HIGHLY EFFECTIVE TREATMENT OF CD38 POSITIVE EXPERIMENTAL LYMPHOMA WITH $^{225}\text{AC}_\text{TINNIUM-DARATUMUMAB}$

Wojciech Dawicki, Kevin Allen, Rubin Jiao, Mackenzie Malo, Mark Burger, Dale Ludwig and Ekaterina Dadachova

Actinium Pharmaceuticals, Inc.
ERADICATING TUMOR CELLS WITH ALPHA-PARTICLES

- $\alpha$-particle emitting isotopes ($^{225}$Ac) are highly cytotoxic to tumor cells
- $\alpha$-particles have high linear energy transfer
- One nuclear transversal can kill a cell
- $\alpha$-particles only travel several cells diameters (~100μm)
- $\alpha$-particles have been shown to be effective in killing cancers resistant to beta- or gamma-radiation
- Low probability of resistance development
ERADICATING TUMOR CELLS WITH $^{225}$Ac

- Half-life of 10 days
- Emits net 4 alpha particles per decay
- Antibodies can be effectively labeled with $^{225}$Ac
- $^{225}$Ac labeled antibodies have been investigated in clinical studies
Targeting $^{225}$Ac to Multiple Myeloma Tumors with Daratumumab Antibodies

- CD38 is expressed on multiple myeloma (MM) cancer cells
- Unlabeled Daratumumab is a CD38 specific antibody that is being used to treat MM patients
- 30% of relapsed/refractory MM patients respond to treatment with Daratumumab
- Increasing the efficacy of Daratumumab may increase the number of patients who respond to anti-CD38 therapy and reduce the number of infusions needed to effect a response

Goal

Attaching $^{225}$Ac to Daratumumab to increase its efficacy, without affecting intrinsic cytotoxic properties
LABELING OF ANTIBODIES WITH $^{225}\text{Ac}$

- DOTA is first conjugated to lysines on antibody
- DOTA-conjugated antibody is subsequently labeled with $^{225}\text{Ac}$
- Labeling efficiency of >95%
- No further purification is required
CONJUGATION OF DOTA TO DARATUMUMAB DOES NOT EFFECT BINDING TO CD38
**$^{225}$Ac-labeled Daratumumab Kills Tumor Cells**

- **Daudi**
- **KMS28BM**
- **KMS28PE**

Graphs showing the percentage of cell death (% Dead) in different concentrations of antibodies (mAb, ug/mL): 0, 0.02, 0.04, 0.06, 0.1.

- **$^{225}$Ac-daratumumab**
- **$^{225}$Ac-IgG**
- **Daratumumab**
IS $^{225}\text{Ac}$-DARATUMUMAB EFFECTIVE IN CONTROLLING TUMORS IN MICE?
DARATUMUMAB DELIVERS RADIOACTIVITY TO TUMORS
$^{225}\text{Ac-DARATUMUMAB CONTROLS THE GROWTH OF CD38 POSITIVE TUMORS}$

**Daudi**

**KMS28BM**

![Graphs showing tumor growth over days post treatment for Daudi and KMS28BM with different treatments: $^{225}\text{Ac-Daratumumab}$, Daratumumab, Saline.](image)
LABELING DARATUMUMAB WITH $^{225}$AC INCREASES ITS POTENCY ~30 FOLD
$^{225}\text{Ac-DARATUMUMAB INCREASES LIFE EXPECTANCY OF TUMOR-BEARING MICE}$
$^{225}$Ac Treatment Has a Transient Effect on Body Weight
Treatment with $^{225}$Ac Labeled anti-murine CD38 Antibody Has no Systemic Toxicity
SUMMARY

- Conjugation of daratumumab to DOTA does not compromise CD38 binding
- Conjugation of daratumumab to DOTA does not affect binding of DARA to complement (C1q)
- Conjugation of daratumumab to DOTA does not inhibit ADCC
- Daratumumab rapidly accumulates in the tumor by 24h and is retained selectively in the tumor by day 7
- The conjugation of daratumumab with $^{225}$Ac dramatically increases the anti-tumor potency of the anti-CD38 antibody in a Daudi and multiple myeloma xenografts.
- $^{225}$Ac-daratatumumab conjugate was well tolerated and increased the in vivo potency of the antibody by at least 30-fold.
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