Treatment of Melanoma Brain Metastases and Leptomeningeal Disease

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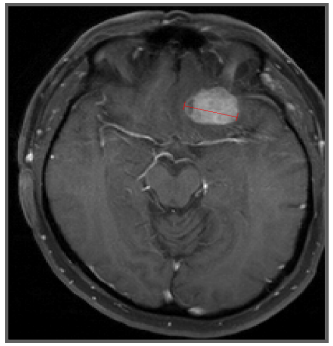
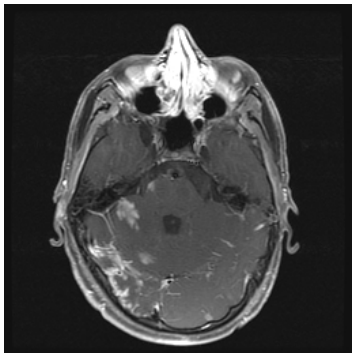


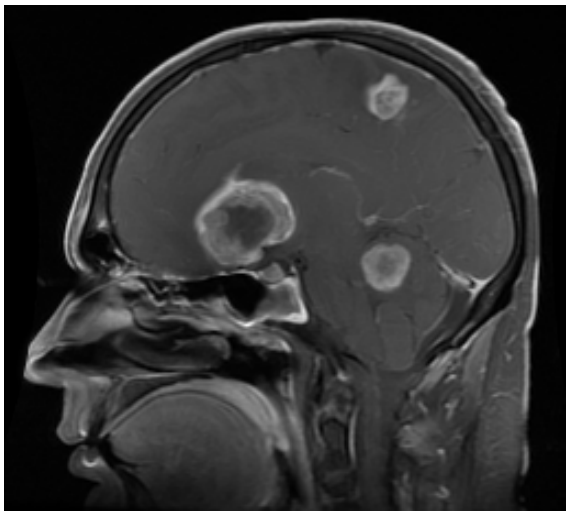
Art and Science of Managing the New Melanoma Landscape

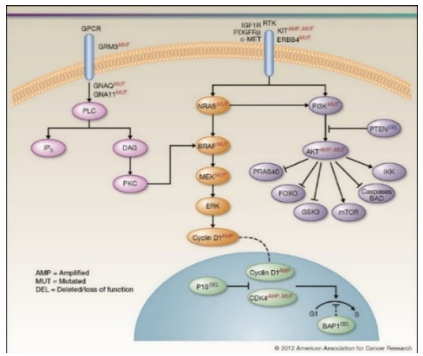
October 2020



Outline- Breakthroughs in the Understanding & Treatment of CNS Metastases: *Melanoma*

- Background
- Treatment
  - Systemic Treatments for Brain Metastases
    - *Immunotherapy*
    - *Targeted Therapy*
  - Leptomeningeal Disease-
    - *1 Slides only!!!!*
- Challenges, Outlook, Opportunities
  - Insights into Pathogenesis and Resistance of Brain Metastases
- Questions

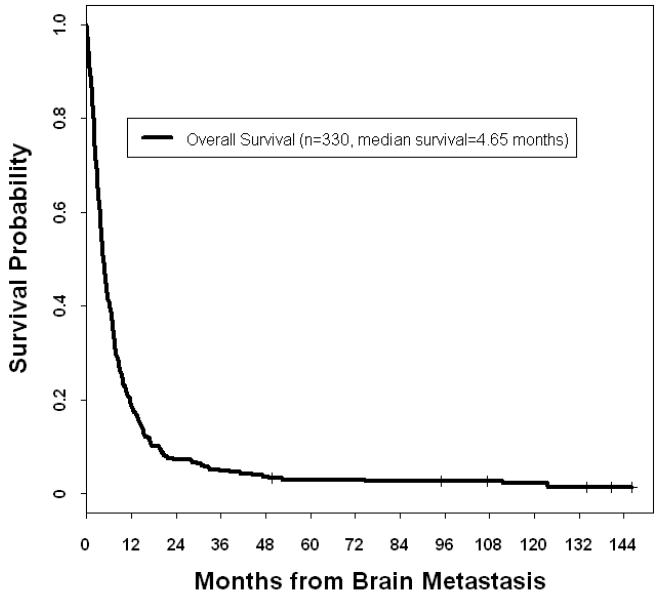




Melanoma Brain Metastases (MBMs)

- Melanoma: the most aggressive of the common forms of skin cancer
- Has among the highest risk of CNS metastasis among solid tumors
  - 10-20% at diagnosis of stage IV,
  - Up to 50% over course of disease
  - Common initial site of treatment failure, especially for chemotherapy, biochemotherapy, and targeted therapy
- Historically median OS ~ 4 months from CNS mets
  - Worst outcomes with leptomeningeal disease (LMD)
- BBB-penetrating chemotherapies achieve intracranial responses in ≤ 10%

MBM: OS

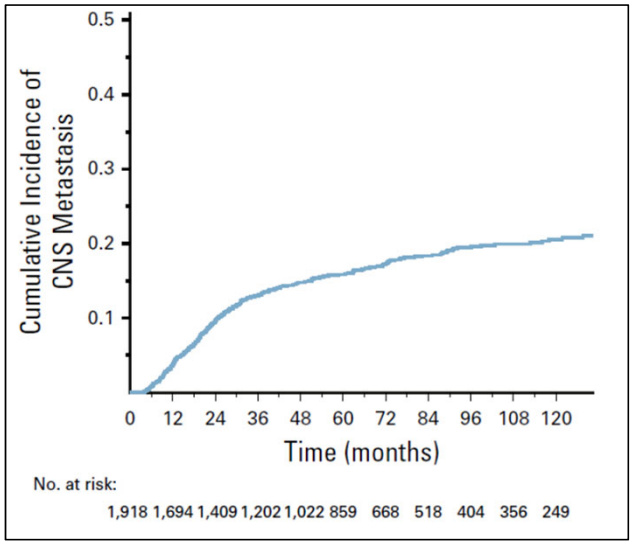


Davies, *Cancer,* 2011
Cohen et al, *PCMR,* 2016

Stage III Melanoma: Prevalence, Timing and Risk Factors for CNS Metastasis

- MD Anderson + MIA Retrospective Cohort (n=1,918)
  - Initial presentation with AJCC 8th edition Stage III melanoma 1998-2014
  - Brain imaging within 4 months of diagnosis (staging window)
  - Cumulative incidence of CNS (brain or leptomeningeal) metastasis
  - Competing risks regression (accounts for death before CNS metastasis)

Cumulative incidence of CNS metastasis – 16.7% (45.1% among patients with distant mets)



Haydu, et al, JCO, 2020

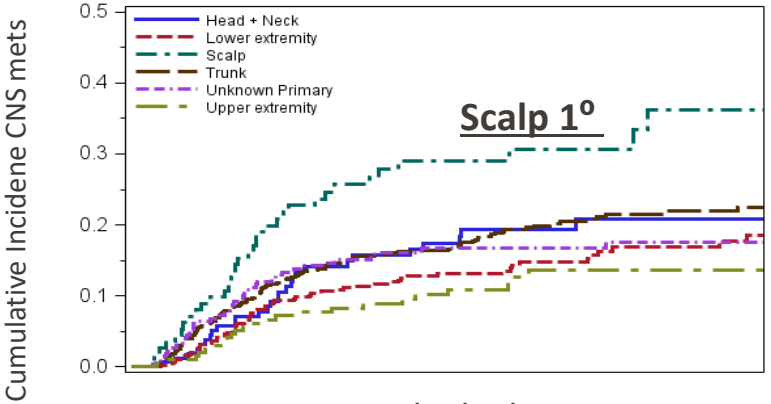
Risk Factors for CNS Metastasis: Primary Tumor Location & Mitotic Rate

- Increased risk of CNS metastasis: male gender, ↓ age, ↑ AJCC stage
  - *IIID: CNS metastases predominantly in first years after stage III diagnosis*
  - *IIIA/B steady increase over time*

In Melanoma also increased incidence among:

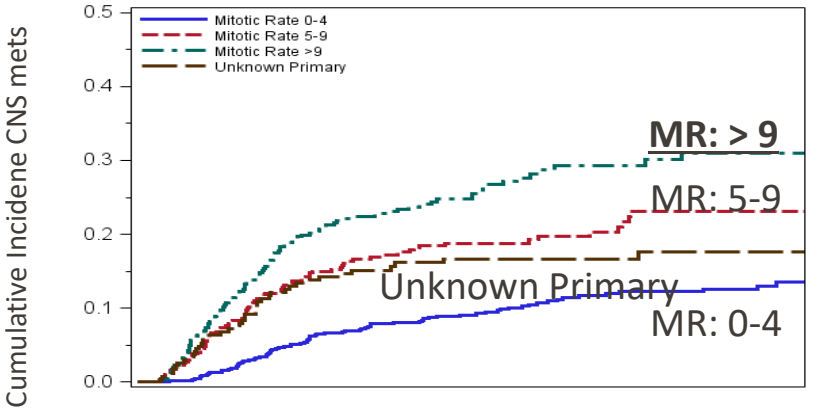
- *BRAF & NRAS* mutant
- Loss of PTEN

Primary Tumor Site



Scalp primary: ↑↑↑ risk CNS mets

Primary Tumor Mitotic Rate



MR > 9: Significant at all timepoints

Haydu, et al, JCO, 2020
Bucheit, *CCR,* 2014

Immunotherapy: Single-Agent ICI

Ipilimumab

- Cohort A: Asymptomatic (n=51)
- Cohort B: Requiring steroids (n=21)

Outcome n (%) [95% CI]	Cohort A (n=51)	Cohort B (n=21)
CNS objective response	9 (18) [8–31]	1 (5) [0.1–24]
CNS disease control	12 (24) [13–38]	2 (10%) [1–30]
Median Overall Survival (OS)	7.0 mos	3.7 mos

Margolin K, *et al. Lancet Oncol* 2012;13:459–65.

→ ***Pts on steroids excluded from many subsequent studies***

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Pembrolizumab

- Melanoma (n=18) and lung cancer (n=18) pts with BMs not requiring steroids
- Melanoma:
  - **ORR 22%** (4 PR, 3 SD, and 7 PD)
  - PFS in PRs: 6+, 10+, 13+, 17+ mos
  - Median OS not reached
  - Neuro AEs: focal sx related to CNS edema (n = 5), seizure (n = 3), HA (n = 3), dizziness (n = 1) and cog dysfn (n = 1; grade 3/4)

Goldberg SB *et al. Lancet Oncol* 2016: 17: 976-983
Kluger HM *et al. JCO* 2019: 37: 52-60

Almost all intracranial responses in both studies durable = Proof of Principle

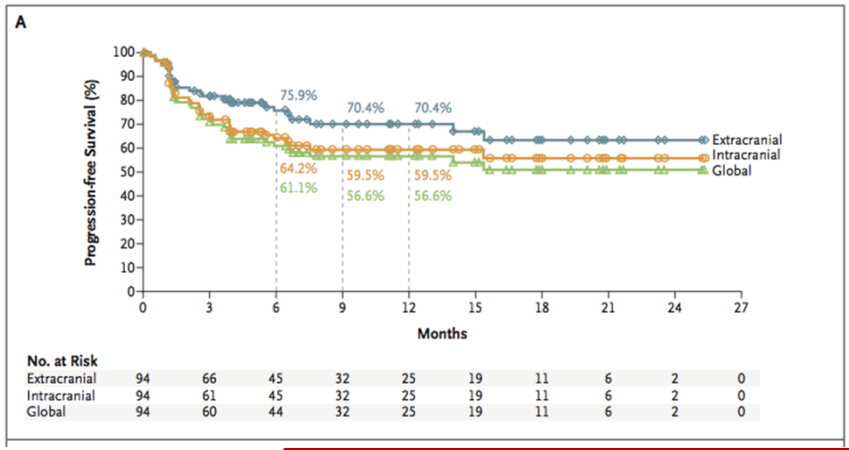
Immunotherapy: Ipilimumab + Nivolumab

- Checkmate 204 (Ipi 3 mg/kg + Nivo 1 mg/kg)
  - 94 patients
    - No steroids; at least 1 met w/o XRT
  - **Intracranial ORR 55%** (CR 26%, PR 30%)
  - 59.5% CNS PFS & 81.5% OS at 12 months
  - No new/unexpected toxicities

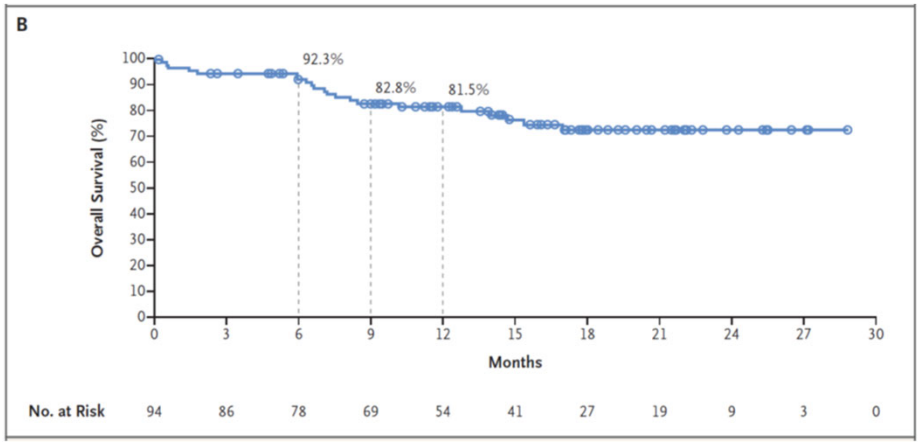
- ABC Trial: Nivo vs Ipi + Nivo (Ipi 3 + Nivo 1)
  - Ipi + Nivo (n=35), Nivo (n=25)
    - No steroids; no prior XRT
  - **Intracranial ORR: 46%** vs 20%
  - No new/unexpected toxicities

Long et al, *Lancet Onc,* 2018

Progression-Free Survival (PFS)



Overall Survival (OS)

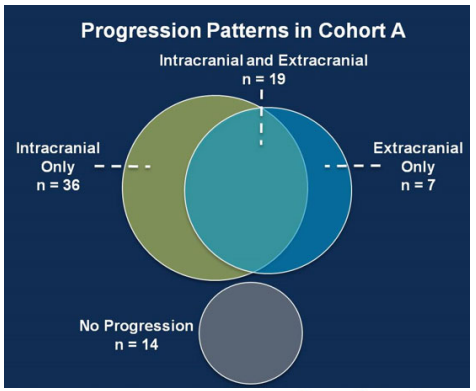


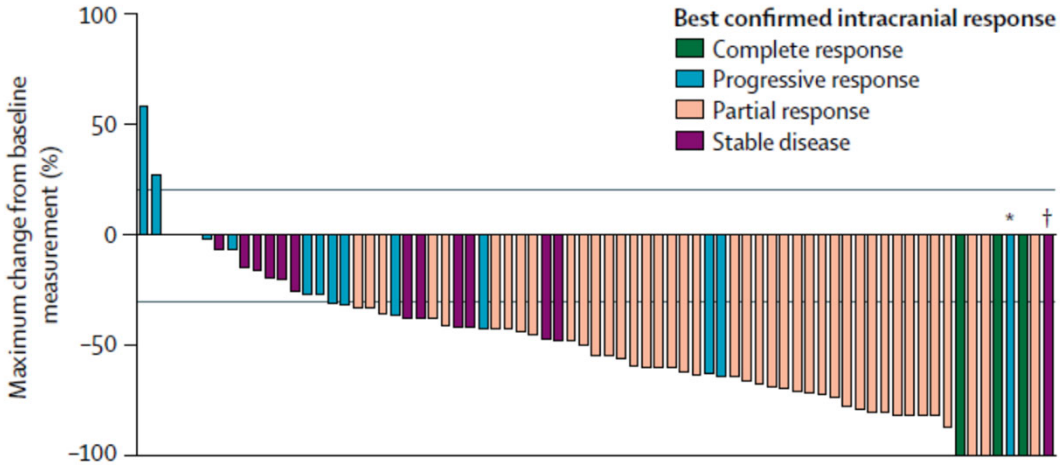
Tawbi et al, *NEJM,* 2018

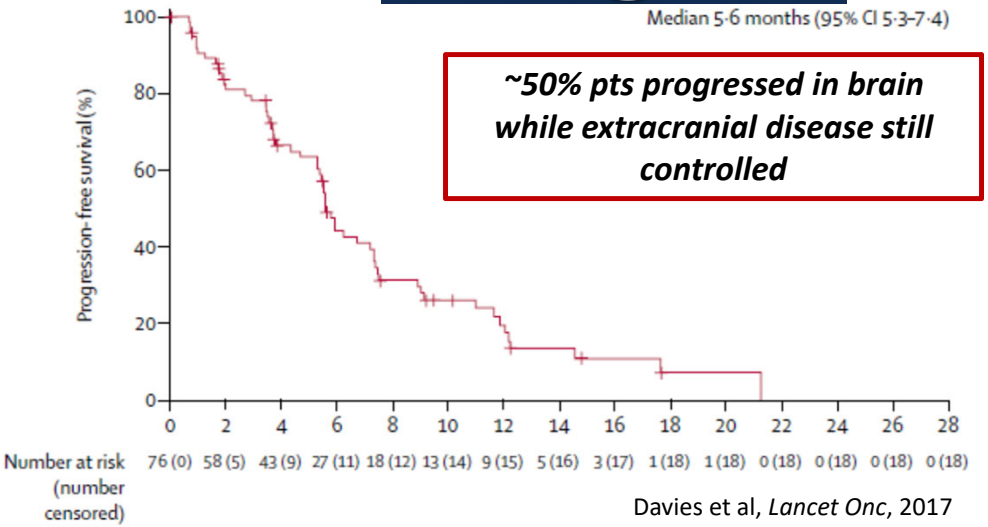
Tawbi et al, ASCO 2019: **Intracranial RR 16.7%** in symptomatic pts

BRAF^{V600} Targeted Therapy: BRAFi + MEKi

- **<u>COMBI-MB:</u>** Phase II study of dabrafenib (150 mg BID) + trametinib (2 mg QD) in BRAF V600-mutant metastatic melanoma patients with new or progressive brain metastases
  - Previously Untx and Previously Tx Brain Met Cohorts
  - Stable or decreasing doses of steroids allowed
- Cohort A: **Intracranial ORR 58%, Intracranial DCR 78%**
  - **<u>BUT</u>** Median Intracranial DOR 6.5 mos, **Median PFS 5.6 mos**
    - Pts without brain mets, Median PFS ~ 12 mos







~50% pts progressed in brain while extracranial disease still controlled

Davies et al, *Lancet Onc*, 2017

Melanoma Brain Metastases: Key Research Findings

- Growing evidence of unique features of brain metastases
  - *Novel Mutations, ↓ Immune Infiltrates, Distinct Oncogenic Pathways & Metabolism*
  - *Some phenotypes of brain metastases appear to be shared across cancer types*
- Many distinct features associated with resistance to therapy
- Insights also suggest rational strategies to improve efficacy/outcomes
  - *XRT + Immunotherapy; PI3K-AKT inhibitors; OXPHOS inhibitors*
- *Overall, findings support need for continued focused research on CNS disease*

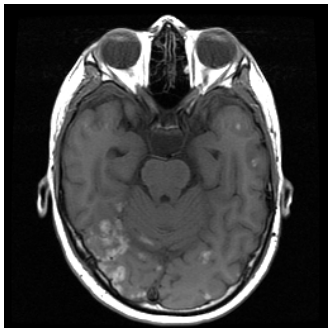
Final Frontier:Leptomeningeal Disease (LMD)

↓↓↓ *survival from CNS metastasis versus brain-only disease*

Recent review showed OS of 3.5 months

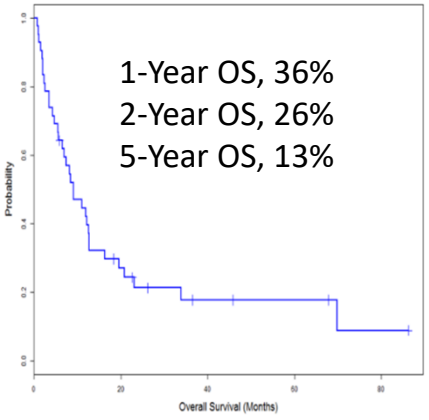
No specific treatment- patients excluded even from trials for brain mets

Very little known about features, pathogenesis of LMD



Intrathecal Immunotherapy Program

Intrathecal IL-2:Overall Survival

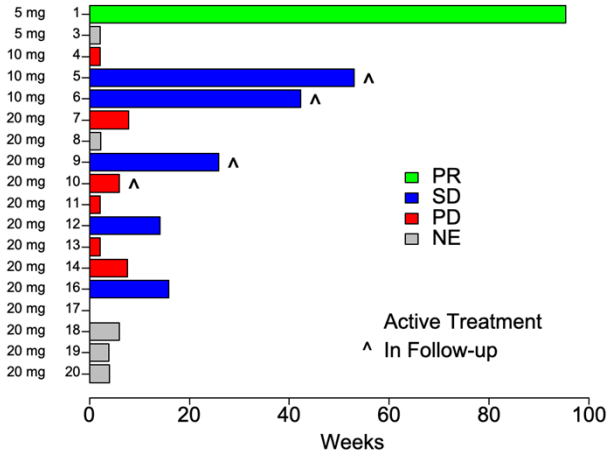


- Initiated 1992
- Treated >150 melanoma LMD patients
- PD-1 is expressed on the surface of immune cells in the CSF

Glitza et al, *ESMO Open Access*, 2018

Phase I IT Nivolumab: Treatment Duration

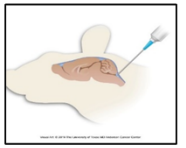
Cycle (14 days each)	Base-line	1				2				3			4		5 and beyond	
Day of cycle		D1	D1 +4 hrs	D2	D8	D1	D1 +4 hrs	D2	D3	D8	D1	D2	D8	D1	D2	D1	D2
Treatment																	
IT Nivo (3 Dose levels: 5, 10, 20 mg)		x				x					x			x		x	
IV Nivo (240 mg)								x				x			x		x

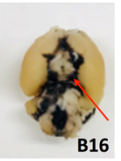


Glitza et al, ASCO 2020

- Treated 21 patients thus far
- No significant toxicities
- Now also open for NSCLC

Melanoma LMD: Model Development





Dr. Ferguson et al., under review

Systemic Therapy for Brain Metastases: Progress, but More Work to Do

- **Immune Therapy**: Ipilimumab + Nivolumab > Single-Agent PD-1
  - *Strengths: ICRR ~50%, most responses to date have been durable, OS*
  - *Weaknesses: 30-40% Progression; Toxicity; Low activity in symptomatic pts*

- **Targeted Therapy**: BRAFi + MEKi- Dabrafenib and trametinib
  - *Strengths: Rapid responses, initial disease control, including in pts on steroids*
  - *Weakness: Most responses are ≤ 6 months; Lack of data for other combos*

- **Current Investigations**: **Combinatorial Approaches**
  - *New immunotherapy combinations, VEGF (avoid/minimize steroids)*
  - *Targeted therapy + immunotherapy*
  - *Combinations/Sequencing with SRS*

- **Leptomeningeal disease: What is the right path moving forward?**
  - *Administration*
  - *Combination with Radiation*