Local Tumor Flare Following Radiosurgery and Ipilimumab (Ipi) for Melanoma Brain Metastases: Increased Immune Response?

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Disclosures

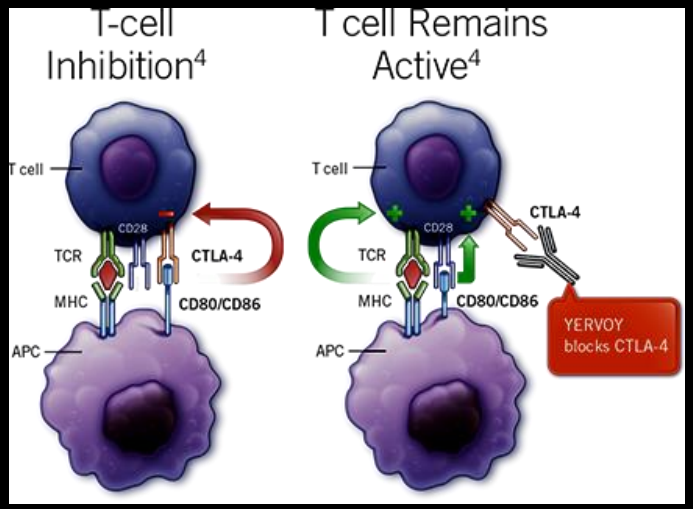
No conflicts of interest to disclose

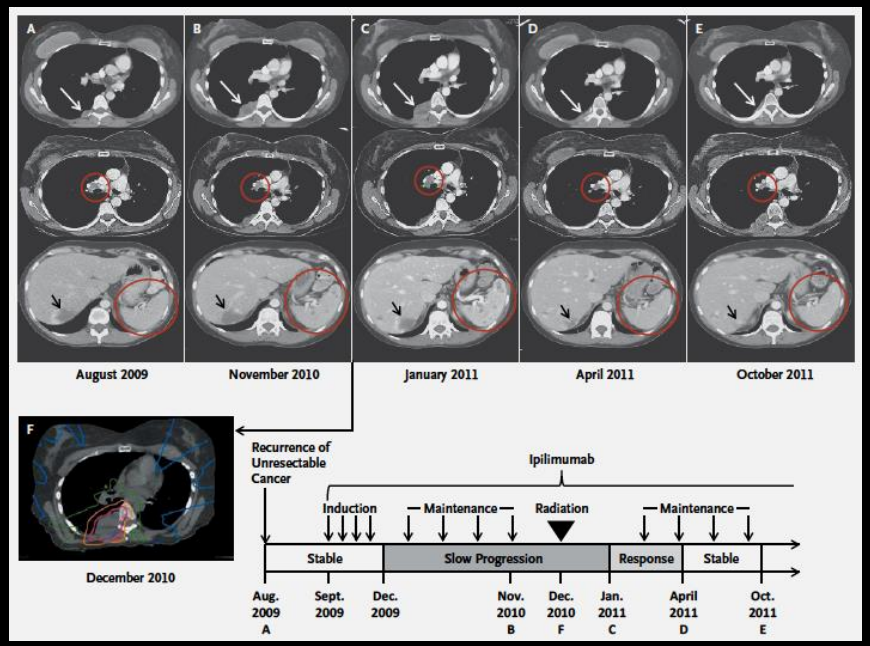
Acknowledgements

Robert and Andree Fitzhenry
Brain Metastases Program

Background

- Ipilumumab is an anti-CTLA4 antibody shown to improve survival in melanoma
- Greater proportion of melanoma patients are developing brain metastases
  - SRS and/or WBRT are mainstay treatments

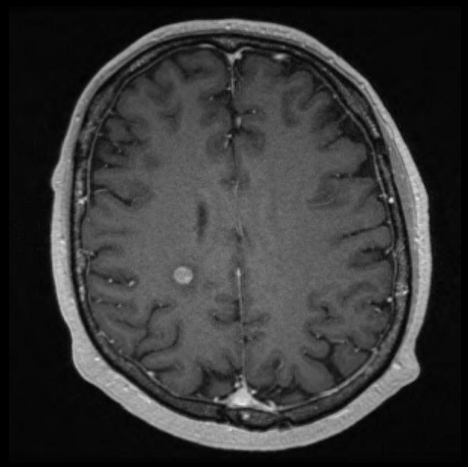




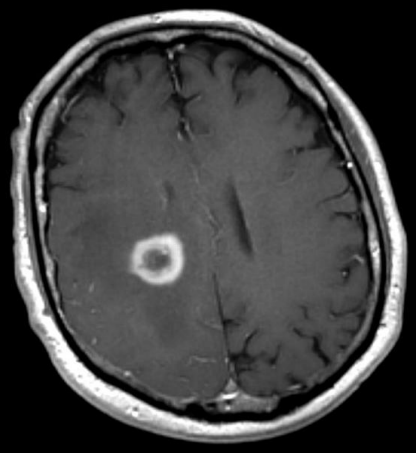
Effect of combining radiotherapy (whole brain radiation and/or radiosurgery) with ipilimumab remain unclear

Postow - NEJM 2012

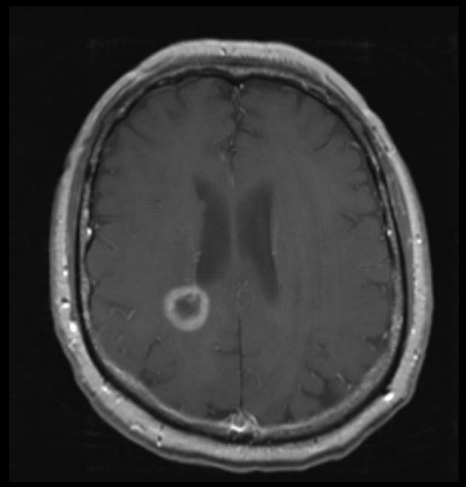
Radionecrosis or
Acute Radiation Effect (ARE) with SRS



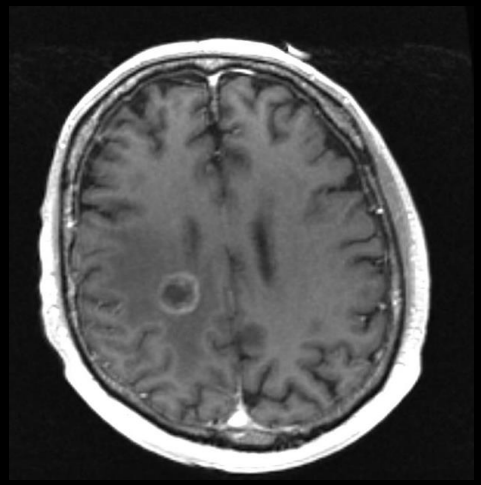
SRS Tx



6-18 months post-SRS

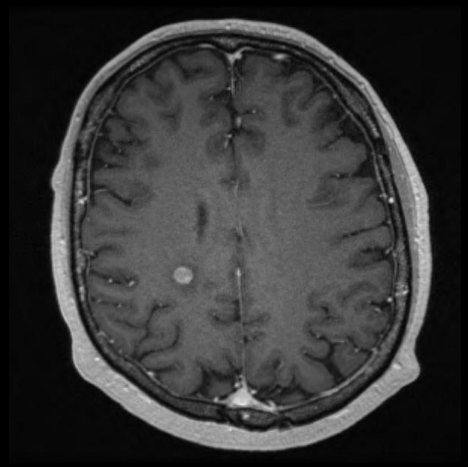


Improvement with dexamethasone

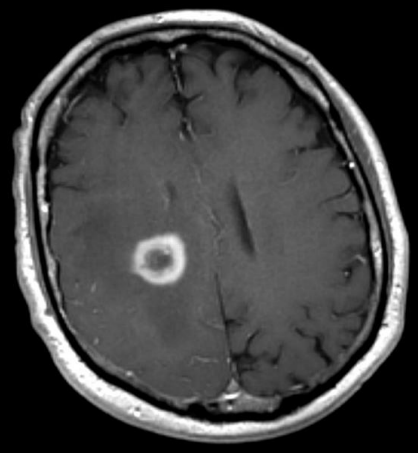


Stability or continued improvement over time

Acute Radiation Effect (ARE) with SRS and Ipilimumab

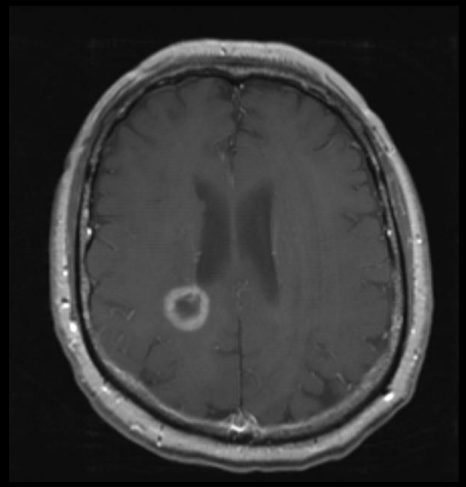


SRS Tx



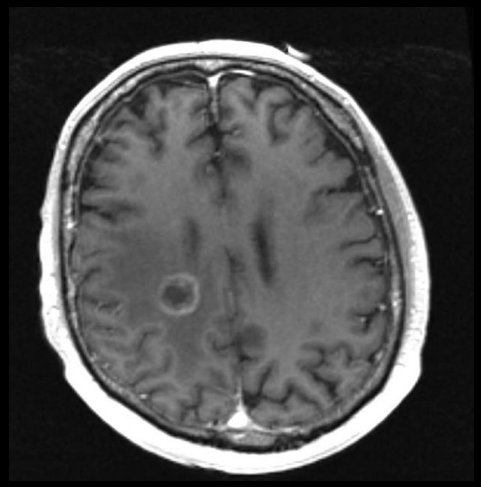
4 months post-SRS
Ipilimumab x 2 doses

Left hemiparesis



After 2 weeks of dexamethasone

Hemiparesis dramatically improved



9 months post SRS

Objectives

- This study evaluated the incidence of acute radiation effect (ARE) and evaluates the factors associated with ARE in patients with melanoma brain metastases treated with ipi and brain RT

Methods

- Retrospective review of a cohort of patients enrolled on a prospective trial of ipilimumab for melanoma, who developed brain metastases (BMs).

Inclusion criteria:

- Metastatic melanoma patients treated with ipilimumab from 2008-2013 at Princess Margaret, who also received radiation for BMs

Results

- 688 patients in our database received SRS as upfront treatment
- 49 pts with 110 brain metastases received SRS +/- WBRT with Ipi
- Median follow-up 7.4 months

Covariate	Full Sample (n=49)	N (n=39)	Y (n=10)	p-value
Gender	**N(%)**	**N(%)**	**N(%)**	0.46
F	18 (37)	13 (33)	5 (50)	
M	31 (63)	26 (67)	5 (50)	
Number of infusions				0.68
1	2 (4)	2 (5)	0 (0)	
2	10 (20)	9 (23)	1 (10)	
3	6 (12)	4 (10)	2 (20)	
4	31 (63)	24 (62)	7 (70)	
Age at first infusion				0.53
Mean (sd)	55.7 (14.3)	55.1 (14.1)	58.3 (15.5)	
Median (Min,Max)	58.2 (24.2,83)	58.2 (24.2,83)	57.6 (31.1,81.8)	

- 9/10 pts required steroids and had symptomatic response within 24 hrs
- 1/10 patient required surgery despite steroids: ++ Tcell infiltrates

ARE Incidence per Metastasis: Timing & Type of Radiation

Covariate	Full Sample (n=110)	SRS only (n=78)	SRS+WBRT (n=9)	WBRT only (n=23)	p-value
ARE	**N(%)**	**N(%)**	**N(%)**	**N(%)**	
N	89 (81)	61 (78)	5 (56)	23 (100)	-
Y	21 (19)	17 (22)	4 (44)	0 (0)	
RT within 4 months Ipi					
N	42 (38)	31 (40)	3 (33)	8 (35)	0.13
Y	68 (62)	47 (60)	6 (67)	15 (65)	

1 metastasis treated with fractionated SRS (8Gy x 3) and Ipi within 4 months was excluded from further analysis, but did not develop ARE

Univariate Analysis for ARE

Variable	Odds Ratio	95% CI	p-value
Brain RT Treatment SRS+WBRT Ref: SRS alone	3.1	0.38-25.6	0.28
RT Timing: Within 4 months Ref: > than 4 months	9.6	0.83-110	0.068
SRS Timing: Within 4 months Ref: > than 4 months	19.4	1.56-241.43	**0.0218**
V12GY	1.2	1.01-1.46	**0.0387**
Target volume	1.48	0.98-2.3	0.0625
SRS Rx Dose	1.004	0.77-1.31	0.9762

Note: fractionated SRS case had Ipi within 4 months and very large V12Gy but did not develop ARE

Multivariable Analysis for ARE

Variable	95% CI	p-value
SRS Timing: Within 4 months Ref: > than 4 months	0.61-58.59	0.123
V12GY	0.99-1.42	0.066

	SRS < 4 months of Ipi	SRS > 4months Ipi
Mean V12Gy	3.65	2.51
Median V12Gy	1.90	1.87

Testing for covariance was not significant p=0.02

Conclusions

- Incidence of ARE was greater in patients treated with SRS + Ipilimumab (26%) vs. SRS alone (11%)
- In a single patient, some metastases may develop ARE and others may not. At the individual metastasis level, ARE was observed in:
  - 24% after SRS + ipilimumab
  - 0% after WBRT + ipilimumab
- Factors associated with ARE:
  - Timing between SRS and ipilimumab
  - V12Gy for SRS

Further Work & Questions

- Relationship between ARE and outcomes:
  - Survival
  - Progression free survival
  - Extracranial disease response

- What is the optimal combination?
  - Timing and Sequence
  - Dose and fractionation of RT
  - Consideration of irradiated volume


Thank you
Questions?