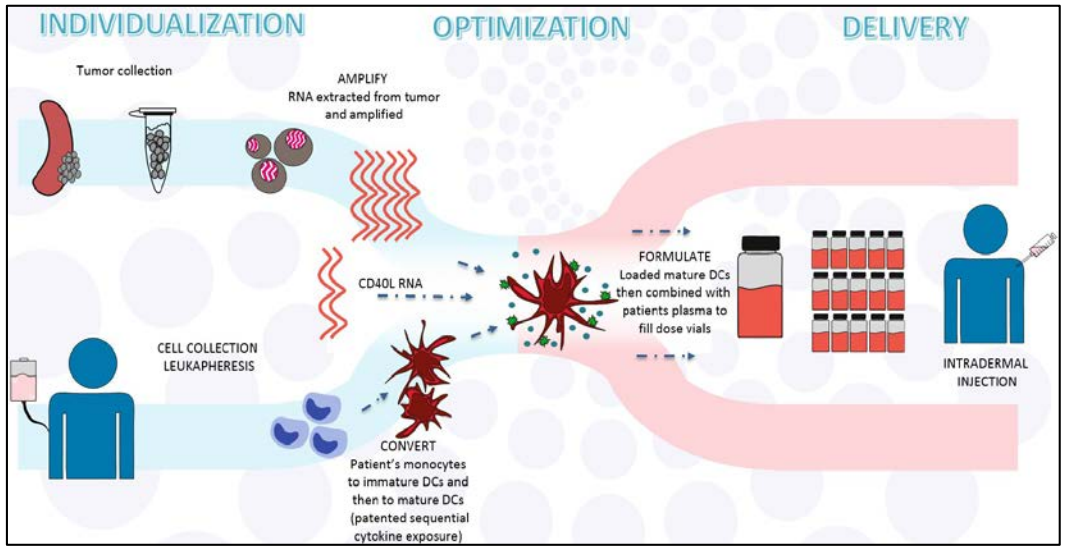
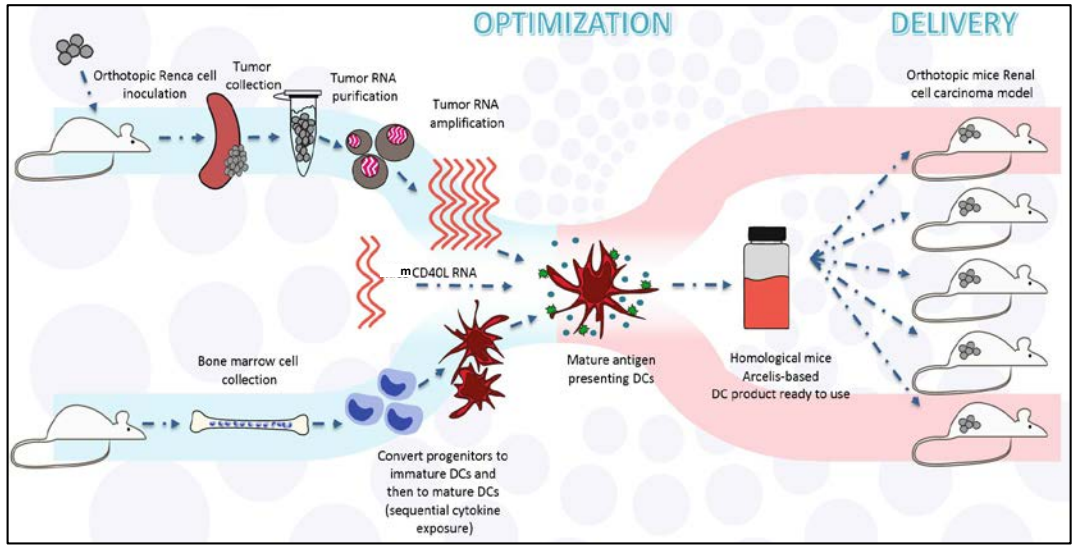
Optimized administration sequence and timing of active dendritic cell immunotherapy with a PD1 checkpoint inhibitor (CPI) resulted in strong synergy in a mouse model of renal cell carcinoma

Mouse analog of Rocapuldencel-T is manufactured similar to the human product

Arcelis®: patented high-yield process



Arcelis®-based mouse product process



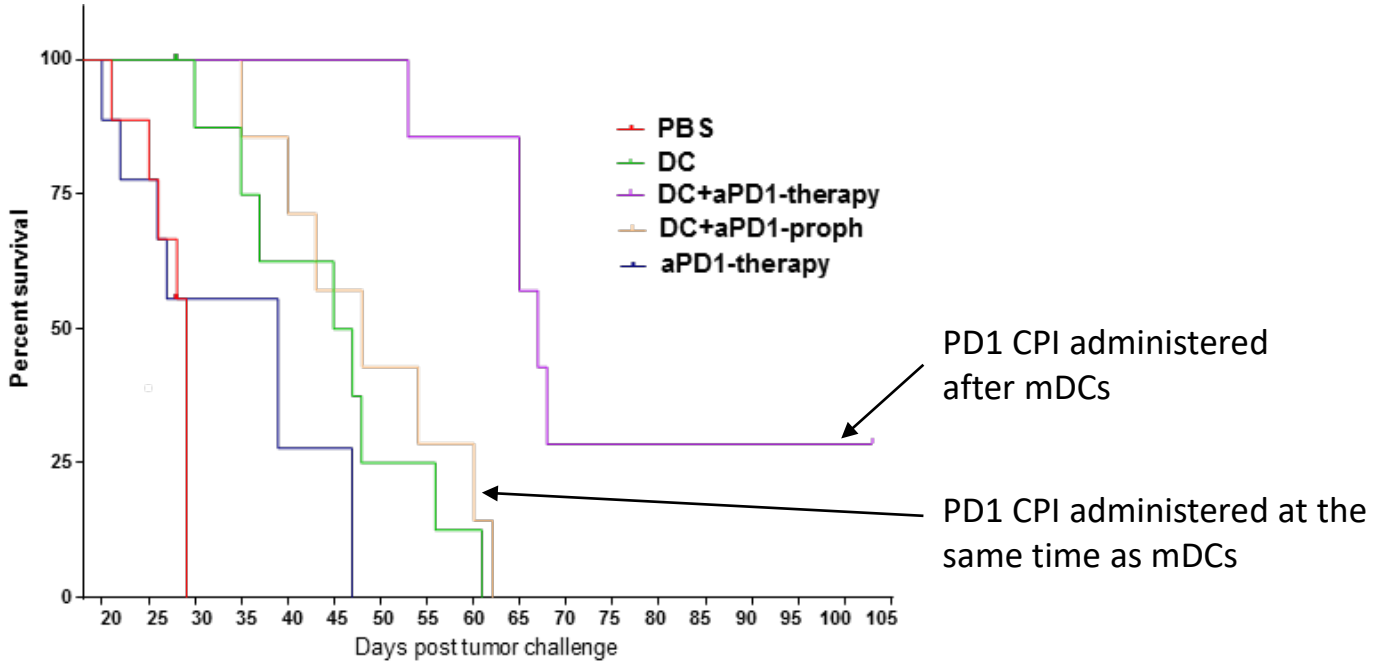
The mouse analog of Rocapuldencel-T:

- Uses the same sequential cytokine maturation process with equivalent murine reagents
- Uses RNA encoding murine CD40L
- Has the same mechanism of action as Rocapuldencel-T (*i.e.,* induction of CD8+CD28+CD45RA- memory T cells)*

*Reported previously at the annual SITC conference in 2016

Synergy with combination therapy was only observed when the PD1 Checkpoint Inhibitor (CPI) was administered after the dendritic cell product

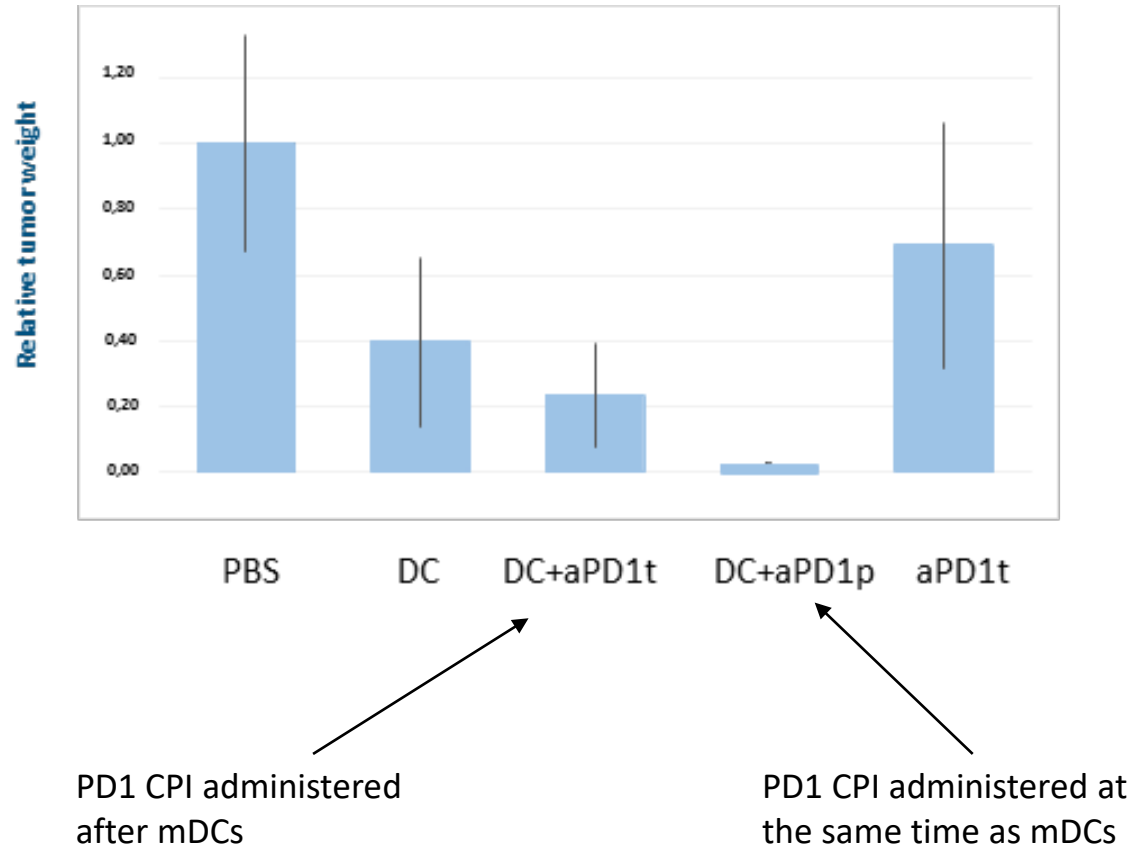
Survival curves of murine dendritic cell (mDC) combination therapy with anti-PD1 murine antibody (aPD1 mAb) in mouse renal cell cacinoma (RCC) model



	PBS	DC	DC + aPD1-therapy	DC + aPD1-proph	aPD1-therapy
Median survival	29	46	67	48	39

Control of tumor growth at day 26 was greatest with combination therapies

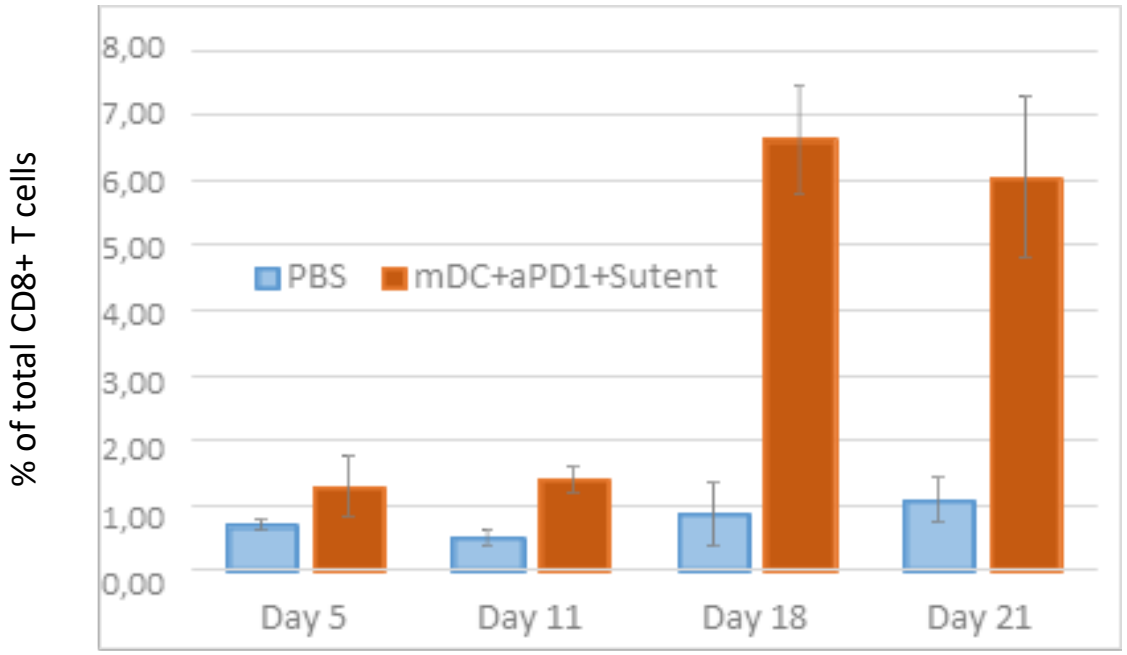
Relative tumor weight on day 26 after the orthotopic Renca cell inoculation



- The greatest control of tumor growth (mDC and CPI administered at the same time) did not translate into long-term survival
- The PD1 CPI may interfere with the development of memory T cells (not tested in this experiment)
- Suggests that progression free survival (PFS) may not always be an accurate surrogate for overall survival (OS)

CD8+CD28+CD45RA- memory T cells were induced by the optimized combination therapy (Similar mechanism of action (MOA) as Rocapuldencel-T)

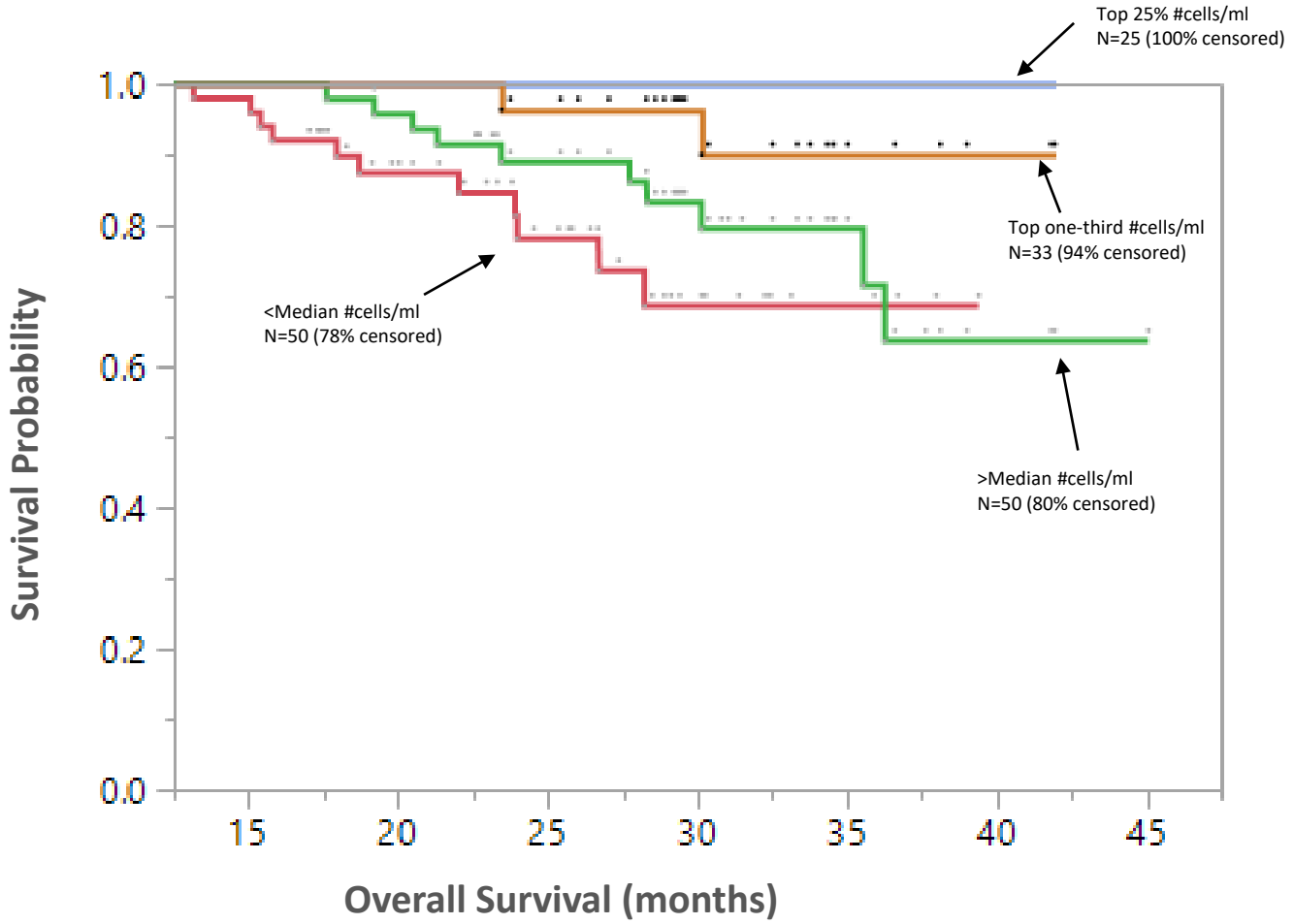
Total % of memory T cells ($CD8^+/CD28^+/CD45RA^-$) in splenocytes increased in response to combination therapy after the orthotopic Renca cell inoculation



- Similar to the observation in the Phase 3 ADAPT trial, the induction of memory T cells had a delayed effect after a single administration
- In the ADAPT trial the memory T cell response became a statistically significant correlate to OS after 7 doses

Rocapuldencel-T MOA: Induced number of memory T cells correlate with OS in the Phase 3 ADAPT trial

The change in the number of antigen-specific memory T cells/ml correlated with OS after 7 doses (Spearman's Rho=0.40, p<0.0001)



- Analysis included 100 patients who received at least 7 doses out of the 146 patients analyzed for immune response.
- Median change = 4,796 cells/ml

**Memory T cells defined as CD8+CD28+CD45RA- cells reactive with antigens encoded by autologous tumor RNA*

Note: Data from patients enrolled at North American sites

Conclusions

- The mouse analog of Rocapuldencel-T induced the same type of memory T cells as the human product
- Similar to the human product, the induction of mouse memory T cells was delayed with respect to immunization (18-21 days)
- Only one combination setting (PD1 CPI administered after mDCs) resulted in a significant synergistic effect on survival
- Administration of PD1 CPI at the same time as mDCs resulted in the best control of tumor growth but had no significant effect on survival over mDCs alone

Implications and considerations for clinical development of combination CPI / Rocapuldencel-T therapies

- PD1 CPIs are becoming accepted standards of care in several indications but may benefit only a minority of patients
- Combinations with PD1 CPIs are actively being studied to improve overall efficacy
- The mouse model system described here may provide a guide for intelligently combining active immunotherapy with PD1 CPIs. We note the limitation of mouse models, however, useful testable hypotheses are being generated which can be prospectively tested in human clinical trials
- The data suggest that inducing memory T cell responses prior to administering a PD1 CPI may result in substantial synergy
- The observations from this study, if confirmed in human trials, may not be limited to Rocapuldencel-T but may more generally apply to other active immunotherapies