Is There a Role for Radiation Therapy and Immunotherapy?

Eric Shinohara, MD, MSCI
Associate Professor
Dept of Radiation Oncology
Vanderbilt University Medical Center

I have no conflicts of interest

There will be discussion about the use of products for non-FDA approved indications in this presentation.

Radiation Therapy

- Local disease
  - Traditional role of radiation for local control
  - A great deal of time spent focusing on the physics of radiation delivery (example: protons)

- Distant disease
  - Established thinking is that the use of radiation in the metastatic setting is limited to palliation
  - Is there a role for radiation in the non-palliative treatment of patients with metastatic disease?
    - Role in oligometastatic disease?
    - Effect on distant lesions?

Radiation Therapy

- Conventionally fractionated radiation (1.8-3 Gy per fraction)
  - Tumor death through creation of oxidative radicals damaging DNA inducing mitotic cell death
  - Vascular endothelial growth may actually be induced
  - Local control can be poor in certain histologies with conventional fractionation

Radiation Therapy: Hypofractionation

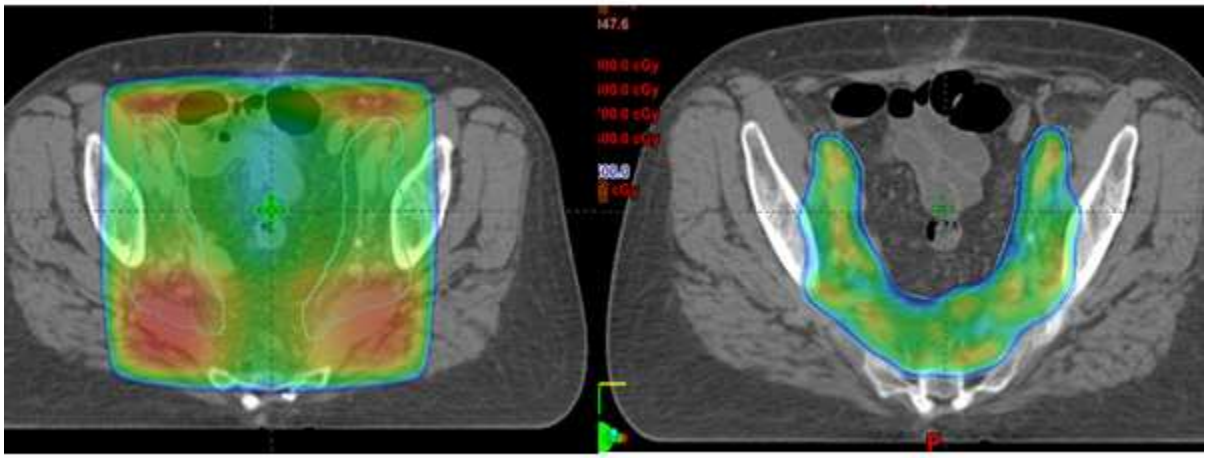
- Larger dose per fraction are given
  - Induction of endothelial cell death occurs by mechanism that appear to be DNA damage independent (10-20 Gy per fraction)
    - Induction of acid sphingomyelinase -> hydrolysis of sphingomyelin -> generate ceremide -> apoptosis)
  - May be why there is an effect in traditionally radiation resistant tumors

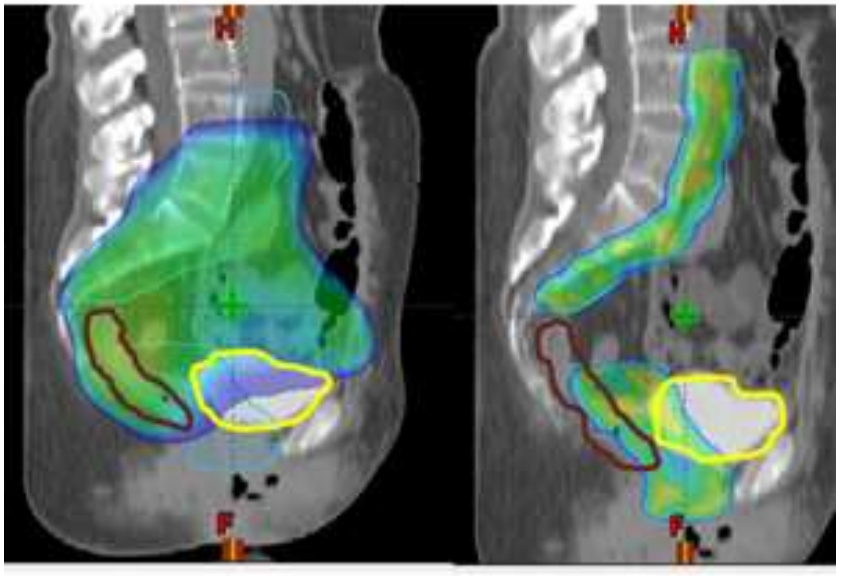
Kolesnick R, Oncogene, 2003
Garcia-Barros M, Science, 2003

Radiation Therapy: SABR

- Normal tissue toxicity has limited the dose that can be given per day, in the past
  - Technological advances have allowed higher, more conformal doses to be given to improve local control
  - Stereotactic Body RadioTherapy (SBRT) or Stereotactic ABlative Radiotherapy (SABR) -> allow higher daily doses to be given
  - Now widely used in many cancers including, CNS, lung, and liver

Radiation Therapy : Improved Conformality





Use in Oligometastatic Disease

- Several studies suggest that SBRT used to treat metastatic lung disease results in excellent local control rates (80-90%) when 8-12 Gy is used over 5 fractions

- Currently there are clinical trials looking at SBRT for oligometastatic disease in several sites including, breast, prostate, lung, Ewing's sarcoma and melanoma

Reference	No. of Patients	No. of Targets	Radiation Dose	Median Follow-Up (Months)	Outcomes
Fractionated/Single Fraction SABR					
Onimaru et al.[27]	20	32	48 Gy/8 fx, 60 Gy/8 fx	18	48% 2-yr OS, 69.6% 3-yr LC for 48 Gy, 100% 3-yr LC for 60 Gy
Yoon et al.[26]	53	80	30 Gy/3 fx, 40 Gy/4 fx, 48 Gy/4 fx	14	70% LC for 30 Gy, 77% for 40 Gy, 100% LC for 48 Gy, 51% all 2-yr OS
Okunieff et al.[29]	50	125	50 Gy/10 fx, 48 Gy/6 fx, 57 Gy/3 fx	18.7	91% 3-yr LC, 50% 2-yr OS
Norihisa et al.[19]	34	43	48 Gy/4 fx, 60 Gy/5 fx, at isocenter	27	90% 2-yr LC, 84% 2-yr OS
Brown et al.[25]	35	69	5 Gy/1 fx to 60 Gy/4 fx	18	77% crude LC, 72.5% 2-yr OS
Rusthoven et al.[12]	38	63	60 Gy/3 fx at 80%	15.4	96% 2-yr LC, 39% 2-yr OS
Wulf et al.[24]	41	51	30 Gy/3 fx, 36 Gy/3 fx, 26 Gy/1 fx at 100%	13	80% 1-yr LC, 33% 2-yr OS
Ricardi et al.[23]	61	77	45 Gy/3 fx, 26 Gy/1 fx at 80%	20.4	89% 2-yr LC, 66.5% 2-yr OS
Single Fraction SABR Only					
Hof et al.[30]	61	71	12 to 30 Gy at isocenter	14	65.1% 2-yr OS
Filippi et al.[28]	67	90	26 Gy at 80%	24	88.1% 2-yr LC, 70.5% 2-yr OS

Singh D, J Thorac Dis, 2014
Collen C, Ann Oncol, 2014
Decaestecker, K, BMC Cancer, 2014
Shultz DB, JTO, 2014

Abscopal Effect

- Latin for “away from target”: treatment of a lesion with subsequent tumor response in non-irradiated lesions

- Rarely seen with radiation alone, but has been reported in medulloblastoma, melanoma, lymphoma and renal cell carcinoma

Meerleer GD, Lancet Oncology, 2014

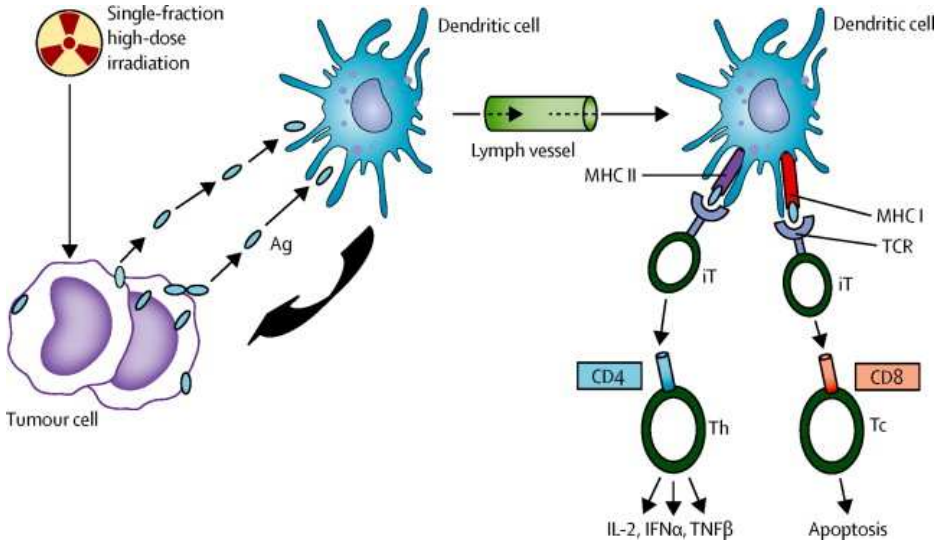
Abscopal Effect: Mechanism

- Mechanism is not fully understood
  - Inhibition of production of growth/proangiogenic factors as a direct result of tumor destruction
  - Increasing local production of local anti-tumor/angiogenic proteins (ex TNF α, IL-1 α, IL-1β, IL-6 etc)
  - Activation of immune system by releasing tumor antigens

Ludgate CM, Clin Cancer Res, 2012
Fairlamb DJ, Cancer, 1981

Abscopal Effect: Mechanism

- Activation of T-cells appears to be an important part of the abscopal effect
  - T-cell depleted mice do not demonstrate an abscopal effect with radiation
- Inflammation and apoptosis recruit dendritic cells to area, which then adopt antigens and present them in regional nodes -> T-cell activation



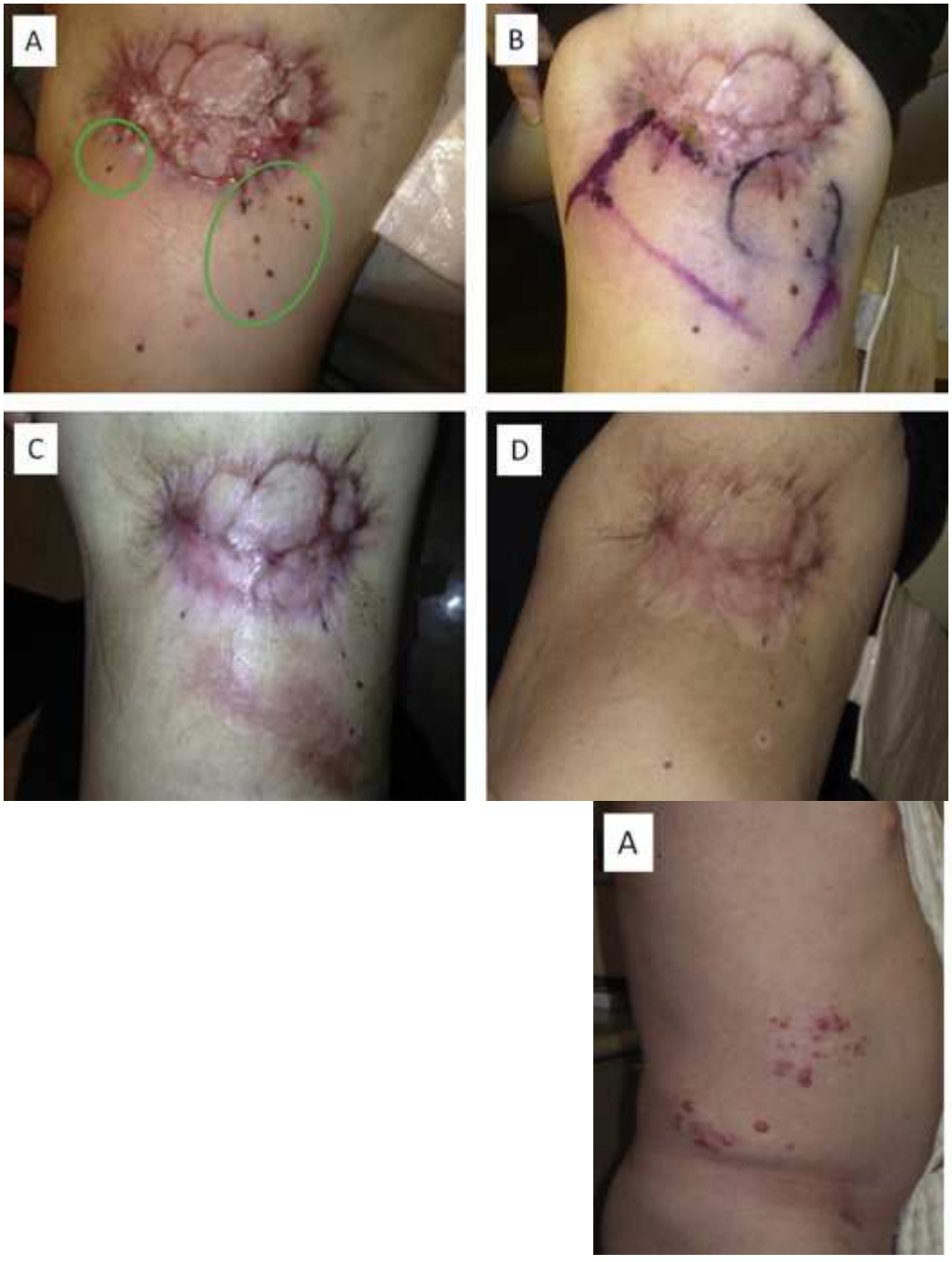
Schmid TE, Front Oncol, 2012
Meerleer GD, Lancet Oncology, 2014

Abscopal Effect: Hypofractionation

- Larger, fractionated doses of radiation appear to be more effective at inducing an abscopal effect that conventional fractionation

- Though hypofractionation appears to increase T- cell activation, still rarely seen with radiation alone, but immunomodulators may potentiate this

Dewan MZ, Clin Cancer Res, 2009
Pilones KA, Clin Cancer Res, 2009


A
B
C
D
A
B
C

Abscopal Effect: GM-CSF

- Sipuleucel-T:
  - Immunotherapy to stimulate T-cell immunity against prostatic acid phosphatase (PAP) in patients with metastatic, castrate resistant prostate cancer
  - Dendritic cells treated with PAP and GM-CSF to mature them -> improved OS (25.9 vs 21.4 months)

Small EJ, JCO, 2006

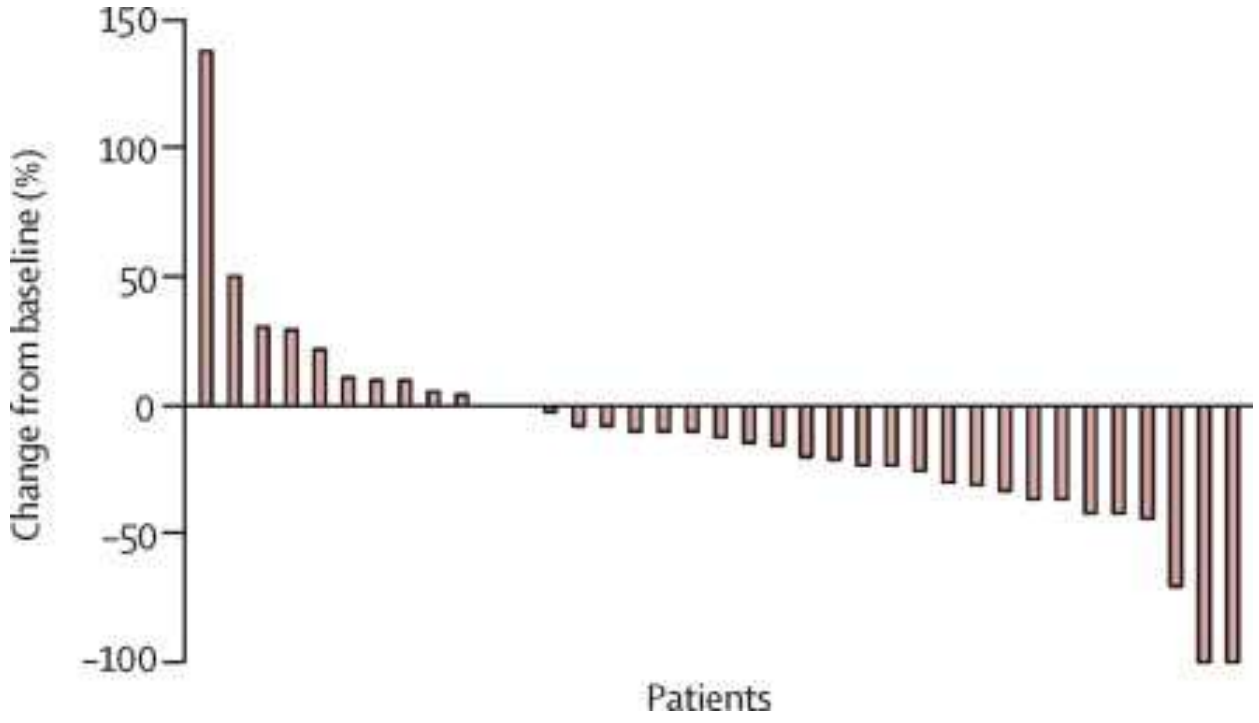
Abscopal Effect: GM-CSF

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) -> induce dendritic cells to develop immune response
- Combination of GM-CSF with concurrent radiation 35 Gy in 10 fractions to a target lesion in pts with predominantly NSCLC and breast cancer with at least 3 sites of disease
- Decrease of at least 30% in a non-target lesion interpreted as an abscopal response

Golden, EB Lancet Oncology, 2015

Abscopal Effect: GM-CSF

- 27% abscopal response noted



Golden, EB Lancet Oncology, 2015

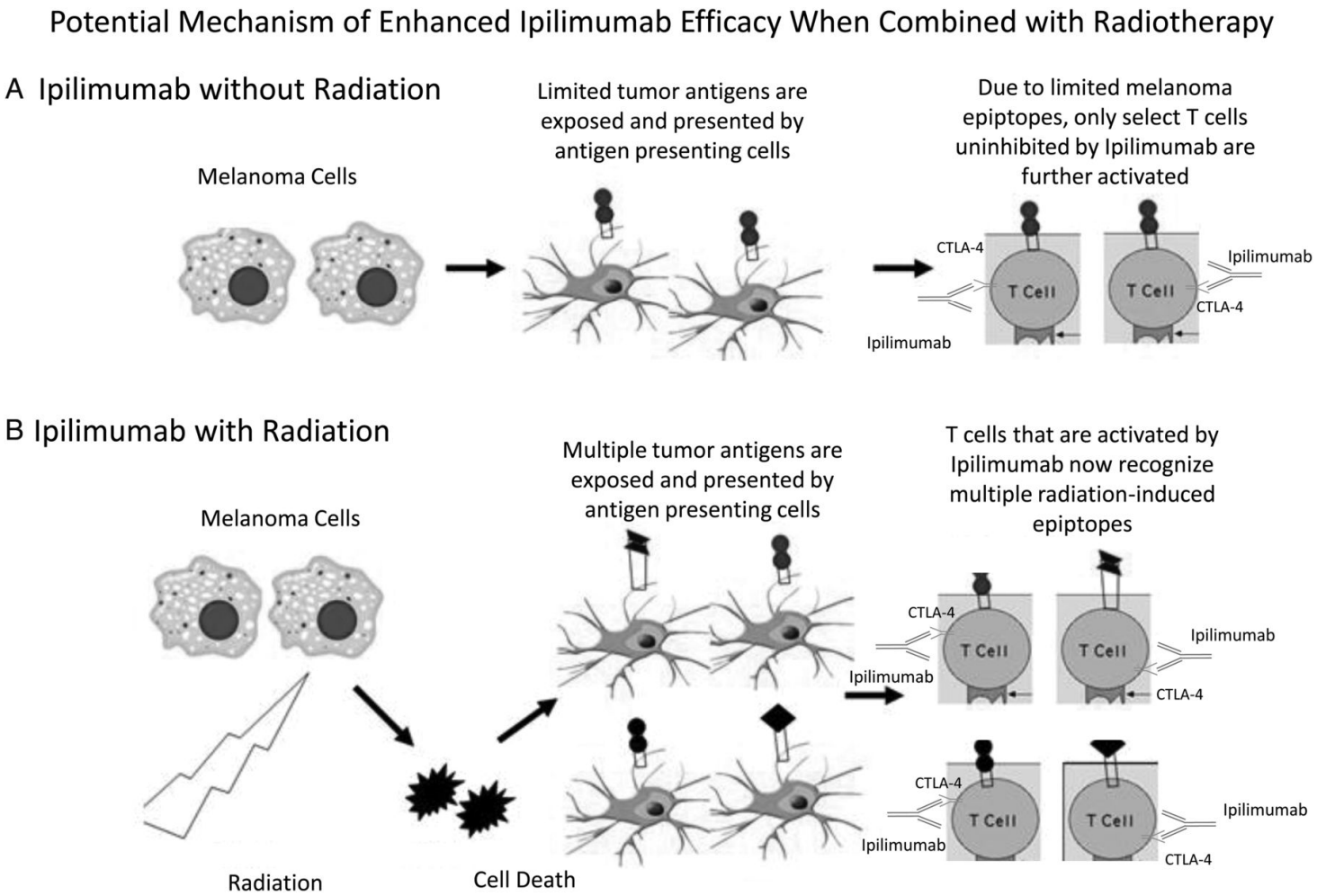
Abscopal Effect: Ipilimumab

- CTLA4 inhibitions leads to enhancement of T-cell activation -> can inhibitors like ipilimumab enhance radiation induced abscopal effect?

- There have been several case reports of abscopal effect with CTLA4 inhibitors, but no randomized studies.

Postow MA, NEJM, 2012
Hiniker SM, Transl Oncol, 2012
Golden EB, Immunol Res, 2013
Grimaldi AM, Oncoimmunology, 2014

Abscopal Effect: Ipilimumab



Patel KR, Neuro Oncol, 2015

Proof of Concept: Case Report

- 33 yo lady with cutaneous melanoma
  - 2003: primary resected – nodes, did well initially
  - 2008: Solitary, biopsy proven, pulmonary metastases 4 years later -> Cis, Vin, Temozolimide ->resected
  - 2009: paraspinal and R hilar mass -> ipilimumab 10 mg/kg q 3 weeks, 4 cycles (induction) -> initially slight enlargement -> continued on maintenance ipi

Postow, MA, NEJM, 2012

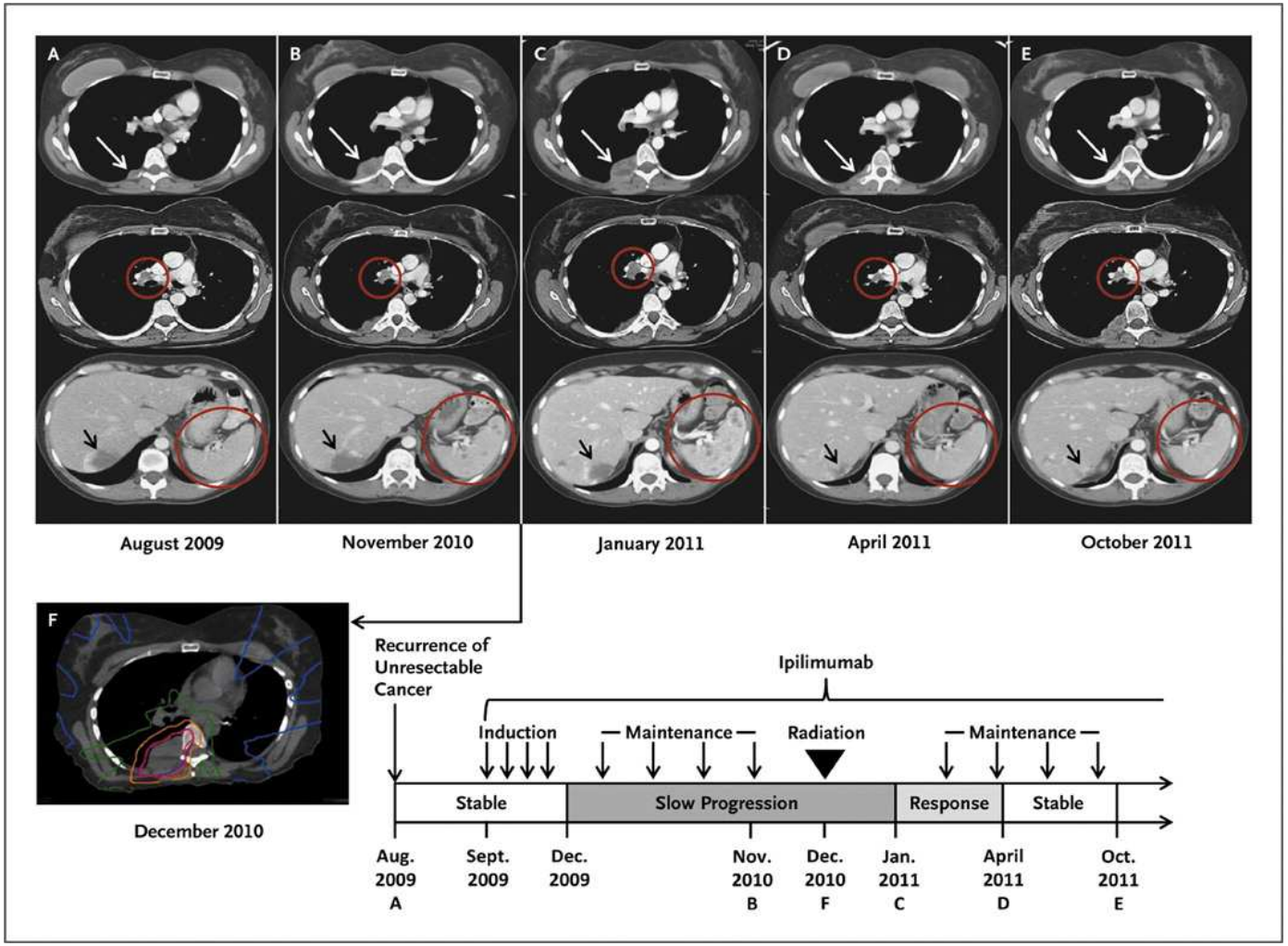
Proof of Concept: Case Report

- November 2010: further progression with splenic mets and back pain due to paraspinal mass
  - 2850 cGy given in 3 fx for palliation over 7 days

- April 2011: Scans demonstrated regression of primary and non-target lesions

Postow, MA, NEJM, 2012

Proof of Concept: Case Report



Postow, MA, NEJM, 2012

Stereotactic Brain Radiation

- Stereotactic radiation commonly used in brain mets, particularly melanoma
- Several studies have investigated ipilimumab in the treatment of brain metastases
  - Phase II studies have suggested that ipilimumab is effective with doses of 3 mg/kg or higher
  - Some have suggested an improvement in OS in pts treated with ipilimumab
  - May be associated with more intracranial swelling, may require dexamethasone, which may reduce efficacy of ipilimumab

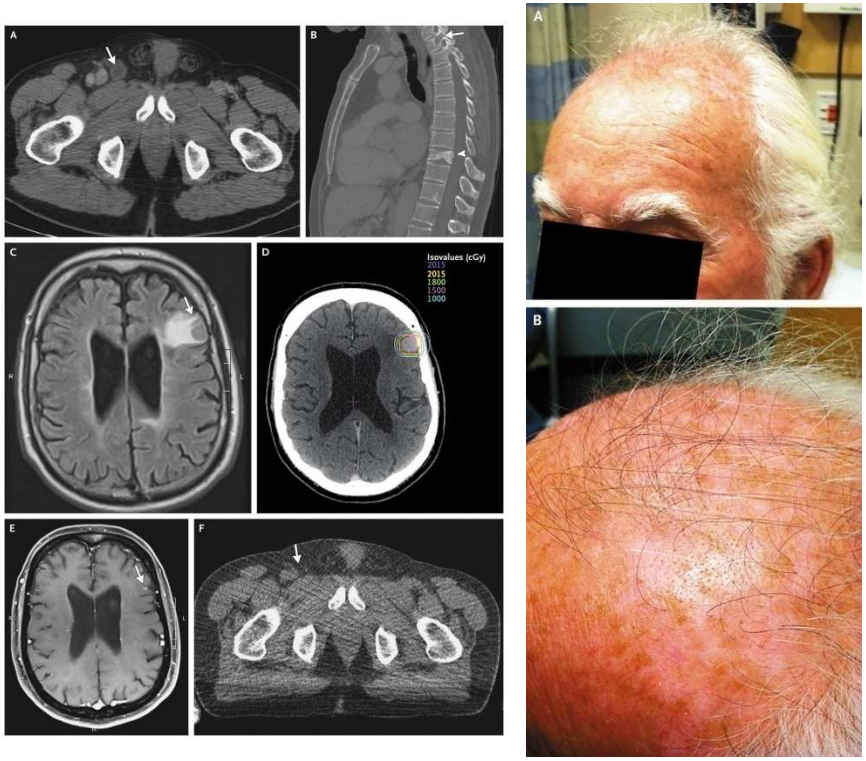
Maya M, Melanoma Res, 2013
Kiess AP, IJORBP, 2015
Naamit K, Journal of Neuro-Onc, 2015
Patel, KR, Neuro Onc, 2015

Stereotactic Brain Radiation

- Combined use of ipilimumab and radiation in brain mets
  - Whole brain given within 30 days of ipilimumab -> 10/10 patients either developed hemorrhage or had worsening of bleeding
  - Smaller studies have been conflicting with some demonstrating better OS and less regional recurrences when treated with SRS before or during ipilimumab, while others do not
  - Sequential treatment may be safer, 40% of patients treated with SRS during ipilimumab treatment developed hemorrhage

Maya M, Melanoma Res, 2013
Kiess AP, IJORBP, 2015
Naamit K, Journal of Neuro-Onc, 2015

Abscopal Effect with SRS?



- Pt treated with vemurafenib with partial response then progression at 39 weeks
- Treated with SRS with regression of groin nodes, developed depigmentation of hair and vitiligo of the scalp

Sullivan RJ, NEJM, 2013

Numerous Current Clinical Trials

Trial	Histology	Phase	Immunomodulator	Fractionation	
NYU S12-02746	Melanoma	Phase II	Anti-CTLA-4	6 Gy x5	
NYU S14-00208	NSCLC	Phase II	Anti-CTLA-4	6 Gy x5	
NCT01416831	Melanoma	Phase II	IL-2	20 Gy x 1 or 2	
PH&S IRB 12-017A	Met breast	Phase I	Anti-CTLA-4	15 Gy x1	
Stanford	Mel/NHL/ Colorectal	Phase I-II	Anti-CTLA-4	2-10 Gy x2	
NIH/NCI (pending)	Colorectal	Phase I	Anti-Pd-1	8 Gy x 1-3	

Crittenden, M Sem in Rad Onc, 2015

Future Directions

- Combined inhibition of CTLA4 and PD-1 appears to be tolerable and be more effective than either agent alone

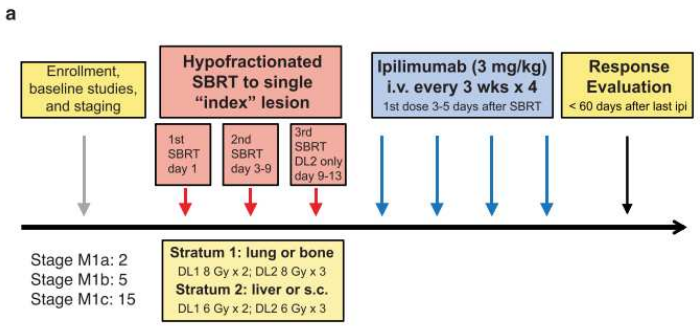
- The combination may further potentiate the abscopal effect

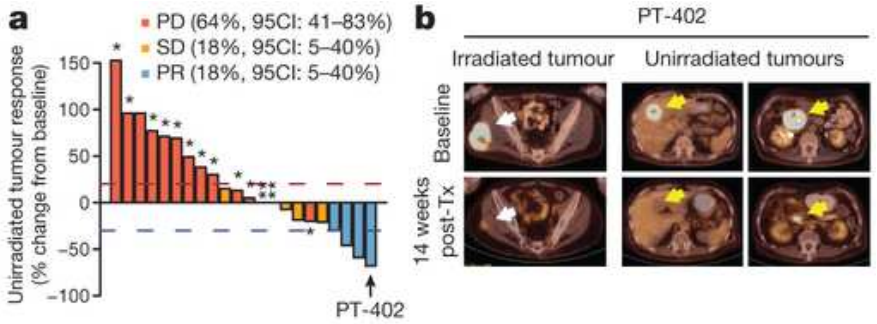
Wolchok JD, NEJM, 2015
Twyman-Saint Victor C, Nature, 2015

Combination Therapy?

- RADVAX: Phase I/II dose escalation study treating ipilimumab naïve melanoma pts with 1-3 fractions of 8 Gy or 6 Gy (lung/bone vs skin/liver mets) followed by ipilimumab

- Response rates of the combination of SBRT and ipilimumab in both melanoma patients and murine models ~18%

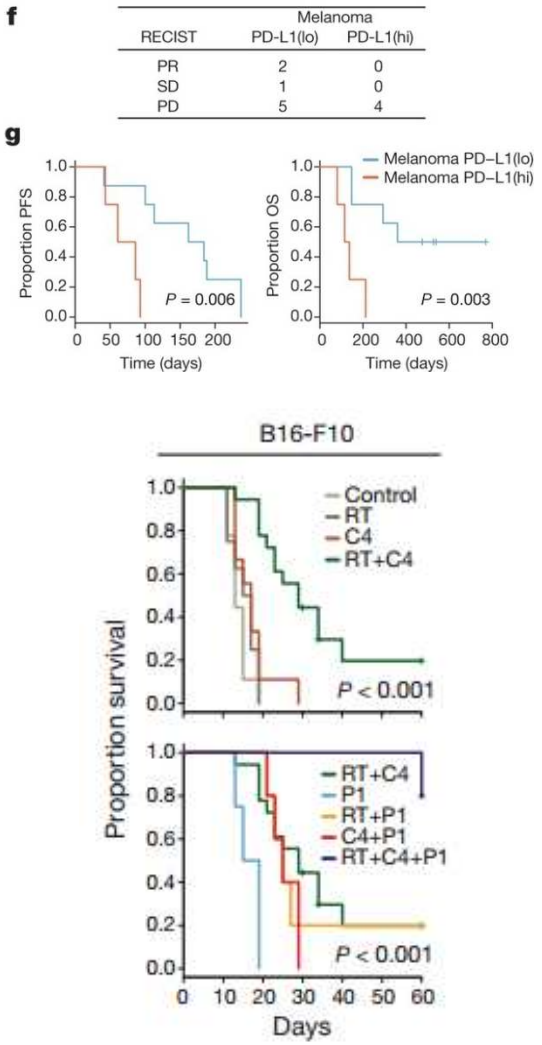




Twyman-Saint Victor C, Nature, 2015

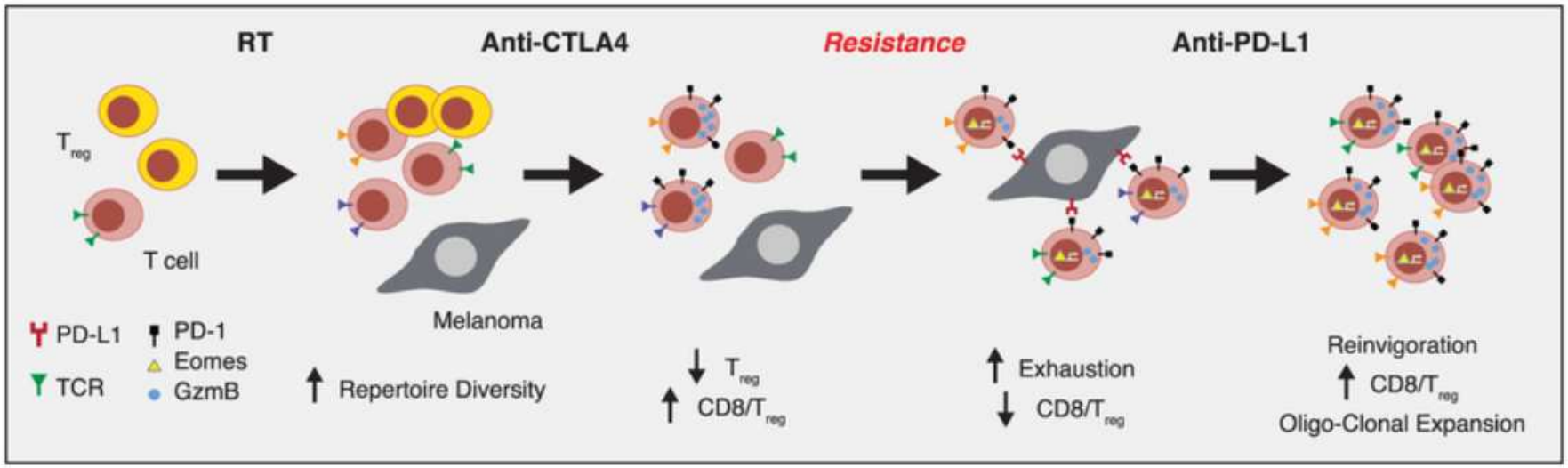
Combination Therapy with SBRT?

- Combination of ipi and radiation demonstrated strong upregulation of PD-L1 and suppression of T-cell function
- In murine models better responses with addition of PD-L1 or PD-1 inhibitors (80%)
- Pts with response to CTLA4 inhibitor and radiation had low tumor expression of PD-L1



Twyman-Saint Victor C, Nature, 2015

Combination Therapy with SBRT?



Thank you for your attention!