



Targeted Alpha Therapy (TAT) Use of Actinium-225

Regulatory Interactions Now and
Tomorrow

I am an employee of Fusion Pharmaceuticals

The views and opinions expressed during my presentation are my own and do not necessarily reflect the official policy or position of Fusion Pharmaceuticals

“Radioactive drugs are regulated by the FDA to the same extent that FDA regulates other drugs. With the exception of certain research uses of radioactive drugs (as specified in 21 CFR 361.1), all radiopharmaceuticals are considered to be new drugs and subject to the applicable provisions of the Federal Food, Drug, and Cosmetic Act and the drug regulations issued under Title 21 of the Code of Federal Regulations”- FDA

July 28, 2021:

**Fusion Pharmaceuticals Announces FDA Clearance
of IND for FPI-1966, an Investigational
Radiopharmaceutical for the Treatment of Head and
Neck and Bladder Cancers Expressing FGFR3**

and other FGFR3 expressing tumors: CRC, Breast, Lung, Liver

Common- Industry-wide- IND Deficiencies*: Radiopharma Development is Still Drug Development



- Frequent IND CMC Deficiencies
 - Incomplete information regarding:
 - Quality of the materials used to make the product
 - Manufacturing process development (e.g., no process development runs)
 - Safety, quality and stability testing (e.g., inappropriate testing, sampling)
 - Cross referenced information (e.g., wrong cross ref, cross ref is deficient)
 - Manufacturing facility, QA/QC, shipping
 - Poorly organized submissions
 - Lack of alignment of CMC development with clinical timeline
 - No comparability plans when planning is needed
- Common IND Pharm/Tox Deficiencies
 - Preclinical testing program not comprehensive enough
 - Differences between the preclinical and clinical product
 - Inadequate preclinical study designs
 - Study conduct issues
 - Safety concerns based on toxicity profile

*Sourced from FDA presentations, RAPS and industry surveys

● General Expectations

- Demonstration of potency, sterility, identity and purity (impurities)
- Understand critical quality attributes
- Chemical, physical, biological and microbiological attributes that can be defined, measured and monitored to ensure final product outputs remain within acceptable quality limits.
- Establish a standard for risk and control in clinical studies
- Robust analytics enable manufacturing changes- during development and post approval

● Regulatory Considerations

- 1 theragnostic pair, 2 IND's that have 70% overlap with simultaneous reviews; conducted in parallel in two separate divisions (DOP and DIRM)
- Multiple DS Sections

● CMC

- Our drug products, due to their very nature, decay over time
 - Retrospective analysis of the DP is therefore impossible
- The only CMC guidance is a PET guidance
- Exceptions in USP's for radiopharmaceuticals (i.e., SVP testing and metal impurities)

● Non-clinical Assessments

- Certain cell-based nonclinical safety studies may not be addressable or relevant as the therapeutic isotope may impact the test system and/or the effects observed may be specific (due to the radionuclide)
 - Justification of approach, including the use of cold equivalents, must be developed and provided

● Specific Quality Expectations

- Batch data results must be provided for radionuclidic purity and submitted in the IND
- Demonstrate that manufacturing processes are capable of purging the Ac-225 decay products. The fate of radioactive decay products during the shelf life of the Ac-225 containing product should also be in the IND
- **Are generator and accelerator produced Ac-225 nitrate products of equivalent quality?** Data for both generator and accelerator Ac-225 must be in the IND. Certificates of analyses for generator and accelerator derived material must also be provided.

● Specific Quality Expectations (continued)

- Details regarding the method used to determine radionuclide impurity should be included in the IND
- Details on the methods used to quantitate other alpha and beta emitting impurities that may be present in Ac-225 should be detailed in the IND

- Regulatory agencies globally need to be prepared for new approaches in nuclear medicine and must be flexible in regulatory approach, case-by-case should be the new, old, paradigm
 - Different nuclides can be used for diagnostic and therapeutic application
 - Different investigational products require separate INDs even when there is only one clinical program
 - Regulatory agencies need to work with sponsors to streamline theragnostic development
 - The theragnostic approach allows for targeted patient selection while increasing the likelihood of a strong therapeutic effect
 - Is the imaging agent a “companion diagnostic”, a “diagnostic imaging agent”, or something else when co-developed? This is not just semantics

- Complex supply chains and manufacturing processes are hurdles to be overcome
- Logistics of clinical supply can be a huge challenge, particularly with multinational studies

- Co-production of Ac-227 as a known, or specified, impurity:
 - The supply of generator produced Ac-225 is at capacity
 - Additional generator supplies won't be available in the near term to support clinical trials
 - Accelerator-produced actinium must be used until additional technologies become available
 - However, this material contains a long-lived radionuclide impurity
 - Process qualification information must be generated
 - Radionuclidic impurity limit must be provided as a specification and justified
 - Justification for the use of material containing this “long lived radionuclidic impurity” must be provided in the IND
 - NRC/RAM licensing concerns
 - Waste disposal concerns

- Demonstration of comparability/interchangeability of generator and accelerator produced Ac-225
 - Technological improvements?
- Waste disposal at clinical sites and also once approved
- Global acceptability of the Ac-227 impurity
- Multiple INDs for a single theragnostic pair
 - Managing expectations of more than one review team
 - Communicating similar or identical information to more than one division
 - Coordination of Information Requests across review divisions

- Improving the public perception of radiopharmaceuticals
- Establishment of clinical/medical disciplines that focus solely on radiopharmaceutical therapies
- “Partnering” with regulators to develop combination therapies which capitalize on patient dosimetry, imaging and therapy
- Technological advancement of Ac-225 production and increased interactions between suppliers, FDA and radiopharma companies

(Genus Med. Techs., LLC v. FDA, 2021 U.S. App. Lexis 10928)

“The FDA has long regulated imaging agents as drugs, rather than devices, even though some imaging agents meet the definition of both a drug and a device

Imaging agents were regulated by FDA as drugs regardless of whether they serve as an enhancement for imaging devices like ultrasound, CT, MRI, and radiology devices, or are necessary to produce an image, such as in the case of radiopharmaceutical imaging.”- RAPS

At present, this seems to implicate only barium contrast agents but history (specified biologics moved to CDER from CBER) show that migration of product regulation within FDA cannot be easily predicted by industry

● **MEET WITH REGULATORS!**

- Take full advantage of every meeting available
- Know the “Formal Meetings...” Guidance

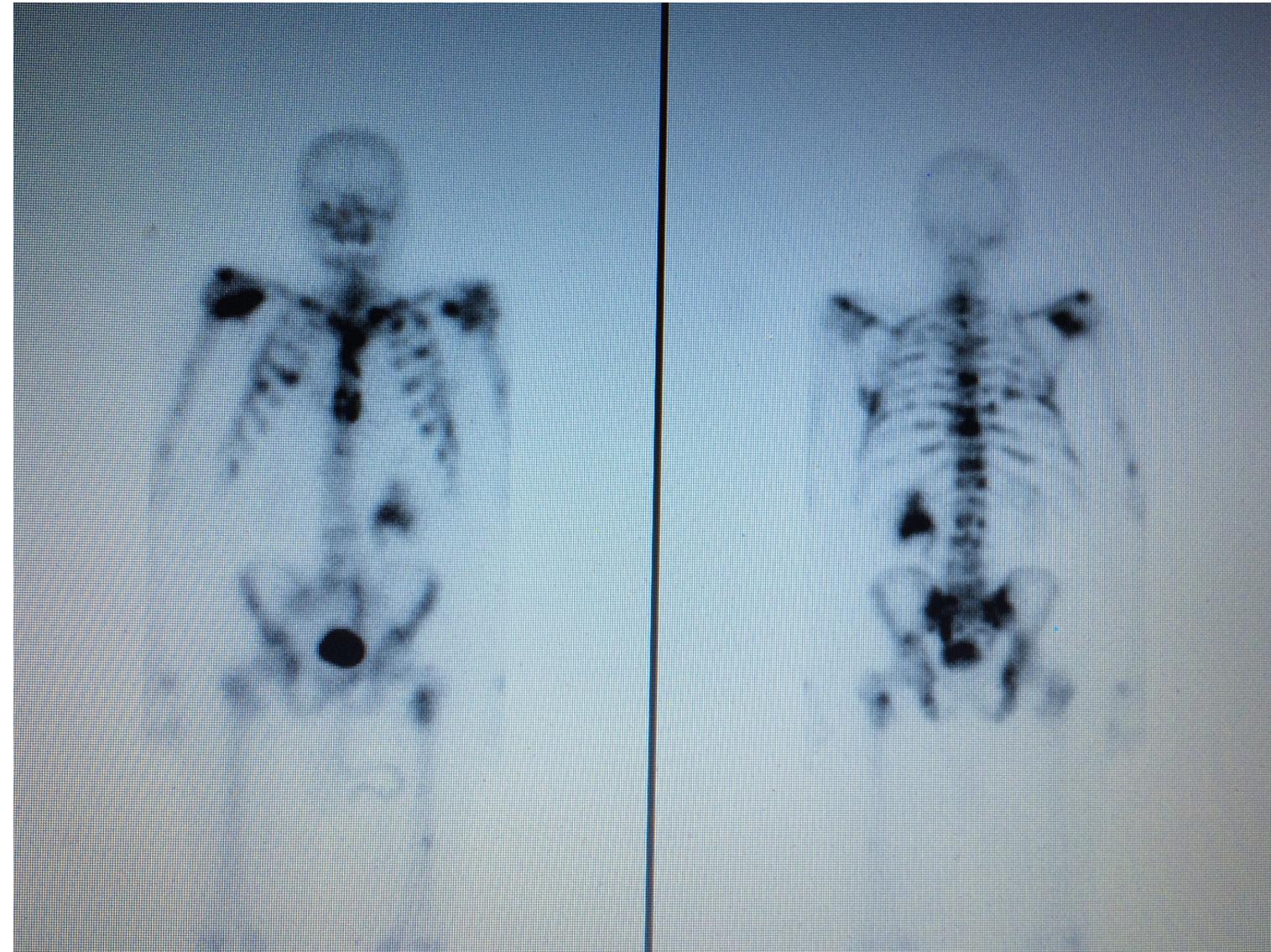
● Address every concern raised by the Regulator before you submit an application

● Do not submit an application before it is ready- beware the desire for speed

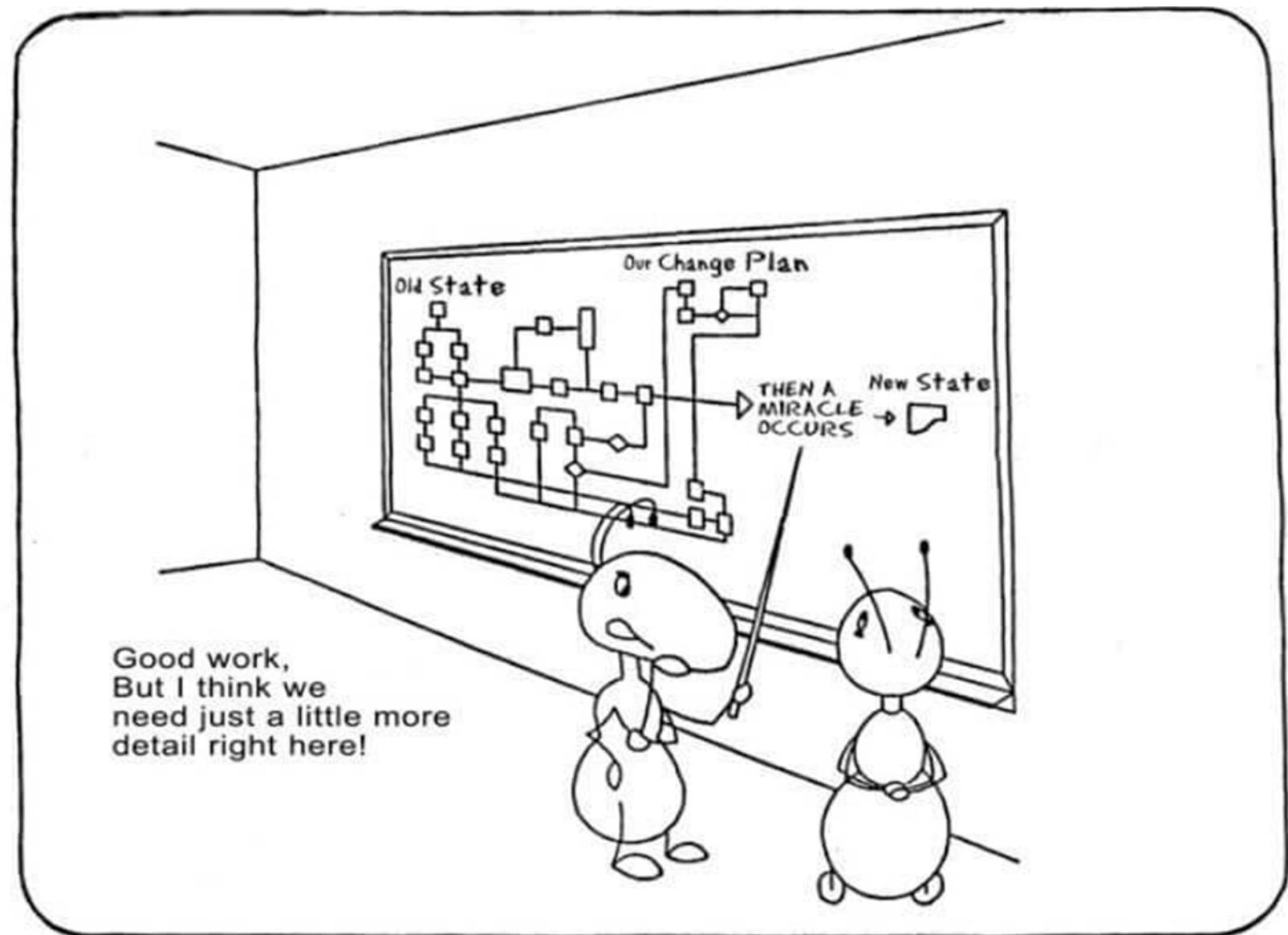
● NEVER submit an incomplete application

● Information Requests happen, always anticipate

Different things provide career motivation



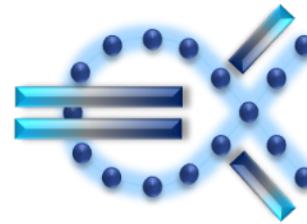
Thank you.



Industry Experience in the Development and Clinical Testing of Actinium-225-Based Radio-Conjugates

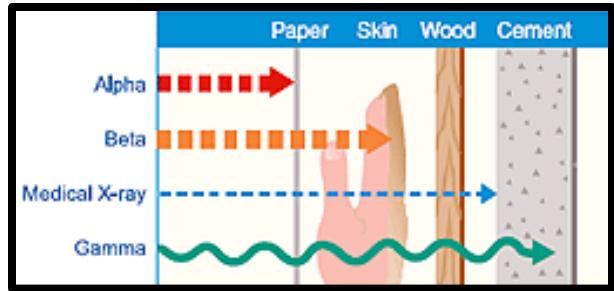
Mark S. Berger, MD
Chief Medical Officer
Actinium Pharmaceuticals

22 Sep. 2021

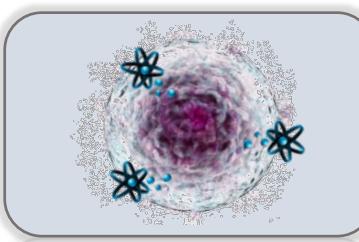
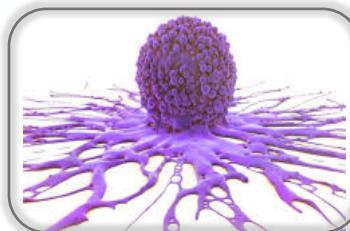
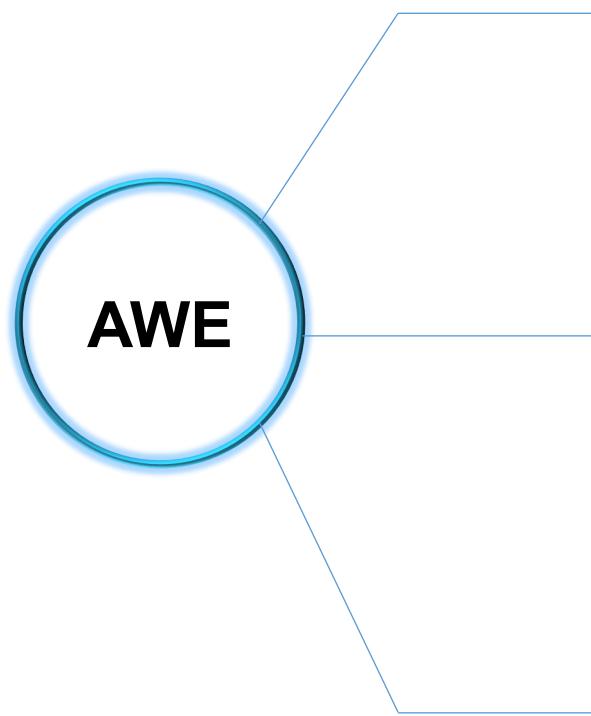


Actinium-225-Based Antibody Radio-Conjugates (ARCs)

- ◆ Actinium-225-based ARCs have desirable characteristics for industry development
- ◆ High Energy = High Potency
 - 5-8 MeV via emission of 4 α -particles
 - Cell kill possible with 1 α -particle hit to DNA
- ◆ Short Pathlength = Safety Potential
 - Approximately 4 cell lengths (50-80 microns)
 - Hit what you aim at and little else
- ◆ 10 day half-life provides time for manufacturing and distribution
- ◆ Lack of restrictions on patients after administration
 - Can go to the mall
- ◆ Actimab-A is an example of industry development of ARCs
 - Actimab-A refers to the anti-CD33 antibody lintuzumab labeled with Actinium-225
 - Distinguish from earlier use of lintuzumab labeled with Bismuth-213
 - Actimab-A was first Actinium-225 labeled agent in clinical trials
 - Largest clinical experience of Actinium-225 labeled agents



AWE (Antibody Warhead Enabling) Technology



AWE Platform Flexibility

- Multiple isotopes
- Applicable to any targeting agent

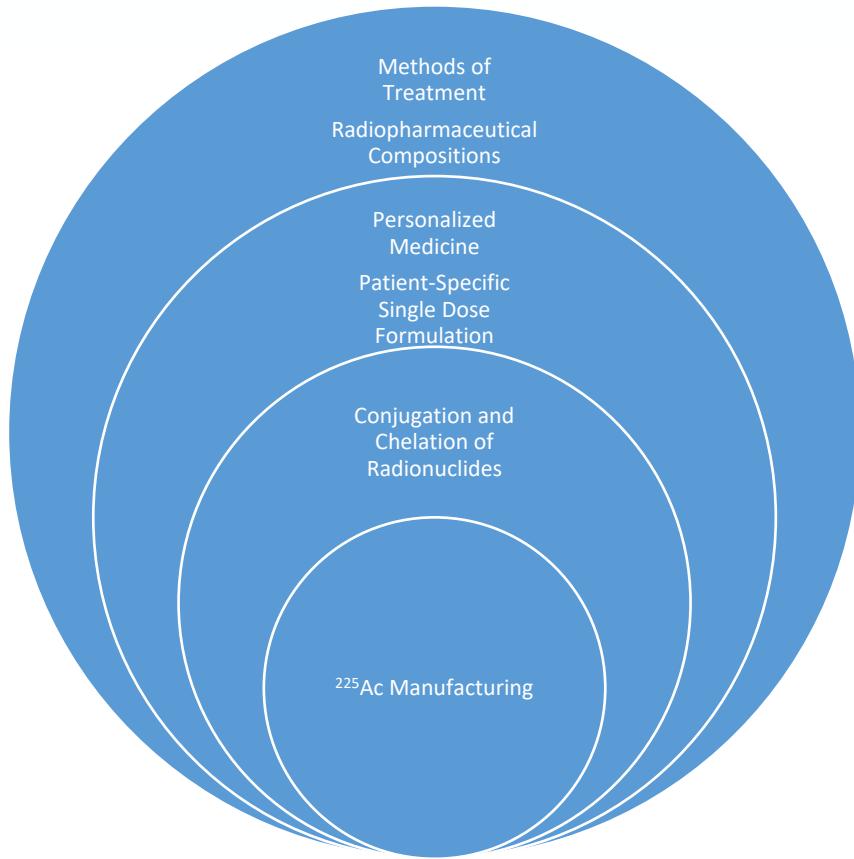
Next Generation ARCs

- Dramatically increase the potency of antibodies and other targeting agents
- Both solid and hematopoietic targets are amenable to ARCs
- Molecularly targeted to malignant cells

Combination Therapy

- Targeted delivery of radiation payload
- Potential synergy with chemotherapy, targeted agents, and immunotherapy

Leading IP Around Actinium-225 and ARCs

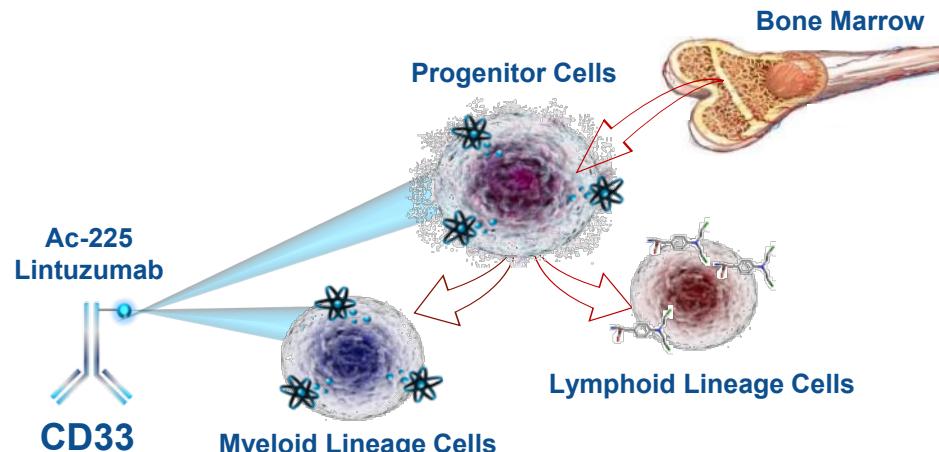


Multipronged Patent Portfolio

- 37 patent families
- >160 issued or pending patents worldwide
- Scope of IP ranges from ²²⁵Ac manufacturing to methods of treatment

CD33 - Target for Actinium-225-based Radio-conjugates

- ◆ Expressed on AML cells of 90% of patients
 - Also expressed on normal myeloid cells, and on myeloid and platelet precursors
 - Therefore anti-CD33 agents have class effect of myelosuppression
 - ANC and platelet count decreased
 - Decrease in platelets lasts longer than decrease of ANC
 - Not on mature RBCs, platelets
- ◆ Validated target
 - Antibody drug conjugate Mylotarg approved for treatment of AML
- ◆ CD33 is internalized on antibody binding
 - Internalization is required for anti-body drug conjugates such as Mylotarg
 - Not required for radio-conjugates as radioactivity will penetrate the cell



Prior Trials Facilitating Actimab-A Development

Previous trials with lintuzumab antibody alone and with lintuzumab labeled with Bismuth-213 led to further development with Actinium-225

‘Naked’ Lintuzumab Phase 2b Study

‘Naked’ Lintuzumab Phase 3 Study

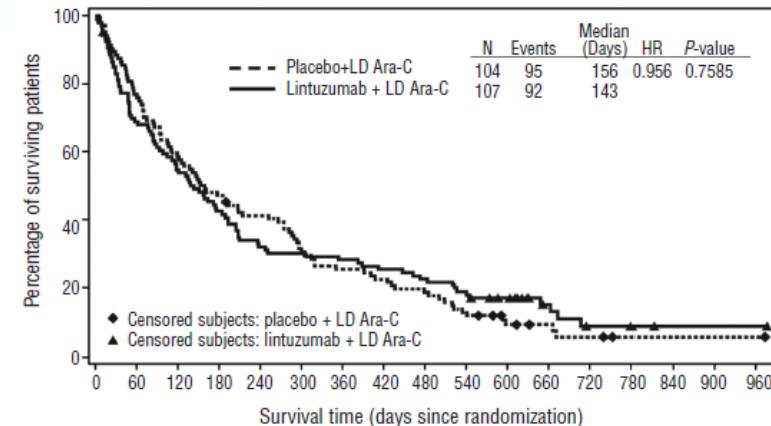
Lintuzumab-Bismuth-213 Single Agent

Cytarabine & Lintuzumab-Bismuth-213
Phase 1/2

“Naked” Lintuzumab Not Effective AML Treatment

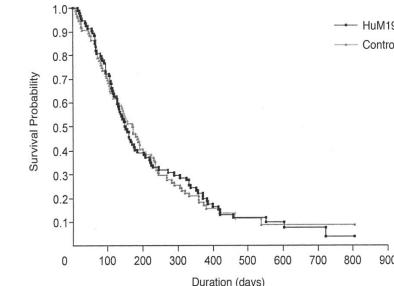
- ◆ A randomized Phase 2b study showed no benefit of adding “naked” lintuzumab antibody to low-dose cytarabine¹

- 211 patients ≥ 60 yrs with untreated AML
- No survival advantage



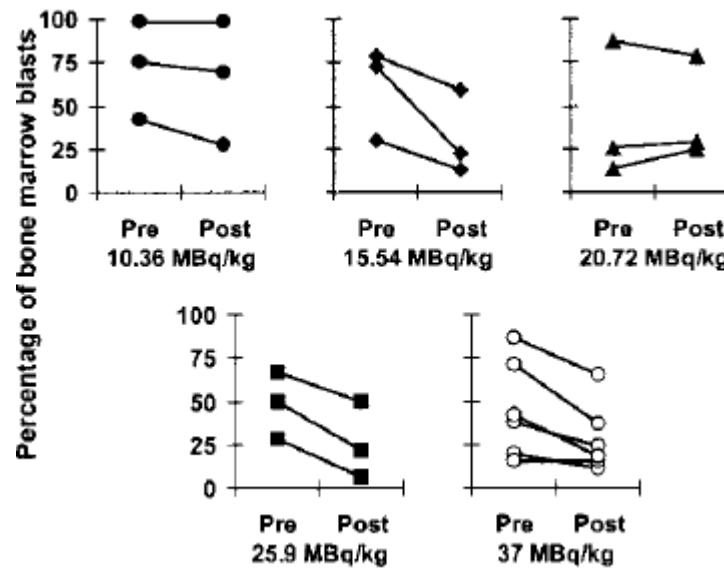
- ◆ A Phase 3 study showed no benefit of adding “naked” lintuzumab antibody to MEC (mitoxantrone, etoposide, cytarabine) chemotherapy²

	Lintuzumab & MEC		MEC Alone	
	# Patients	%	# Patients	%
Overall Response Rate (CR + CRp)	34/94	36	27/97	28
$P = 0.28$				



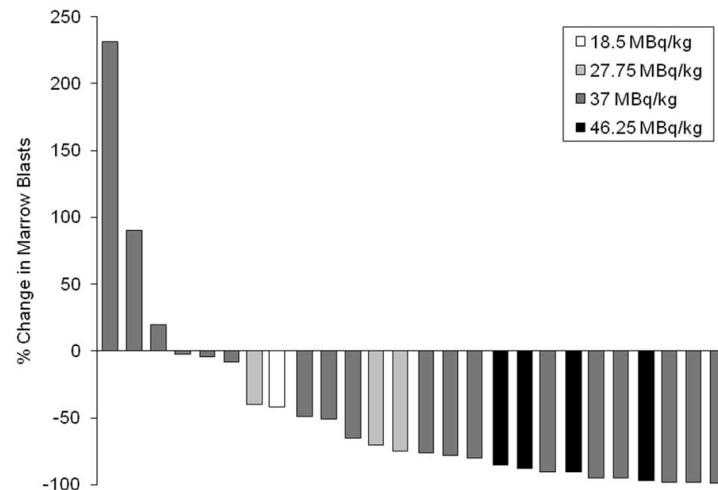
Lintuzumab-Bismuth-213 – AML Proof of Concept

- ◆ Academic clinical data with bismuth-213
 - 46 minute half life not amenable to development by industry
 - Phase 1 single agent study in relapsed/refractory AML
 - 14/18 (78%) had decreases in bone marrow blasts after 7-10 days¹
- ◆ Provided proof of concept data for alpha particle therapy in AML



Cytarabine & Lintuzumab-Bismuth-213 Clinical Trial

- ◆ Academic combination Phase 1/2 clinical trial
 - Continuous infusion cytarabine 200 mg/m² daily x 5 days
 - Then lintuzumab-bismuth-213 administered
 - Bone marrow blasts decreased at all doses
 - MTD determined to be 37 MBq/kg (1000 µCi)
 - Grade 4 leukopenia lasting ≥35 days
 - Responses in patients receiving ≥37 MBq/kg (1000 µCi)
 - 2 CRs, 2 CRi, and 2 PR
 - 46 minute half-life limited utility of this regimen



Actimab-A Development Program – Prior Trials

Several Phase 1 and Phase 2 trials inform our current Actimab-A development program

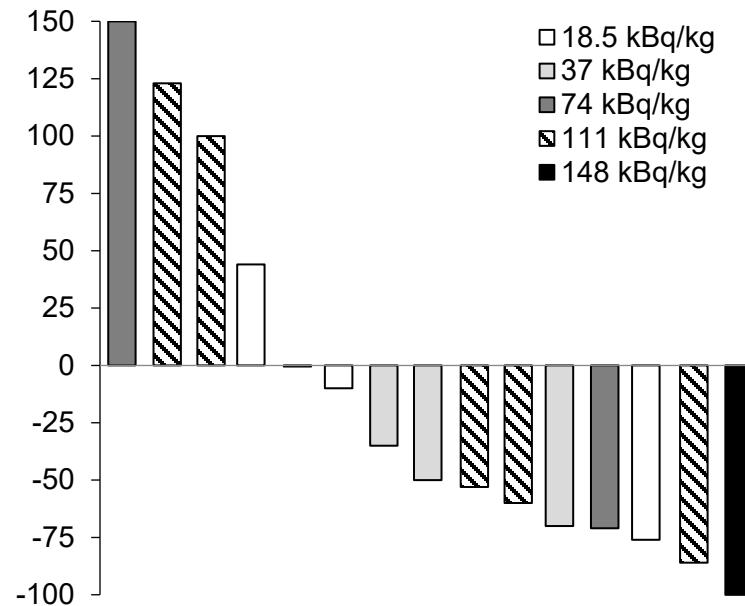
Single Dose Actimab-A Trial

Fractionated Dose Phase 1
Actimab-A Trial

Fractionated Dose Phase 2
Actimab-A Trial

Single Dose Actimab-A Trial

- ◆ Phase 1 single dose trial
 - Phase 1 study in relapsed, refractory AML
 - $0.5-4.0 \mu\text{Ci/kg}$ ($18.5-148 \text{ kBq/kg}$)
 - 18 patients
 - Dose Limiting Toxicity at $4 \mu\text{Ci/kg}$ (148 kBq/kg)
 - Prolonged myelosuppression was DLT
 - Bone marrow blasts decreased in 10/15 evaluable patients
 - Some patients had significant decreases in BM blasts



Fractionated Dose Phase 1 Trial - Safety

- ◆ Phase 1 study in relapsed, refractory AML
 - Fractionated dose trial - same dose administered day 1 and 8
 - Combination with low-dose Ara-C
 - Actinium-225 0.5-2.0 μ Ci/kg/fraction; 18 patients
 - Dose Limiting Toxicity in 2 patients
 - Gr 4 thrombocytopenia with marrow aplasia for > 6 weeks
 - 1 each at 1 μ Ci/kg/fraction and 2 μ Ci/kg/fraction
 - 2 μ Ci/kg/fraction chosen as Phase 2 dose
 - Maximum Tolerated Dose not reached
 - Dose chosen to limit prolonged myelosuppression

Selected Gr 3/4 AEs	Dose Level (μ Ci/kg/fraction)				Total
	0.5 (n=3)	1 (n=6)	1.5 (n=3)	2 (n=6)	n=18
Neutropenia	2	1	0	2	5 (32%)
Thrombocytopenia	0	3*	2	4*	9 (11%)
Febrile Neutropenia	1	4	0	1	6 (33%)
Pneumonia	0	3	1	1	5 (28%)

* 1 DLT

Fractionated Dose Phase 1 Trial - Efficacy

- ♦ ORR – 5/18 patients = 28%
 - Responses seen only at dose levels above 0.5 $\mu\text{Ci}/\text{kg}/\text{fraction}$
 - 4/5 responses seen at two highest dose levels

Response	Dose Level ($\mu\text{Ci}/\text{kg}/\text{fraction}$)				Total
	0.5 (n=3)	1 (n=6)	1.5 (n=3)	2 (n=6)	
CR	0	0	1	0	1 (6%)
CRp	0	1	0	1	2 (11%)
CRi	0	0	1	1	2 (11%)
ORR	0	1 (6%)	2 (11%)	2 (11%)	5 (28%)

CR = complete remission

CRp = CR with incomplete platelet count recovery

CRi = CR with incomplete blood count recovery

Fractionated Dose Phase 2 Trial

- ◆ Phase 2 study in older patients with no prior AML therapy
- ◆ Phase 2 fractionated dosing (Day 1 & 8)
 - 2.0 uCi/kg/fraction dose based on Phase 1 trial safety results
 - Single agent – no LDAC
 - 13 patients treated
 - High investigator accessed ORR of 69% but also high rate of Gr 4 myelosuppression for > 6 weeks
 - Dose reduced to 1.5 uCi/kg/fraction
 - 27 patients treated
 - Lower investigator accessed ORR of 22% but still high rate of Gr 4 myelosuppression for > 6 weeks

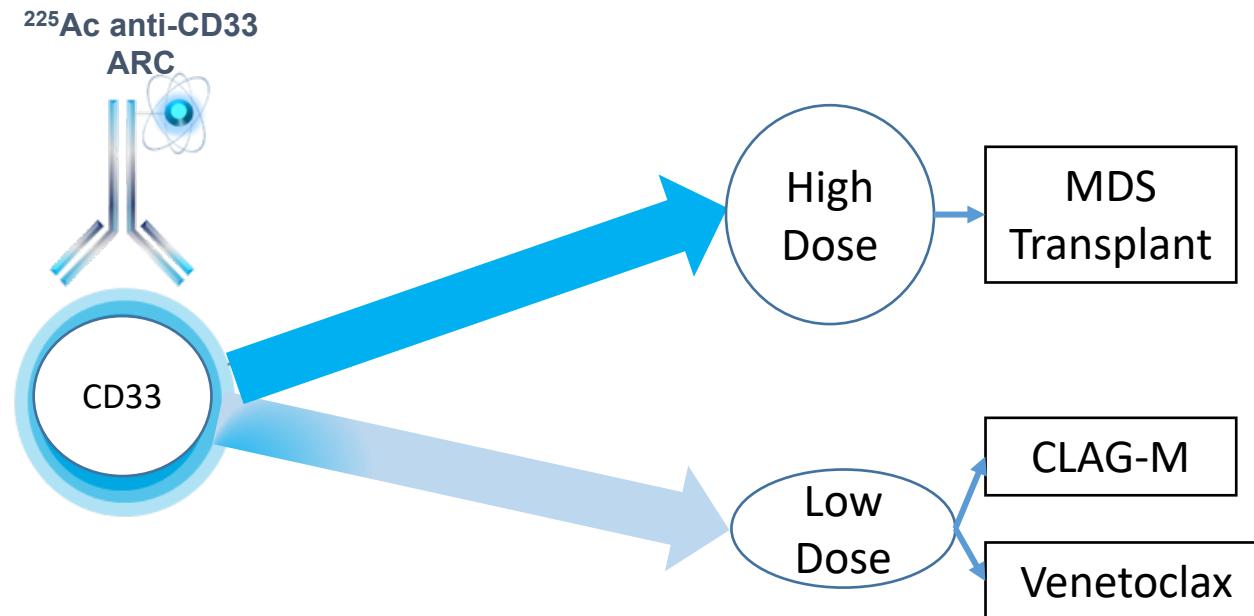
Dose Level (Day 1 & Day 8)	# Patients (N = 40)	Response Rate	Myelosuppression	
			Gr 4 thrombocytopenia for >6 wks (% Pts)	Gr 4 neutropenia for >6 wks (% Pts)
2.0 μ Ci/kg	13	69% 1 CR, 2 CRp, 6 CRI	46%	38%
1.5 μ Ci/kg	27	22% 3 CRp, 3 CRI	30%	40%

Lessons from Actimab-A Clinical Trials

- ◆ Actimab-A has advantages over lintuzumab-bismuth-213
 - Half-life of 10 days provides time for manufacture and distribution
 - Actimab-A is dramatically more potent than lintuzumab-Bismuth-213
 - Releases 4 alpha particles compared to 1
- ◆ No significant non-hematopoietic adverse events
 - Depletes myeloid cells and platelets
 - No veno-occlusive disease (VOD)
 - VOD seen with anti-CD33 antibody drug conjugate Mylotarg
- ◆ Actimab-A is a potent anti-leukemic drug
 - 69% Overall Response Rate at 2.0 uCi/kg/fraction
- ◆ Myelosuppression is dose related

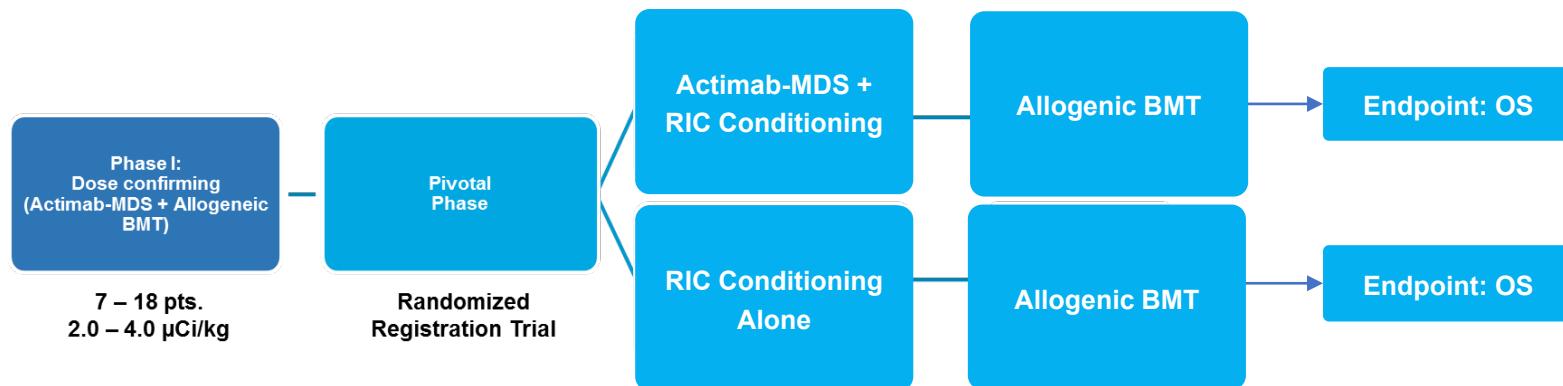
High Dose/Low Dose Approach

- ◆ High dose
 - Prior to hematopoietic cellular transplant where myelosuppression will be limited in time – rescued by the transplant
- ◆ Low dose
 - Use lower doses in combination with other AML drugs
 - Limits myelosuppression
 - Combines drugs with different mechanisms of action



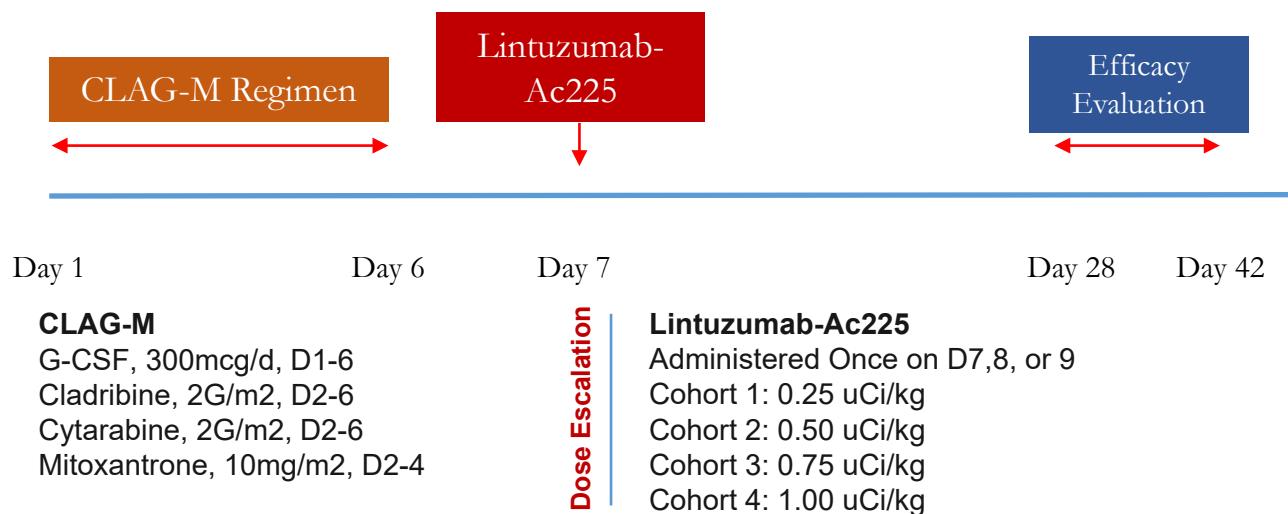
High Dose – MDS Transplant

- Only curative therapy for myelodysplastic syndrome (MDS) is allogeneic transplant
- CD33 expressed in vast majority of MDS patients
- Planning study to use high doses of Actimab-A as conditioning for allogeneic transplant in MDS
 - Requires standard conditioning agent to deplete lymphocytes



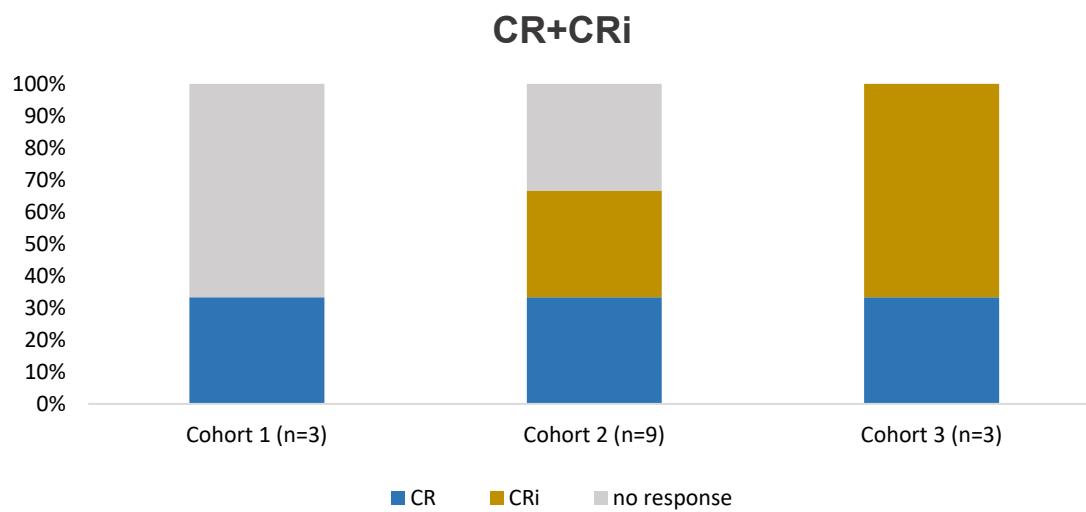
CLAG-M/Actimab-A Study Design

- ◆ CLAG-M is AML salvage chemotherapy regimen
 - Used for younger patients with relapsed or refractory AML
 - Actimab-A administered on day 7 after CLAG-M regimen
 - Adds targeted radiation modality to chemotherapy regimen

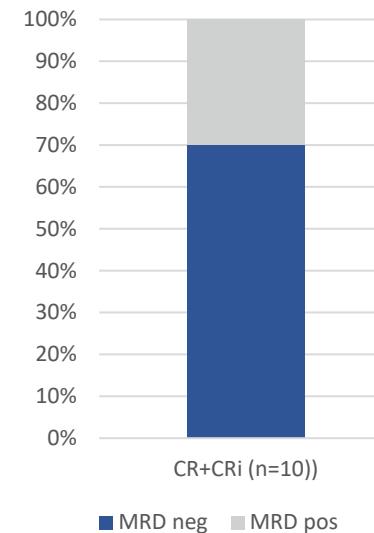


CLAG-M/Actimab-A Clinical Trial

- ◆ CLAG-M salvage regimen had 54% CR rate (CR & CRi) in relapsed, refractory AML
- ◆ Study shows increasing CR rate with Actimab-A dose
 - Third cohort (0.75 uCi/kg) has 100% CR rate (CR+CRi)
- ◆ Importantly, 7/10 remissions are deep remissions which are negative for measurable residual disease (MRD) by multiparameter flow cytometry (MFC)
- ◆ Dose escalation continues to 1.00 uCi/kg

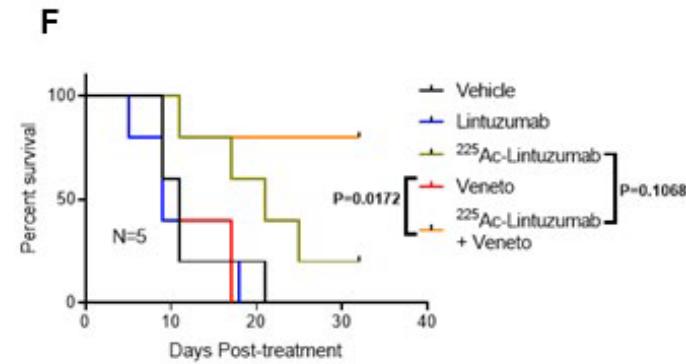
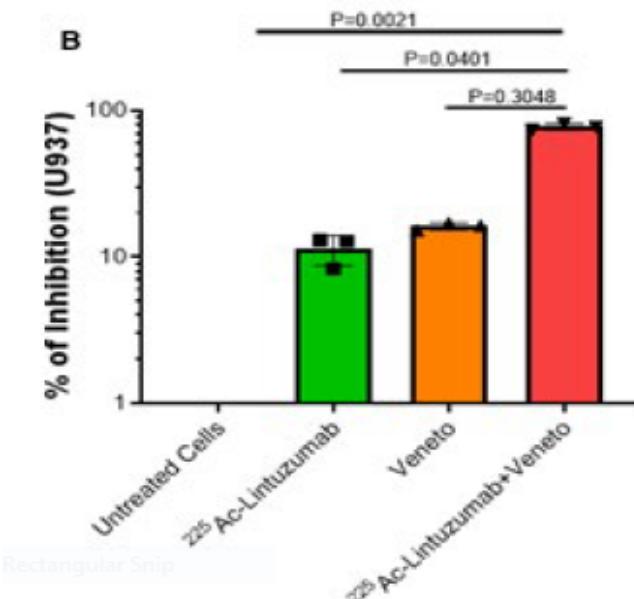


MFC MRD Status



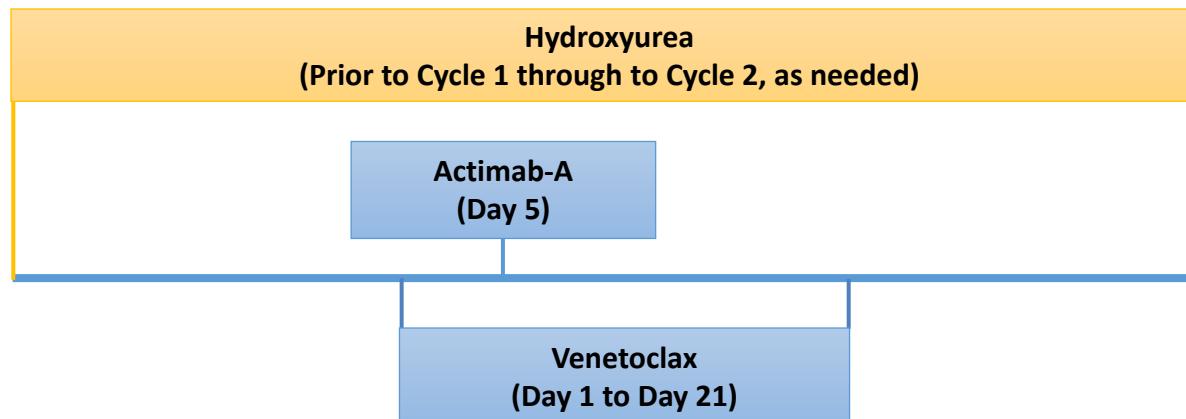
Venetoclax/Actimab-A Synergy

- ◆ Venetoclax is a Bcl-2 inhibitor commonly used in older patients with AML
- ◆ Increased MCL-1 is a common mechanism of Venetoclax resistance
- ◆ Actimab-A restores sensitivity to venetoclax in venetoclax-resistant AML cell lines
 - Demonstrated by increased inhibition of cell growth in vitro
 - Combination therapy led to increased survival in mouse xenograft models
 - Mechanism of synergy shown to be decreased levels of MCL-1



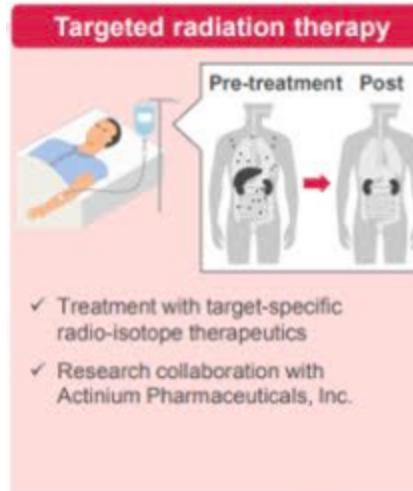
Venetoclax/Actimab-A Clinical Trial

- ◆ Builds on pre-clinical studies showing combination synergy
- ◆ Patients with relapsed or refractory AML
- ◆ Planned dose levels for Actimab-A are 0.5, 1.0, and 1.5 μ Ci/kg
- ◆ Venetoclax administered at 400 mg daily (Days 1-21)
 - Dose ramp up in cycle 1
- ◆ First dose cohort 0.5 μ Ci/kg had 1 PR and 1 CRi
 - No safety issues
 - Dose has been escalated



Actinium AWE Platform Deployment in Solid Tumors

- ◆ Collaboration with Astellas
 - Solid tumor targets
 - To develop both target-specific radioisotope diagnostics and therapeutics
- ◆ Targeted radiation has multiple applications in solid tumors
 - Direct treatment of primary tumors
 - Treatment of metastatic lesions
 - Unlike external beam radiation therapy, targeted radiation will home to metastases even if they have not been identified by imaging studies



Summary

- ◆ Actinium-225-based radio-conjugates have desirable characteristics for development by industry
- ◆ CD33 is an attractive target for targeted radiation in hematologic malignancies
- ◆ Development was facilitated by previous studies of naked lintuzumab and of lintuzumab-Bismuth-213
- ◆ Actimab-A was first targeted Actinium-225 labeled therapy in clinical development
 - Largest clinical experience of Actinium-225 labeled agents
- ◆ Actimab-A currently being developed in combination with
 - CLAG-M chemotherapy for younger patients with relapsed/refractory AML
 - Venetoclax for older patients with relapsed/refractory AML
- ◆ Expansion to the solid tumor space including collaboration with Astellas
- ◆ Further expansion of the Actinium-225 antibody radio-conjugate space is expected



Radiation Safety Considerations for Novel Radionuclide Therapies

Megan Shober

Nuclear Safety Specialist

September 22, 2021



Abbreviations

- Ac-225: Actinium-225
- Ac-227: Actinium-227
- cpm: counts per minute
- dpm: disintegrations per minute
- NUREG: [not an abbreviation]



Overview

- Actinium-225 (Ac-225) regulatory challenges
- Radiation safety
- Available guidance
- Licensing users
- Licensing producers



Current Ac-225 Licensees

- Benchtop research (millicuries)
- Animal studies (millicuries)
- Radiopharmacy (millicuries)
- Medical use (microcuries)



Regulatory framework

- Medical use licensees have general authorization for unsealed material requiring a written directive.
 - Notification to regulator not needed.
- Broad scope and pharmacy licensees may need specific authorization.
 - Amend license due to high atomic number.
- Impurities are typically not listed on licenses.



Regulatory framework

Impurities can present substantial challenges.

Decommissioning financial assurance is required for actinium-227 exceeding 10 microcuries.

Do we...

- Limit licensees to Ac-225 from only certain production methods?
- Require financial assurance for all licensees authorized for Ac-225?



Radiation Safety Issues

- Contamination
- Chemical separation
- Bioassay
- Engineering controls
- Action levels
- Skin overexposure
- Training
- Waste disposal

Isotope	Annual Limit on Intake
Fluorine-18	50,000 microcuries
Lutetium-177	2000 microcuries
Radium-223	0.7 microcuries
Actinium-225	0.3 microcuries
Actinium-227	0.0004 microcuries



Available Guidance

Nuclear Regulatory Commission

- Radiopharmacy NUREG (Revision 2) and Research and Development NUREG (Revision 1)
 - No action level for Ac-225
 - 20 dpm for Ac-227
- Medical NUREG (Revision 3)
 - 200 dpm alphas in restricted areas
 - 100 dpm Ac-225, 20 dpm Ac-227 in unrestricted areas



Available Guidance

University radiation safety material

- Design engineering controls to limit potential skin exposure.
- Detect Ac-225 and progeny with standard survey meters.
- Expect contamination.
- Count wipes on liquid scintillation counters when possible.
- Use net 20 cpm action level.



Available Guidance

Licensee research

- Detect Ac-225 and progeny with standard survey meters.
- Determine efficiency for well counters or dose calibrators.
- Increase action level. 20 dpm is not reasonable due to extremely long count time in well counter.



Licensing Ac-225 Users

- Contamination ✓ Day of use wipe surveys
- Chemical separation ✓ No separation
- Bioassay ✓ Did not require bioassay
- Engineering controls ✓ Required controls
- Action levels ✓ 200 dpm
- Skin overexposure ✓ Double gloves
- Training ✓ Isotope-specific training
- Waste disposal ? Decay-in-storage



Licensing Ac-225 Producers

- Reduce production of impurities
- Manage radium targets
- Control radon gas
- Manage waste streams
- Decommissioning funding plan
- Emergency planning



Licensing Ac-225 Producers

- Shielding design
- Engineering controls
- Respiratory protection
- Air monitoring
- Bioassay strategies





Questions?

Megan Shober
megan.shober@dhs.wisconsin.gov

Wisconsin Division of Public Health
Bureau of Environmental and Occupational Health