



ZIOPHARM Oncology

NIH OBA Protocol #1210-1189 (ATI001-201) RAC Public Review Slides

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Protocol #1210-1189: Presentation Overview

- Overview of Protocol #1210-1189
- Review of clinical/nonclinical information to address comments received from Primary RAC Reviewers

A Phase II Randomized, Open Label Study of Ad-RTS-hIL-12 Monotherapy or Combination with Palifosfamide-tris in Subjects with Recurrent/Metastatic Breast Cancer with Accessible Lesions

Population

- Recurrent/metastatic breast adenocarcinoma with accessible tumor(s) not amenable to surgical resection or radiation with curative intent
- At least one accessible lesion
- ECOG PS 0-2

Primary Endpoints

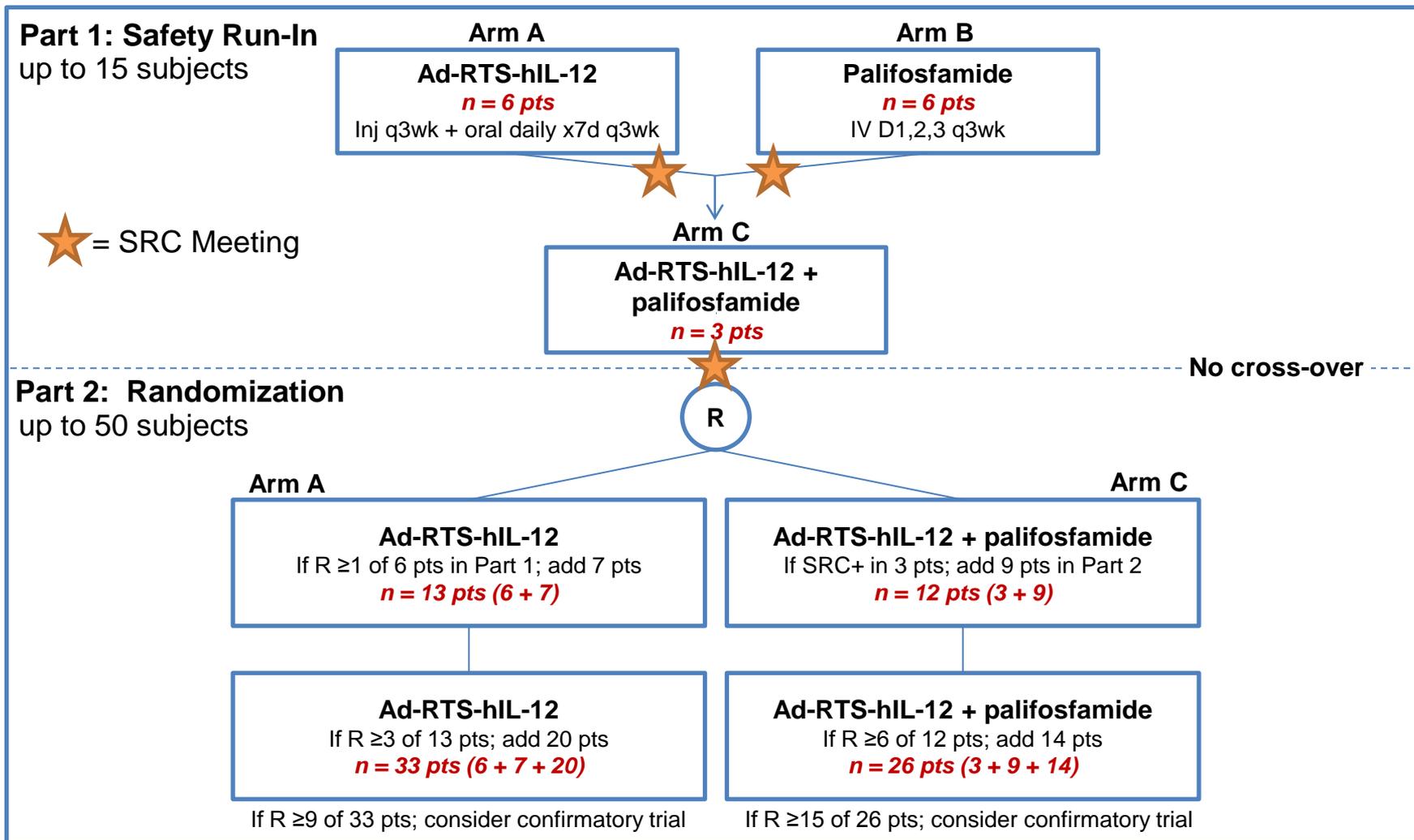
- Safety and tolerability of therapy
- The proportion of subjects who survive progression-free at week 16

2 Part Study Design

- **Part 1** - safety run-in: safety assessment will be performed after 1 cycle of therapy
 - Ad-RTS-hIL-12 monotherapy (Arm A: n=6)
 - palifosfamide monotherapy (Arm B: n=6)
 - Ad-RTS-hIL-12 + palifosfamide (Arm C: n=3)
- **Part 2** - subjects randomly assigned to active treatment arms A or C

ATI001-201: 2 Part Study Design

Ad-RTS-hIL-12 = INXN-1001 + INXN-2001
 Palifosfamide = palifosfamide-tris
 Response (R): progression-free at week 16 as measured by RECIST



Key Inclusion & Exclusion Criteria

Inclusion Criteria

1. Locally recurrent or metastatic breast cancer with injectable lesions, for which no proven effective therapy exists
2. Adequate renal liver, hematologic and electrolyte function
3. Failed or progressed on at least one prior systemic chemotherapy regimen \pm biologic/experimental therapy
4. Males or females \geq 18 years of age

Exclusion Criteria

1. *HER2/neu*-positive
2. Concomitant potent CYP3A4 inhibitors/inducers
3. Localized infection at injection site

Rationale for IL-12 as a Cancer Immunotherapeutic

- IL-12 is a heterodimeric (p35, p40 subunits) glycoprotein cytokine
- Mainly produced by innate immune cells
 - Dendritic cells (DC), NK cells, neutrophils and macrophages
- Enhances CD8+ maturation – increased CTL activity
- A key mediator for the generation of Th1 CD4+ effector T cells
- Augments antigen-specific anti-tumor responses
- Induces maturation of DC
 - Upregulation of costimulatory molecules and MHC class II
- Stimulates NK cell cytotoxicity and production of IFN- γ
 - Induces Ig class switching by B cells
 - Induces production of anti-angiogenic factors by tumor cells

Rationale for IL-12 as a Cancer Immunotherapeutic

- Shown to have anti-tumor activity in several animal models
- Tested clinically in Melanoma, Head and Neck, Kaposi's Sarcoma, with varying levels of efficacy
- Administration of IL-12 systemically has resulted in induction of immune responses in some subjects and limited clinical improvement, but has been associated with severe toxicity
- Toxicities in patients treated for melanoma or renal cell cancer include:
 - Elevated transaminases
 - Rapid transient leukopenia
 - Flu like-symptoms
 - GI toxicity and/or liver dysfunction

Robertson MJ et al. Clin Cancer Res. 1999; Atkins MB et al. Clin Cancer Res. 1997; Gollob JA et al. Clin Cancer Res. 2000; Lenzi R et al. J Transl Med. 2007; Alatrash G et al. J. Clin. Oncol. 2004; Gollob JA et al. J Clin Oncol. 2003; Eisenbeis CF et al. J Clin Oncol. 2005; Portielje JE et al. Immunother. 2003; Van Herpen CM et al. Clin Cancer Res. 2003; Leonard JP et al. Blood. 1997

Rationale for IL-12 Delivery Mechanism

Injection of plasmids or adenovirus containing *hIL-12* genes to cancer patients has proven to limit or abrogate the toxic effects of hIL-12, thus providing an effective way to deliver this potent immunomodulatory cytokine.

Sangro B et al. J Clin Oncol. 2004; Triozzi P et al. Clin Cancer Res. 2005; Mazzolini, G et al. J Clin Oncol. 2005; Daud AI et al. J Clin Oncol. 2008; Heinzerling L et al. Hum Gene Ther. 2005; Anwer K et al. Gene Ther. 2010

Human Safety Assessment (Healthy Volunteers): INXN-1001

- 129 subjects were treated in 4 studies in Healthy Volunteers*
- INXN-1001 doses ranged from 0.7 to 200 mg
- Well-tolerated up to 200mg
- Mild to moderate tachycardia were observed at the 200 mg dose

* *Excellent safety demonstrated in preclinical toxicology (mice, rats, dogs)*

Clinical Safety Assessment: RTS-M101b & ATI001-101

26 subjects have been treated in 2 clinical studies thus far

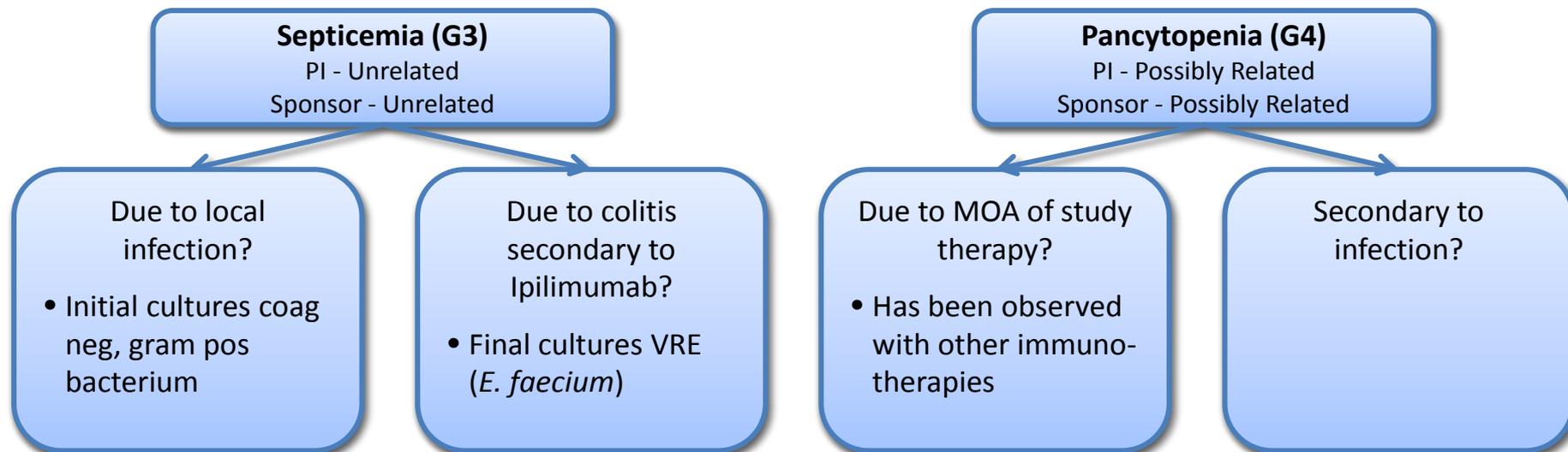
- 12 subjects were dosed in the RTS-M101b Study (INXN-1001 + INXN-3001)
 - INXN-1001 doses ranged from 0.6 mg to 200 mg
 - INXN-2001 dose 1×10^{12} vp by autologous transduction of DCs (INXN-3001)
- 14 subjects were dosed in the ATI001-101 Study thus far (INXN-1001 + INXN-2001)
 - INXN-1001 doses ranged from 5 mg to 160 mg
 - INXN-2001 dose 1×10^{12} vp

1 SAE observed in the RTS-M101b

- 73 y/o, morbidly obese, white male
- Advanced unresectable malignant melanoma on left leg
- Concurrent medication – Benicar® for hypertension
- Presented with voluminous diarrhea (RELATED) and vomiting (RELATED) leading to dehydration and hypotension
- Remained immobile on the floor for 8hrs
- Resulted in rhabdomyolysis (UNRELATED) and subsequent acute kidney injury (UNRELATED)

3 SAEs observed in the AT1001-101

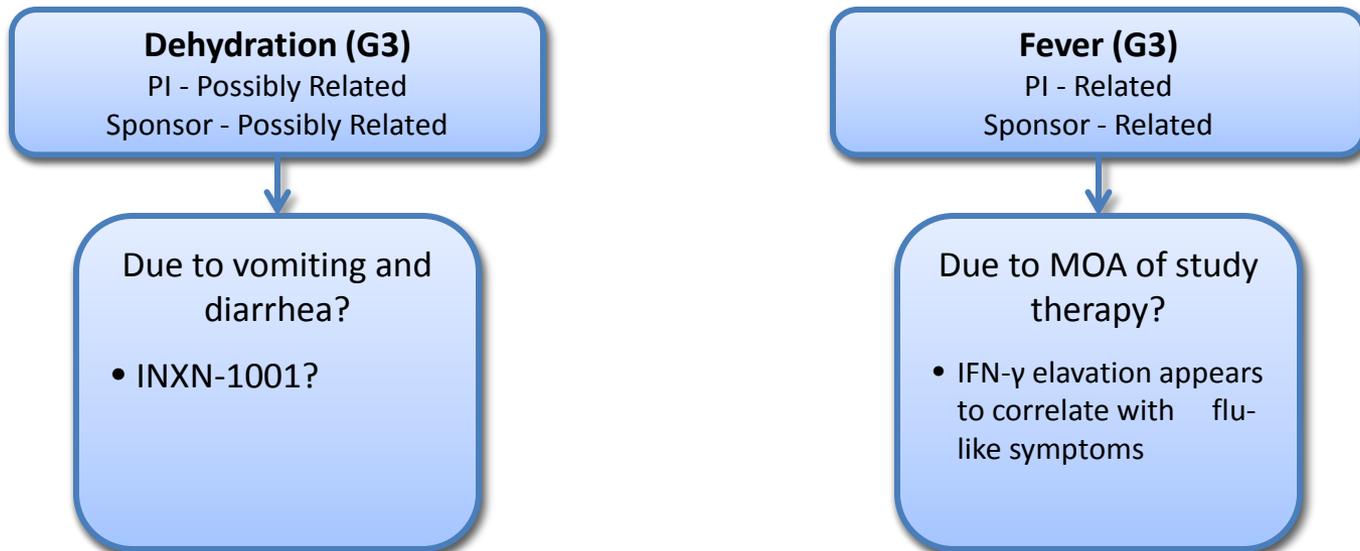
1. DVT (UNRELATED)
2. Septicemia (UNRELATED) & Pancytopenia (POSSIBLY RELATED)
 - 62 y/o female with h/o breast cancer treated and in remission and high BMI
 - Stage IV micrometastatic acral melanoma (T4b, N3, M1a)
 - Concurrent Fentanyl and Oxycodone (two drugs that interact with CYP3A4)
 - Treated with ipilimumab, complicated by colitis and required steroids
 - Cellulitis on her left lower extremity, required treatment with systemic antibiotics



3 SAEs observed in the ATI001-101 (cont.)

3. Pyrexia (RELATED) & Dehydration (POSSIBLY RELATED) – *During Cycle 4*

- 60 y/o male, Stage IV melanoma (M1c)
- Presents with high fever, chills, leukopenia at each cycle. Fully recovered within a week after initial dose
- Hospitalized (for IV hydration and antipyretics) on C4D3 for dehydration secondary to diarrhea
- Discharged with full recovery four days later



Analysis of Most Frequent AEs from 2 Clinical Studies

| | | Grade 1 | Grade 2 | Grade 3 | UN-Related | Possibly Related | Related |
|------------|-------------------|------------|-----------|----------|------------|------------------|------------|
| RTS-M101b | Flu-like Symptoms | 17 (85%) | 3 (15%) | 0 (0%) | 6 (30%) | 12 (60%) | 1 (5%) |
| | GI Symptoms | 12 (80%) | 2 (13.3%) | 1 (6.7%) | 6 (40%) | 8 (53.3%) | 1 (6.7%) |
| ATI001-101 | Flu-like Symptoms | 35 (79.5%) | 8 (18.2%) | 1 (2.3%) | 2 (4.5%) | 17 (38.6%) | 25 (56.8%) |
| | GI Symptoms | 13 (92.9%) | 1 (7.1%) | 0 (0%) | 0 (0%) | 17 (38.6%) | 25 (56.8%) |

Palifosfamide

- Palifosfamide is the active metabolite of ifosfamide that avoids the debilitating toxicities inherent to the alternate metabolites of the parent molecule^{1,2}
 - In the same class of agents as bendamustine, cyclophosphamide, and ifosfamide
- Novel bifunctional DNA-alkylating agent that is not metabolized by ALDH^{1,2}
- Generates DNA crosslinks leading to genomic damage and the stimulation of cell apoptosis^{1,2}

1. Struck RF, et al. *Cancer Chemother Pharmacol.* 1994;34:191-196.
2. Zhang J, et al. *Curr Cancer Drug Targets.* 2006;5:385-407.

Palifosfamide Clinical Safety Information

- A total of 8 clinical trials with palifosfamide have been conducted.
- An estimated 400 patients receiving treatment with palifosfamide monotherapy or in combination in Phase 1 through Phase 3 clinical trials.
- Tolerance demonstrated at 130 or 150 mg/m² x3 q 31 days
- The most commonly reported (≥50%) adverse events include:
 - Nausea (62% subjects)
 - Fatigue (55% subjects)
 - Alopecia (59%). Notably, alopecia was not observed when palifosfamide-tris was administered as monotherapy (zero of a total of 21 subjects)
- The most commonly-occurring Grade ≥3 AEs (≥10%) include:
 - Neutropenia (22%)
 - Anaemia (13%)
 - Febrile neutropenia (13%)
- In addition, subjects receiving palifosfamide-tris as monotherapy reported ≥Grade 3 Fatigue (3 subjects, 14%).

Potential Toxicity of Ad-RTS-hIL-12 + Palifosfamide Combination

- Potential overlapping toxicities for Ad-RTS-hIL-12 (INXN-2001), INXN-1001, and palifosfamide include:
 - fatigue, nausea, vomiting, fever and dehydration
- As such, there is existing language in the protocol to prophylactically manage the potential for dehydration and high fevers (eg, oral hydration, antiemetics, and antipyretics)

Summary of Tumor Inhibition and Safety in Murine Tumor Models to Ad-RTS-mIL-12 plus INXN-1001

| Tumor Type | Cell Line | % Tumor Growth Inhibition ¹ | p-value | # Deaths ² |
|---------------------|-----------|--|----------|-----------------------|
| Metastatic melanoma | B16F0 | 98% | < 0.0005 | 0 |
| Colorectal | CT26-1uc | 100% | < 0.0005 | 0 |
| Pancreatic | Pan02 | 97% | < 0.0005 | 0 |
| Lung | LLC | 78% | < 0.0005 | 0 |
| Breast | 4T1 | 82% | < 0.005 | 0 |

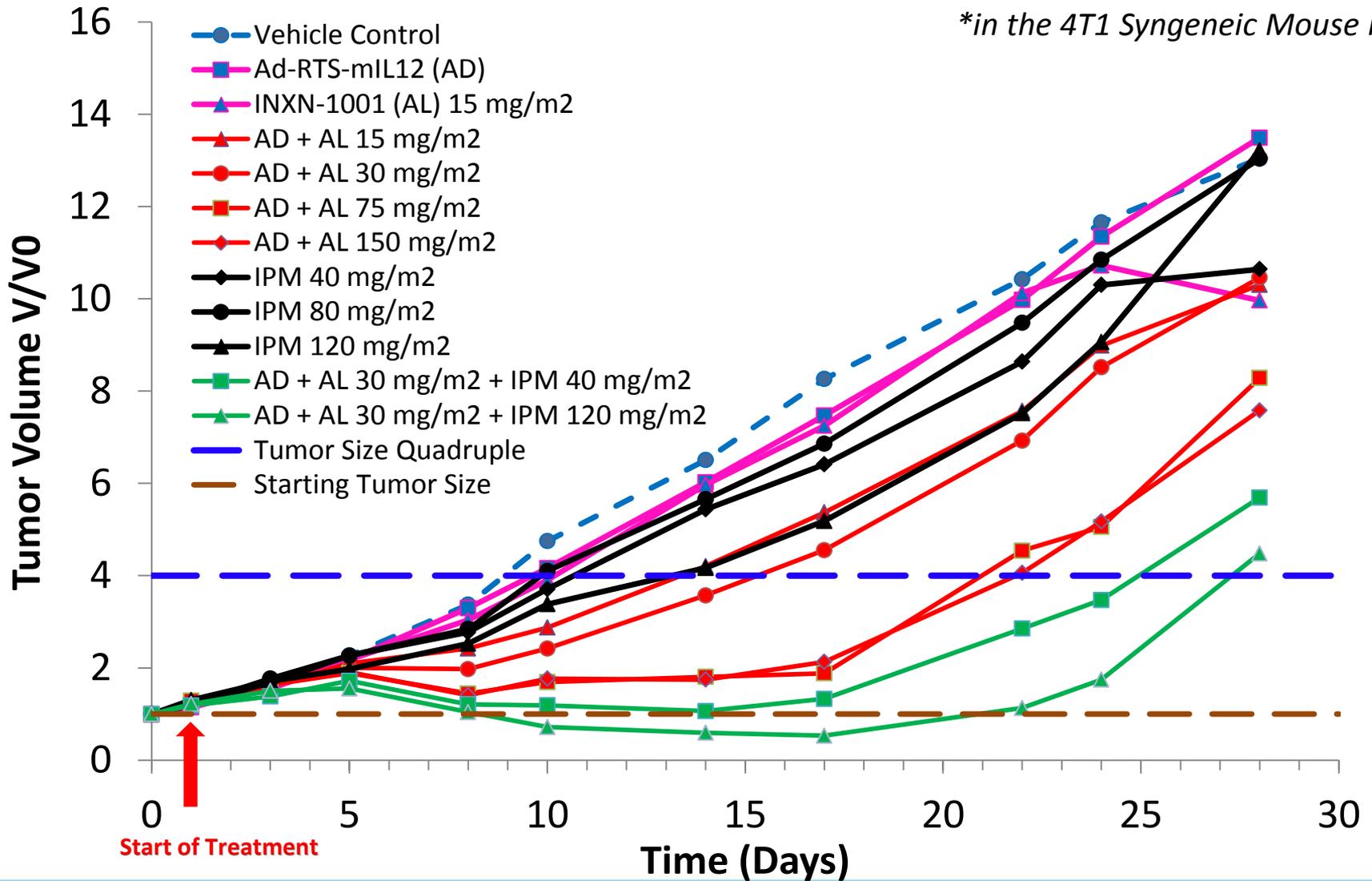
¹ Tumor growth inhibition and corresponding p-value for Ad-RTS-mIL-12 plus INXN-1001 treated animals as compared to untreated controls.

² Number of deaths observed in Ad-RTS-mIL-12 plus INXN-1001 treated animals.

- 5 animals per group
- No significant reduction in body weight

The Combination of IPM + Ad-RTS-mIL-12 + INXN-1001 Enhances the Reduction in Tumor Growth Rate

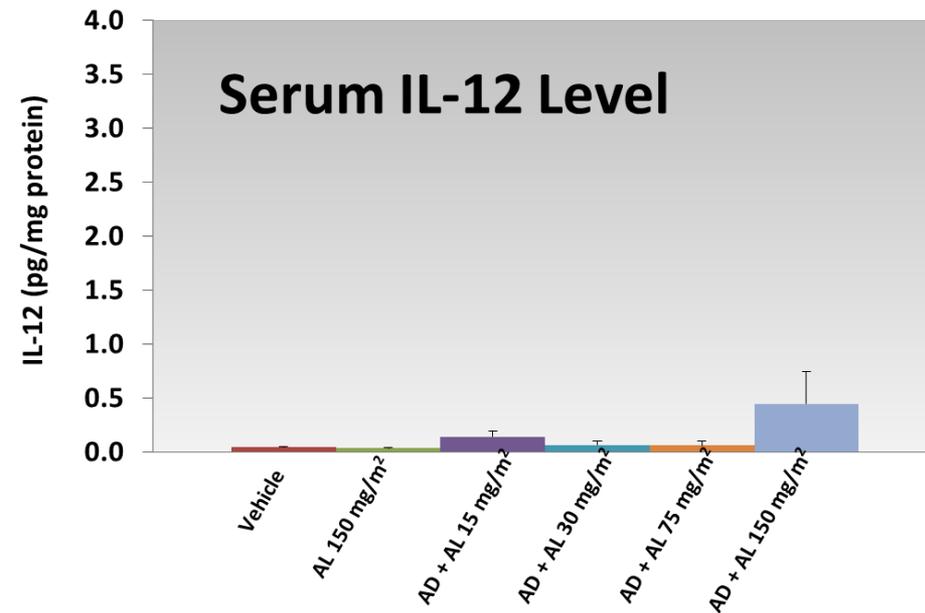
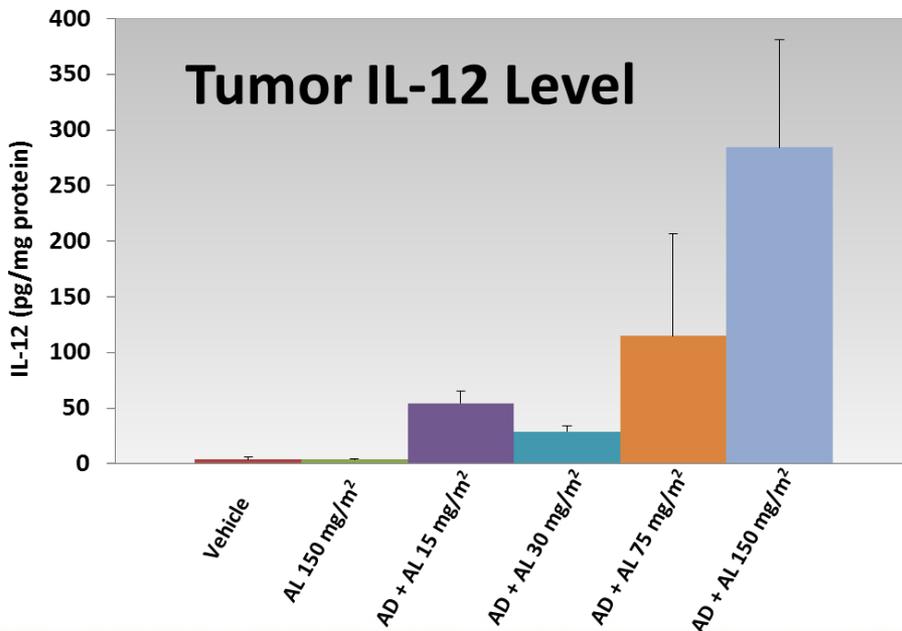
**in the 4T1 Syngeneic Mouse Model*



Effects of Ad-RTS-mIL-12 + INXN-1001 on Tumor and Serum IL-12 Production

**in the 4T1 Syngeneic Mouse Model*

- Dose-dependent increase in expression of tumor IL-12 in response to activator ligand
- No increase in serum IL-12 level
- INXN-2001 on D1, INXN-1001 Daily x 7, data shown below from D4



NIH OBA Protocol # 1007-1060 (ATI001-101)

Ad-IL-12 FIH Phase I/II Study in Melanoma

- **Primary objective**
 - Evaluate the safety and tolerability of intratumoral injections of INXN-2001 in a constant dose in combination with intra-cohort escalating doses of INXN-1001 (activator ligand) in subjects with unresectable stage II or IV melanoma.
- **Secondary objectives**
 - Evaluate immunological effect of treatment includes monitoring of IL-12 and IFN- γ
 - Assess pharmacokinetics of INXN-1001
 - Assess preliminary anti-tumor activity (RECIST v1.1)

NIH OBA Protocol # 1007-1060 (ATI001-101)

Preliminary Ad-IL-12 Melanoma Study Results

- Tumor shrinkage in two subjects in the 100 mg cohort (107 & 109)
- Tumor shrinkage/flattening in three subjects in the 160 mg cohort (110, 111 & 113)
- After C3D1, subject 110 presented new lesions; however, they decreased in size by C3D5.
 - Coincided with prominent lymphadenopathy after each cycle
- Stable Disease (SD) in one subject for at least 16wks (111)
- Response appears to be associated with:
 - Leukopenia
 - High Fevers
 - Chills

Subject 107 Clinical History

- 71 y/o female
- History of vaginal carcinoma (1998), lung cancer (2009), Schwannoma of the brain, renal insufficiency coronary artery disease.
- Presents with a metastatic malignant melanoma (T4N2a M1a)
- ECOG - 0
- Previously treated with Interferon and Leukin (2009), right arm melanoma excision, right arm axillary LN dissection

Clinical Observations Correlate with Increased Levels of IFN- γ

C1D1



C1D16



- Initial increase in lesion size due to inflammatory response seen at Cycle 1 Day 16
- Lesion was undetectable at Cycle 2 Day 1
- Subject ultimately progressed and was taken off study

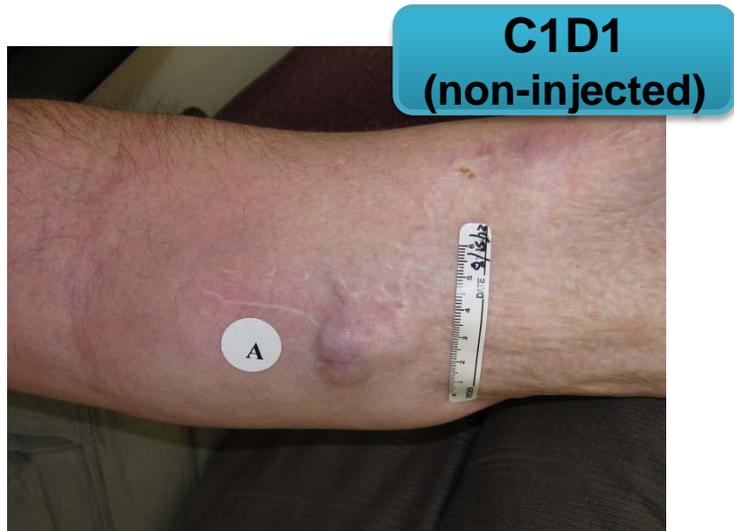
C2D1



Subject 113 Clinical History

- 60 y/o male
- History of anxiety disorder, weight loss and general pain
- Dx on registration malignant metastatic melanoma
- Prior therapy Included
 - Surgery
 - Oncovex virus 2/2011 – 3/2011
 - Ipilimumab 6/2011 - 8/2011
 - Dacarbazine 9/2011 – 7/2012
 - Presents with 4 target lesions and 5 non-target lesion

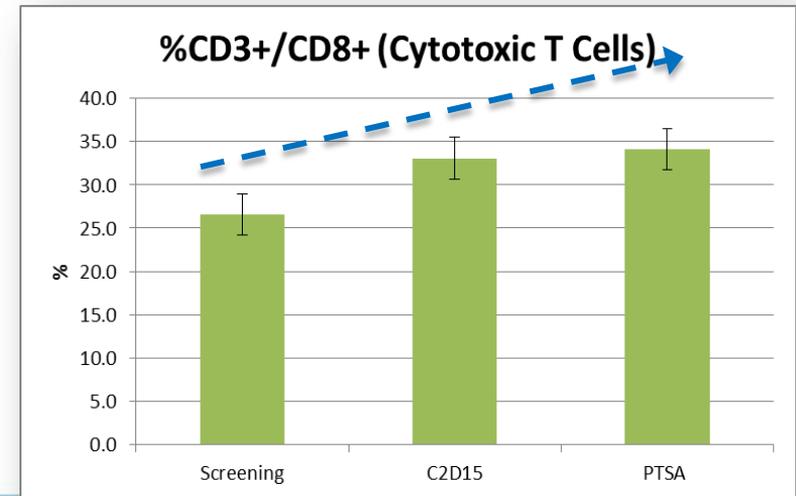
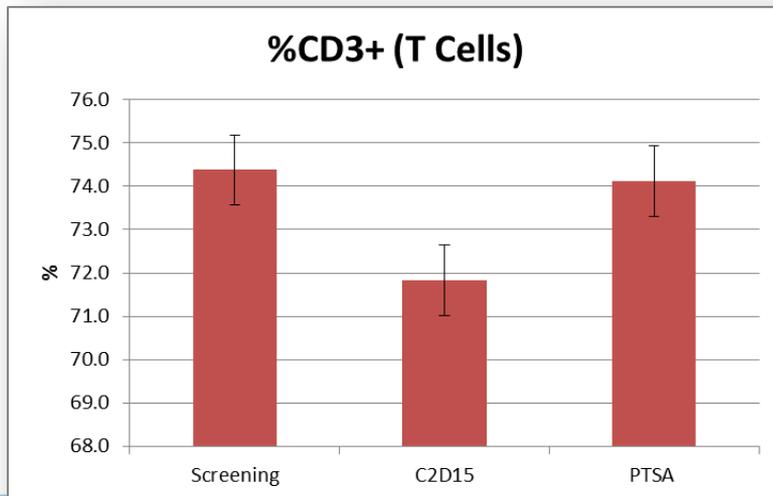
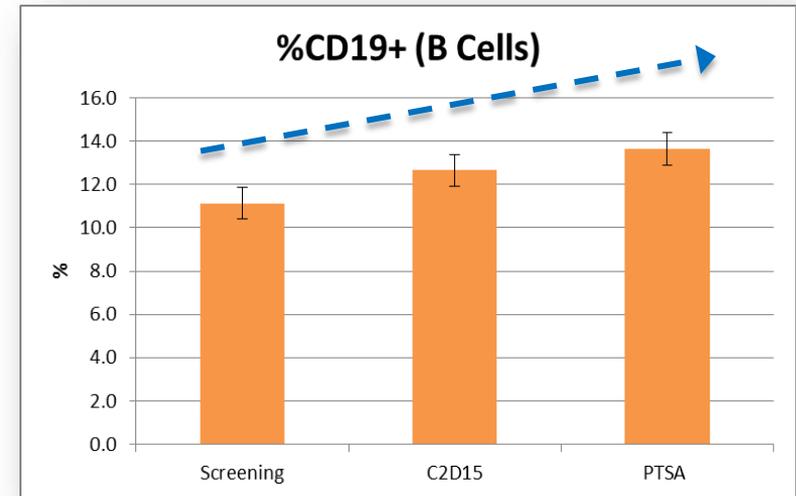
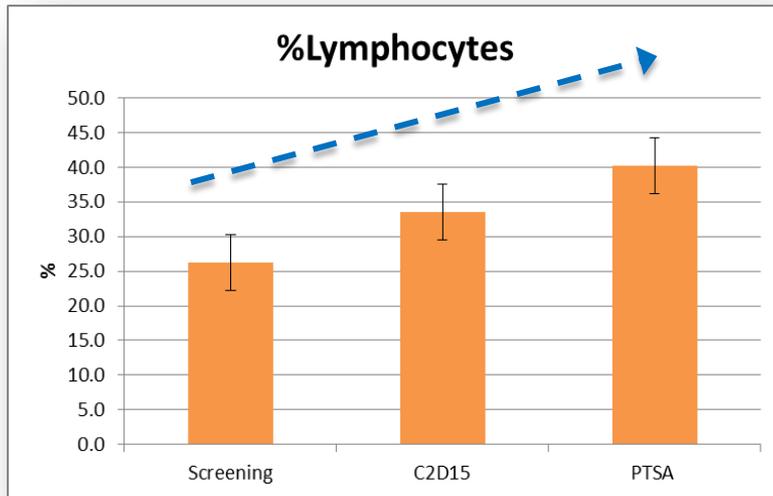
Subject 113 Digital Photography



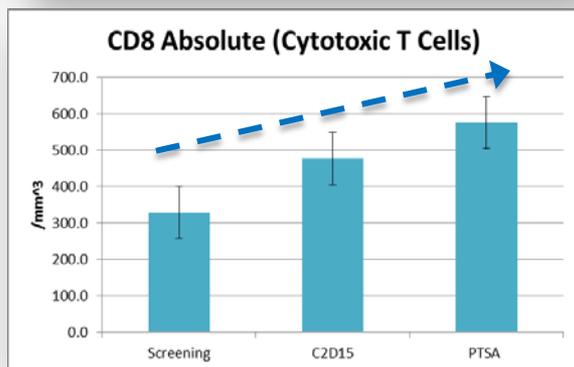
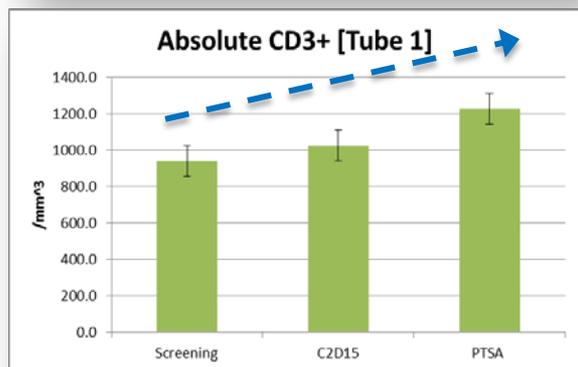
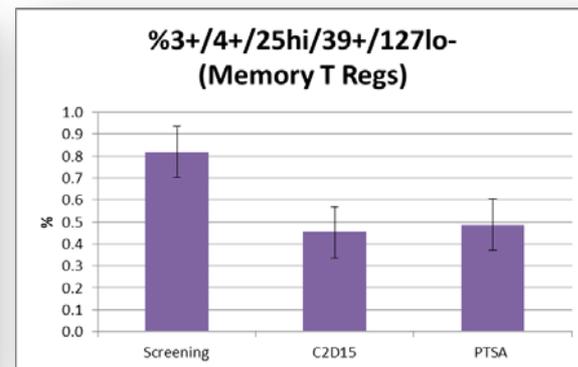
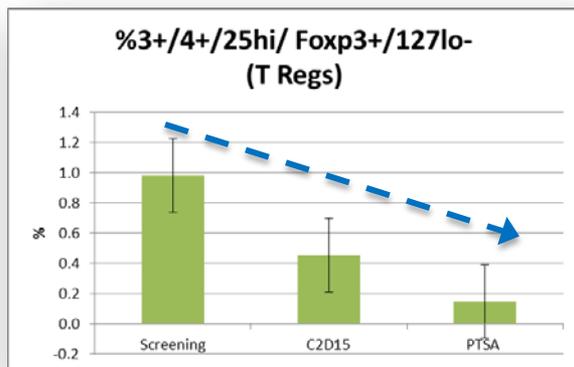
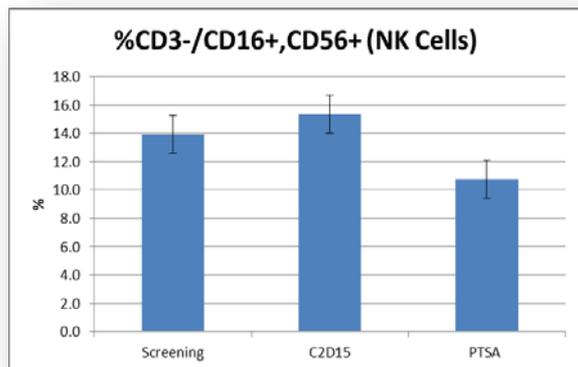
Conclusions

- Analysis of the emerging safety profile from the melanoma studies along with safety mitigation measures have enabled exploration of the use INXN-1001 and INXN-2001 in other indications.
- Compelling nonclinical data support pursuing this combination study in advanced breast cancer combining INXN-1001 and INXN-2001 with palifosfamide.

General Trends for Aggregate Flow Cytometry Data



General Trends for Aggregate Flow Cytometry Data



Mean increase in ALC during ipi treatment correlates with dose
At 3mg/kg, ALC ≥ 1000 at wk 7 (vs < 1000) is significantly associated with improved OS

Postow MA et al. Evaluation of the absolute lymphocyte count as a biomarker for melanoma patients treated with the commercially available dose of ipilimumab (3mg/kg). J Clin Oncol 30, 2012 (suppl; abstr 8575)