

# NCI Experience Using Yeast-Brachyury Vaccine (GI-6301) in Patients with Advanced Chordoma

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## Abstract

**Background:** *Saccharomyces cerevisiae* has been genetically modified to express Brachyury (Br) protein and developed under a CRADA with GlobeImmune/NCI as a heat-killed immune-stimulating therapeutic cancer vaccine (GI-6301). Br is a member of the T-box family of transcription factors and is a key factor in embryonic (mesoderm) development. Chordoma, a rare tumor of the notochord (derived from mesoderm) is known to over-express Br while expression in normal adult tissue is minimal or not present. Preclinical work has demonstrated Br specific T cells stimulated by GI-6301 can lyse human chordoma cells expressing Br in an MHC restricted fashion.

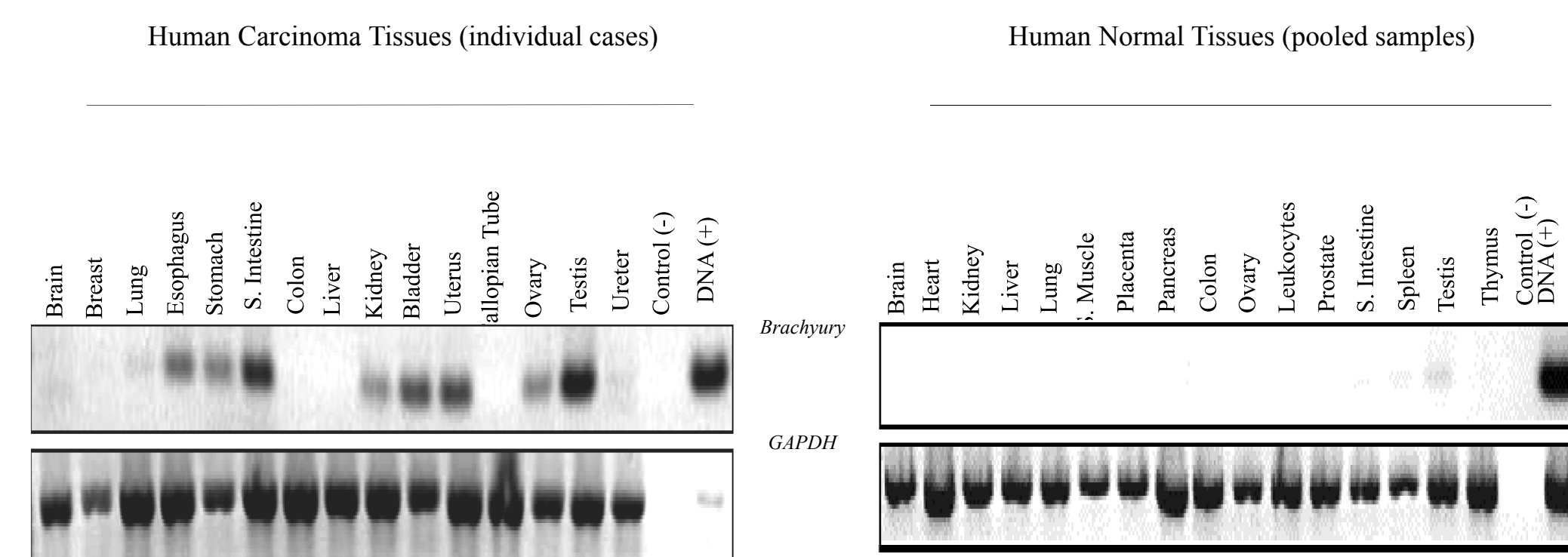
**Methods:** We enrolled a cohort of 7 pts with advanced chordoma in an expansion cohort of a phase I study (NCT01519817) and evaluated their clinical and immunologic outcomes. All patients had undergone previous radiation (median 470 days since radiation; range 111-1183). All received 40 yeast units of vaccine every 2 weeks x 7 with first restaging at day 85. If stable, pts went on to monthly dosing with restaging scans every 2 months. The primary endpoint was safety, but clinical outcomes were followed as well. Br-specific T cell responses were also analyzed by flow cytometry intracellular staining (ICS) of CD4 and CD8 T lymphocytes for the cytokines IFN-g, TNF, and IL-1.

**Results:** All 7 pts had undergone extensive previous treatment. Median age was 59 (41-66). Two pts had relatively stable disease for 6 and 12 months, respectively, before coming on the study, and both remain stable at day 141 and 197 restaging, respectively. The remaining 5 had progressive disease at enrollment. Of those 5, 1 had a decrease in index lesions >30% at day 141 with a confirmed PR on repeat scan 4 weeks later. 1 has stable disease through day 141 restaging. The other 3 progressed at day 141 restaging. Adverse events were minimal with injection site reaction being the most common (13 events in 63 doses (21%), 6 of 7 pts (86%)). Three of 7 pts had a Br-specific T cell response by ICS.

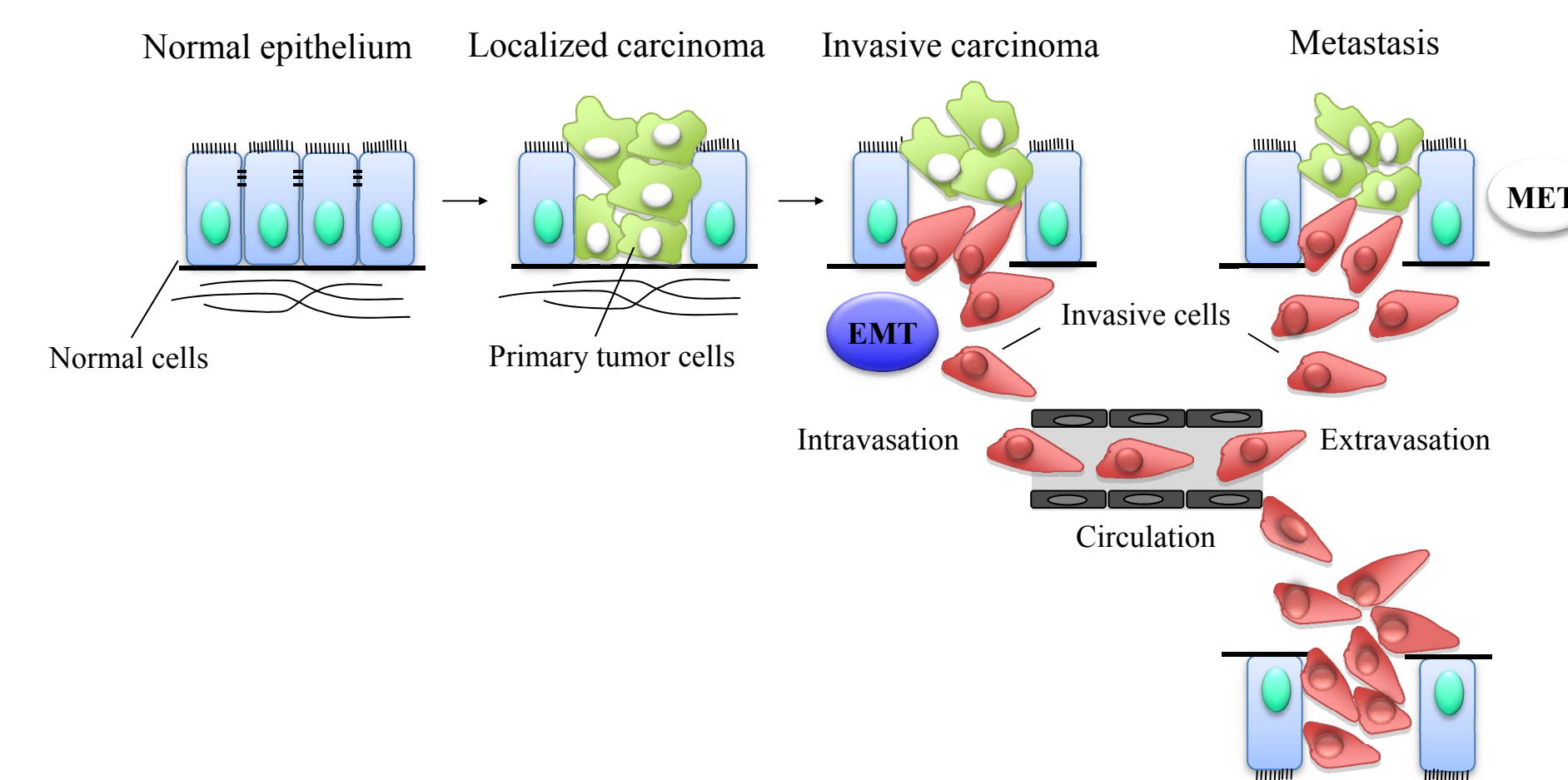
**Conclusions:** This cohort of pts with advanced chordoma in the phase I study with GI-6301 vaccine demonstrated an acceptable safety profile and enhanced immune response with a confirmed PR. These findings are encouraging and warrant further study using this vaccine in pts with chordoma.

## Background

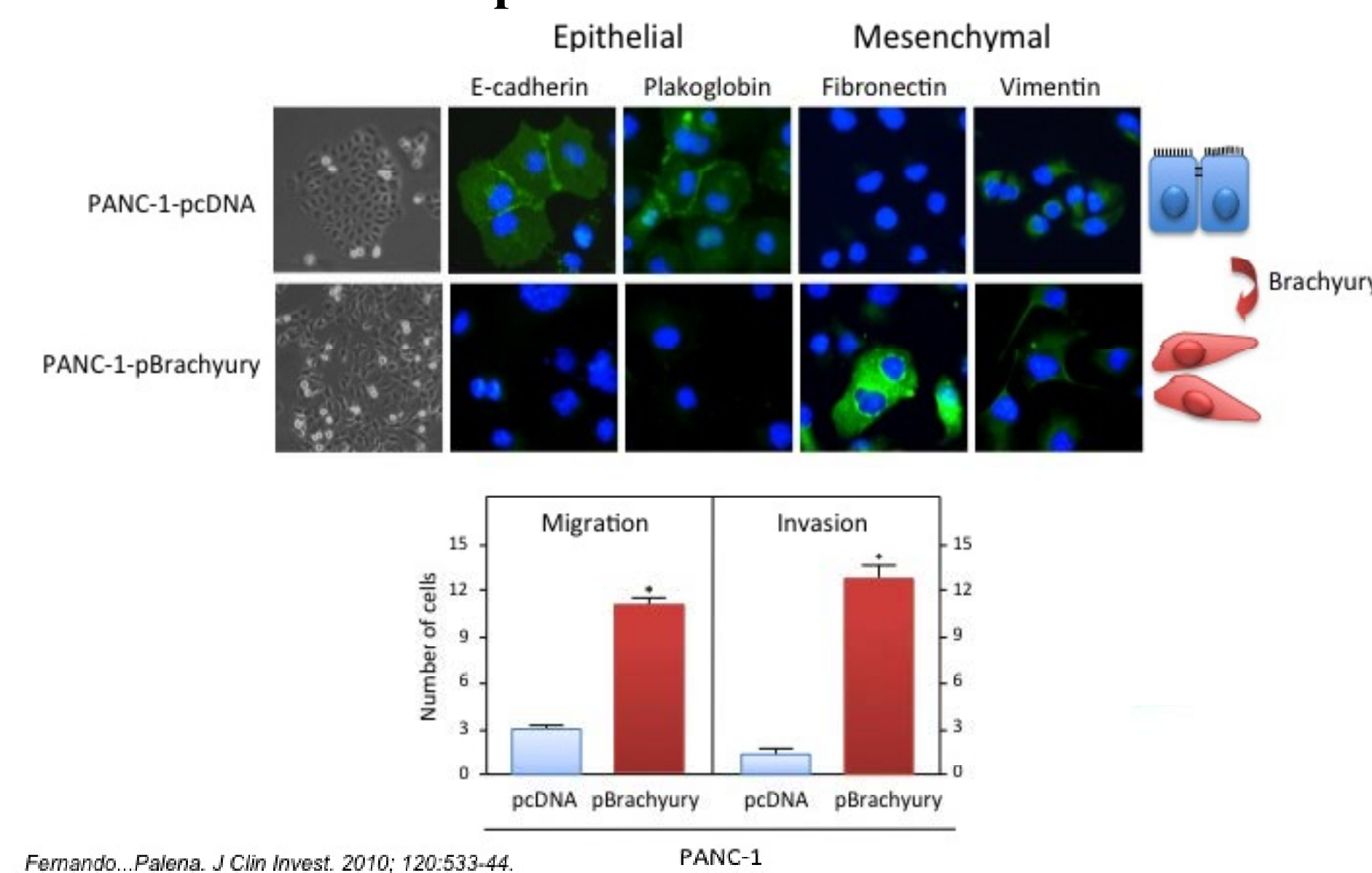
### Brachyury is Expressed in Human Carcinoma Tissues and Rarely Expressed in Normal Human Tissue



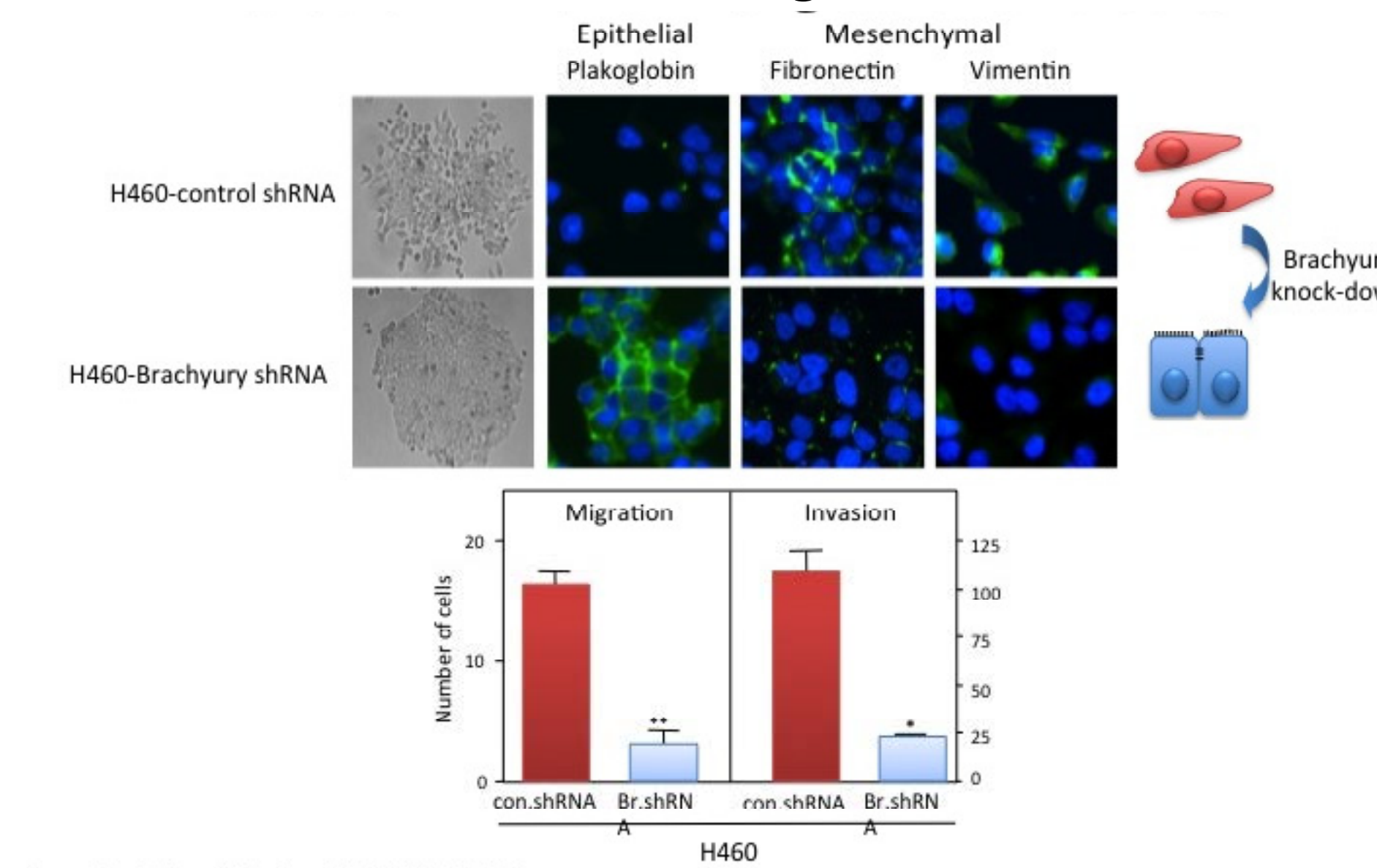
### Epithelial-to-Mesenchymal Transition (EMT): an Opportunity for Interventions Against Tumor Progression



### Brachyury Over-Expression Induces EMT in Epithelial Tumor Cells



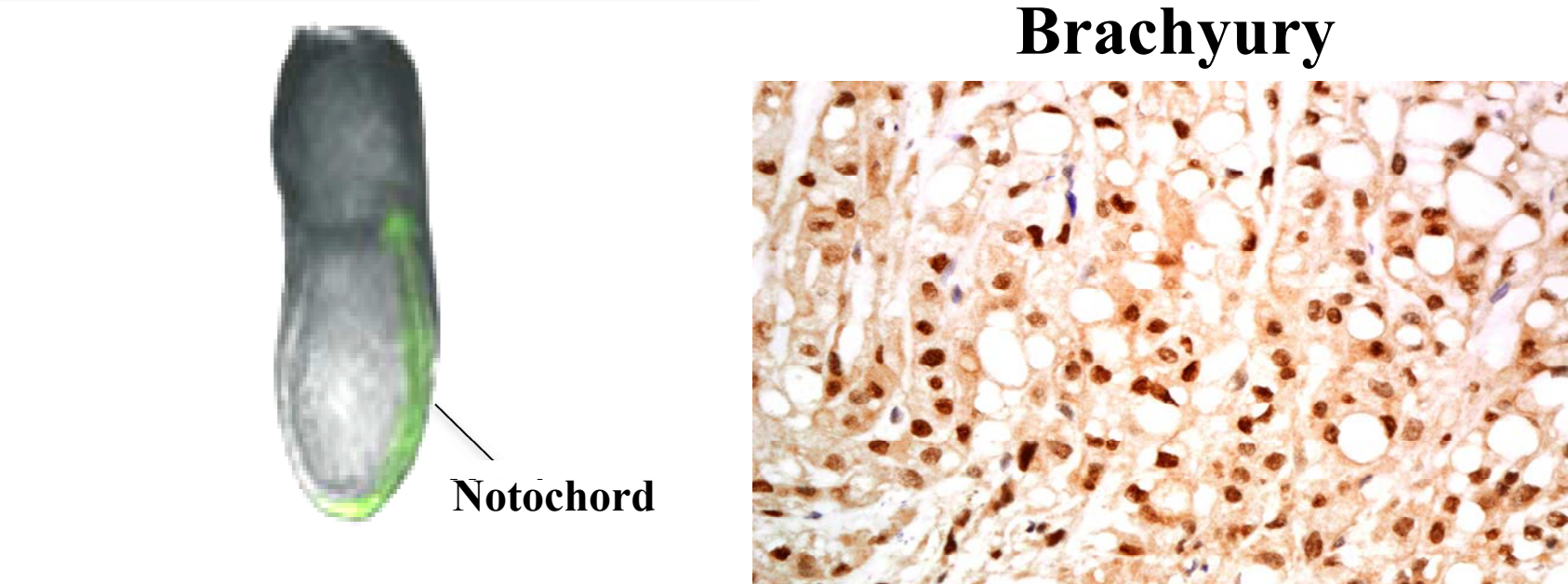
### Brachyury Inhibition Induces Mesenchymal-Epithelial Transition in Human Lung Carcinoma Cells



## Chordoma Overview

- Rare tumor (~300 cases/year)
- Arises from residual notochord (mesoderm)
- Develops in axial spine (clivus, spinal, sacral)
- Brachyury expression is a diagnostic criterion
- No approved therapy for advanced disease

### Brachyury is Expressed in the Embryonic Mesoderm Immunohistochemistry Staining of Chordoma for Brachyury



From Haber et al, Nature 2004; 432:625

### Brachyury is Highly Expressed in Chordoma

Chordoma type	Site	Number of cases analyzed by IHC	n (% cases with Brachyury expression by IHC)
Classical chordoma	Sacral	24	23 (95%)
	Clival	3	3 (100%)
Chordomas with focal areas of chondroid differentiation	Sacral	10	10 (100%)
Chondroid chordoma	Clival	3	3 (100%)
Dedifferentiated chordoma	Sacral	3	3 (100%)
Metastatic chordoma		5	5 (100%)
<b>Total</b>		<b>54</b>	<b>53 (98%)</b>

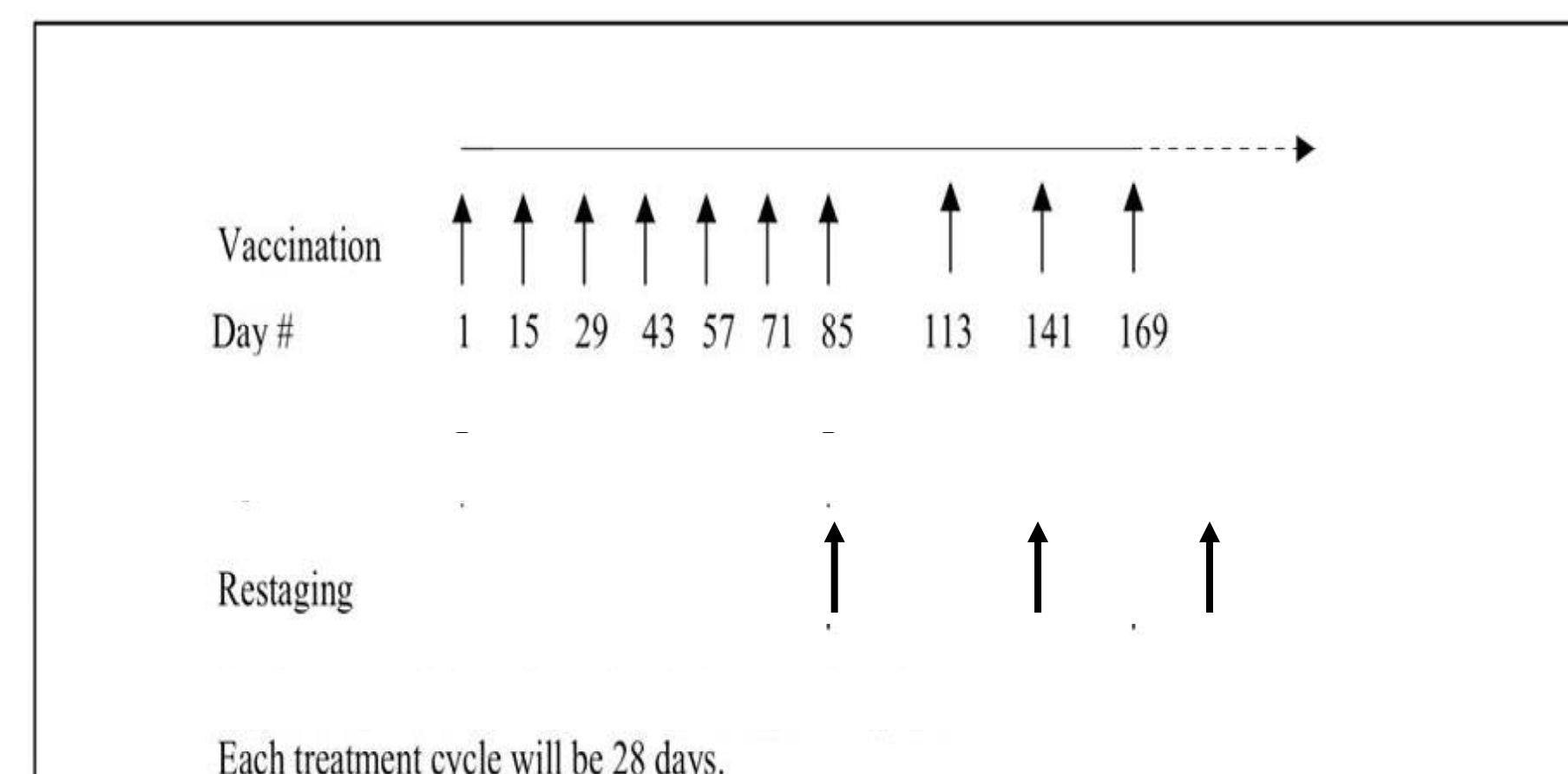
From Vujovic et al, Journal of Pathology 2006; 209: 159

## Design

### Dose Escalation Schedule

Dose Level	Dose and Schedule
1 n = 4	1 Yeast Unit (1 YU = 10 <sup>7</sup> yeast particles) per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until progression
2 n = 3	4 Yeast Units per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until Progression
3 n = 16 Expansion	10 Yeast Units per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until Progression
4 n = 3 (planned 10)	20 Yeast Units per site administered subcutaneously at 4 sites every 2 weeks x 7 courses, if no evidence of progression, then every 4 weeks until Progression

### Dosing Schema and Design



### Baseline Clinical Characteristics (chordoma only)

Chordoma (n = 7)	
Gender	# (%)
Male	7 (100)
Female	0 (0)
Age - Median (range)	59 (41-66)
Primary diagnostic site	# (%)
Clival	2 (28)
Sacral	3 (43)
Spinal	2 (28)
Prior therapy	# (%)
Surgery	7 (100)
Radiation	7 (100)
Tyrosine kinase inhibitors	2 (28)
Additional therapies	3 (43)
Disease at study entry	# (%)
Stable Disease (SD)	2 (28)
Progressive Disease (PD)	5 (71)

### Adverse Events (all patients enrolled)

Likely/Possibly related	Grade 1		Grade 2	
	# events (% doses)	# pts (% of pts)	# events (% doses)	# pts (% of pts)
Injection site reaction	38 (16)	20 (74)	7 (3)	5 (19)
Fever	1 (0.4)	1 (3.7)	0 (0)	0 (0)
Flu-like symptoms	1 (0.4)	1 (3.7)	0 (0)	0 (0)
Lymphocyte count decreased	5 (2)	2 (7.4)	2 (0.8)	2 (7.4)
Joint effusion/joint swelling	1 (0.4)	1 (3.7)	0 (0)	0 (0)
Myalgias/body aches	1 (0.4)	1 (3.7)	0 (0)	0 (0)
Pruritus	1 (0.4)	1 (3.7)	0 (0)	0 (0)

Calculation based on 237 administered doses.  
No events greater than grade 2 attributed to IND.

## Immune Responses

### 15-mer peptides:

- Brachyury with TP2 agonist
- HLA negative control
- CEFT positive control (for 5 samples)

### Readouts:

- Intracellular cytokine staining in CD4 and CD8 for INFγ, TNF, IL2, CD107a

### Response Criteria:

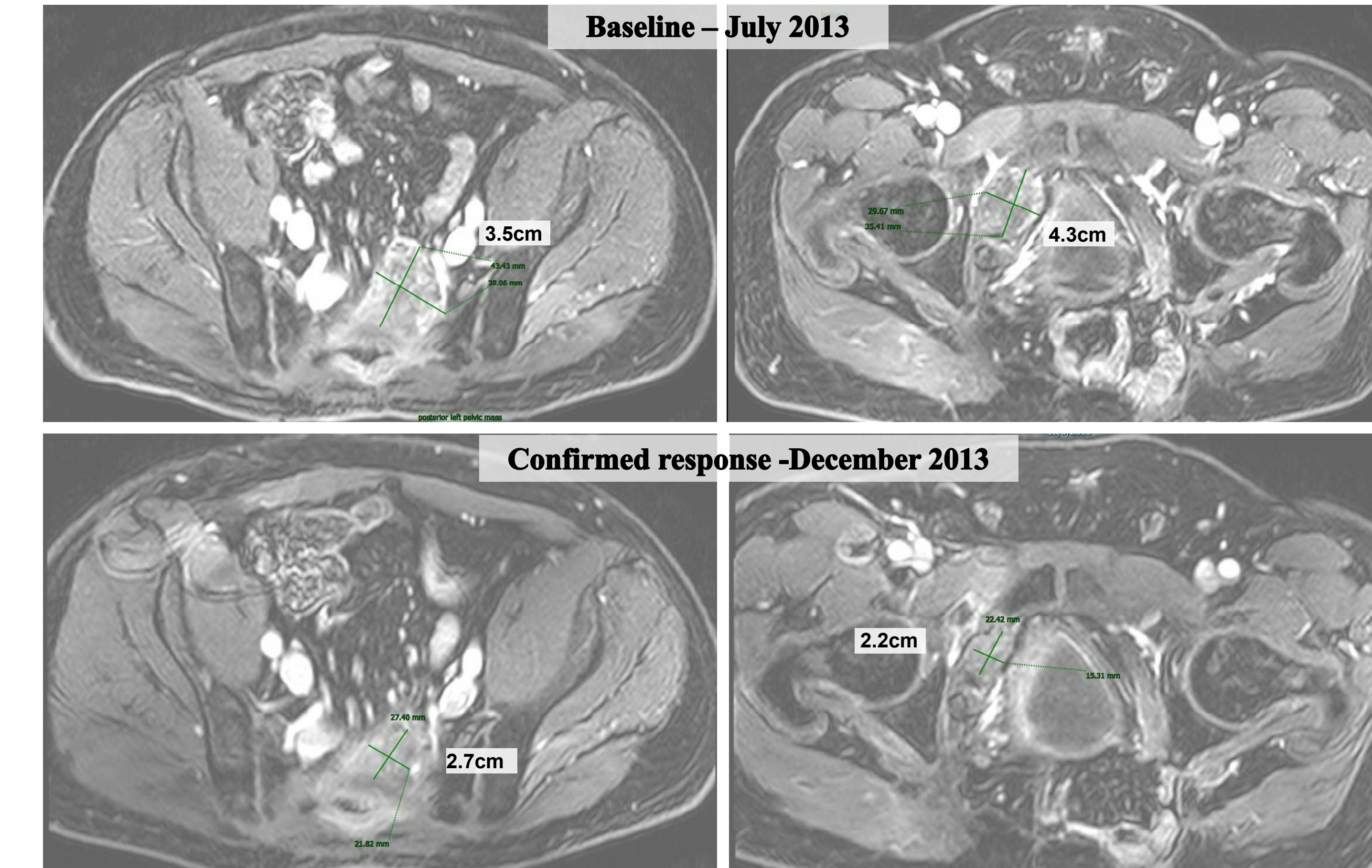
- ≥50% increase in response to Brachyury in post vs pre
- ≥50% increase in response to Brachyury at post vs HLA at post
- ≥0.05% of CD4 or CD8 T cells

Cancer Type	Dose	Immune Response to Brachyury stimulation							
		CD4				CD8			
		IFNγ	TNF	IL2	CD107a	IFNγ	TNF	IL2	CD107a
PT #15	Chordoma	-	-	-	-	-	-	-	-
PT #16	Chordoma	-	-	-	-	-	-	-	-
PT #17	Chordoma	+	+	-	+	+	+	+	+
PT #18	Chordoma	-	-	-	-	-	-	-	-
PT #19	Chordoma	+	-	-	-	-	-	-	-
PT #21	Chordoma	-	-	-	-	-	-	-	-
PT #22	Chordoma	+	+	-	-	-	-	-	-

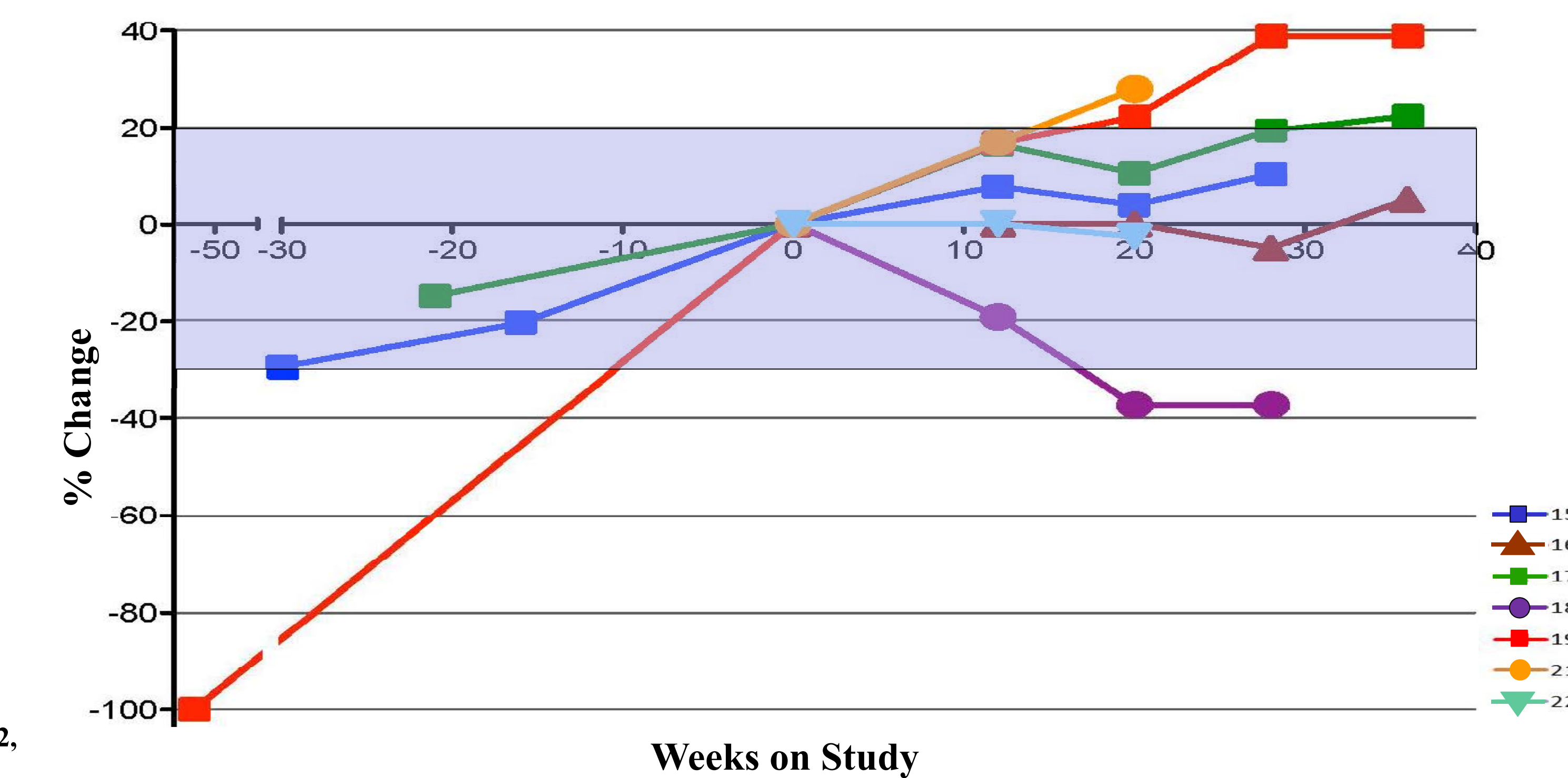
10 out of 21 patients demonstrated a Br-specific CD8+ and/or CD4+ T cell response pre and post vaccination. 3 out of 7 tested chordoma patients had a response.

## Results

### Confirmed Partial Response in Patient with Sacral Chordoma (Patient 18)



### Yeast-Brachyury Phase I expansion phase Chordoma Cohort Percentage Change in Tumor Volume by RECIST



## Conclusions

This Phase I study with GI-6301 Brachyury vaccine demonstrated:

- An acceptable safety profile
- Capability of induction of immune response against a transcription factor, Brachyury
- One confirmed PR in a patient with chordoma.

These results are encouraging and warrant further study using this vaccine in patients with chordoma.

A phase II study for patients with chordoma using GI-6301 Brachyury vaccine is planned.