

Phase I clinical results of an APC-targeted hCG β vaccine (CDX-1307) with TLR agonists.

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Disclosure Slide

- Michael Morse
 - No disclosures related to this presentation

Challenges in Immunotherapy

- Choosing target antigens to which tolerance may be broken
- Efficient delivery of antigen to APCs
- Presentation to CD8+ and CD4 + T cells
- Providing “danger signals” to APCs that lead to enhanced activation of T cells

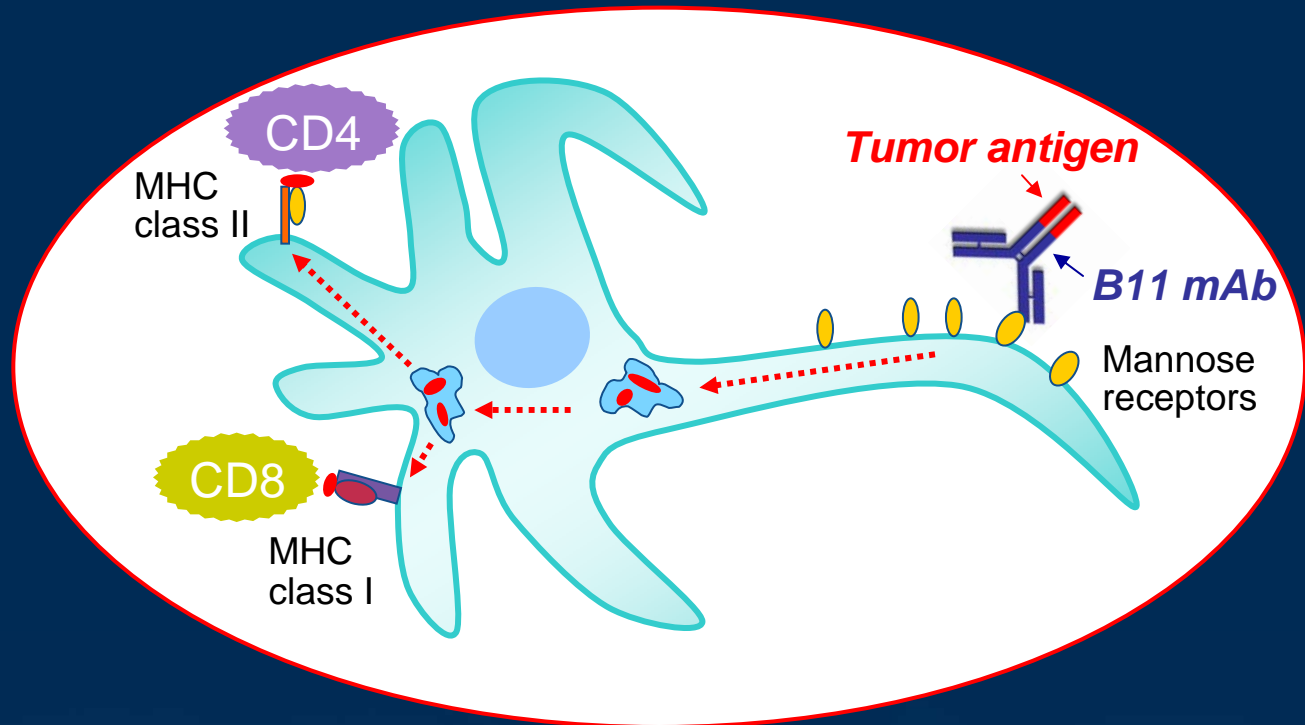
Targeting Ag to APC with Mannose Receptor-Binding Ab

- Tumor antigen delivered to dendritic cells and macrophages

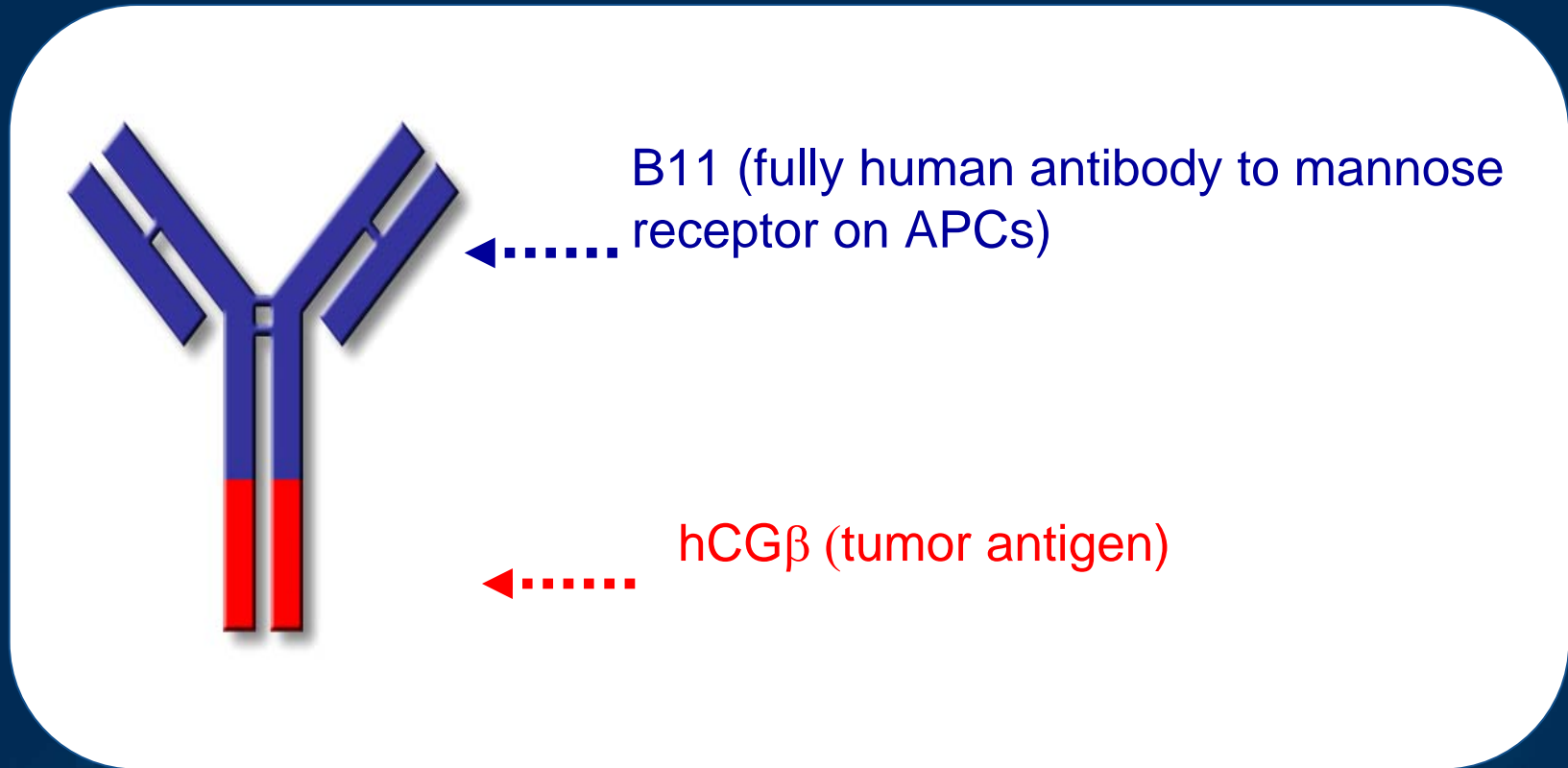
- Efficient uptake
- Presentation of multiple epitopes (MHC-I and -II)

- Antibody and T cell immune responses

- Allows potential access to a larger APC population compared to standard protein vaccination strategies



CDX-1307: APC-targeted hCG β vaccine



Rationale for targeting hCG β in cancer immunotherapy

- overexpressed by common cancers; few normal tissues¹
- Implicated in survival and growth of cancer cells
- Elevated expression associated with poor prognosis
- Anti-hCG β Ab response associated with improved survival²
- Tolerance to hCG β may be broken
 - specific cytotoxic T cells can be generated from PBL of healthy donors and cancer patients

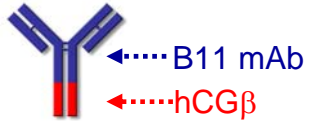
In vitro targeting of B11-hCG β (CDX-1307) to human dendritic cells

0 min

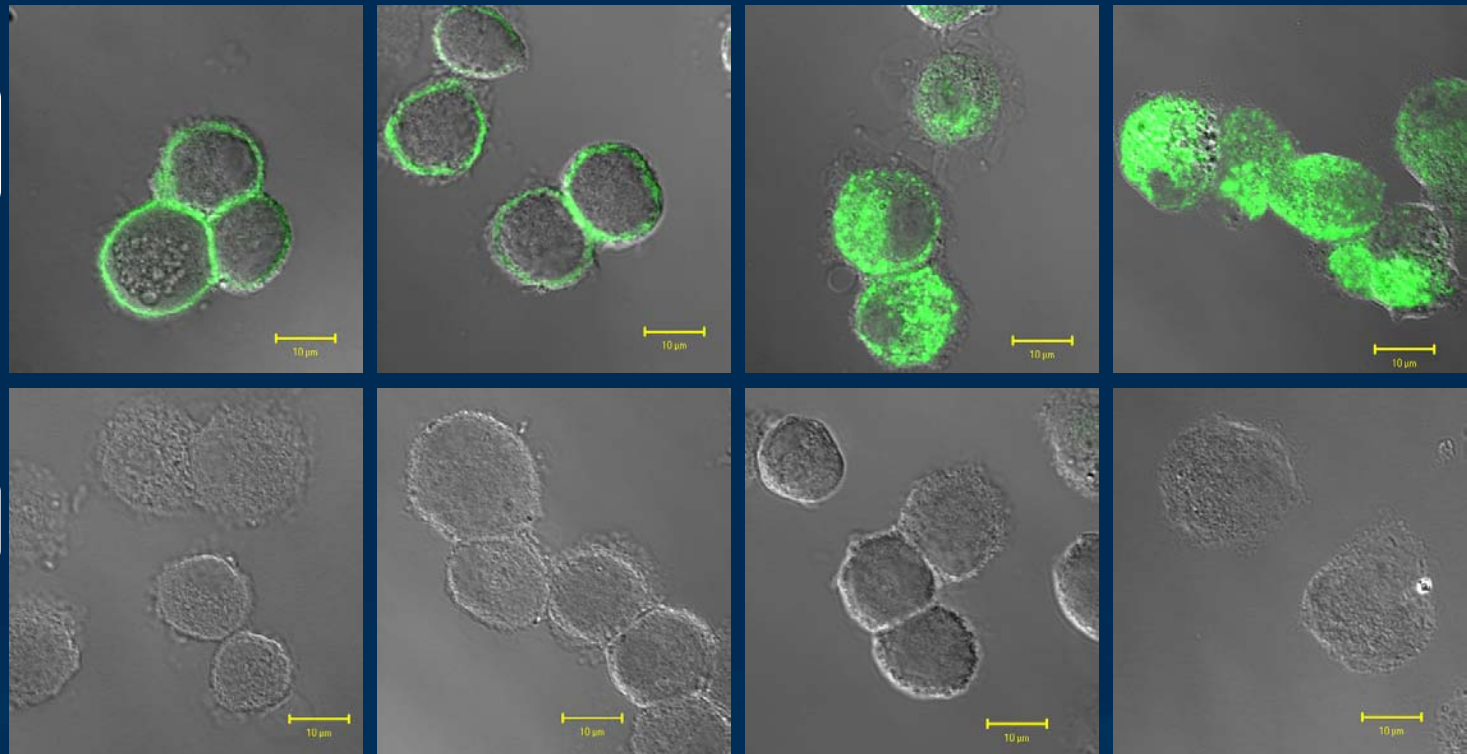
10 min

60 min

120 min



B11-hCG β -FITC
0.25 μ M

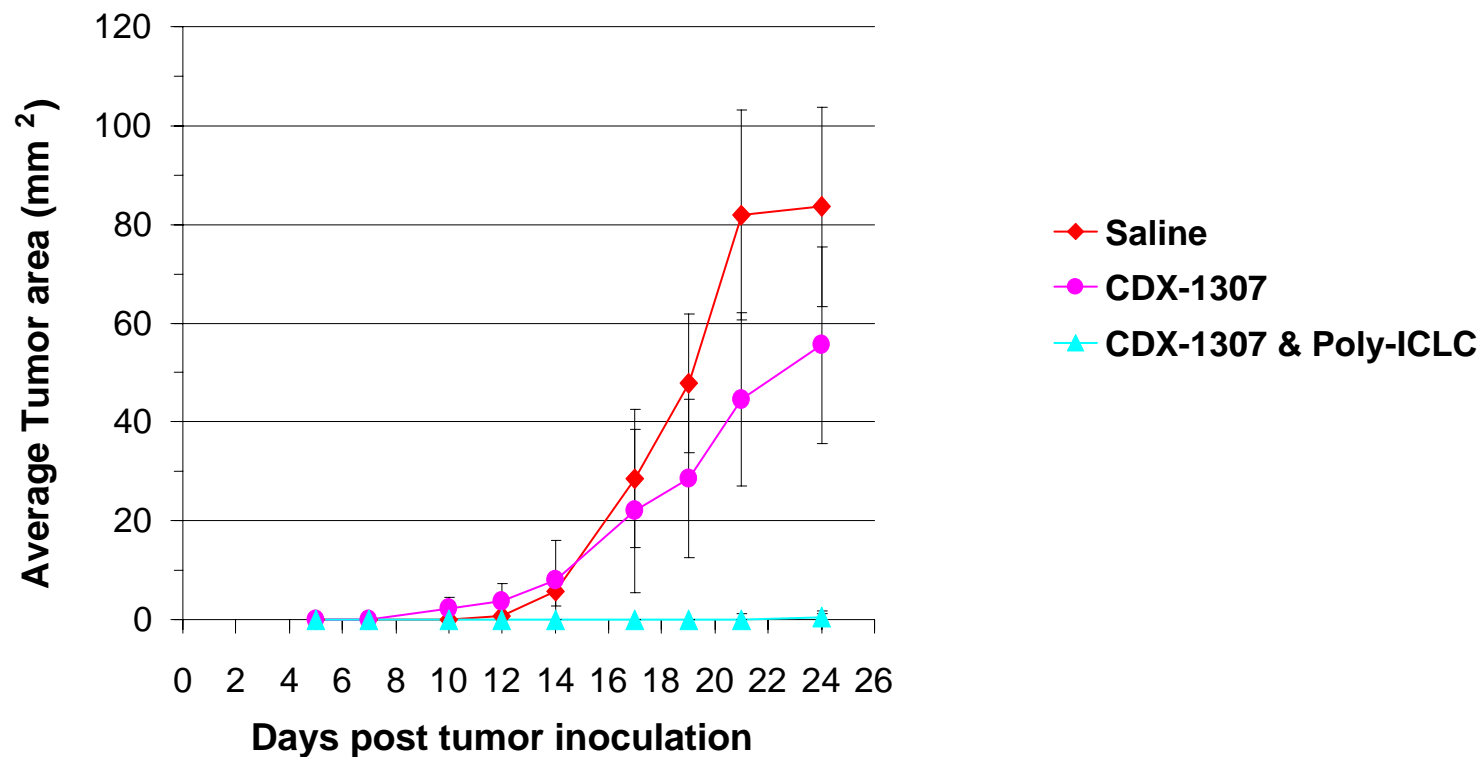


hCG β -FITC
0.5 μ M

Adjuvants provide additional signals for APC activation

- **GM-CSF**
 - Local recruitment and maturation of DCs
 - Up-regulation of mannose receptors
- **TLR agonists**
 - Trigger maturation and activation of APCs
 - enhance co-stimulatory signals and release of cytokines
 - **Poly-ICLC (Hiltonol: Oncovir, Inc.):** ds RNA with poly lysine and carboxymethylcellulose; activates TLR3
 - **Resiquimod/R848 (3M):** synthetic, imadazoquinoline; activates TLR7/8

Combination with TLR-Agonists Generates Anti-Tumor Immunity



CDX-1307: Clinical Studies

- Two Phase I studies:
 - Intravenous vs. intradermal delivery
- Advanced breast, colorectal, pancreatic, ovarian or bladder cancer
- Objectives:
 - Safety and tolerability;
 - Immune responses
 - Clinical activity (ORR, TTP)

Clinical Study Cohorts

Intradermal/Intracutaneous Study

Intravenous Study

**CDX-1307
(no adjuvants)**

0.3 mg (n=6)

1.0 mg (n=6)

2.5 mg (n=6)

1 mg (n=4)

3 mg (n=4)

10 mg (n=3)

30 mg (n=5)

**CDX-1307 +
GM-CSF**

2.5 mg + GM-CSF (n=7)

10 mg + GM-CSF (n=5)

30 mg + GM-CSF (n=3)

**CDX-1307 +
GM-CSF +
TLR
Agonists**

2.5 mg + GM-CSF + Hiltonol (n=6)

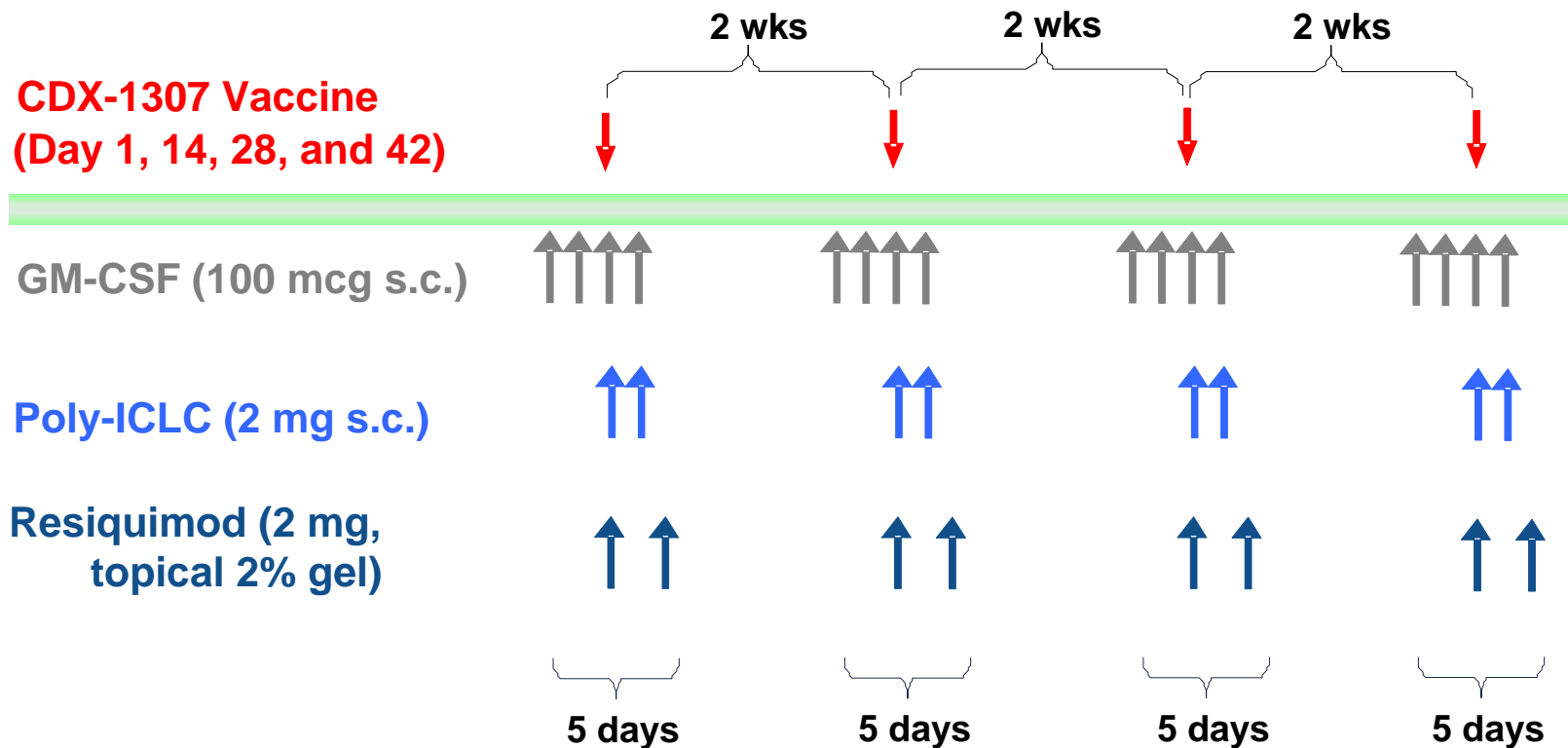
2.5 mg + GM-CSF + Resiquimod (n=7)

2.5 mg + GM-CSF + Poly-ICLC + Resiquimod (n=8+)

30 mg + GM-CSF +
Hiltonol (n=6)

Currently enrolling

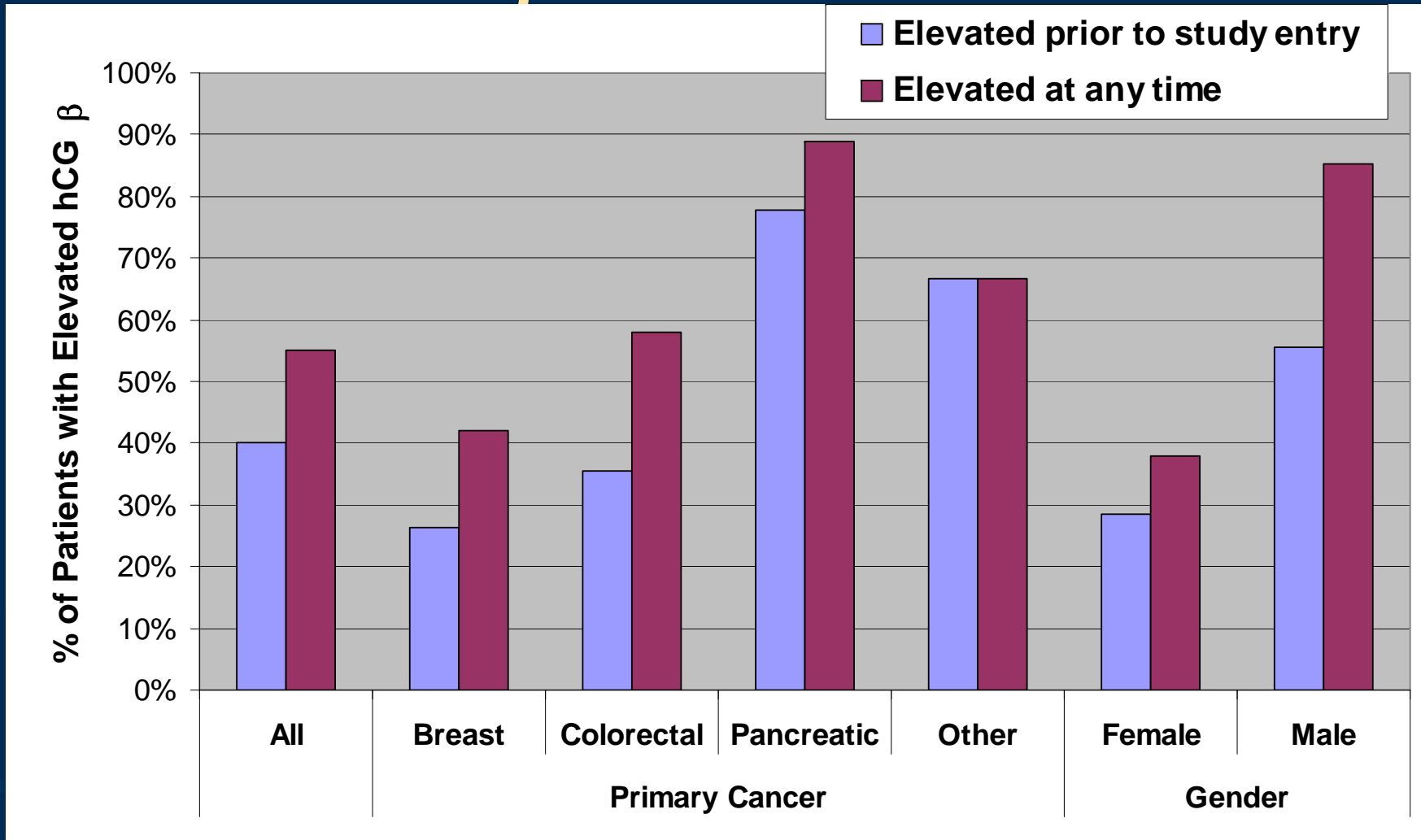
Treatment Regimen



Baseline Characteristics

Characteristic	All Patients (n=68)
Median age (years [range])	60 (35-81)
Male	40%
ECOG Performance Status	
0	49%
1	50%
2	1%
Primary Cancer	
Pancreatic	13%
Colorectal	46%
Breast	37%
Other	4%
Number of prior chemotherapy regimens (Mean)	4.5
Received prior radiotherapy	59%
Elevated Serum hCG- β	42%

Serum hCG β Measurements

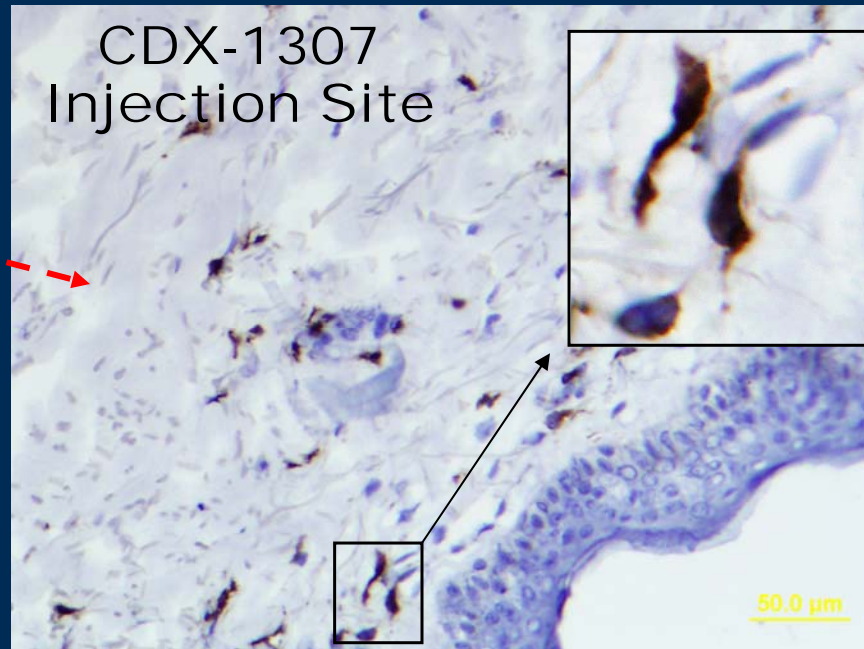


- Elevated hCG β found commonly in cancer patients

CDX-1307 Tolerability & PK

- No DLTs or treatment discontinuation due to toxicity
- 4 patients treated with 2nd cycle
- Treatment-related AEs:
 - G1-2 administration site reactions (23%)
 - CDX-1307 locally (17%); addition of adjuvants (55%)
 - G1-3 fatigue (21%), G1 flu-like illness (10%), G1 diarrhea (6%), G1 myalgia (6%), G1 pyrexia (6%)
- No significant circulating levels of CDX-1307 at doses below 30 mg
 - 30 mg dose IV ~ 1 µg/ml at 2 hr post infusion

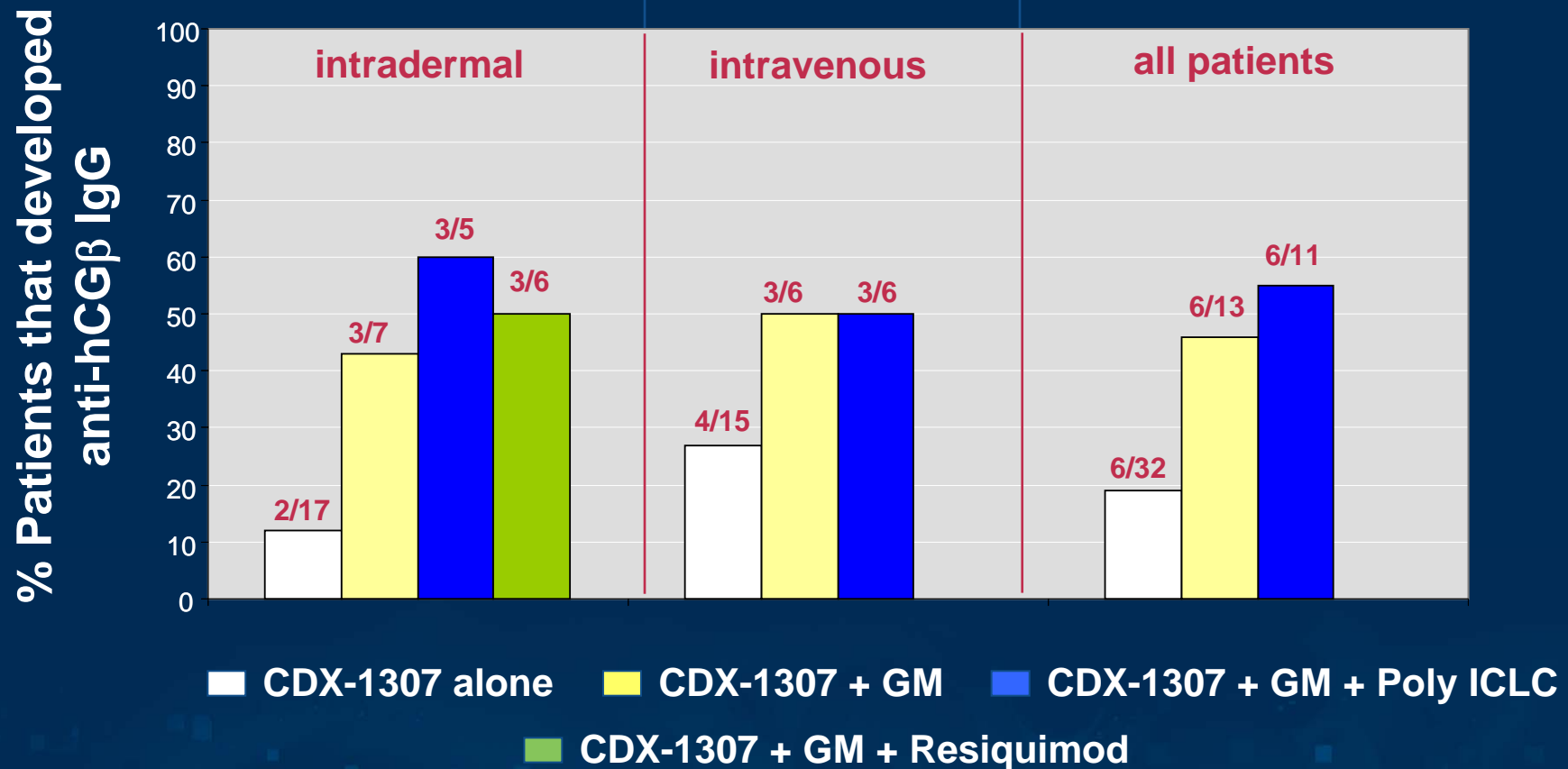
Accumulation of hCG β in dermal dendritic cells and macrophages



Skin punch-biopsies taken from injection site and opposite limb 48 hrs post CDX-1307 (1 mg, i.d.)

IHC - rabbit anti-hCG β

Humoral Immune Responses



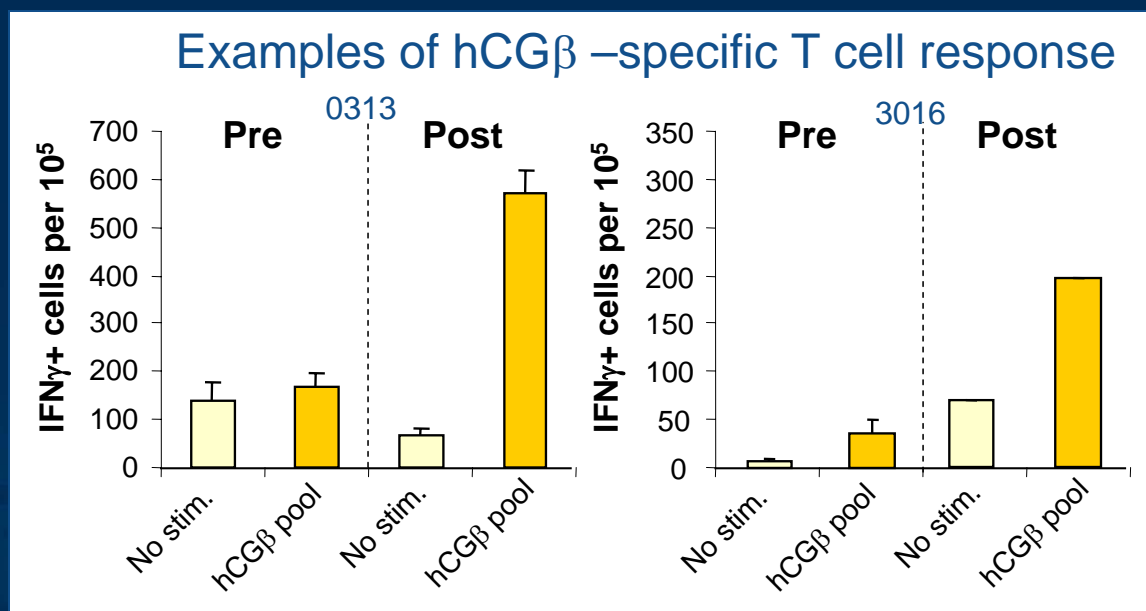
- Similar outcome with i.d. and i.v. administration

Correlates of Anti-hCG- β Immune Response

- Highest titers in GM + TLR combination
 - Titers ranged to $> 1/200,000$
- Similar response in males (44%) and females (52%)
- Anti-hCG β response despite elevated serum hCG β
- Anti-hCG β response in 3 of 4 patients receiving retreatment
- In adjuvant groups
 - 75 % (9/12) of breast cancer patients had Anti-hCG β response
 - 36% (5/14) of colorectal Ca patients had Anti-hCG β response

Cellular Immune Responses

- Analysis not complete
 - Monitored from 90ml blood samples
 - In vitro re-stimulation to expand T cells
 - Analysis by ELISPOT with hCG β peptide pool
- Enhanced T cell responses observed in some patients



Emerging data: CDX-1307 plus combined TLR agonists

3 of 3 with + humoral immune response

d1



d3



d4



Enhanced local response with combined TLR agonists

Clinical Outcomes

- Tumor response:
 - 1 mixed response seen in Pancreatic Cancer
 - 7 patients with SD for 2.2+ to 6.5+ months (5 breast cancer, 1 colorectal, 1 pancreatic)
- Tumor markers
 - Robust humoral response in 1 colon cancer patient - coinciding with decrease in CEA
 - Second patient (testicular cancer) with humoral immune response had improvement in AFP

Summary/Conclusions

- CDX-1307 is designed for delivery of hCG- β to APCs
- Administration of CDX-1307 is well tolerated
- hCG- β localization in APCs demonstrated
- Anti-hCG β immune responses observed in combination with adjuvants
- No clear differentiation between systemic and local administration
- 1 mixed response and 7 patients with stable disease
- Combination of TLR agonists may prime for additional anti-tumor activity

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