Lm-Based Immunotherapies: Leveraging the Advantages of a Unique Vector to Attack Cancer

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Advaxis Overview

- *Listeria monocytogenes (Lm):* Bacterial vector optimized to deliver large antigen payloads directly inside dendritic/antigen presenting cells
- Ability to generate CD8+T cells **rapidly** and against **large percentage** of peptide/neoantigen targets
  - > 90% in pre-clinical studies
- Preliminary clinical data in neoantigen-directed program suggests **best-in-class** CD8+T cell response
  - > 80% of neoantigen pools
  - T cell responses observed 1 week after initial/priming dose
- Leveraging the large, antigen-payload capacity of our *Lm* vector in our neoantigen-directed programs
- Antigen spreading demonstrated in clinical trials including our neoantigen-directed drug constructs
- Efficacy signals include: Single agent Complete Responses (CRs), prevention of recurrence and improved survival
- Manageable safety profile – nearly 500 patients treated to date with mostly Grade 1 and 2 TRAEs
- *Lm*-platform enables broad pipeline
  - **ADXS-HPV** (AXAL) in Phase 3 for high-risk cervical cancer
  - **ADXS-PSA** in Phase 1/2, Keynote-046 combination with pembrolizumab in advanced prostate cancer
  - **ADXS-NEO,** personalized-drug constructs, in Phase 1 for multiple cancers
  - **ADXS-HOT:** > 12 “off-the-shelf” hotspot, neoantigen-targeting drug constructs with first candidate, **ADXS-503** (HOT Lung) for NSCLC about to enter the clinic

Anti-Tumor Immunity: Building Blocks for Clinical Success

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Induction of peripheral immune responses ✓

- ✓ CD8+, CD4+, increased Myeloid proliferation, Decreased Tregs & MDSCs[1]
- ✓ HPV, PSA, HER2, ADXS-NEO, ADXS-HOT (In vitro[2])

Priming of T cell response ✓

- ✓ **Neoantigen Specific T cells after 1 week**
- ✓ 90% of neoantigens generate CD8+ T cells in *Lm* vectors (In vitro, clinical data pending)[3]
- ✓ **Non-immunogenic neoantigens *are* immunogenic** when presented by *Lm* vector[3]

Convert "cold" tumors into "hot" tumors ✓

- ✓ Preclinical Models: Upregulates PD-L1[4]
- ✓ Reduces Tregs, MDSCs[5], M2 TAMs (M2-M1 shift)[2]

Vaccine-induced T cells infiltrate to the tumor ✓

- ✓ **Chemokines traffic T cells into TME[8]**
- ✓ Clinical Evidence: HPV+ Head and Neck[6], ADXS-NEO (pending)
- ✓ In Vitro: All Constructs Including ADXS-NEO[3] and ADXS-HOT[8] (prototype)

Promote antigen spreading ✓

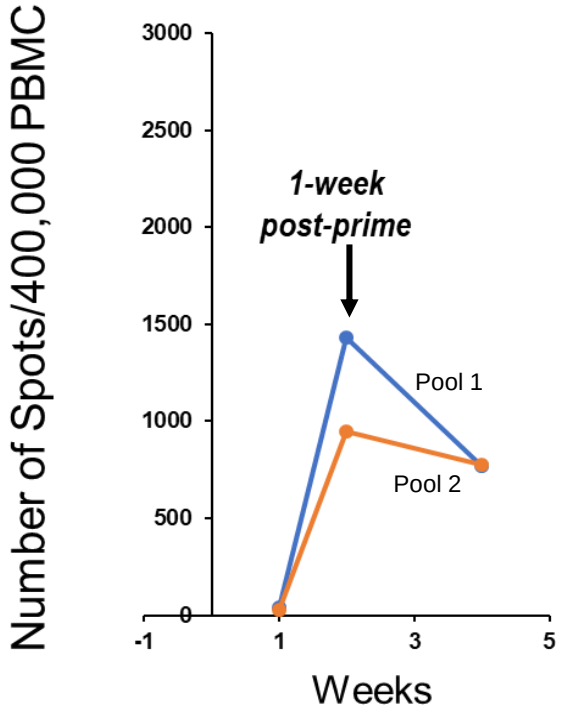
- ✓ Demonstrated with 5 different constructs in clinical trials[6,7]
- ✓ Multiple targets not included in the vaccine
- ✓ Magnitude of T cell response vs. target is associated with **increased antigen spreading** and clinical outcomes[8]

Lm-based drug candidates have demonstrated broad anti-tumor immunity through achieving these

Best-in-Class Potential in Neoantigen Field

- Advaxis neoantigen programs leverage our *Lm* vector's capacity for large number of antigens
  - ADXS-NEO constructs currently utilize **40 *private* neoantigens per patient**
  - ADXS-HOT constructs utilize **> 30 *public* hotspots + other immunogenic antigens**
- Preliminary clinical data from ADXS-NEO clinical trials demonstrate broad and rapid anti-tumor immunity
  - Strong T cell **neoantigen responses 1 week after priming/initial dose**
  - **T cell responses in >80% of neoantigen pools** tested (individual peptide data pending)
- Antigen spreading documented in both single antigen Advaxis clinical constructs as well as in ADXS-NEO
  - Immunologic context promotes antigen spreading, extending effects beyond included targets
  - Magnitude of T cell response to primary targets correlated with antigen spreading and clinical outcomes
- Repeat dosing without neutralizing antibodies

ELISPOT data
ADXS-NEO
MSS-CRC patient



MSS CRC, microsatellite stable colon cancer

ADXS-HPV: Vaccine Expressing HPV 16 (tLLO-E7)

IV administration every 3-4 weeks at 1X10^9 CFU

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ADXS-HPV (AXAL)

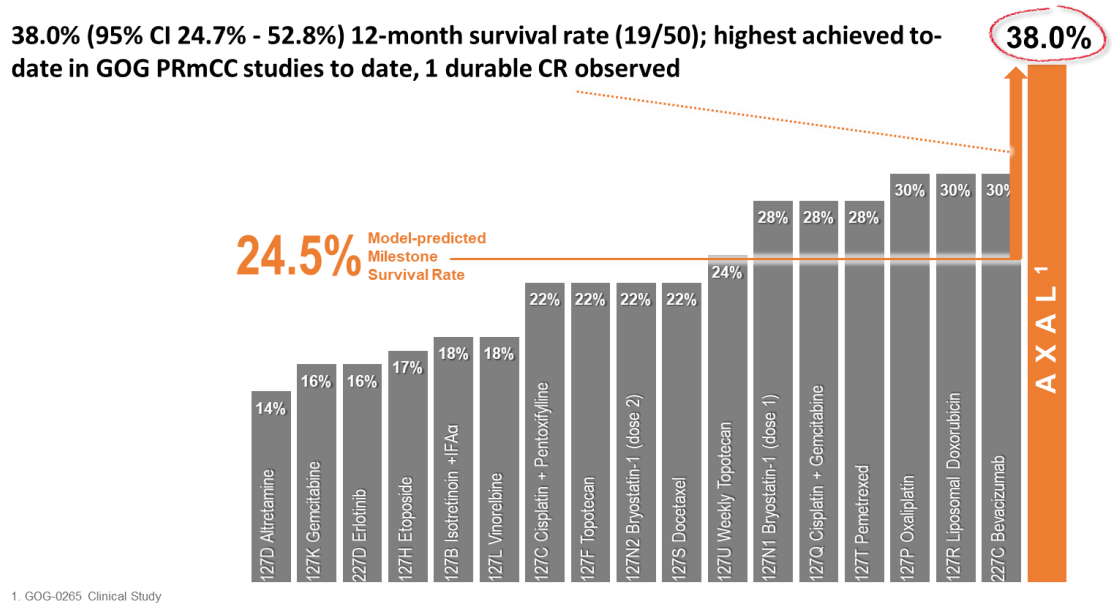
Clinical data:
Prolonged survival and ***complete responses*** in cervical and anal cancer subjects and ***antigen spreading*** observed

GOG-0265

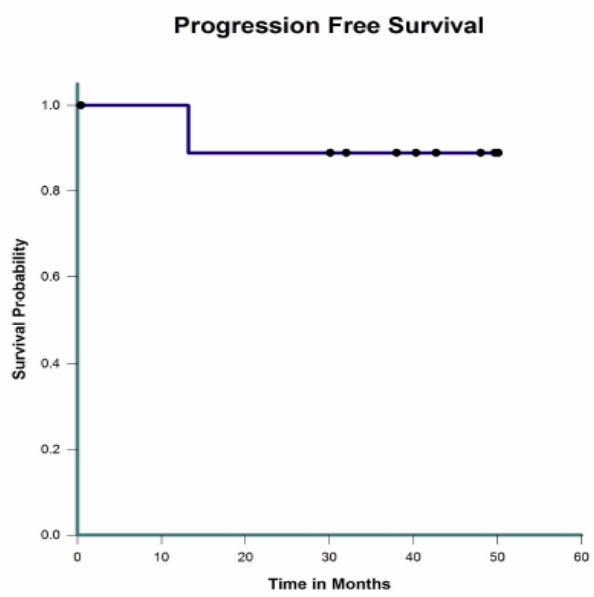
- Phase 2 (n=50)
- Recurrent metastatic cervical cancer
- Comparison to historical GOG studies

BrUOG-276

- Phase 1-2 (n=11)
- Adjuvant therapy with CCRT– anal cancer



1. GOG-0265 Clinical Study



- Mostly Grade 1-2 (mild-moderate) chills, pyrexia, nausea, fatigue, headache and hypotension, shortly after infusion.
- High grade, manageable hypotension has been reported in up to 7% of subjects after infusion
- AEs usually resolve within 2 to 4 hours after infusion with symptomatic treatment

Hu W et.al. AXAL-GOG0265. SGO Annual Meeting, 2017; Safran H et.al. Int J Radiat Oncol Biol Phys. 2018

AXAL Phase 3 AIM2CERV – Registration Trial[1]

HPV+ Cervical Cancer

Study Design

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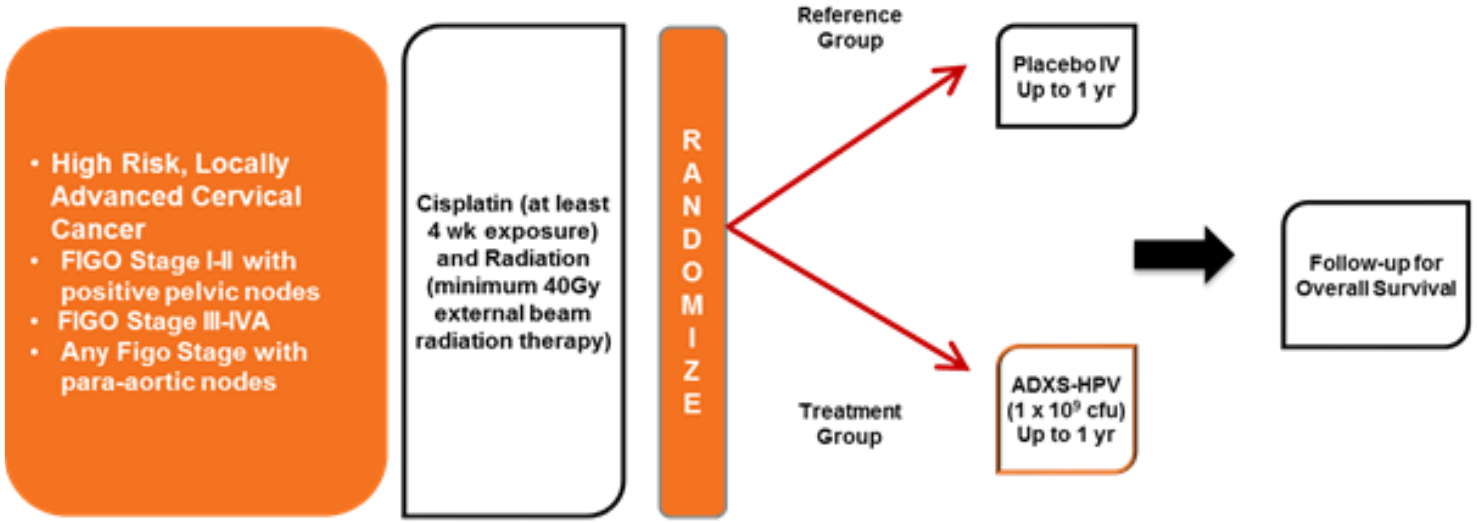
FDA Orphan | FDA SPA | FDA FastTrack

Adjuvant AXAL Following Chemo/Radiation to Prevent Recurrence in HRLA Cervical Cancer

Total no. patients = 450



Baseline tumor imaging must be performed within 28 days prior to the first study treatment infusion

Randomization 1:2 Reference and Treatment Groups

Primary Objective is Disease Free Survival

Primary Endpoint:

- Disease-free survival

Secondary Outcome Measures:

- Safety & Tolerability
- Overall survival
- Patient reported outcomes
- **Exploratory:**
- Association between biomarkers of immunologic response

Advaxis addressing FDA's comments on CMC package and inclusion of second interim analysis

1 FDA has placed a partial clinical hold on this study due to CMC requests which allows continued dosing of already enrolled patients but which prevents enrollment of new patients until resolution of this partial hold.

Herzog T, et al. Poster Presentation at SITC 2016; https://clinicaltrials.gov/ct2/show/NCT02853604

"FIGO: International Federation of Gynecology and Obstetrics; HRLACC: high-risk locally advanced cervical cancer; IV, intravenous; SPA: Special Protocol Assessment".

AIM2CERV: AXAL Immunotherapy Following Chemo/Radiation in Patients who have High Risk Locally Advanced Cervical Cancer (HRLACC)

GOG Gynecologic Oncology Group

ADXS-PSA ± Pembrolizumab in Metastatic Castration Resistant Prostate Cancer
Phase 1 /2 Clinical Study: Keynote 046

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ADXS-PSA

Clinical evidence of ***disease stabilization*** and ***antigen spreading*** in prostate cancer subjects along with reductions in levels of PSA

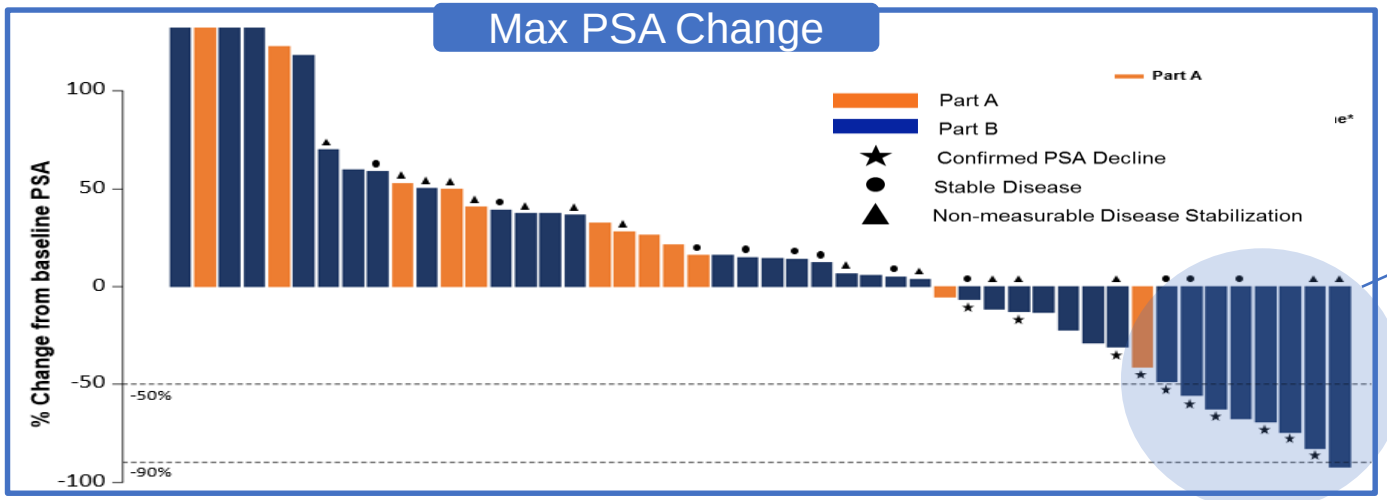
50* subjects, predominantly bone disease only
Part A (ADXS-PSA monotherapy; N=13)
Part B (ADXS-PSA + pembrolizumab; N=37)

In collaboration with: MERCK

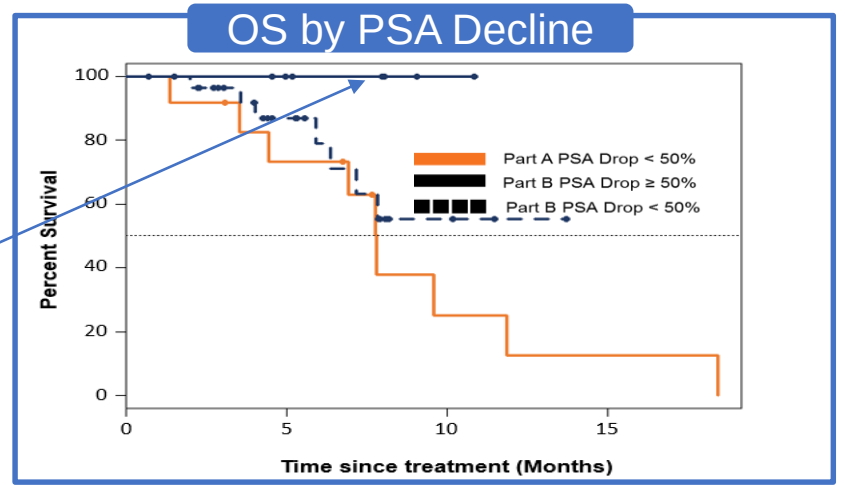
No added toxicity with PSA-pembro combination treatment was observed
- Most commonly Grade 1-2 chills, pyrexia, nausea, fatigue, headache and hypotension shortly after the infusion.

Improvement in survival observed in subjects with ≥ 50% PSA declines from baseline

Max PSA Change



OS by PSA Decline



Stein M et.al. Keynote 046. ASCO 2018

ClinicalTrials.gov Identifier: NCT02325557

Update on Survival Rates and Correlative Biomarker Analysis Anticipated in Q1 2019

*31 patients had grade 1-2 events, 18 patients (5 Part A and 13 Part B) had grade 3-4 events, 1 discontinued for grade 4 event

ADXS-NEO: Personalized Neoantigen Vaccine

Phase 1 Clinical Study Design – Initiated June 2018

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ADXS-NEO

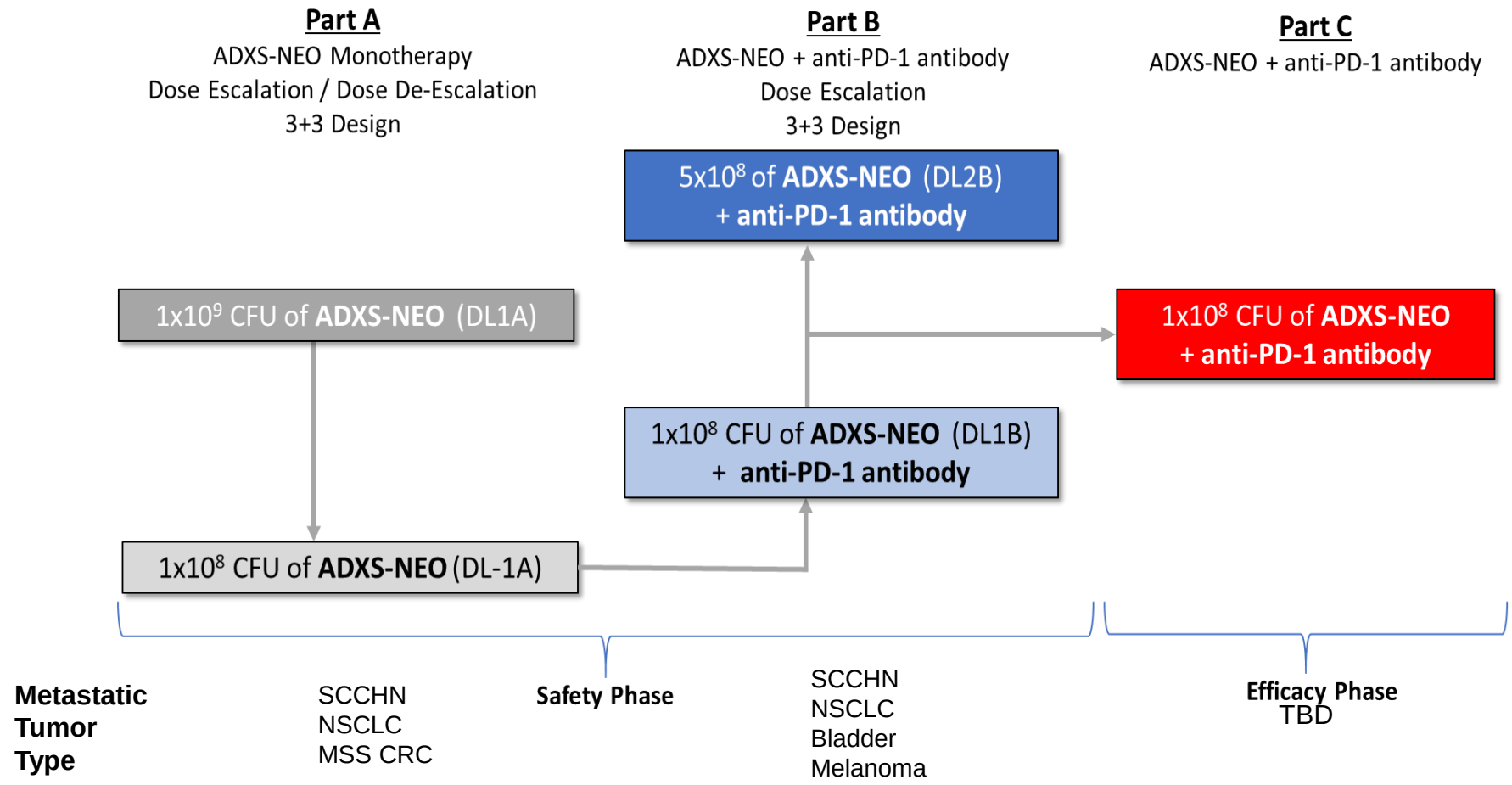
Personalized, patient-specific candidates based on sequencing of each subject's tumor

Endpoints:

Primary
Tolerability/ Safety

Secondary
Clinical activity
RP2D

Exploratory
Immunological



CFU, Colony-Forming Unit; SCCHN, squamous cell carcinoma head and neck; NSCLC, non-small cell lung cancer; MSS CRC, microsatellite stable colon cancer; RP2D, recommended phase 2 dose

Clinical Data From Initial Cohort (safety, immune response)
Anticipated 1H 2019

ClinicalTrials.gov Id: NCT03265080

ADXS-HOT (503): NSCLC-Specific Vaccine

Phase 1/2 Clinical Study Design: Open to enrollment

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ADXS-HOT

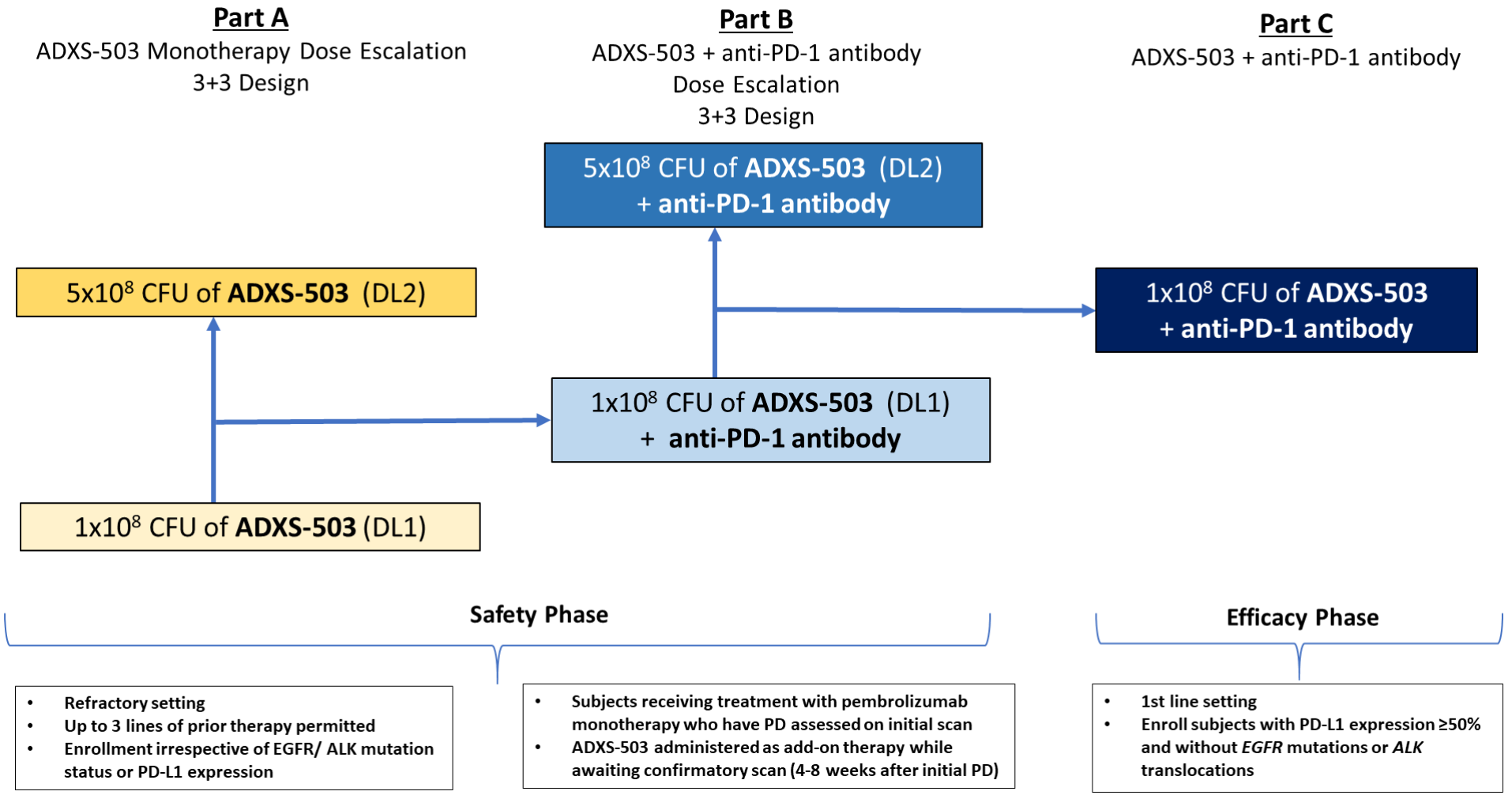
Cancer type-specific candidates based on commonly expressed public hotspot mutations and proprietary cancer antigens

Endpoints:

Primary
Tolerability/ Safety

Secondary
Clinical activity
RP2D

Exploratory
Immunological



Clinical Data From Initial Cohort (safety, immune response) Anticipated 1H 2019

Next-Generation Cancer Immunotherapies Using a Proprietary *Lm* Platform

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- Leveraging unique properties of *Lm* vector
  - Capable of delivering large antigen payloads directly inside dendritic/antigen presenting cells
- Broad pipeline of drug candidates for multiple cancer types
  - From Phase 1 to Phase 3 programs in several solid tumor types
- Preliminary clinical data from first neoantigen-directed program demonstrate broad and rapid anti-tumor immunity
  - Ability to generate CD8+T cells rapidly and against large percentage of peptide/neoantigen targets
- Clinical and correlative immune data readouts anticipated throughout 2019

References

1. Wood L, Paterson Y. Front Cell Infect Microbiol. 2014;4:51.
2. Coder B. Targeting shared hotspot cancer mutations with a Listeria monocytogenes immunotherapy induce potent anti-tumor immunity. Poster Presentation, AACR 2018. *Manuscript in preparation.*
3. Coder B. Neoantigens that fail to elicit measurable T cell responses following peptide immunization can control tumor growth when delivered using a Listeria-based immunotherapy platform. Poster Presentation, AACR 2018, *Manuscript in preparation.*
4. Data on file at Advaxis
5. Kosoff R. Advaxis' Listeria monocytogenes-based immunotherapies rapidly impair intratumoral regulatory T cell survival and function and promote effector T cell recruitment, activation and differentiation SITC, November 13, 2017
6. Krupar R. HPV E7 antigen-expressing Listeria-based immunotherapy (ADXS11-001) prior to robotic surgery for HPV-positive oropharyngeal cancer enhances HPV-specific T cell immunity. AACR 2017 Poster Discussion (#7632)
7. Villareal D. Targeting shared hotspot cancer mutations with a Listeria monocytogenes immunotherapy induce potent anti-tumor immunity. AACR 2018
8. Hayes S. Magnitude of anti-PSA T cell response is associated with antigen spreading and slowing in PSA and PAP velocity in ADXS-PSA-treated mCRPC patients. Oral and poster presentation, Keystone Cancer Vaccines, January 2019