AB12 tumor cells (AB12-luc) on day 0, IP. On days 12, 15, 19 and 22, mice were treated IP with 200µg anti-CTLA-4 (BioXcell) and/ or 5 or $20x10^6$ Allocetra-OTS cells. Mice were monitored daily for clinical score and survival **B.** IVIS imaging on day 81. IVIS was performed at days 6, 11, 18, 25, 39, 53, 67 and 81 (Perkin-Elmer, Lumina III).

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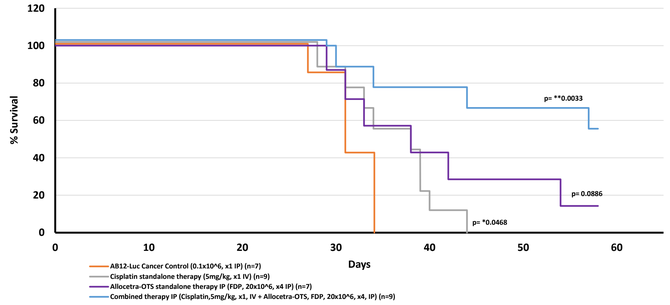

Figure 2. BALB/c mice (female, 7 weeks) received 0.1×10^6 luciferase-expressing AB12 tumor cells (AB12-luc) on day 0, IP. On days 12, 15, 19, and 22, mice were treated IP with 20×10^6 Allocetra-OTS cells (FDP) and on day 13, mice were treated IV with 5mg/kg Cisplatin (Abiplatin, TEVA). Mice were monitored daily for clinical score and survival.

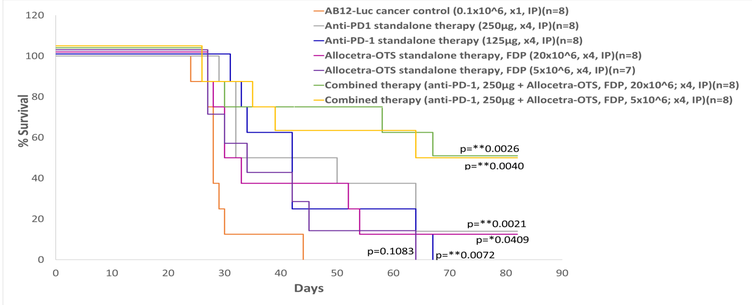

Figure 3. BALB/c mice (female, 7 weeks) received 0.1×10^6 luciferase-expressing AB12 tumor cells (AB12-luc) on day 0. On days 12, 15, 19, and 22, mice were treated IP with 125µg or 250µg anti-PD-1 (BioXcell, BE0146) and/or $5x10^6$ or $20x10^6$ Allocetra-OTS cells (FDP) at a 1-hour interval. Mice were monitored daily for clinical score and survival

Conclusion

During intraperitoneal tumor progression, Allocetra-OTS as standalone therapy or in combination with ICI, cisplatin or CAR-T therapy, significantly reduced tumor size and resulted in complete remission in up to 100% treated mice.

Based on excellent safety profile in > 40 patients treated in prior clinical trials for sepsis and COVID-19, Phase I/II clinical trial of Allocetra-OTS plus chemotherapy started on July 2022, and a second Phase I/II clinical trial of Allocetra-OTS plus anti-PD1, as a second- and third-line therapy in various cancers, is planned for Q4 2022.