Improved anti-tumor immunity and efficacy upon combination of the IDO1 inhibitor GDC-0919 with α-PD-L1 blockade versus α-PD-L1 alone in preclinical studies

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INTRODUCTION

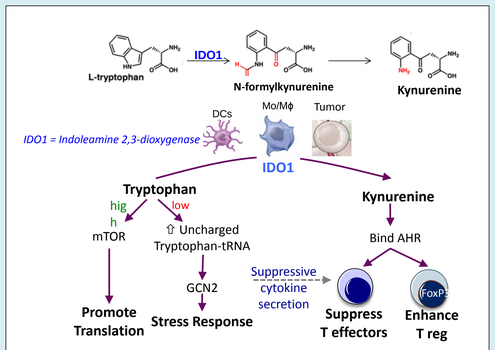
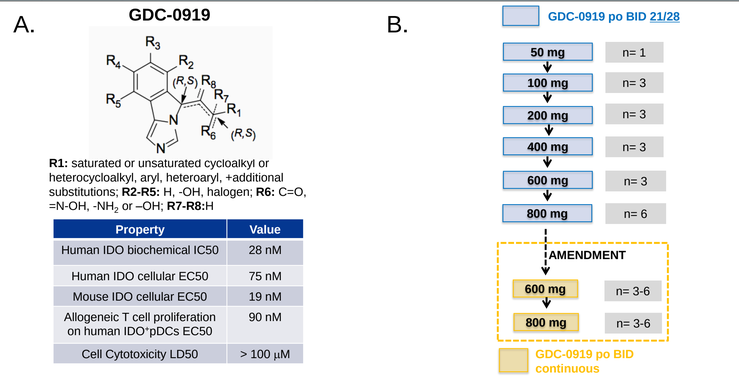


Figure 1. IDO1 Creates an Immunosuppressive Tumor Microenvironment Through Metabolic Modulation

Indoleamine 2,3-dioxygenase (IDO1) is a tryptophan-catabolizing enzyme that plays a key role in immune suppression (Figure 1). Breakdown of tryptophan (Trp), generation of kynurenine (Kyn) and additional Trp metabolites result in the suppression of T effector function and the potentiation of regulatory T cell (Treg) function. IDO1 is therefore a promising target for Cancer Immunotherapy (CIT) and IDO inhibitors are currently in clinical trials. Accumulating data suggest that durable anti-tumor responses require combinations of different CIT agents. Atezolizumab (anti-PD-L1 mAb) targets a key negative immune checkpoint and has shown promising results in critical trials. Combination of GDC-0919 and Atezolizumab is a promising strategy for inhibiting two critical immune regulators.



Property	Value
Human IDO biochemical IC50	28 nM
Human IDO cellular EC50	75 nM
Mouse IDO cellular EC50	19 nM
Allogeneic T cell proliferation on human IDO+pDCs EC50	90 nM
Cell Cytotoxicity LD50	> 100 μM

Figure 2. GDC-0919 is a potent IDO1 inhibitor that has completed Phase 1A studies. A. GDC-0919 key properties. B. Phase IA design: patients received escalating doses of GDC-0919 BID for 21 days followed by a 7 day break. Safety, PK and peripheral PD endpoints were analyzed and previously reported (Nayak A. et al, 2015). Protocol amended to test 600 and 800 mg BID continuously with safety, PK and PD endpoints.

GDC-0919 (previously NLG919) is a potent, selective small molecule IDO1 inhibitor (Mautino et al.; 2013), intended for use in combination as a Cancer Immunotherapy target. 19 patients were dosed in PhIA with a 50-800 mg BID 21/28 days regimen. GDC-0919 was well tolerated and MTD was not reached. PK was approximately dose proportional with a $t_{1/2}$ ~ 12 hrs. Peripheral blood testing of Kyn and Trp levels showed GDC-0919 transiently decreased plasma Kyn beyond 95% CI, in a manner consistent with its PK profile. No significant modulation of plasma Trp observed, as expected (Nayak A. et al, 2015).

RESULTS

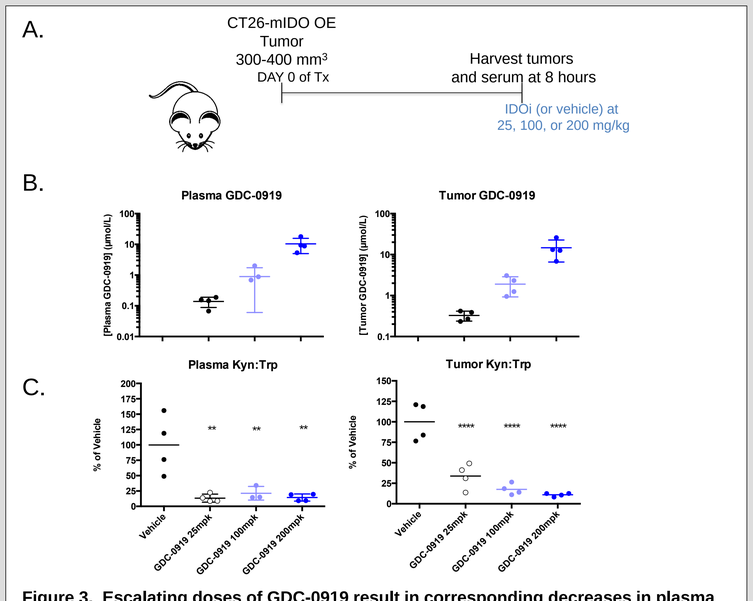


Figure 3. Escalating doses of GDC-0919 result in corresponding decreases in plasma and tumor Kyn:Trp ratios. A. Schematic of experimental design. Balb/c mice were inoculated with CT26 cells overexpressing murine IDO1. When tumors reached 300-400 mm^3, mice were grouped out. The following day, mice were treated with varying doses of GDC-0919 and plasma and tumors were harvested 8 hours later. B. Plasma and tumor drug levels increase with increasing doses of GDC-0919. C. Ratio of Kynurenine to Tryptophan decreases with increasing doses of GDC-0919. No changes in Trp were observed. Asterisks indicate statistical significance relative to vehicle.

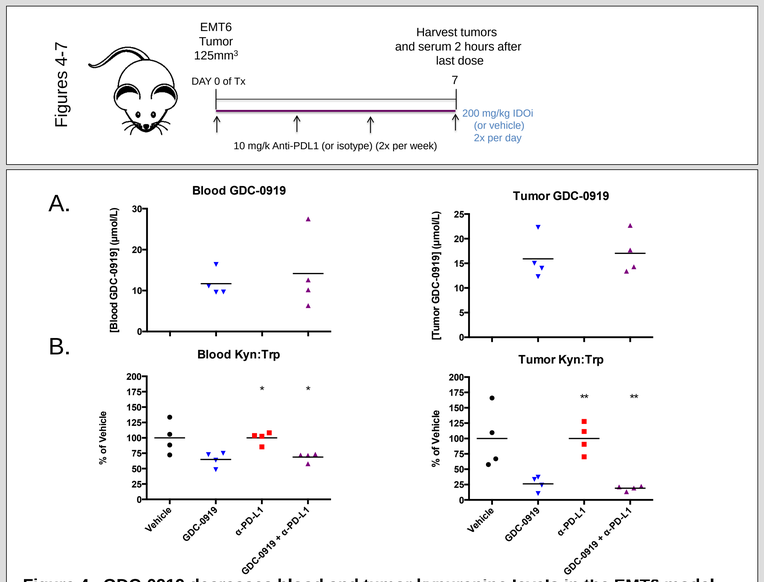


Figure 4. GDC-0919 decreases blood and tumor kynurenine levels in the EMT6 model. Balb/c mice were injected with EMT6 cells followed by treatment with α-PD-L1 alone (10 mg/kg, 2x/week), GDC-0919 alone (200 mg/kg twice daily), or a combination of the two. At 2 hrs post-last-dose, blood and tumors were assessed for GDC-0919 (A) and kynurenine:tryptophan (B) concentrations. Asterisks indicate statistical significance relative to vehicle.

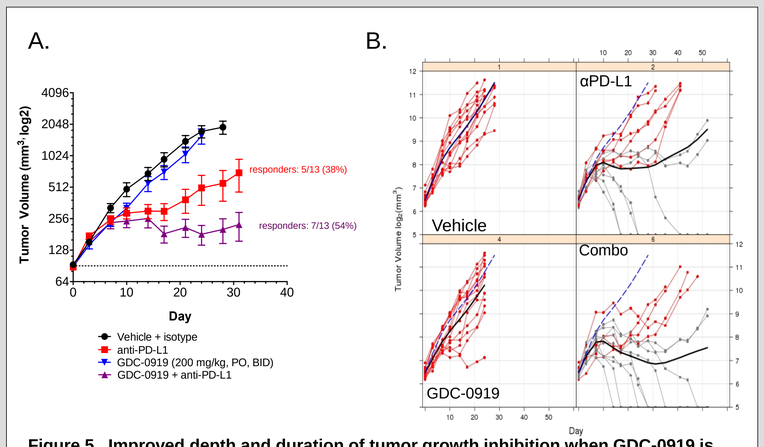


Figure 5. Improved depth and duration of tumor growth inhibition when GDC-0919 is combined with αPD-L1 *in vivo*. Balb/c mice were injected with EMT6 tumors followed by treatment with either αPD-L1 alone, GDC-0919 alone, or the two in combination. Tumors were measured twice weekly. A. Average tumor volumes. B. Individual mice tumor growth curves.

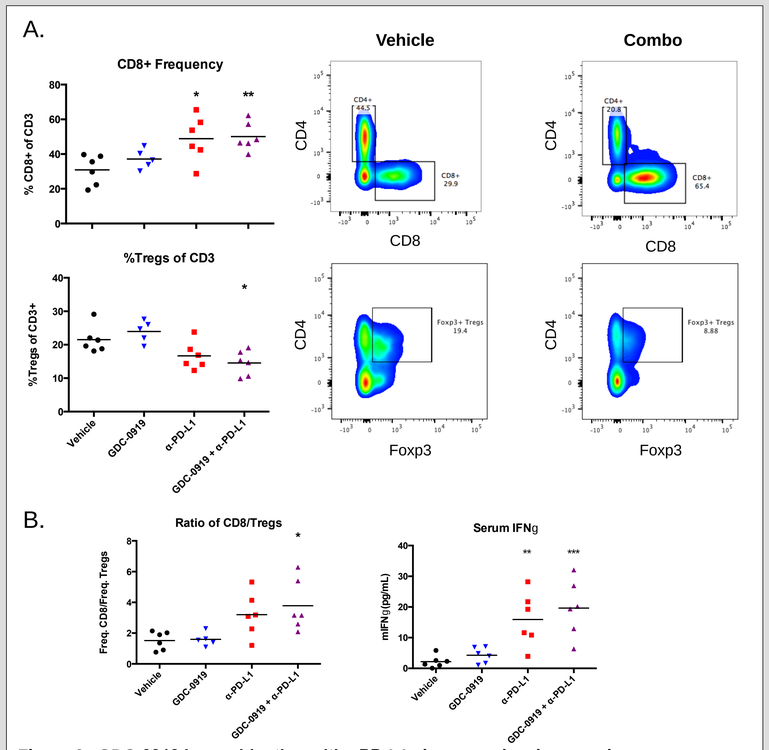


Figure 6. GDC-0919 in combination with αPD-L1 shows modest but consistent improvement of adaptive immune response markers versus αPD-L1 alone in EMT6 model. A. Top, CD8$^+$/CD3$^+$ T cell frequency with representative dot plots on the right. Bottom, Treg/CD3$^+$ T cell frequency with representative dot plots. B. CD8:Treg ratio (left) and serum IFNγ levels (right) across treatment groups. Asterisks indicate statistical significance relative to vehicle group.

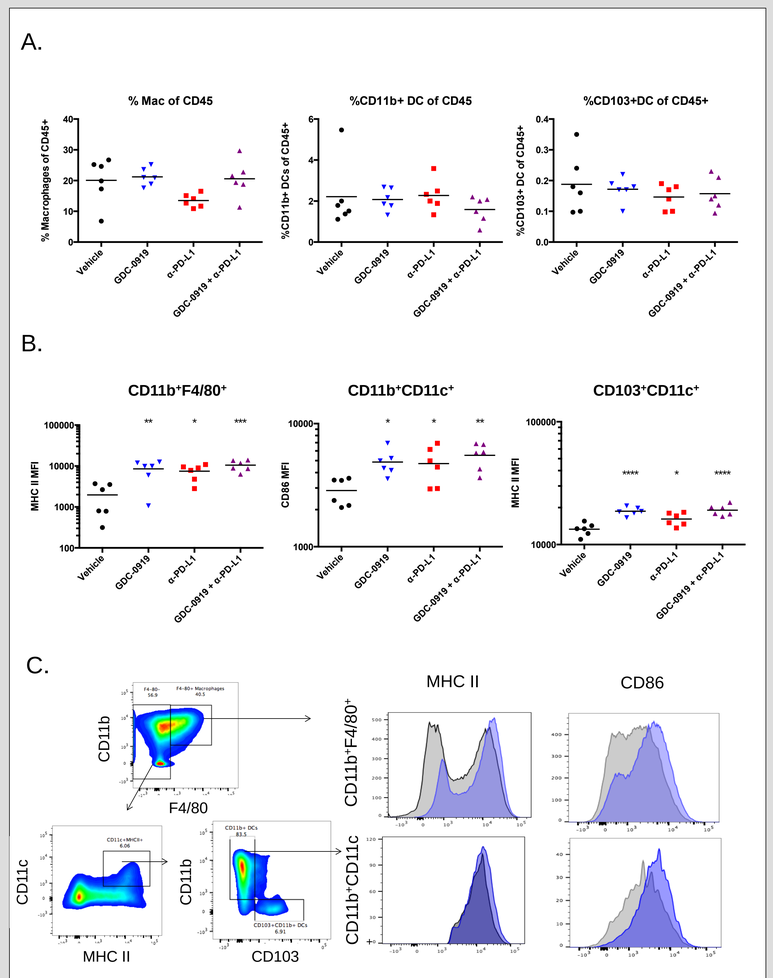


Figure 7. GDC-0919 alone induces myeloid cell activation markers which is maintained and modestly improved in αPD-L1 combo in EMT6 model. A. Percentage of macrophages (left), CD11b$^+$ DCs, (middle), and CD103$^+$ DCs (right) of CD45$^+$ cells does not change with treatment. B. Summary graph of CD11b$^+$F4/80$^+$ MHC II (left), CD11b$^+$CD11c$^+$ DC CD86 (middle), and CD103$^+$CD11c$^+$ DC MHC II expression (right).B. Histograms of CD11b$^+$F4/80$^+$, CD11b$^+$CD11c$^+$ DC, and CD103$^+$CD11c$^+$ DC MHC II (left) and CD86 (right) levels. Gray:Vehicle, Blue: GDC-0919. Asterisks show significance relative to vehicle.

SUMMARY AND CONCLUSIONS

- In the clinic, peripheral blood testing of Kyn levels showed GDC-0919 transiently decreasing plasma Kyn beyond 95% CI, in a manner consistent with its PK profile; PK was approximately dose proportional with a $t_{1/2}$ ~ 12 hrs (Nayak et al.)
- Preclinically, GDC-0919 decreased plasma and tumor Kyn levels in tumor-bearing mice in a dose-dependent manner
- A combination treatment of GDC-0919 with αPD-L1 in the EMT6 syngeneic model resulted in improved anti-tumor activity compared with αPD-L1 alone
- EMT6 treatment of GDC-0919 in combination with αPD-L1 led to increased CD8$^+$/Treg ratio and increased serum levels of IFNγ consistent with a stronger adaptive anti-tumor immune response
- GDC-0919 induces activation of intratumoral CD11b$^+$F4/80$^+$ macrophages as well as CD11b$^+$CD11c$^+$ and CD103$^+$CD11c$^+$ DCs as single agent and in combo
- **A phase 1b study of GDC-0919 in combination with atezolizumab, αPD-L1 antibody (NCT02471846) is currently ongoing**

ACKNOWLEDGEMENTS & REFERENCES

We thank the entire GDC-0919 Team at GNE and NLG for their contributions

- Mautino et al., AACR 2013, Abstract # 491
- Nayak et al., ECC 2015, Abstract # 346