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

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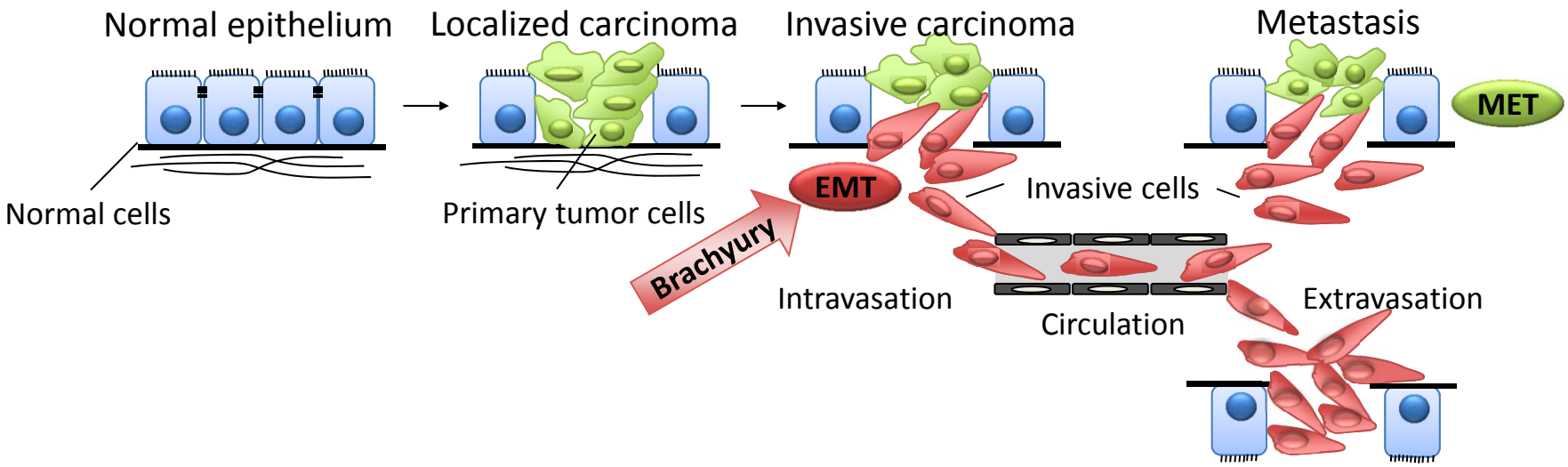
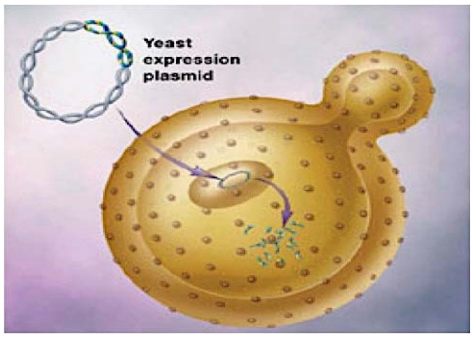
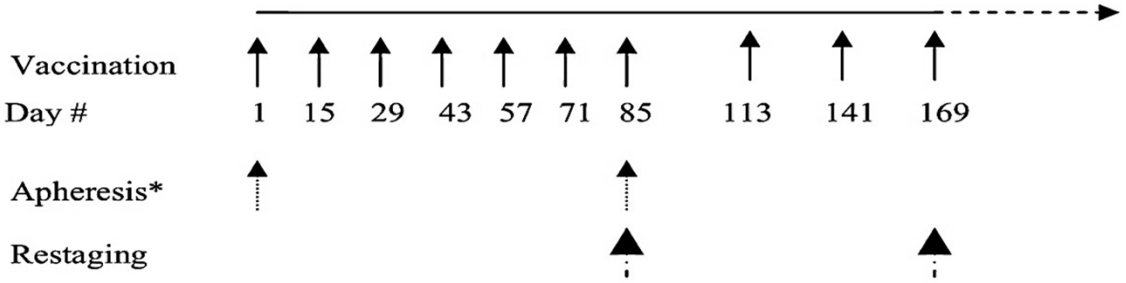
Role Of Brachyury in the Epithelial-to-Mesenchymal (EMT) Transition During Tumor Progression



PHASE I TRIAL OF YEAST-BRACHYURY VACCINE





*Apheresis will be performed only in expansion phase
Each treatment cycle will be 28 days.

Dose Level	Dose and Schedule
1 n = 4	1 Yeast Unit (1 YU = 10^7 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 = 4 (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

PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

Key Eligibility Criteria

Inclusion:

-Solid tumor

-Measurable or non-measurable disease (must be evaluable)

-ECOG 0-1

-Creatinine ≤1.5xULN, ALT, AST≤2.5xULN, Bili≤1.5xULN

-ANC >1500, Platelets >100,000

-Minimum 2 weeks from prior chemotherapy

-Prior immune therapy is allowed

Exclusion:

-HIV, hepatitis

-Pregnant women, breast-feeding women

-Active autoimmune disease

-Systemic steroid use (some exceptions)

-Allergy to yeast based products

-Disease of the central nervous system

-Pericardial mass > 2cm

-Use of tricyclic antidepressants (affects yeast skin test)

PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

END POINTS

Primary: Safety

Secondary:

a. CD8 and CD4 T-cell immune response specific for Brachyury

b. Clinical benefit (describe PFS, tumor marker changes or rate of change)

c. Other
   Immune subsets
   Cytokines

PATIENT CHARACTERISTICS

All cancers (n = 34)	
Gender	***# (%)***
Male	19 (56)
Female	15 (54)
Age - Median (range)	58 (32-79)
Advanced cancer	***# (%)***
Colorectal	11 (32)
Chordoma	11 (32)
Breast	5 (15)
Pancreatic	3 (9)
Other	4 (20)

Chordoma (n = 11)	
Gender	***# (%)***
Male	10 (91)
Female	1 (9)
Age - Median (range)	58.5 (32-66)
Primary diagnostic site	***# (%)***
Clival	3 (27)
Sacral	6 (55)
Spinal	2 (18)
Prior therapy	***# (%)***
Surgery	11 (100)
Radiation	11 (100)
Systemic therapy	5 (45)
Disease at study entry	***# (%)***
Stable Disease (SD)	2 (18)
Progressive Disease (PD)	9 (82)

ADVERSE EVENTS

	Grade 1		Grade 2	
	# events (% doses)	# pts (% of pts)	# events (% doses)	# pts (% of pts)
Likely/Possibly related				
Injection site reaction	48 (18)	24 (71)	8 (2)	7 (21)
Fever	1 (0.4)	1 (2.9)	0 (0)	0 (0)
Flu-like symptoms	1 (0.4)	1 (2.9)	0 (0)	0 (0)
Lymphocyte count decreased	4 (1.5)	2 (6)	2 (0.8)	2 (6)
Joint effusion/joint swelling	1 (0.4)	1 (2.9)	0 (0)	0(0)
Myalgias/body aches	1 (0.4)	1 (2.9)	0 (0)	0(0)
Pruritus	1 (0.4)	1 (2.9)	0 (0)	0(0)

Calculation based on 266 administered doses.
No events greater than grade 2 attributed to IND.

IMMUNE RESPONSES

13 out of 21 patients evaluated to date showed a Brachyury-specific immune response post vaccine by ICS

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Chordoma cohort

Study Status

- 7 of 11 patients have come off study for disease progression
- 4 of 11 patients remain on study (2 on DL3, 2 on DL4)
  - 3 of those 4 had progressive disease coming on study

Best Response

- 1 of 11 patients achieved a Partial Response at Day 85 restaging
- 8 of 11 patients had Stable Disease at Day 85 restaging
  - 2 of these patients had SD coming on study

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Confirmed Partial Response – Case History

- 47 year old male
- Diagnosed in 2004 (12cm)

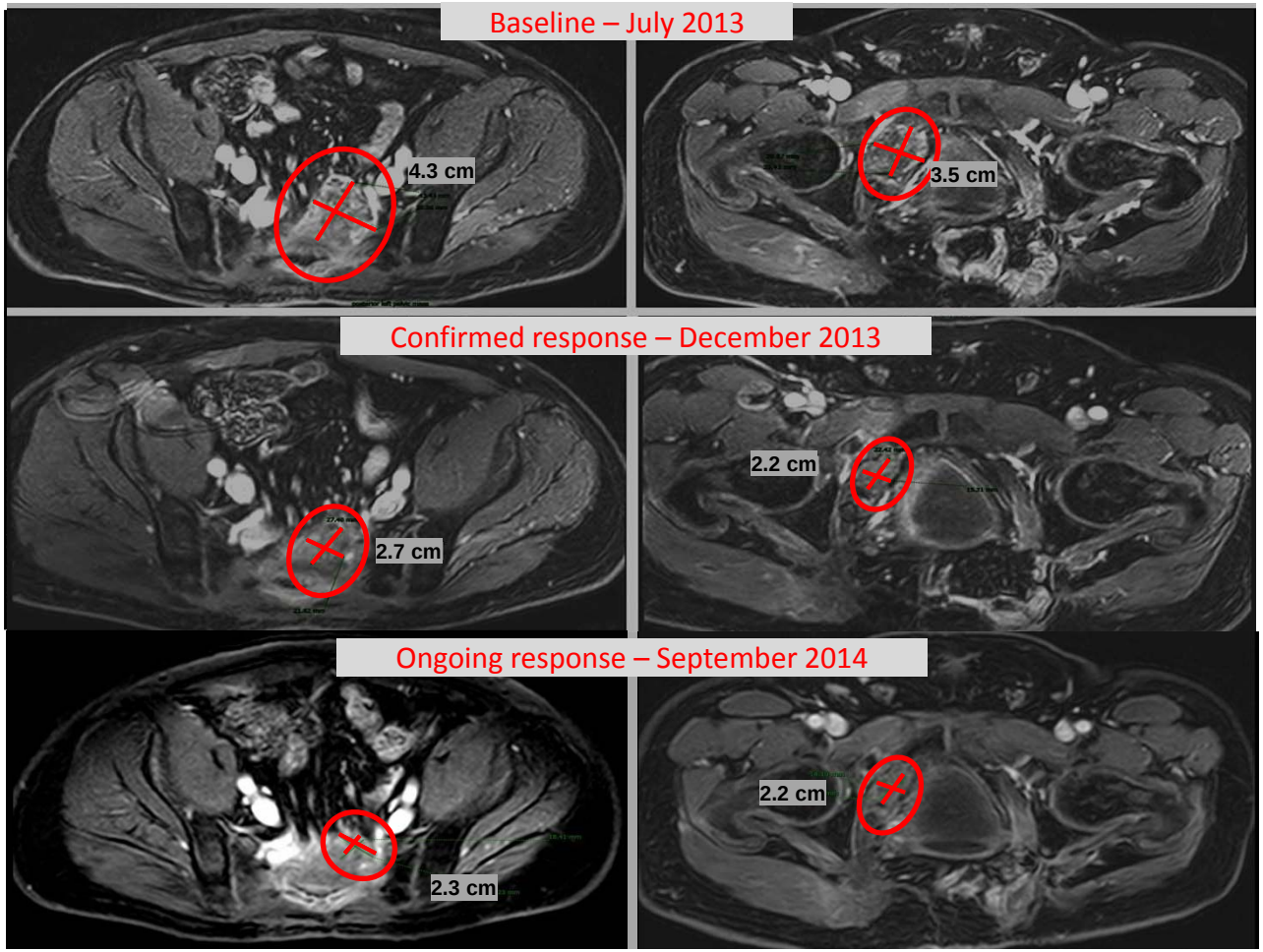
- Surgery → Radiation → recurrence in 1 year

- Radiation → no effect → surgery → radiation to tumor bed → recurrence 2 years later

- Surgery → recurrence 2 years later → experimental therapy 2012, no effect

- Hypofractionated radiation March 2013 → enrolled July 2013

- **PR December 2013 (8 doses), confirmed January 2014 (9 doses), ongoing response (42% decrease) September 2014**



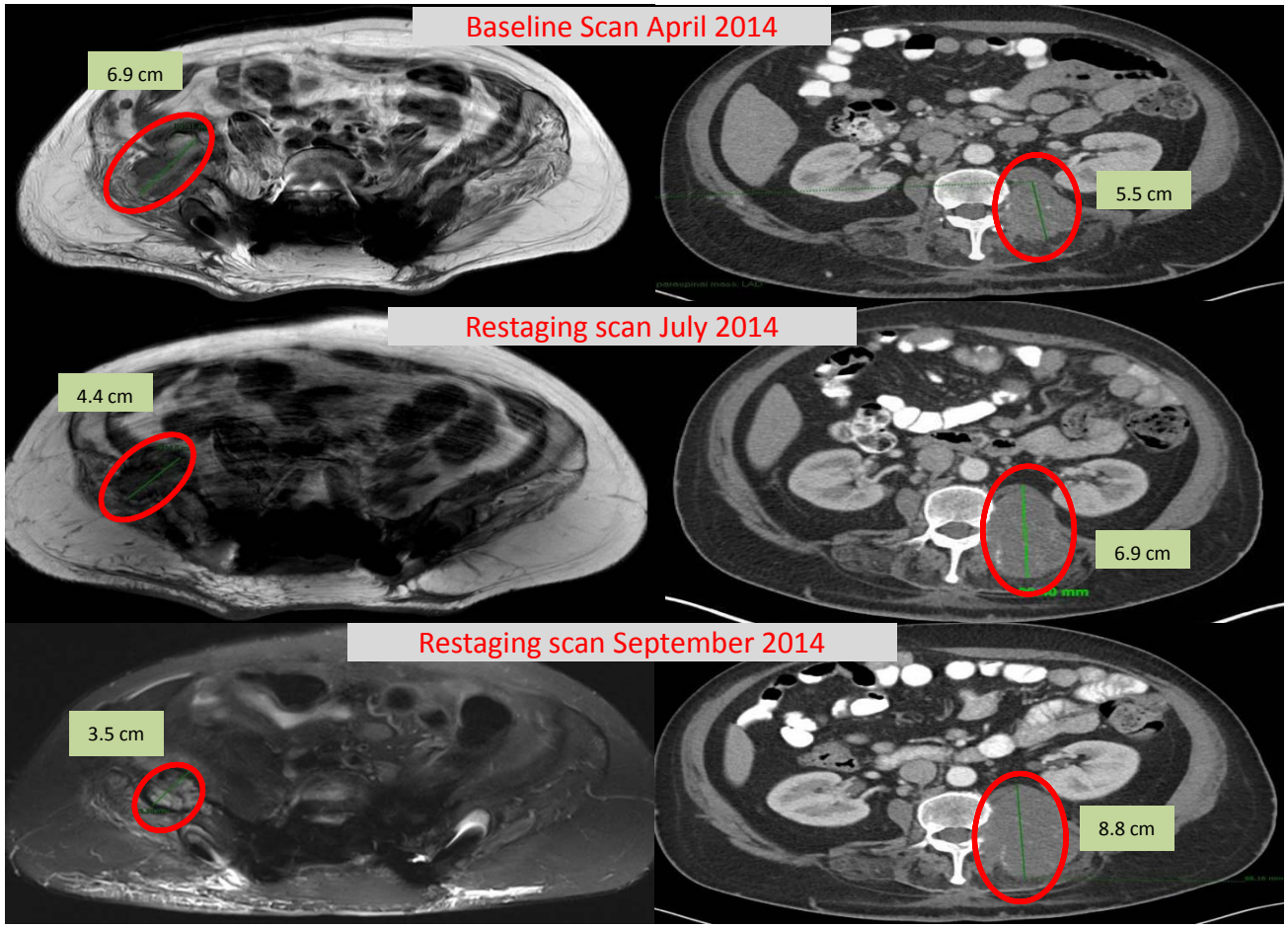
PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

- 61 year old male
- Diagnosed in 2008 (sacral chordoma)

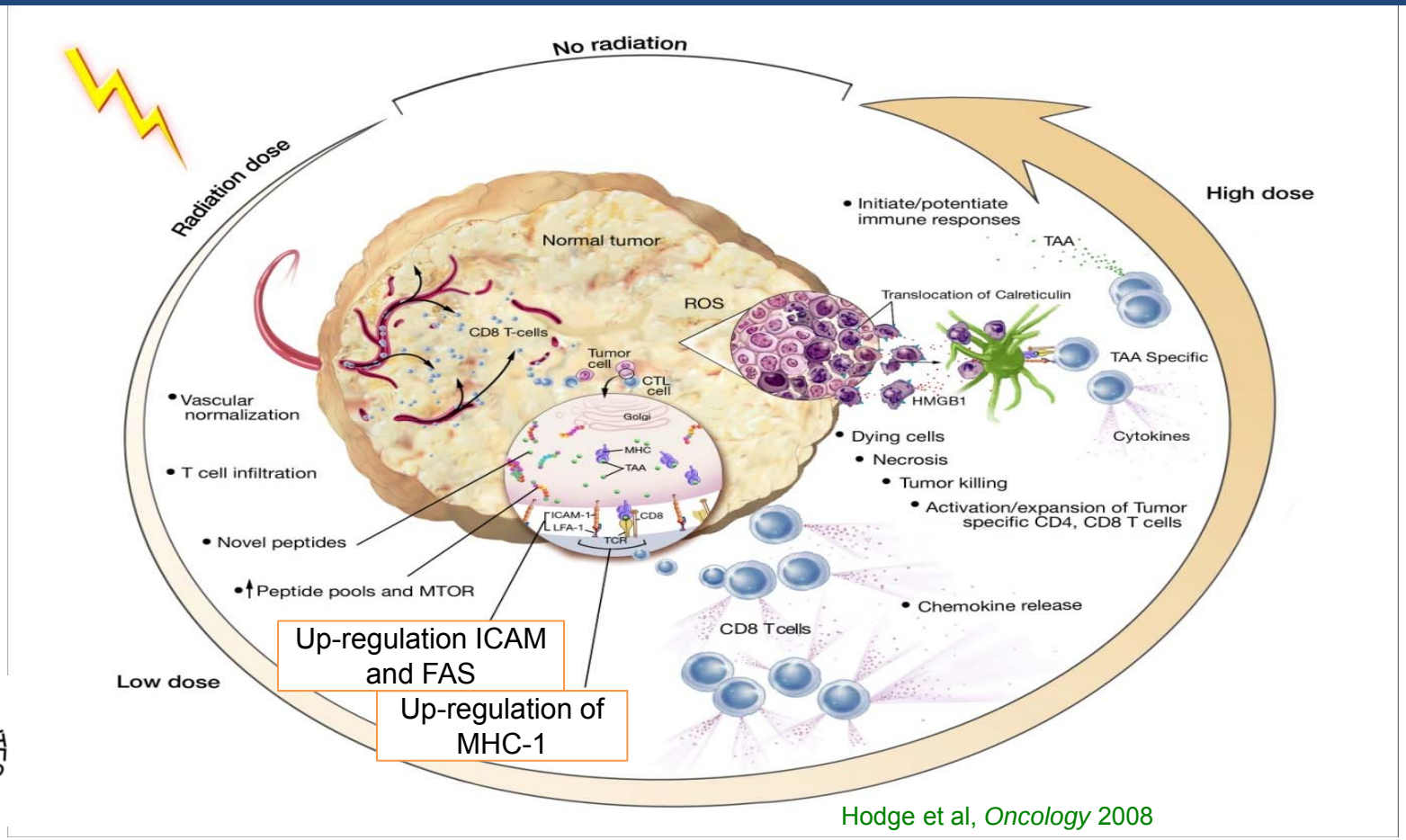
- Gleevec, Rapamycin → Surgery → recurrence in 1 year to wrist, right iliac bone

- Radiation to iliac bone November 2013 → progression of disease January 2014 to pelvis, lumbar spine

- Gleevec February 2014 → discontinued due to side effects → enrolled April 2014



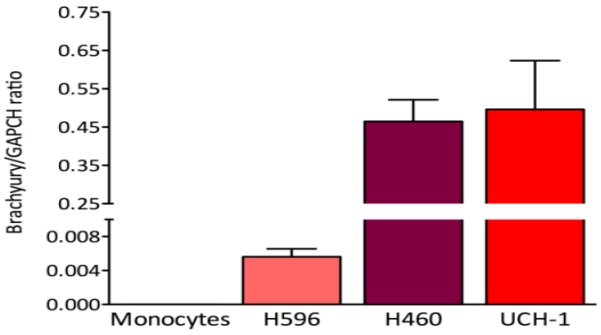
Potential Multiple Effects of Local Irradiation of Tumors



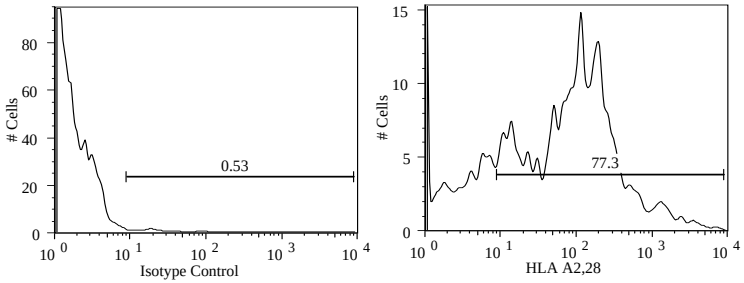
Hodge et al, *Oncology* 2008

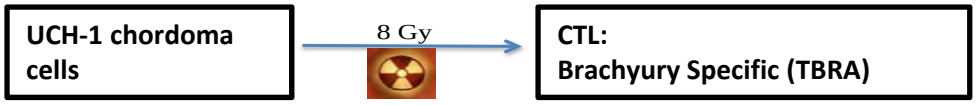
Improving T-Cell Lysis of Chordoma Tumor Cells with Radiation

Brachyury mRNA in UCH-1 chordoma cells



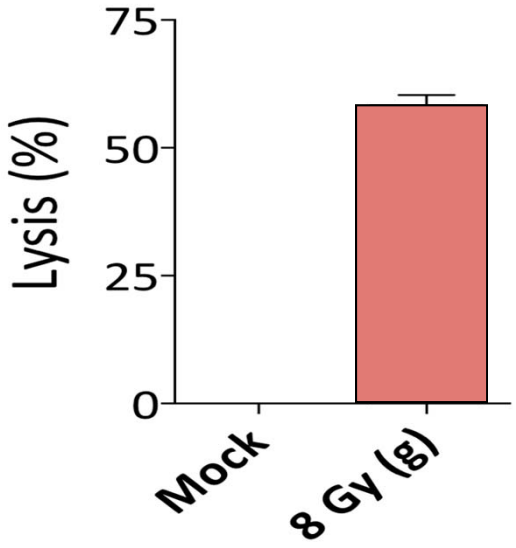
FACS analysis for HLA-A2 expression





Brachyury Specific-CTL

Preliminary Data



James Hodge Lab in Collaboration with Palena Lab

PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

In this phase 1 study, GI-6301 has been **well tolerated, immunogenic**, and has **evidence of clinical activity** in both advanced epithelial cancers and chordomas.

•Well tolerated: most common AEs were injection site reactions

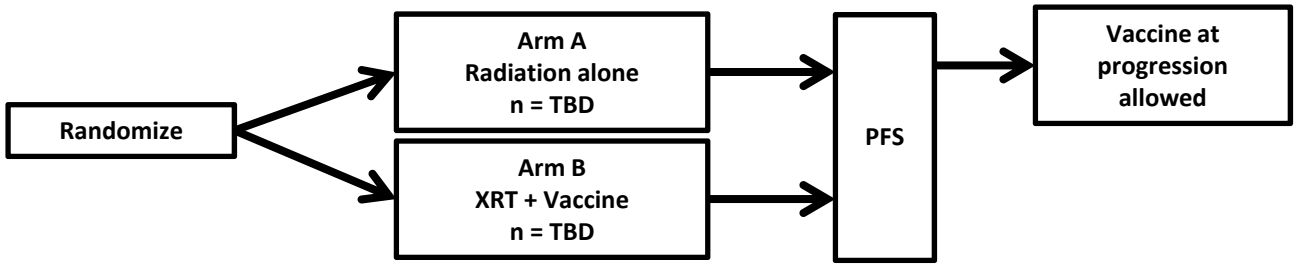
•Immunogenic: 13/21 patients demonstrated immune responses

•Clinical Activity:

- 1 **Partial Response**
- 1 **Mixed Response** in Chordoma patients who received Radiation
  - Provides rationale for Phase II trial design
- 8 of 11 patients had Stable Disease at Day 85 restaging
  - 2 of these patients had SD coming on study
- 1 patient went on to receive anti-PD-L1 and had prolonged stable disease
  - Possible combination to study in the future

Proposed Randomized, Double-Blind Phase II Study Design

Patients with locally advanced, non-resectable, radiation-naïve,
measurable disease required, prior surgery allowed
Eligible for standard radiation for disease control



Primary endpoint:
1. Overall response rate (RECIST, immune related)

Secondary objectives:
-Other radiographic finings (RECIST, Volumetric, Growth rate kinetics, Choi)
-Time to treatment failure (expected median 39 months) Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 5, pp. 1514–1521, 2006
-Immune responses

Statistical assumption:
- Goal: improve response rate from 5% to 30%

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Back Up Slides

CLINICAL INVESTIGATION **Sarcoma**

PHASE II STUDY OF HIGH-DOSE PHOTON/PROTON RADIOTHERAPY IN THE MANAGEMENT OF SPINE SARCOMAS

THOMAS F. DELANEY, M.D.,* NORBERT J. LIEBSCH, M.D., PH.D.,* FRANCIS X. PEDLOW, M.D.,† JUDITH ADAMS, C.M.D.,* SUSAN DEAN, B.A.,* BEOW Y. YEAP, SC.D.,‖ PATRICIA MCMANUS, R.N.,* ANDREW E. ROSENBERG, M.D.,‡ G. PETUR NIELSEN, M.D.,‡ DAVID C. HARMON, M.D.,§ IRA J. SPIRO, M.D., PH.D.,* KEVIN A. RASKIN, M.D.,† HERMAN D. SUIT, M.D., D.PHIL.,* SAM S. YOON, M.D.,¶ AND FRANCIS J. HORNICEK, M.D., PH.D.†

Departments of *Radiation Oncology, †Orthopedic Surgery, ‡Pathology, §Medicine, Division of Hematology Oncology, ‖Biostatistics, and ¶Surgery (Section of Surgical Oncology), Massachusetts General Hospital, Harvard Medical School, Boston, MA

Int. J. Radiation Oncology Biol. Phys. Vol 74 2009

Defines optimal outcomes with maximal surgical resection followed by adjuvant radiation.

Endpoints at 5 years:

- local control (78%)
- recurrence free survival (63%)
- overall survival (87%).

Chordoma Systemic Therapy

Phase II study on lapatinib in advanced EGFR-positive chordoma†

S. Stacchiotti[1*], E. Tamborini[2], S. Lo Vullo[3], F. Bozzi[2], A. Messina[4], C. Morosi[4], A. Casale[4], F. Crippa[5], E. Conca[2], T. Negri[2], E. Palassini[1], A. Marrari[1], E. Palmerini[6], L. Mariani[3], A. Gronchi[7], S. Pilotti[2] & P.G. Casali[1]

[1]Sarcoma Unit, Departments of Cancer Medicine; [2]Pathology, Laboratory of Molecular Pathology; [3]Unit of Clinical Epidemiology and Trial Organization; Departments of [4]Radiology; [5]Nuclear Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [6]Chemotherapy Unit, Istituto Ortopedico Rizzoli, Bologna; [7]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

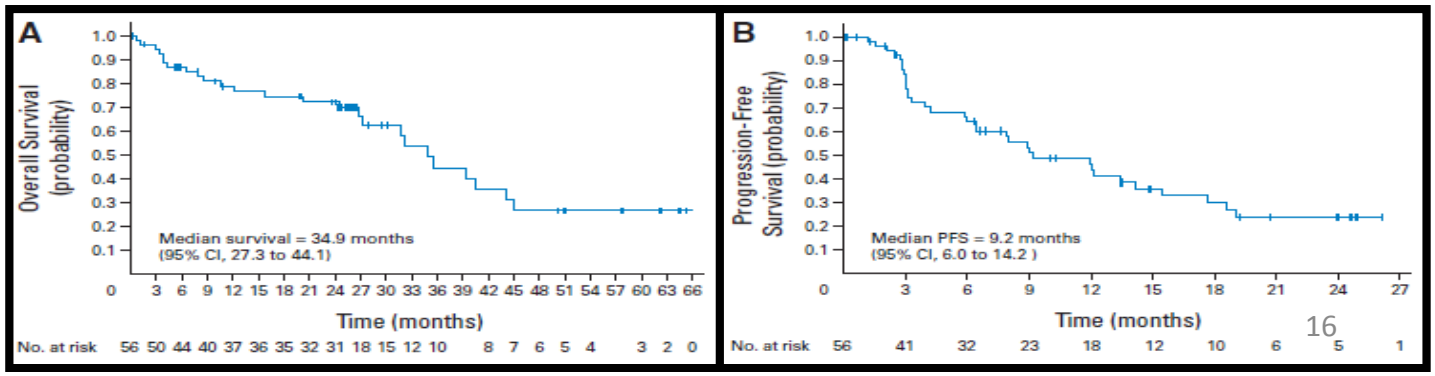
- 6/18 (33.3%) had PR by Choi (>10% decrease size, >15% decrease density, >15% increase in TSE T2-weighted signal intensity, >15% decrease TSE T1-weighted CE
- 7/18 (38.9%) had SD by Choi
- Median PFS was
  - 6 months (range 3-8) by Choi
  - 8 months (4-12) by RECIST

Phase II Study of Imatinib in Advanced Chordoma

Silvia Stacchiotti, Alessandra Longhi, Virginia Ferraresi, Giovanni Grignani, Alessandro Comandone, Roger Stupp, Alexia Bertuzzi, Elena Tamborini, Silvana Pilotti, Antonella Messina, Carlo Spreafico, Alessandro Gronchi, Paola Amore, Vincenza Vinaccia, and Paolo Giovanni Casali

See accompanying editorial on page 896

- 56 patients enrolled, all pts had PDGFRB/PDGFB over expression (by one of IHC, Western (phoporylation), PCR)
- RECIST
  - 1 PR (2%)
  - 35 SD (70%)
  - 14 PD (28%)
- PFS
  - Median 9.1 months
  - 8 pts >24 months
- OS
  - Median 26.4 months (24.1-57.8)



CLINICAL INVESTIGATION **Sacrum**

SACRAL CHORDOMAS: IMPACT OF HIGH-DOSE PROTON/PHOTON-BEAM RADIATION THERAPY COMBINED WITH OR WITHOUT SURGERY FOR PRIMARY VERSUS RECURRENT TUMOR

LILY PARK, B.A., THOMAS F. DELANEY, M.D., NORBERT J. LIEBSCH, M.D., PH.D., FRANCIS J. HORNICEK, M.D., PH.D., SAVELI GOLDBERG, PH.D., HENRY MANKIN, M.D., ANDREW E. ROSENBERG, M.D., DANIEL I. ROSENTHAL, M.D., AND HERMAN D. SUIT, M.D., D.PHIL.

Massachusetts General Hospital and Harvard Medical School, Boston, MA

- Excellent local control for primary treatment (90% +)
- For recurrent tumors, local control at 5 years ~50%, 10 years ~20%
- 2/4 patients treated with >73 Gy developed distant metastases
- No data on response rates

Definitive High-Dose Photon/Proton Radiotherapy for Unresected Mobile Spine and Sacral Chordomas

Yen-Lin Chen, MD,*§ Norbert Liebsch, MD, PhD,*§ Wendy Kobayashi, BA,* Saveli Goldberg, PhD,*§ David Kirsch, MD, PhD,‡ Geoffrey Calkins, BS,* Stephanie Childs, MD,* Joseph Schwab, MD, MPH,†§ Francis Hornicek, MD, PhD,†§ and Thomas DeLaney, MD*§

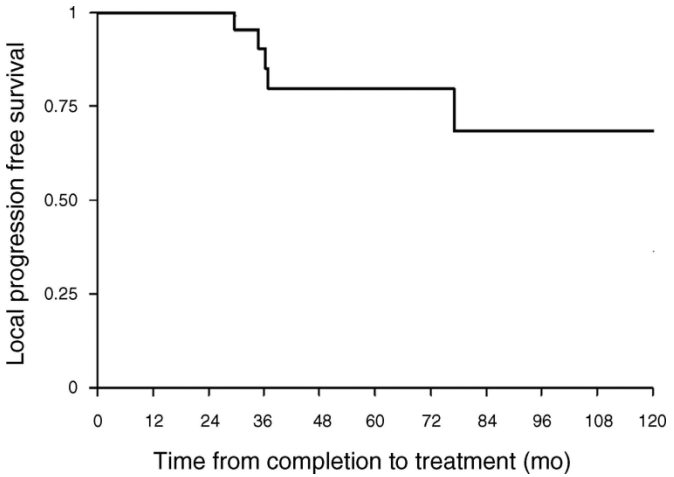


Figure 4. Local progression free survival rates were 90.4% (95% CI: 66.8%–97.5%) at 3 years and 79.8% (95% CI: 54.6%–91.9%) at 5 years.

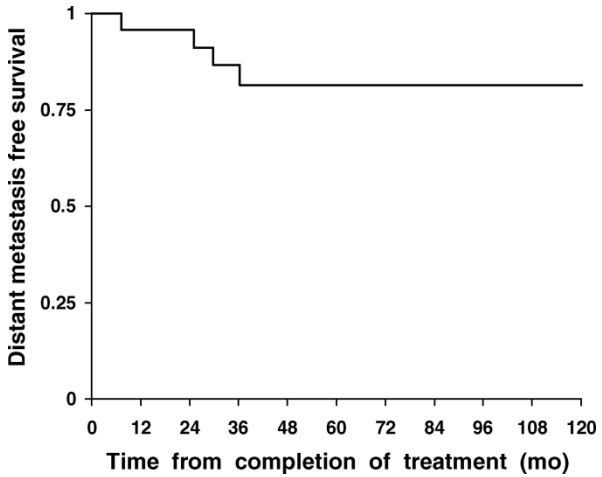
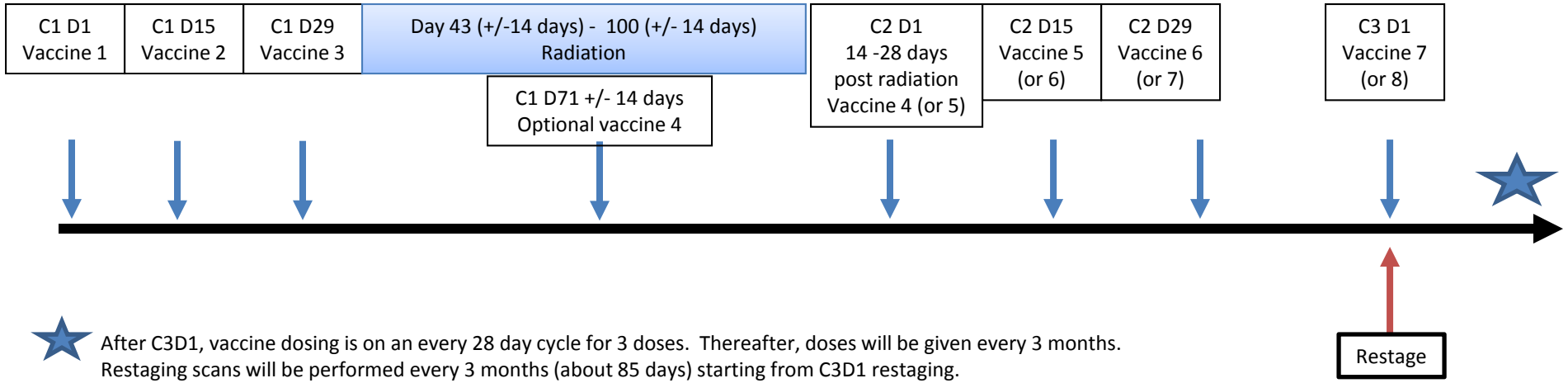


Figure 5. Distant metastases free survival rates were 86.5% (95% CI: 63.8%–95.5%) at 3 years and 81.5% (95% CI: 57.7%–92.6%) at 5 years.

Single Arm Phase 2 Treatment Schema



After C3D1, vaccine dosing is on an every 28 day cycle for 3 doses. Thereafter, doses will be given every 3 months.
Restaging scans will be performed every 3 months (about 85 days) starting from C3D1 restaging.

PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

Table 1: Summary of Subject Disposition (All Subjects)

Summary of Subject Disposition (All Subjects)		4 YU (N=4)	16 YU (N=3)	40 YU (N=16)	80 YU (N=11)	Total (N=34)
Study Disposition	Continuing Study	0 (0%)	0 (0%)	2 (13%)	3 (27%)	5 (15%)
	Off Treatment	4 (100%)	3 (100%)	14 (87%)	8 (73%)	29 (85%)
Reason Off Treatment	Switched to Alternate Treatment	1 (25%)	0 (0%)	0 (0%)	2 (18%)	3 (9%)
	Death on Study	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Disease Progression on Study	2 (50%)	3 (100%)	14 (86%)	5 (5%)	24 (71%)
	Refused Further Treatment	1 (25%)	0 (0%)	0 (0%)	1 (9%)	2 (6%)
	Adverse Events / Side Effects	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Lost to Follow up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

Summary of Subject Disposition (Chordoma Subjects)		4 YU (N=0)	16 YU (N=0)	40 YU (N=7)	80 YU (N=4)	Total (N=11)
Study Disposition	Continuing Study	0 (0%)	0 (0%)	2 (29%)	2 (50%)	4 (36%)
	Off Treatment	0 (0%)	0 (0%)	5 (71%)	2 (50%)	7 (64%)
Reason Off Treatment	Switched to Alternate Treatment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Death on Study	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Disease Progression on Study	0 (0%)	0 (0%)	5 (71%)	2 (50%)	7 (64%)
	Refused Further Treatment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Adverse Events / Side Effects	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Lost to Follow up	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

Best Response Assessment (All Subjects)		4 YU (N=4)	16 YU (N=3)	40 YU (N=16)	80 YU (N=11)	Total (N=34)
Response Assessment	Complete Response	0	0	0	0	0
	Partial Response	0	0	1	0	1
	Stable Disease	2	0	7	5	14
	Progressive Disease	1	3	7	5	16
	Not Evaluable	1	0	1	1	3

Best Response Assessment (Chordoma Subjects)		4 YU (N=0)	16 YU (N=0)	40 YU (N=7)	80 YU (N=4)	Total (N=11)
Response Assessment	Complete Response	0	0	0	0	0
	Partial Response	0	0	1	0	1
	Stable Disease	0	0	6	2	8
	Progressive Disease	0	0	0	1	1
	Not Evaluable	0	0	0	1	1

Brachyury Responses Post Vaccine following *in vitro* stimulation with Brachyury 15-mer pool peptides

Formula:
(Br. POST – HLA POST) – (Br. PRE – HLA PRE)

			Immune Response to Brachyury stimulation							
			CD4				CD8			
	Cancer Type	Dose	IFNg	TNF	IL2	CD107a	IFNg	TNF	IL2	CD107a
PT #01	Colon	4								
PT #02	Colon	4								
PT #03	Colon	4	++	+		++				
PT #04	Colon	16		+	+	++				
PT #05	Colon	16				++				+
PT #07	Colon	16	+	++						
PT #08	Breast	40								
PT #09	Pancreatic	40	+++		++	+++				
PT #10	Urothelial	40								
PT #11	Colon	40		+						
PT #12	Pancreatic	40	+	++				+		
PT #13	Pancreatic	40								
PT #14	Breast	40	+		+++	+++	+++	+++	+	++
PT #15	Chordoma	40								
PT #16	Chordoma	40		++						
PT #17	Chordoma	40	+++	+++	++	++	++	++	+	++
PT #18	Chordoma	40								
PT #19	Chordoma	40	+		+++	+++				+
PT #20	Breast	40								+
PT #21	Chordoma	40								
PT #22	Chordoma	40	++		++					+

	IFNg	TNF	IL2	CD107a
+	140 - 299	740 - 999	400 - 599	70 - 199
++	300 - 600	1,000 - 1499	600 -1,999	200 - 499
+++	600 – 1,000	1,500 – 3,000	2,000 – 3,000	500 – 1,500

Summary of Findings:

Total Increased Responses
13/21 (62%)

- **Response by Dose Level**
  4 YU: 1/3 (33%)
  16 YU: 3/3 (100%)
  40YU: 9/15 (60%)
- **Response by Cancer Type**
  Colon: 5/7 (71%)
  Breast: 2/3 (66%)
  Pancreatic: 2/3 (66%)
  Urothelial: 0/1 (0%)
  Chordoma: 4/7 (57%)

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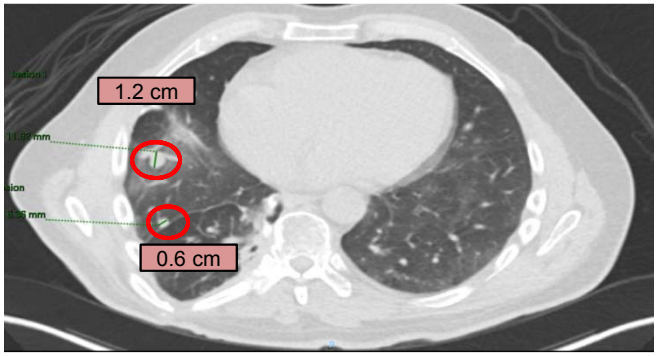
Immune Responses

- 21 pt paired samples have been tested pre- versus post-treatment with vaccine.
- By flow cytometry intracellular staining 62% of all subjects and 57% of chordoma subjects (all in dose level 3) have demonstrated a response by at least one cytokine or marker.
- In dose level 3 (40 YU), 60% of all patients (9/15) tested have had evidence of T cell activation against brachyury.

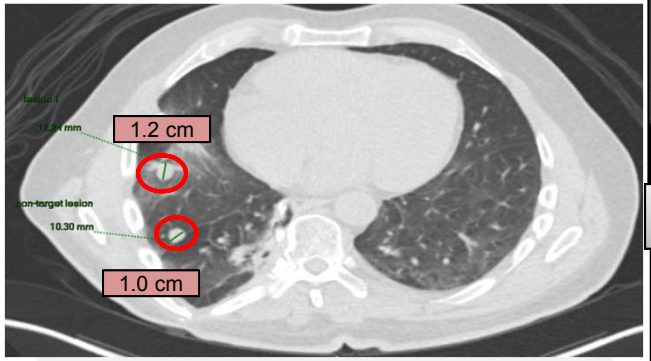
PHASE I TRIAL OF YEAST-BRACHYURY VACCINE

Chordoma with Stable Disease after Vaccine and anti-PDL-1

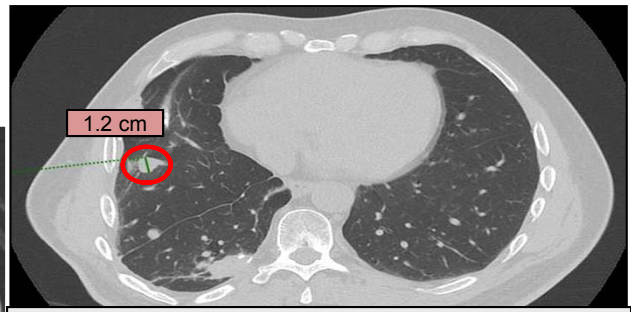
- 58 year old male
- Diagnosed in 2006 with posterior medicastinal mass which was surgically resected
- Radiation to posterior mediastinum 2006
- 2012 → progression with paraspinal mass at T11 → surgical resection
- New Lung lesions
- Enrolled on 12-C-0056 July 2013 → PD after 6 months on vaccine
- Enrolled on 13-C-0063 Anti-PDL-1 → SD for 9 months



7/2013 – start of 12-C-0056



12/2013 – PD after vaccine



9/2014 – SD on anti PDL-1