

Chad Tang, MD
Department of Radiation Oncology
University of Texas MD Anderson Cancer Center

Is There a Role for Radiation Therapy and Immunotherapy?



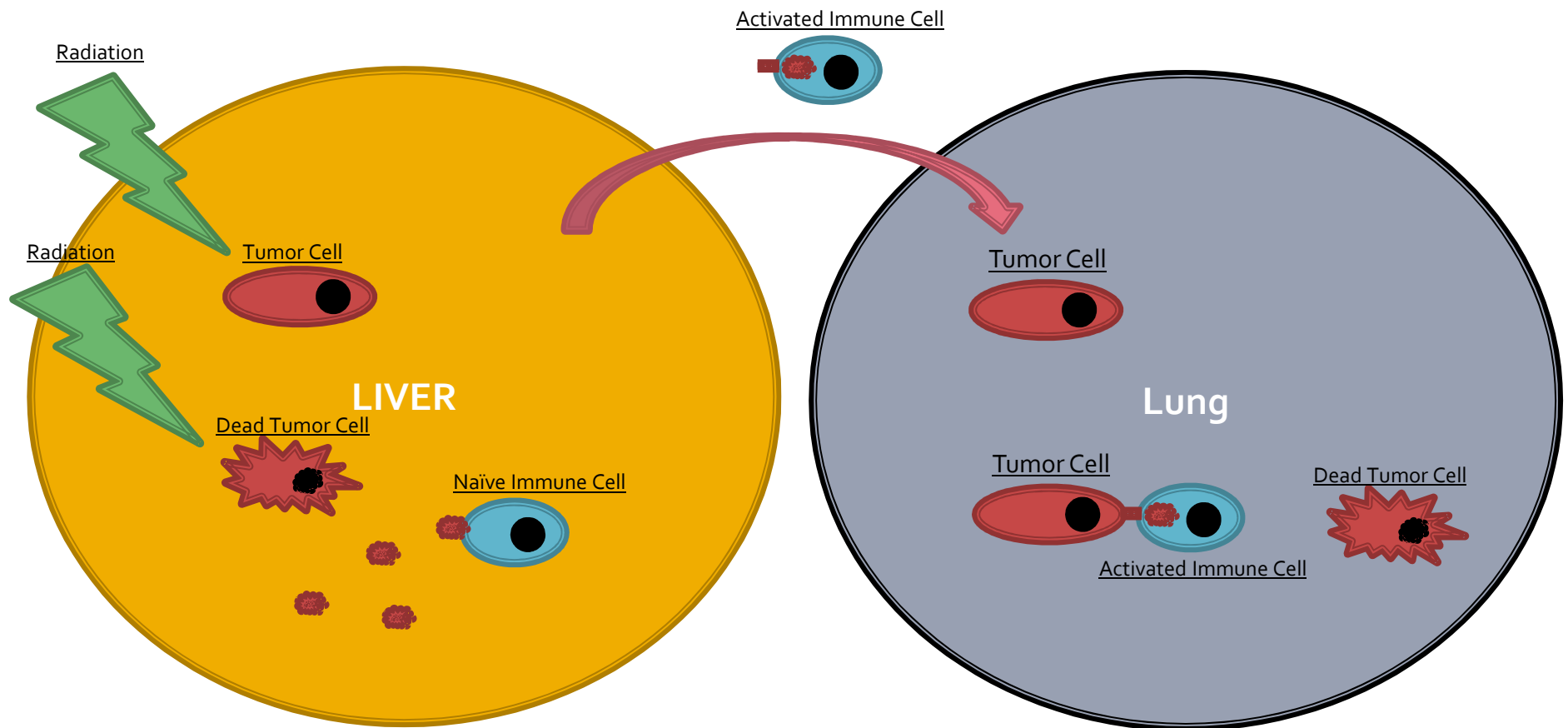
Disclosures

- No Disclosures

Key Concept Outline

- Abscopal Effect
- Available Evidence for the Abscopal Effect
- Ongoing Trials
- Treatment Side Effects

Radiation Abscopal Effect?



BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D.,
Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D.,
Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S.,
Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S.,
Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D.,
Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D.,
Alexander M. Lesokhin, M.D., Sacha Gnjjatic, Ph.D.,
and Jedd D. Wolchok, M.D., Ph.D.

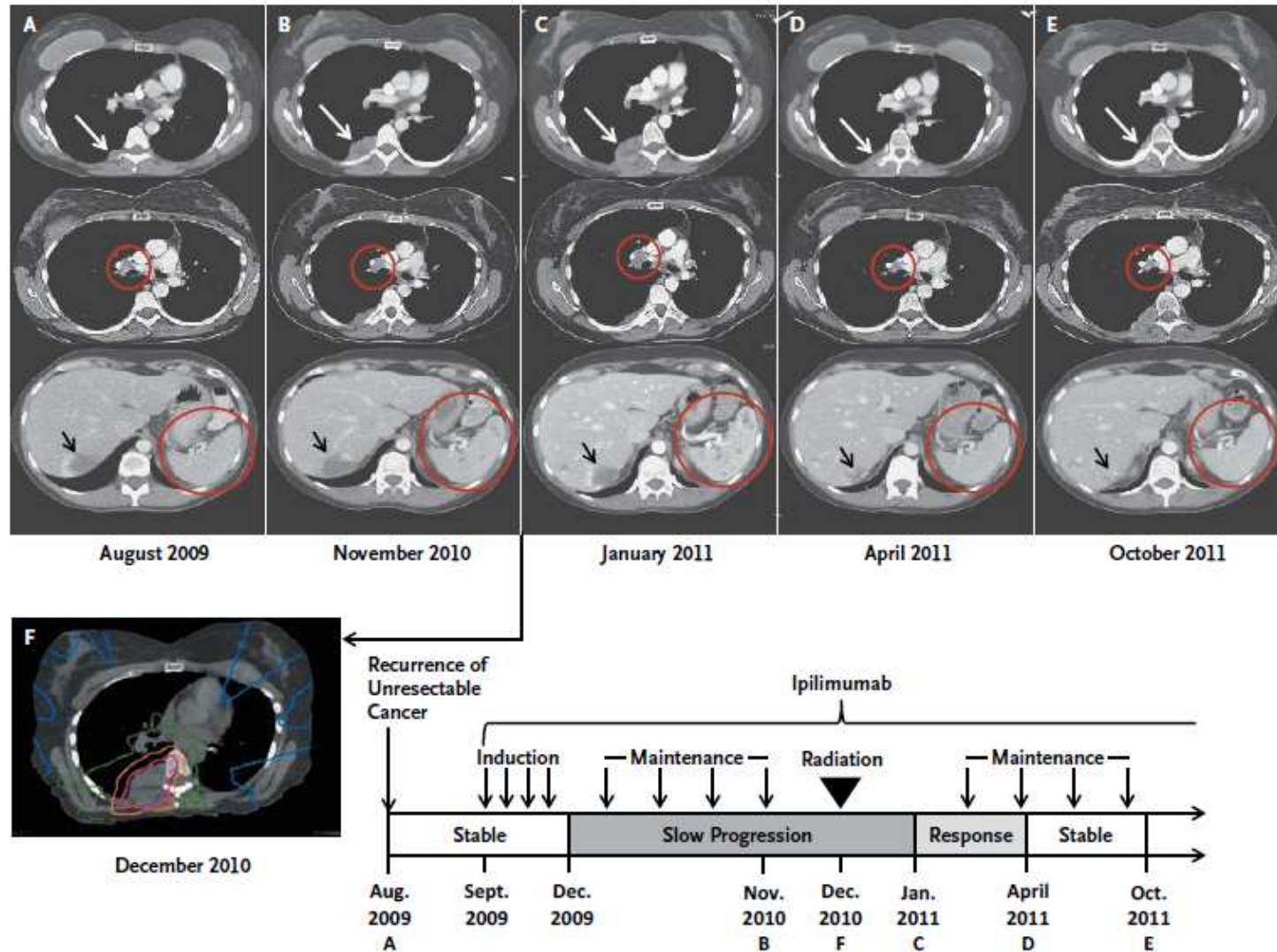
Patient History

- April 2004, 33 yo woman identified a mole in her upper back to be melanoma
- August 2009, surveillance CT detected recurrent new pleural based paraspinal mass and R hilar LAD
- Sept 2009, treated with ipilimumab 10mg/kg q3 wks x4 then maintenance ipilimumab q12 wks.

Patient History Continued

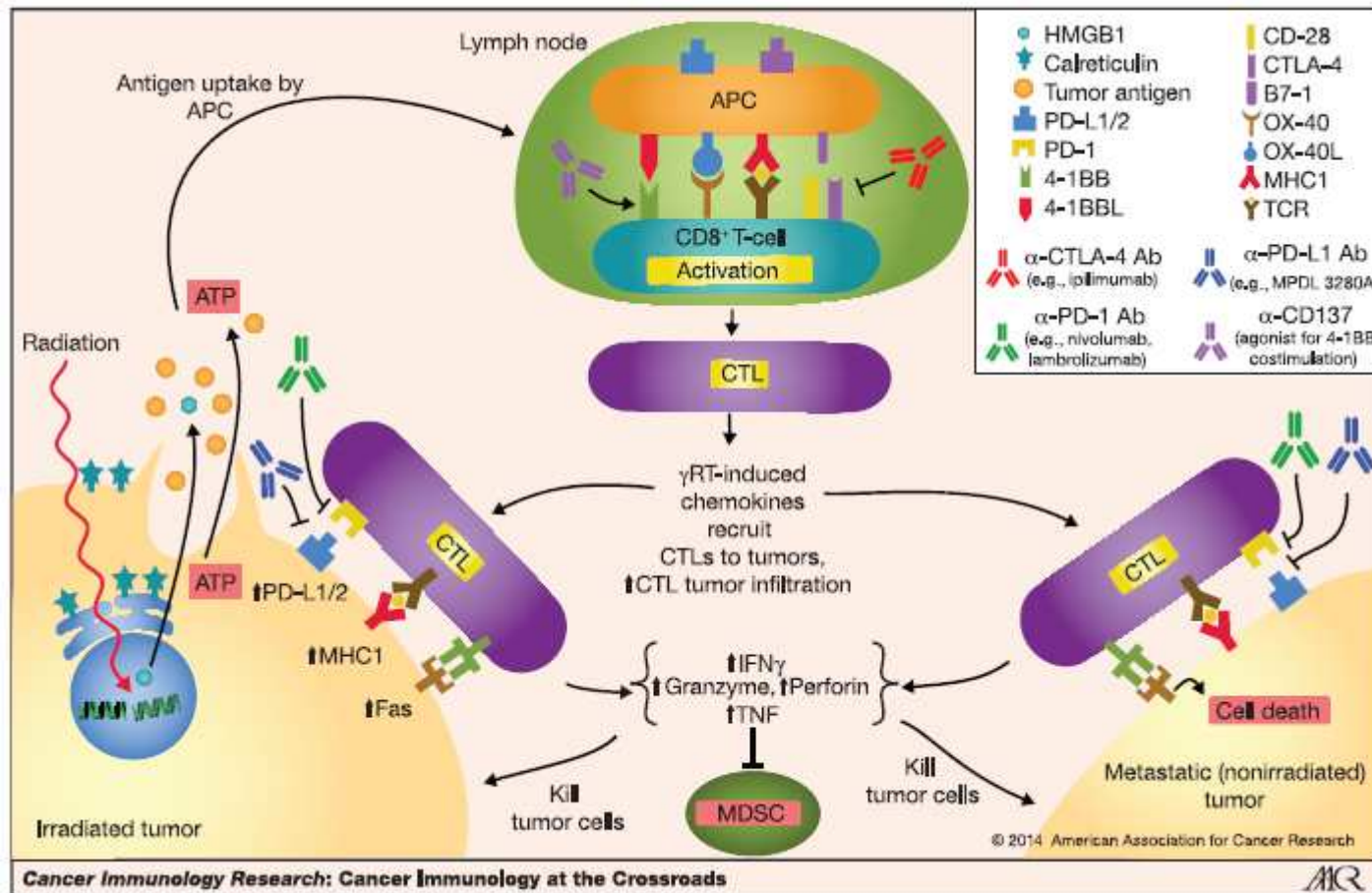
- December 2009, FU CT scan showed SD by immune response criteria. Slow progression noted in the paraspinal mass
- December 2010, received palliative XRT for their slowly enlarging parapsinal mass 28.5 Gy in 3 fractions over 7 days
- October 2011, imaging showed disease response systemically with continued presence of minimal disease

Patient Timeline



Postow et al. NEJM 2012

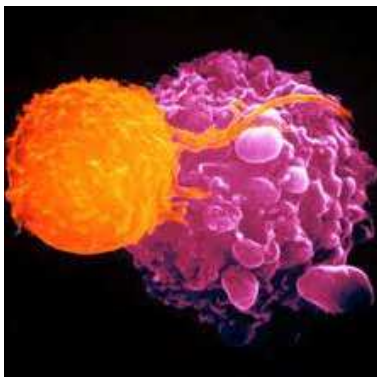
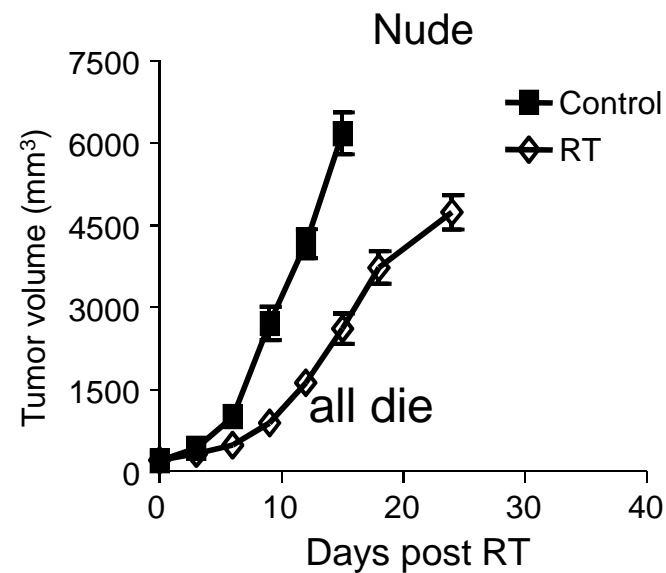
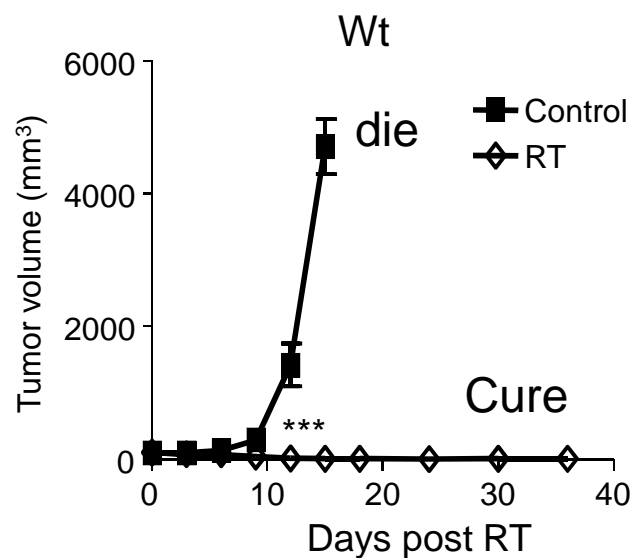
Complex Signaling Pathway



Tang.... Welsh, Cancer Immunol Res 2014

Radiation Effects Requires T cells

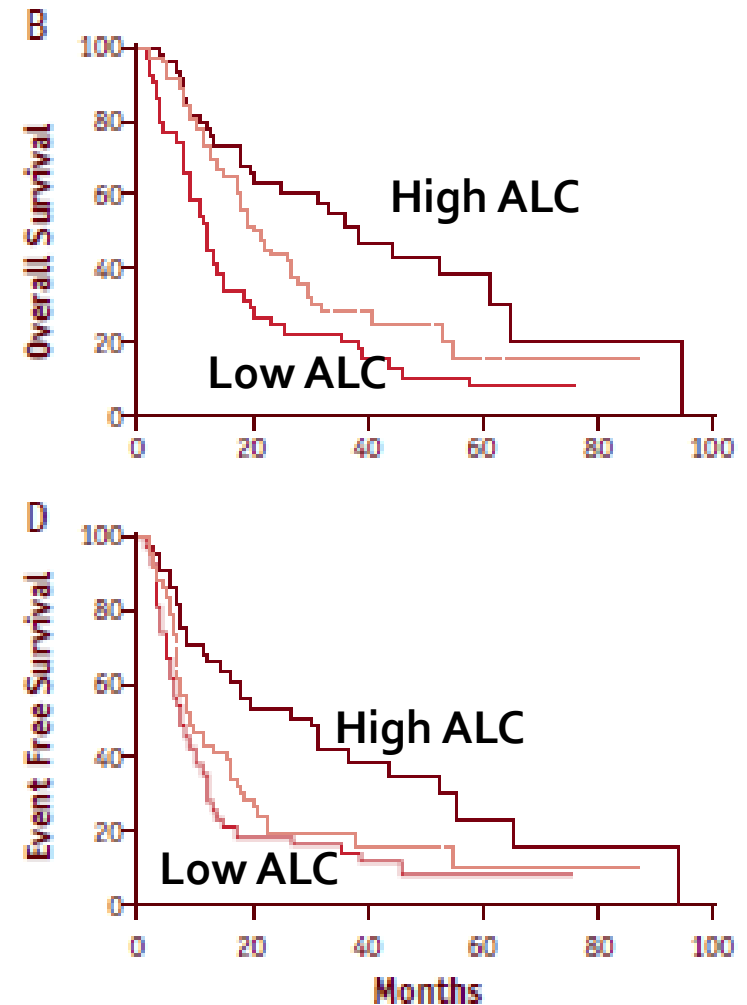
B16-SIY: Single dose 20-25 Gy



Lee et al. Blood 2009

Radiation Effects Requires T cells

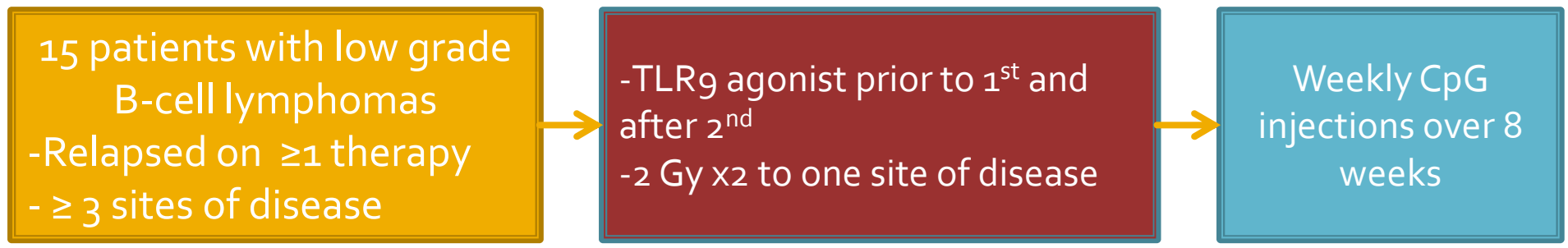
711 NSCLC patients who received definitive radiation therapy for inoperable disease



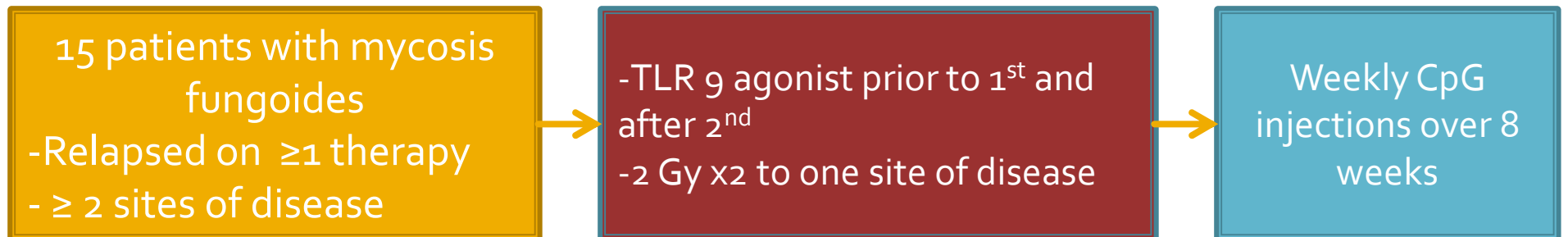
Key Concept Outline

- Abscopal Effect
- Available Evidence for the Abscopal Effect
 - Brody et al. JCO 2010
 - Kim et al. Blood 2012
 - Seung et al. Science Translational Medicine 2012
 - Victor et al. Nature 2015
- Ongoing Trials at MDACC
- Treatment Side Effects

Phase I/II TLR9 vaccine with Radiation

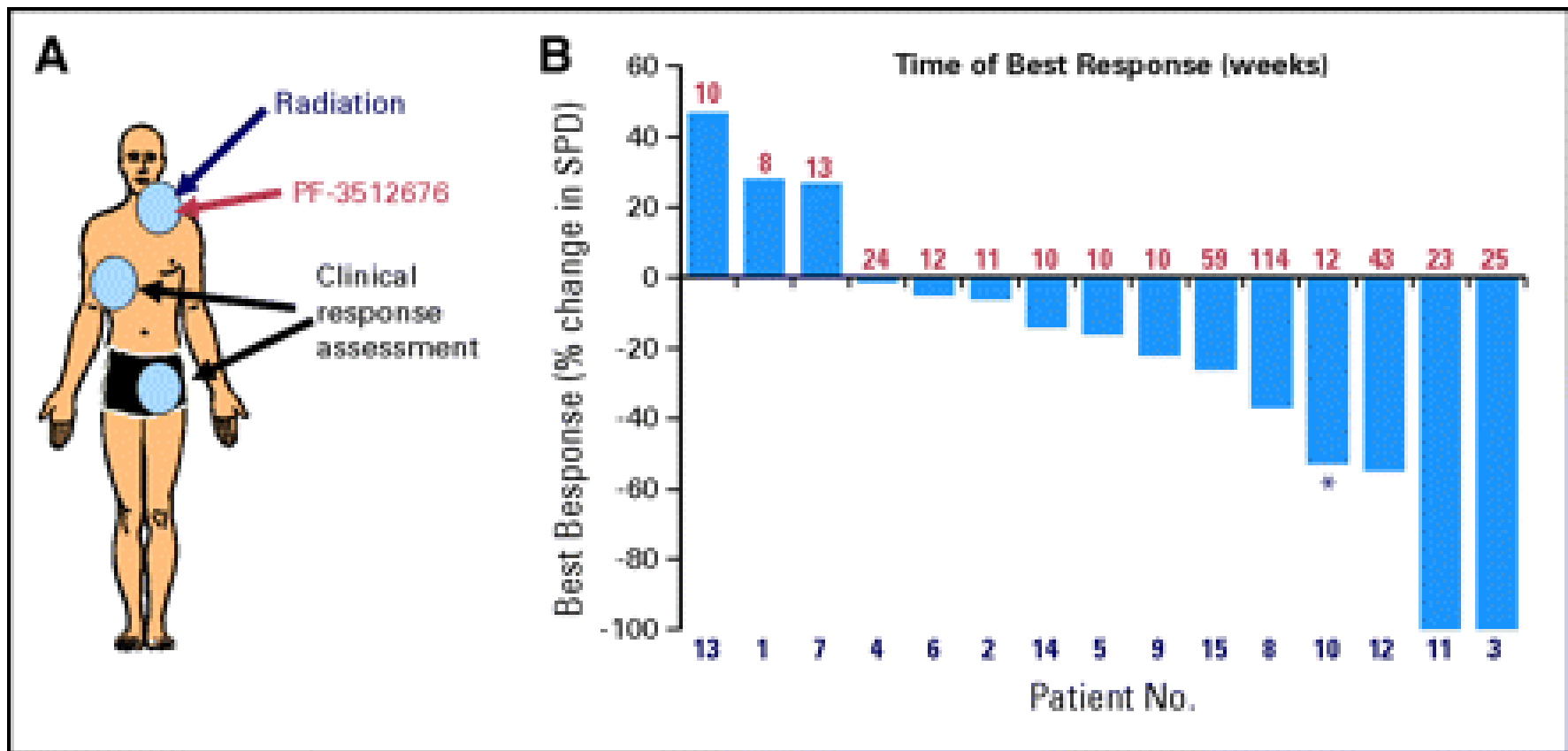


Brody, J Clin Onc 2010



Second immunization procedure for patients 7-15 week 4
Kim, Blood 2012

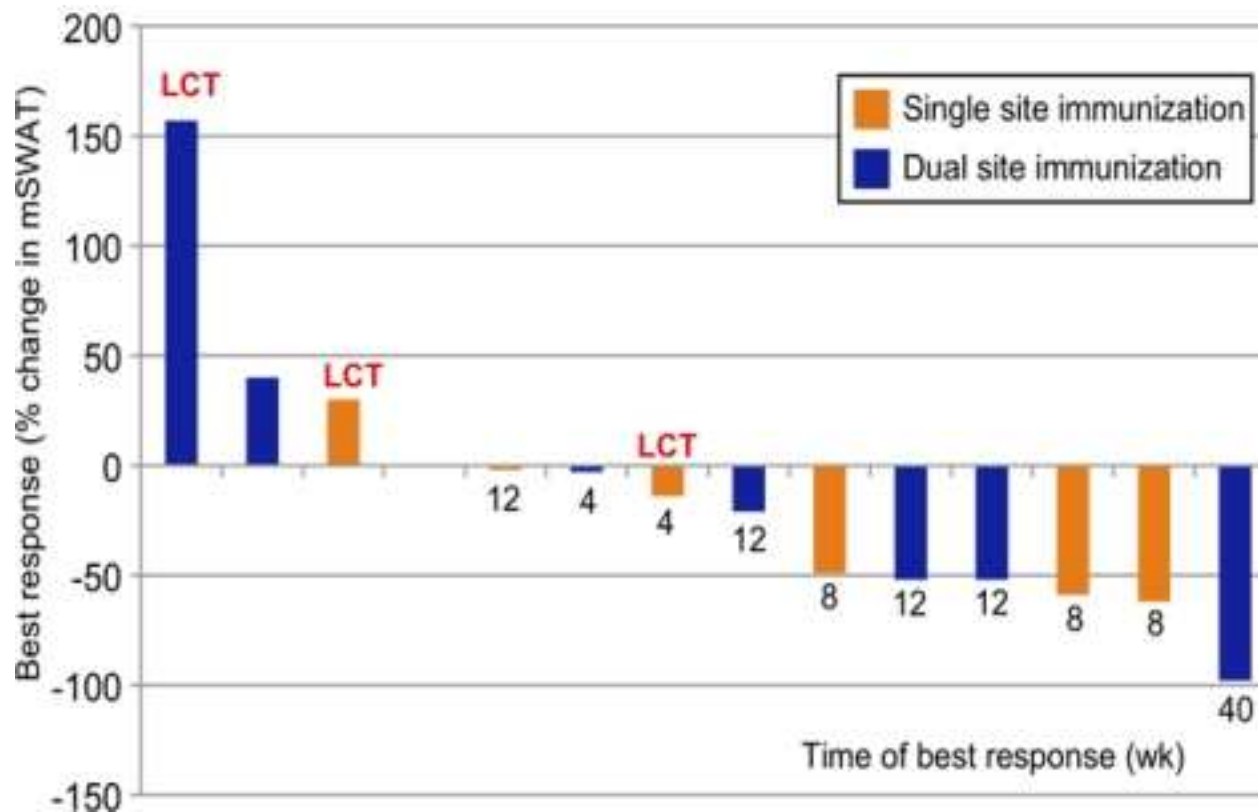
Response Profile (B-cell Lymphomas)



Therapy well tolerated: 1 grade 2 injection site reaction
1 grade 2 systemic flu-like reaction

Brody, J Clin Onc 2010

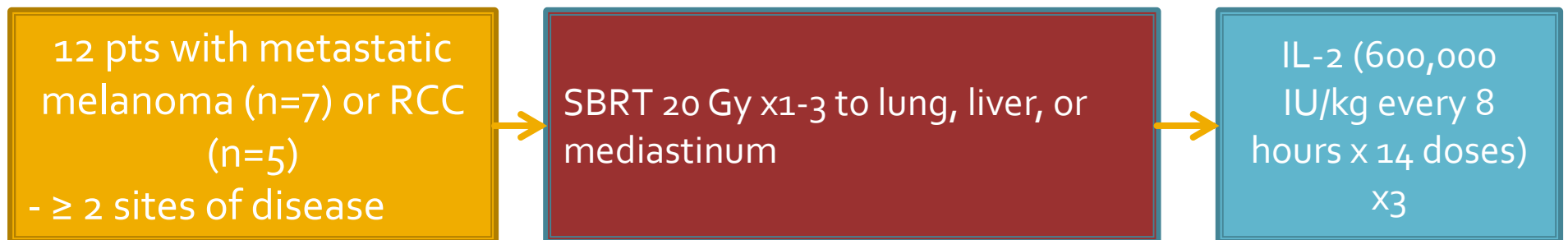
Response Profile (Mycosis Fungoides)



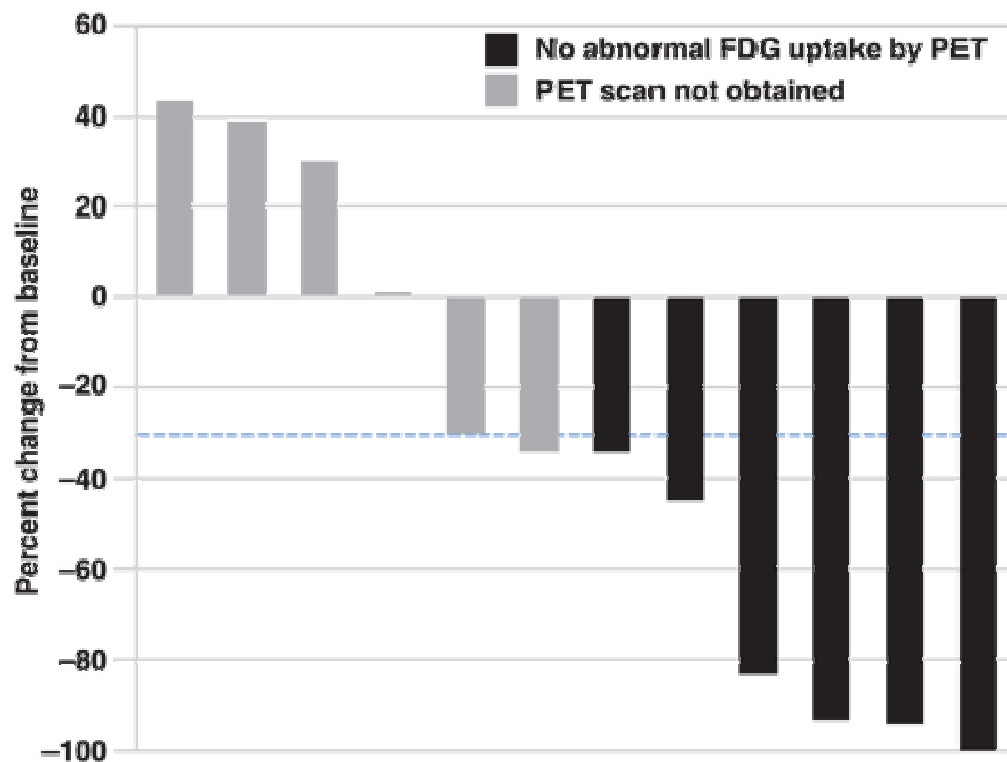
Therapy well tolerated: 1 grade 3 injection site reaction
Numerous Grade 1-2 chills, fatigue, myalgia, fever, arthralgia

Kim, Blood 2010

Phase I Stereotactic Radiation and IL-2



Response Profile (Melanoma and RCC)



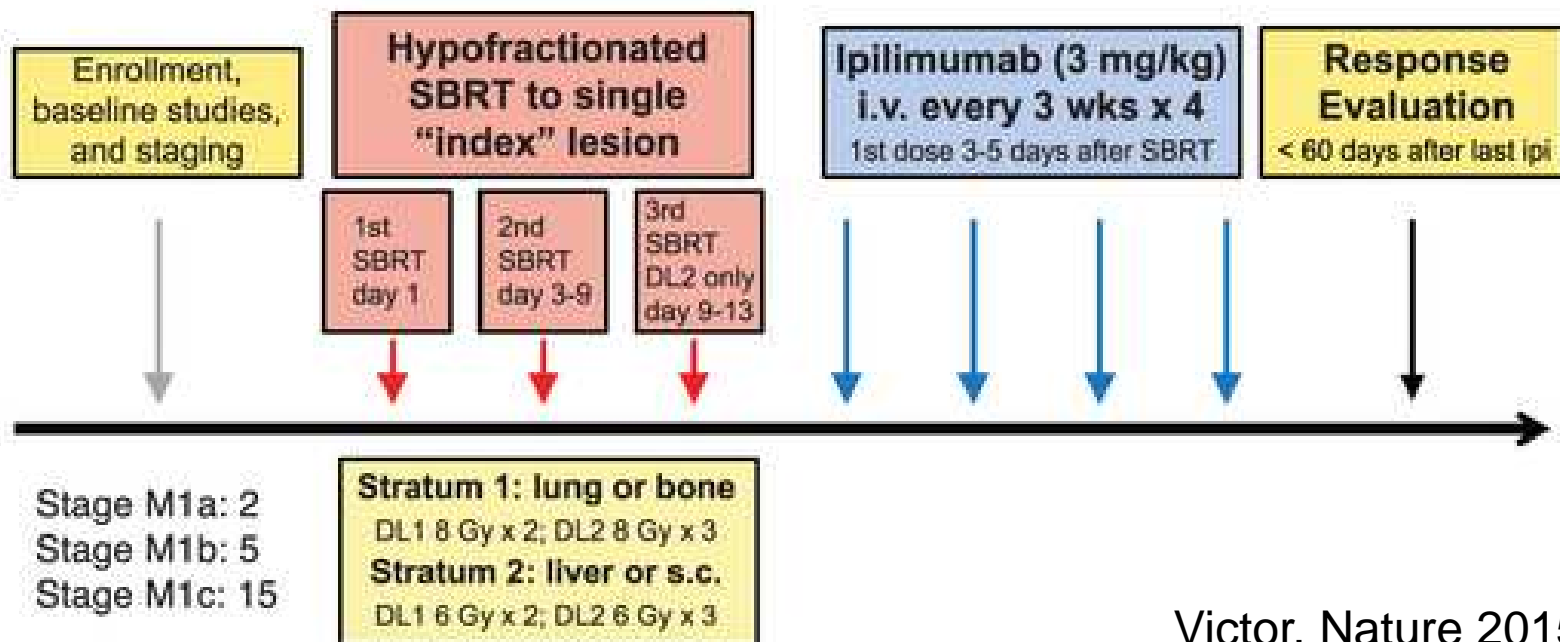
- Maximum tolerated dose (MTD) not reached
- “Anticipated” IL-2 toxicities were observed: hypotension, pulmonary capillary leak, fever, and rigors
- Toxicities resolved after completing IL-2

Phase I Stereotactic Radiation and Ipilimumab (3 of 4 dose levels)

22 pts with metastatic melanoma
- ≥ 2 sites of disease

SBRT to lung, bone, liver, or
subcutaneous lesion 6-8Gy x 2-3

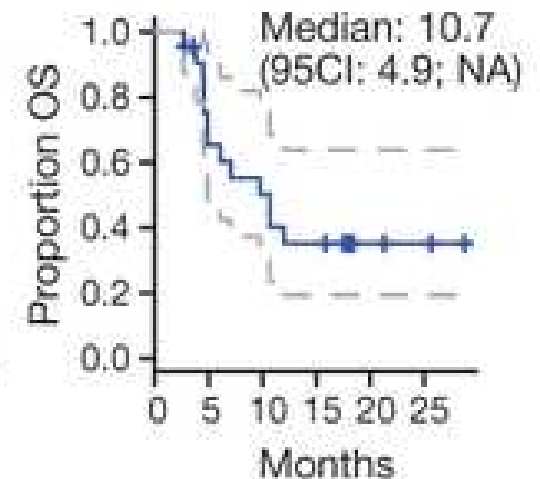
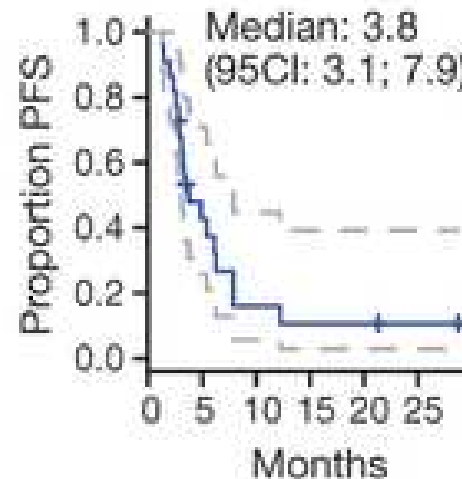
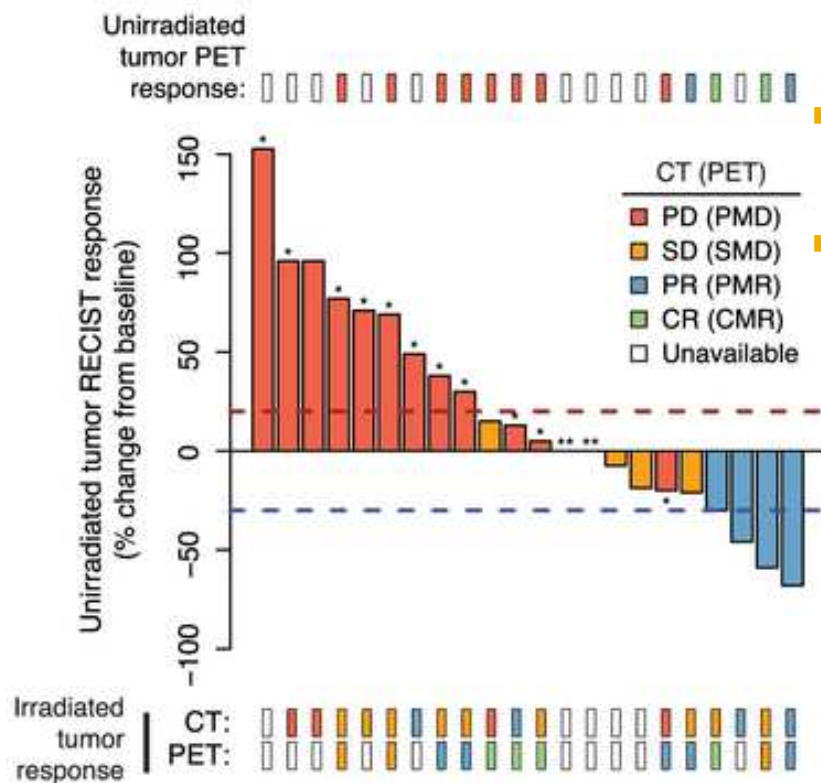
Ipilimumab
3mg/kg every 3
weeks x4



Victor, Nature 2015

Response Profile (Melanoma)

- Ongoing study
- Response measured in a single non-irradiated lesion
- 18% partial response in a single unirradiated lesion
- 18% stable disease



Toxicities

Grade 3 Toxicities*	Radiation Dose				Total
	6Gy x 2 n=6	8Gy x 2 n=6	6Gy x 3 n=6	8Gy x 3 n=4	
Edema		1			1
Anaphylaxis		1			1
Hypotension		1			1
Fatigue		1			1
Anemia	2	1	1		4
Gastric hemorrhage	1				1
Wound infection		1			1
Diarrhea	1				1
Cholecystitis	1				1
Weight loss	1				1
Colitis	1				1
Pneumothorax				1	1

* No Grade 4 toxicities were observed

Prospective Trial Summary

	Tumor Type	Systemic Treatment	Radiation Treatment	Disease Response
Brody et al. JCO 2010	Low Grade B-cell Lymphoma (n=15)	Local TLR9 injection	2 Gy x2	ORR: 4/15 (27%)-modified RECIST
Kim et al. Blood 2012	Mycosis Fungoides (n=15)	Local TLR9 injection	2 Gy x2	ORR: 5/15 (33%) – mSWAT
Seung et al. STM 2012	Melanoma (n=7) and RCC (n=5)	Systemic IL-2	20 Gy x (1-3)	ORR: 8/12 (67%)-modified RECIST
Victor et al. Nature 2015 (ongoing)	Melanoma (n=22)	Ipilimumab	6-8 Gy x (2-3)	ORR: 4/28 (18%) – RECIST non-targeted lesion

Total N=64

Key Concept Outline

- Abscopal Effect
- Available Evidence
- Ongoing Trials at MDACC
- Treatment Side Effects

2013-0882: Ipilimumab + radiation in advanced malignancies

Phase I/II Trial of Ipilimumab (Immunotherapy) and Hypofractionated Stereotactic Radiation Therapy in Patients with Advanced Solid Malignancies

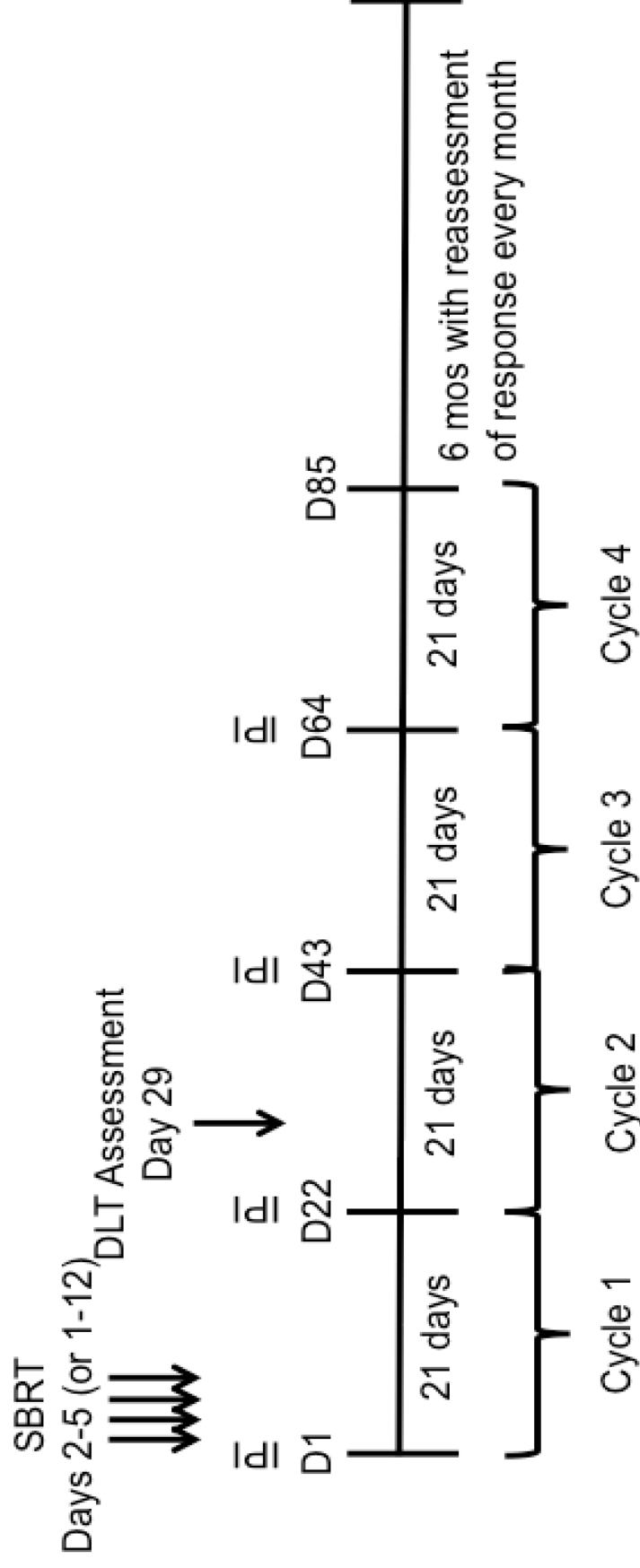
Jim Welsh, Chad Tang, David Hong, Aung Naing

- Goals:
 - To establish the safety of ipilimumab and SBRT
 - To compare safety/efficacy of concurrent vs. sequential RT and ipilimumab
 - To compare safety/efficacy of SBRT to the lung versus the liver
- Patient inclusion criteria:
 - Any refractory solid cancer with advanced metastatic disease
 - Liver or lung lesion amenable to stereotactic radiation therapy
- Trial status:
 - Phase I complete, MTD not reached
 - Phase II ongoing

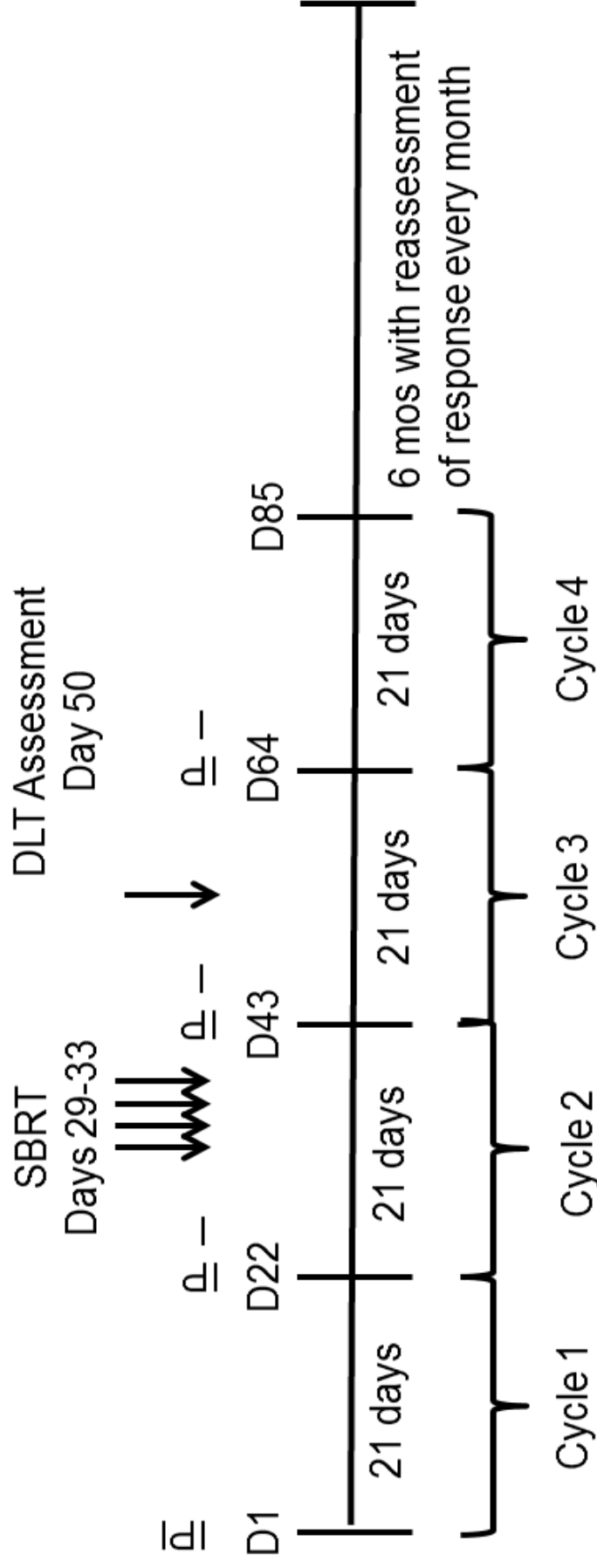
2013-0882: Treatment Schema

Metastatic or primary lesion amenable to SBRT treatment				
Treatment Sequence	Liver lesion treatable with 50 Gy / 4 Fc (n=40)		Lung lesion treatable with 50 Gy / 4 Fc (n=40)	Liver/lung lesion not treatable with 50 Gy/ 4 Fc or adrenal lesion (n=20)
	Concurrent: SBRT (50 Gy/ 4 Fc) + Ipilimumab (n=40)	Treatment Group 1 (n=20)		Treatment Group 3 (n=20)
		Treatment Group 2 (n=20)		
	Sequential: SBRT (50 Gy/ 4 Fc) + Ipilimumab (n=40)	Treatment Group 4 (n=20)		Treatment Group 5 (n=20)
	Sequential: SBRT (60 Gy/ 10 Fc) + Ipilimumab (n=20)			

2013-0882: Treatment Groups 1+3



2013-0882: Treatment Groups 2+4+5



2014-1020 Pembrolizumab (PD-1 inhibitor) + Radiation in NSCLC

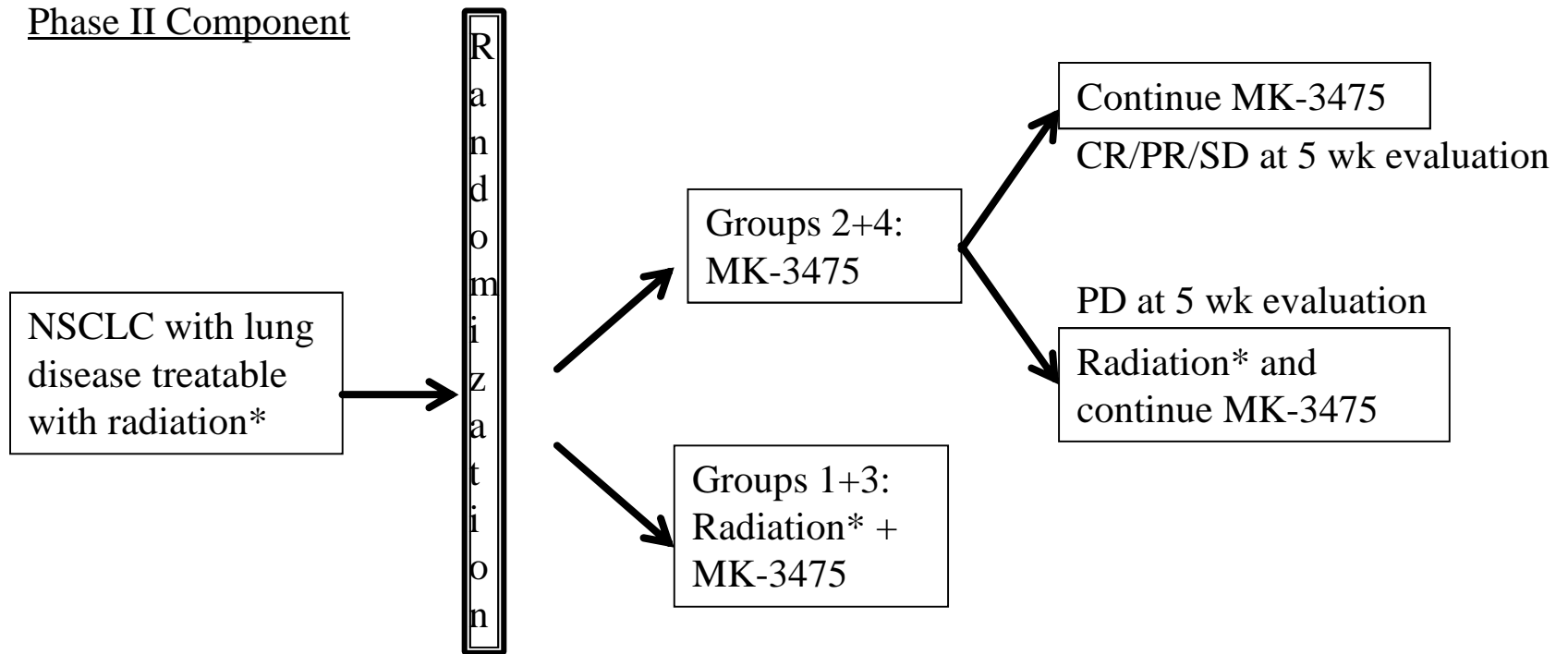
Phase I/II Trial of MK-3475 (Pembrolizumab) and Hypofractionated Stereotactic Radiation Therapy in Patients with NSCLC

Jim Welsh, Chad Tang, John Heymach

- Goals:
 - To establish the safety of pembrolizumab (PD-1 inhibitor) and thoracic radiation (either SBRT or conventional)
 - To compare efficacy/safety of pembrolizumab (PD-1 inhibitor) and radiation with pembrolizumab alone
 - Establish the efficacy of salvage radiation for patients who exhibit disease progression
- Patient inclusion criteria:
 - NSCLC with metastatic disease
 - Lung lesion amenable to radiation
- Trial status:
 - Phase I ongoing

2014-1020 Phase II randomization

Phase II Component



Key Concept Outline

- Abscopal Effect
- Available Evidence
- Ongoing Trials at MDACC
- Treatment Side Effects

Checkpoint Inhibitors Toxicities

- Limited data exists, current phase I trials utilizing ipilimumab + XRT show no significant increase in frequency, quality, or quantity of toxicities.
- No data regarding PD-1 inhibitors, combination PD-1 and CTLA-4 inhibitor, or other emerging checkpoint inhibitors with radiation.
- General Management:
 - Supportive care
 - Steroids
 - Suspension/cessation of treatment
 - Toxicities may herald later responses!

Lessons and Take Home Message

- Radiation abscopal effect is an immunologic-based phenomena where local treatment leads to a systemic immune response
- Contemporary research focuses on potentiating the radiation-induced immune stimulating effect through different immunotherapies
- Data on efficacy is limited with a lack of randomized trials. There is no evidence of increased efficacy combining radiation with current checkpoint inhibitors.
- Data on toxicity is accruing but there is currently no evidence of increased side effects combining radiation + immunotherapy

Thank You

- SITC organizers
- Mentors:
 - Jim Welsh, MD - Dept of radiation oncology
 - David Hong, MD - Dept of investigational therapeutics
 - Eugene Koay, MD, PhD - Dept of radiation oncology

Thank you

- AND YOU!

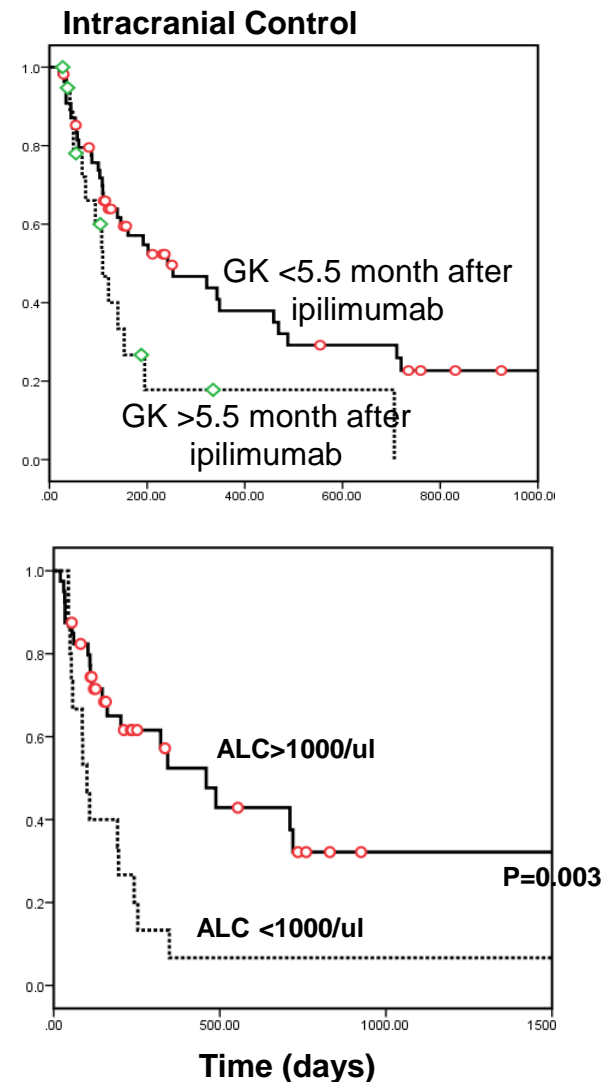
ON TOUR NOW



CNS radiation and Ipilimumab?

Jiang et al. ASTRO 2015

- Retrospective review of patients receiving GK after ipilimumab
- Patients with advanced stage melanoma who received at least 2 cycles of ipilimumab
- All patients received Gamma Knife-based stereotactic radiosurgery (SRS) for brain metastasis



In-Development: Nivolumab +/- ipilimumab and CNS radiation for NSCLC

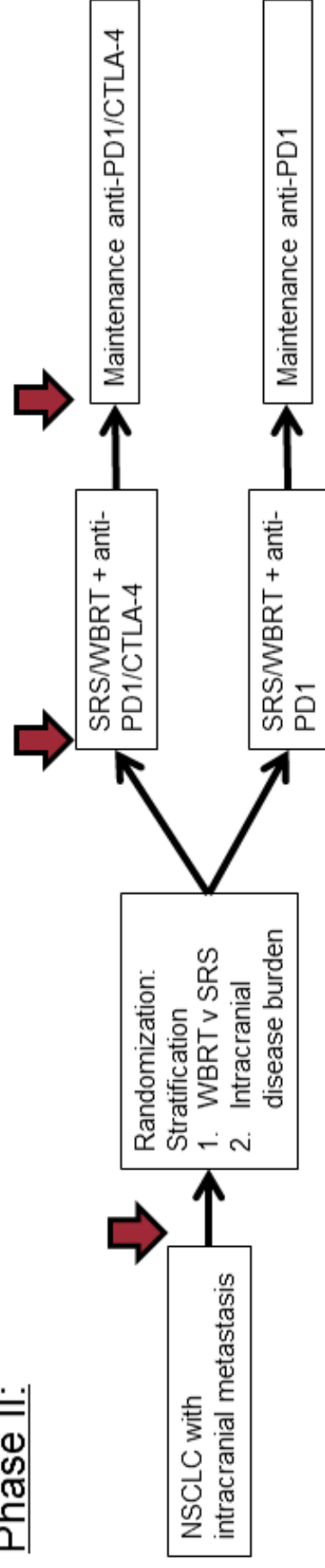
Phase I/II Trial of Nivolumab and Ipilimumab with radiation for the treatment of brain metastases from non-small cell lung cancer

Jing Li, Chad Tang, Jim Welsh, Renata Ferrarotto

- Goals:
 - To establish the safety of nivolumab and CNS radiation
 - To establish the safety of nivolumab+ipilimumab and CNS radiation
 - To compare efficacy of nivolumab and CNS radiation compared with nivolumab+ipilimumab and CNS radiation or CNS radiation alone (historical controls)
- Patient inclusion criteria:
 - NSCLC with CNS metastasis
 - Brain lesion or lesions amenable to Gamma Knife SRS or WBRT
- Trial status:
 - In development, anticipated start in Oct 2015

In Development:

Phase II:



Additional Correlates:

- 1) Immuno markers of interest
- 2) Interval MRI imaging

- We will allow patients with prior immunotherapy
- SRS will be limited to a total of 10 intracranial lesions
- Phase II: NSCLC only (n=60, 30 per arm)
- Primary endpoint: safety
- Secondary endpoints: intracranial PFS, systemic PFS