

Workshop on Product Development for CNS Metastases

March 22, 2019



Session I: Defining the Problem of CNS Metastases

Laleh Amiri-Kordestani, MD, Co-Chair, US Food and Drug Administration

Greg Riely, MD, Co-Chair, Memorial Sloan Kettering Cancer Center



Current Treatments and Investigations for CNS Metastases

Michael A. Davies, M.D., Ph.D.

Associate Professor, Deputy Chairman, Melanoma Medical Oncology
The University of Texas MD Anderson Cancer Center

FDA Brain Metastasis
Workshop:

March 22, 2019



Dr. Paul Brown



Dr. Ross Camidge



Dr. Nancy Lin



Dr. Michael Davies



Dr. Emilie Le Rhun

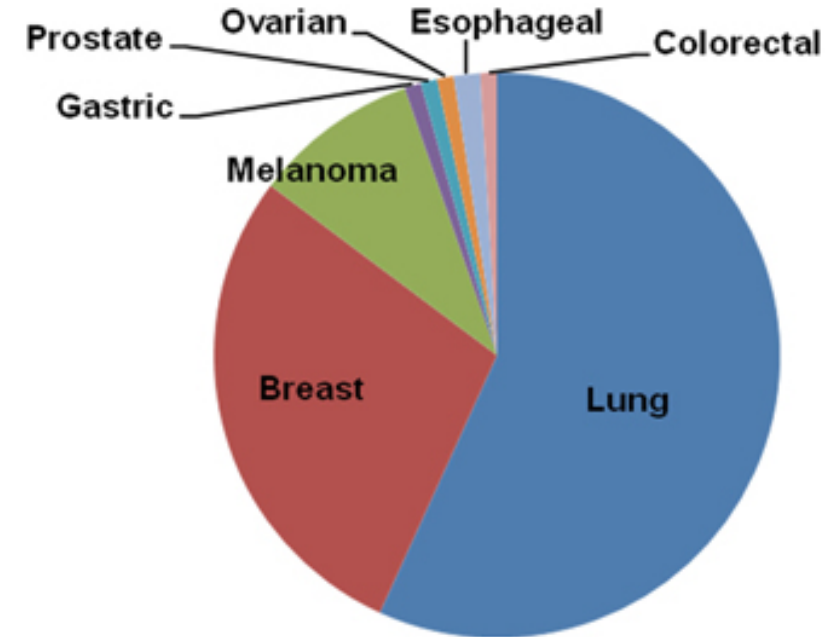
Disclosures

- Research Support from
 - AstraZeneca
 - Roche/Genentech
 - GlaxoSmithKline
 - Myriad
 - Oncothyreon
 - Sanofi-Aventis
- Advisory Board
 - GlaxoSmithKline
 - Roche/Genentech
 - Novartis
 - Array
 - BMS
 - Sanofi-Aventis
 - Vaccinex

Brain Metastases: Significance

Brain Metastases (BM)

- 98,000-170,000 patients diagnosed with BM annually
 - ~10% of all cancer patients
 - up to 40% of pts with metastatic disease
- ~100,000 deaths per year
 - 20-50% of patients dying of cancer have brain metastases



Current Therapeutic Landscape for CNS Metastases, 2019

- Overview of Webinars
 - *Radiation Therapy- Dr. Paul Brown*
 - *Breast Cancer – Dr. Nancy Lin*
 - *Lung Cancer – Dr. Ross Camidge*
 - *Melanoma- Dr. Michael Davies*
 - *Leptomeningeal Disease (LMD) – Dr. Emilie Le Rhun*
- Summary & Key Questions

Radiotherapy in the Management of Brain Metastases

Paul Brown, MD
Professor Radiation Oncology
Mayo Clinic



Radiotherapy for Brain Metastases, 2019

- **SRS:** SOC for oligometastases (<4) and resected brain metastasis (BM)
 - ~90% local control in BM < 2 cm, but high risk of new BMs with SRS alone
 - + WBXRT: ↑control in CNS, but ↑neurocognitive dysfn, ↓QOL, no impact on OS
- **WBXRT:** still reasonable for diffuse brain metastases
 - Reduce neurotoxicity with memantine, hippocampal sparing
- **Key Question: Role/timing with increasingly effective systemic therapies**
 - No strong evidence yet support systemic therapy + WBRT
 - WBRT + systemic therapy trials difficult
 - Concerns regarding toxicity
 - Change in practice patterns (often used near end of disease course)
 - Systemic therapy +/- SRS: **What is the best primary endpoint?**
 - OS, response rates, neurologic death, brain control, etc?
- *Overall: importance of neurocognitive function in addition to ORR, PFS, OS*

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Systemic Therapy for Breast Cancer Brain Metastases



Nancy U. Lin, MD

Associate Chief, Division of Breast Oncology, Dana-Farber Cancer Institute

Associate Professor of Medicine, Harvard Medical School

FDA Brain Metastasis Workshop: Pre-Meeting Webinar

February 14, 2019

Brain Metastasis in Breast Cancer

- Brain metastasis (BM): frequent among patients with advanced breast cancer
 - Risk higher for TNBC and HER2+
 - Relatively uncommon as 1st site of metastasis, but high incidence over time (i.e. ~50% met HER2+; 25-46% with met TNBC)
- There are currently **no systemic therapies with an FDA-approved indication for treatment** of breast cancer brain metastases
- There are currently **no proven prevention** strategies to reduce the risk of CNS involvement in breast cancer
- Historically pts with active BMs largely excluded from clinical trials
 - Review of 1,474 trials through 6/2016: only 39 (2.6%) specifically designed to evaluate efficacy in pts with BMs, only 16 (1%) for breast cancer only
 - Among 165 early phase study for HER2+ MBC, 48.5% excluded any h/o CNS mets

Breast Cancer Brain Metastasis: Systemic Tx

Subtype	Commercially Available	Selected Ongoing Trials (not complete listing)
HER2+	Lapatinib-capecitabine, T-DM1, Neratinib-capecitabine, Anthracyclines (i.e. Trastuzumab-Doxil), Platinums (i.e. Trastuzumab-carboplatin)	Trastuzumab/capecitabine +/- tucatinib; T-DM1/TMZ s/p SRS; Neratinib + T-DM1; Trastuzumab + Pertuzumab + Atezolizumab; Trastuzumab + GDC0084; Tucatinib + Palbociclib + AI; Tucatinib + Abemaciclib + Trastuzumab + AI
TNBC	Anthracyclines, Platinums, Capecitabine, Irinotecan	NKTR-102 (stable/treated BMs); Atezolizumab + SRS; Pembrolizumab; Ipilimumab + Nivolumab; Platinum + Veliparib
ER/PR+	Aromatase inhibitors, Tamoxifen, Abemaciclib (CDK4/6i), Chemotherapy	NKTR-102 (stable/treated BMs), Palbociclib)

Other Targets to Interest: Topo I, PARP, VEGFR, PI3K, Immunotherapy

Breast Cancer: Summary & Future Directions

- HER2+: Multiple active regimens (ORR 20-50%), but median PFS ~6 months
 - Some more durable responses with current regimens- how to understand/predict/mine
 - Continued need/priority for effective strategies to prevent BM development
- Chemotherapy: some effective regimens
 - Still has a role, need for improvement
- Multiple new targets of interest: CDK4/6, PARP, VEGF, PI3K, IO- **Combinations**
- Future Directions/Questions/Opportunities
 - Better preclinical models to understand biology, differential efficacy, prioritize strategies
 - Why does efficacy against established BMs NOT equate to prevention efficacy
 - How to increase inclusion of pts with active brain mets into all phases of clinical testing
 - Sequencing with XRT

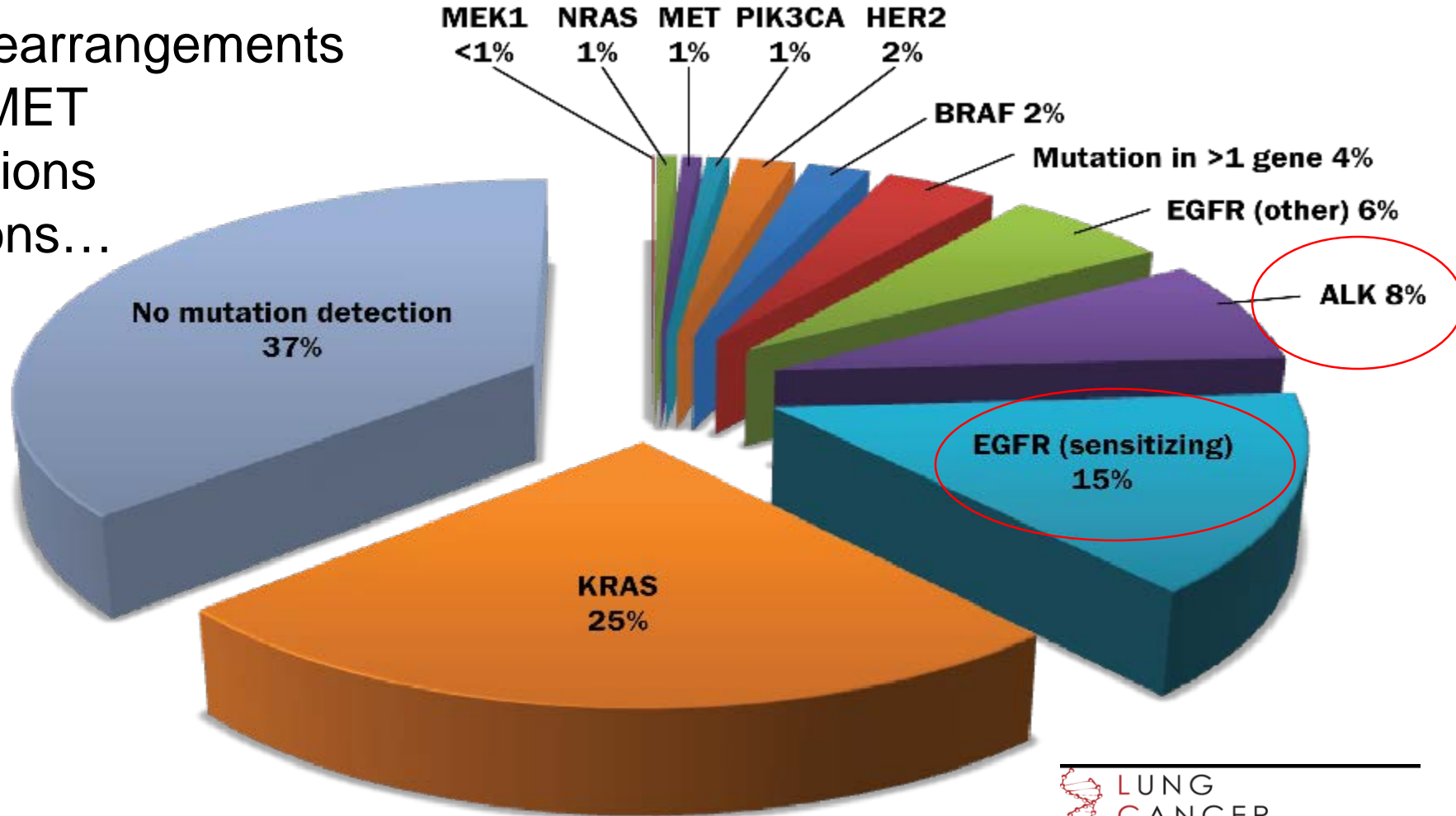
Non-small cell lung cancer and brain metastases: a 'State of the Tumor Address'



D. Ross Camidge, MD PhD
Joyce Zeff Chair in Lung Cancer Research
Director of Thoracic Oncology
University of Colorado Cancer Center

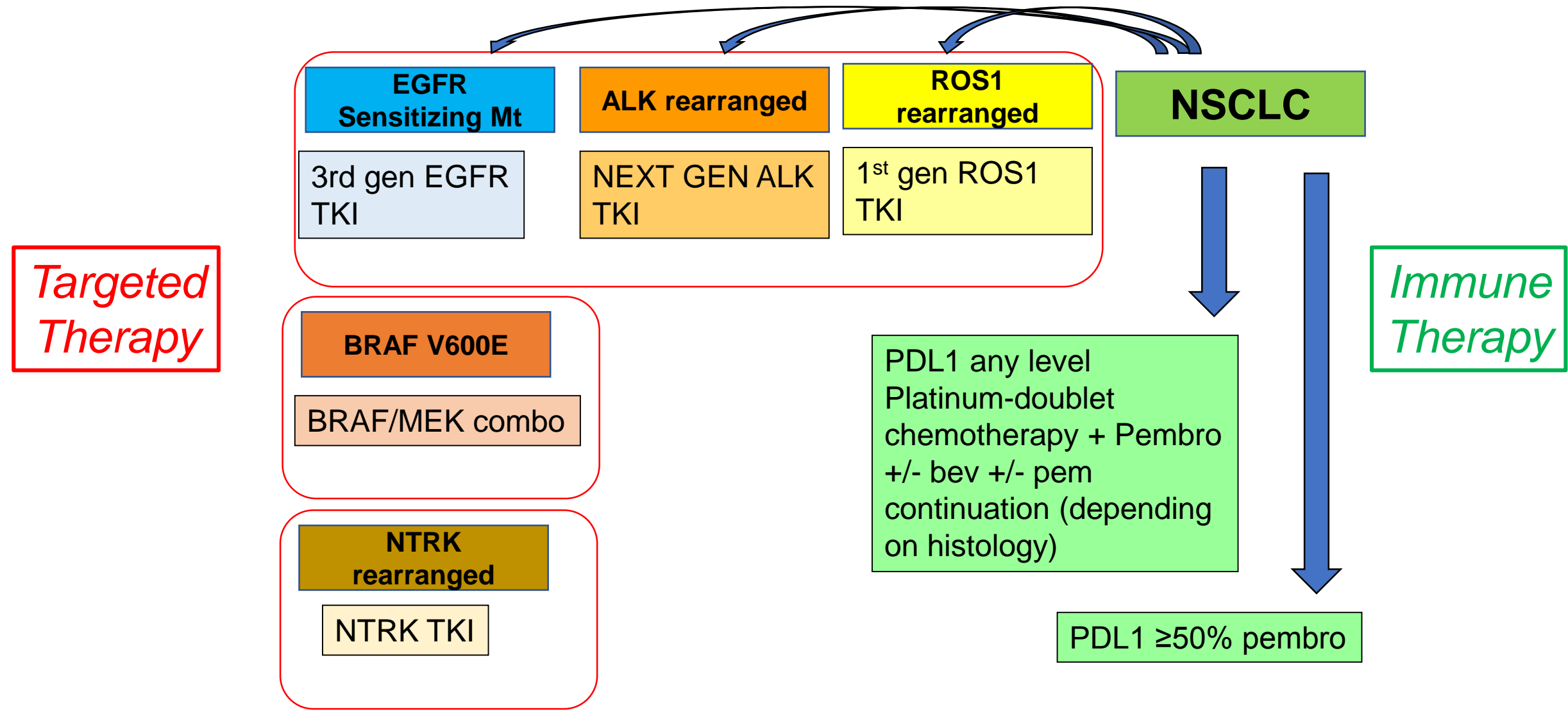
Lung Cancer (adenocarcinoma) The Growing List of 'Genetic' Targets

+ NTRK rearrangements
Exon 14 MET
NRG1 fusions
MET fusions...



97% mutually exclusive

Standard management 1st line stage IV NSCLC. USA



Beyond entry criteria: Appropriately capturing data on the CNS: RANO-BM group

Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group



Nancy U Lin, Eudocia Q Lee, Hidefumi Aoyama, Igor J Barani, Brigitta G Baumert, Paul D Brown, D Ross Camidge, Susan M Chang, Janet Dancey, Laurie E Gaspar, Gordon J Harris, F Stephen Hodi, Steven N Kalkanis, Kathleen R Lamborn, Mark E Linskey, David R Macdonald, Kim Margolin, Minesh P Mehta, David Schiff, Riccardo Soffiatti, John H Suh, Martin J van den Bent, Michael A Vogelbaum, Jeffrey S Wefel, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

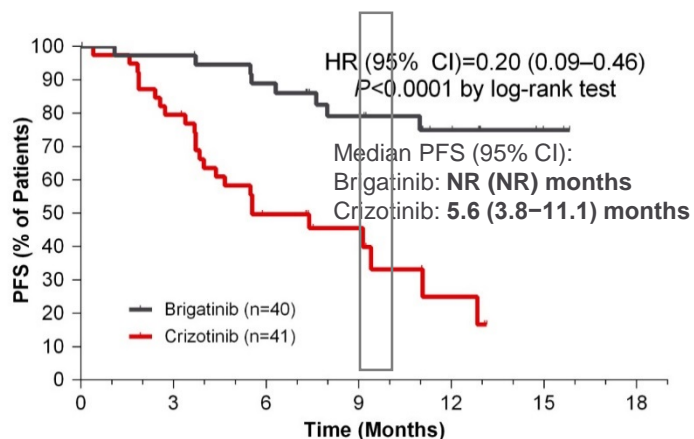
- 'Rookie' mistakes include:

- Not separating treated vs untreated, WBRT vs SRS
- Biasing CNS as 'non-target lesions' and impact on non-CR/non-PD rate
- Presenting overall ORR or PFS by presence/absence of CNS disease without defining if CNS lesions being assessed
- Impact of variation in frequency and modality of CNS surveillance on duration outcomes in those with and without known or proven CNS disease at baseline

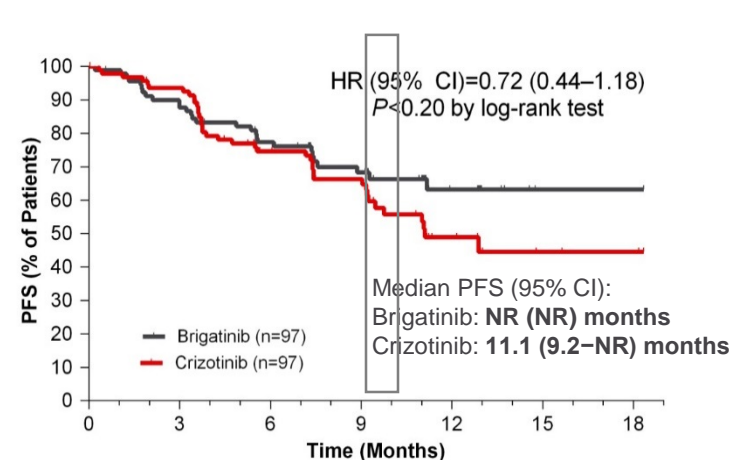
Popat et al, ESMO 2018. Median duration of follow up only 9-11 months in ALTA-1L to date.
Extra-cranial PFS differences yet to fully realise

Whole Body BIRC-assessed PFS

Patients With Brain Metastases at Baseline



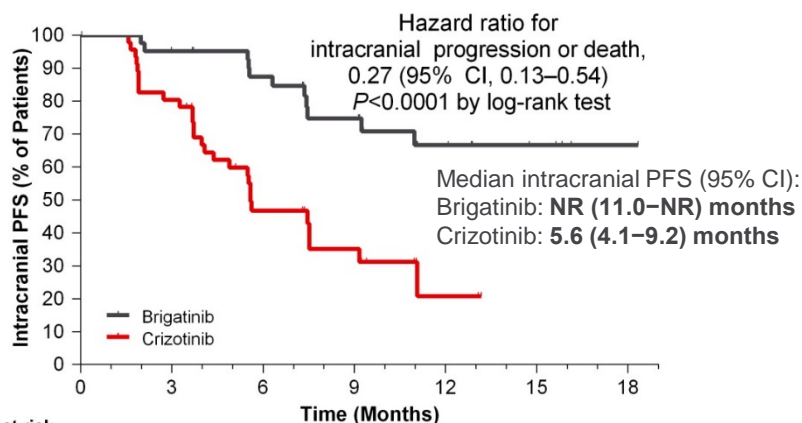
Patients Without Brain Metastases at Baseline



Median follow-up at initial presentation of data

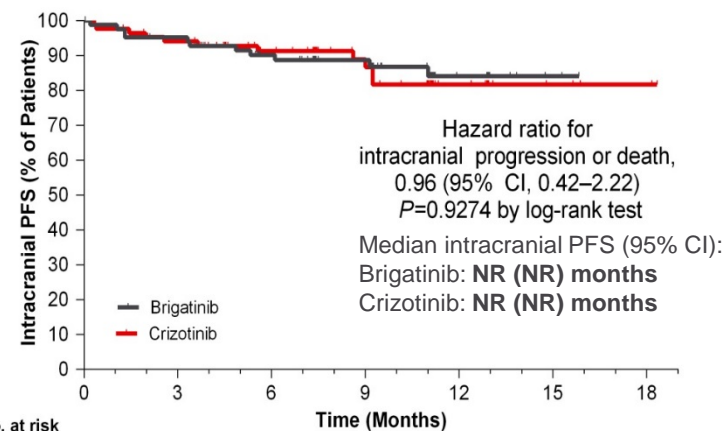
Intracranial PFS

Patients With Any Brain Metastases at Baseline



No. at risk	0	3	6	9	12	15	18
Brigatinib	43	39	32	22	9	5	1
Crizotinib	47	37	16	9	2	0	0

Patients Without Brain Metastases at Baseline



No. at risk	0	3	6	9	12	15	18
Brigatinib	94	78	62	45	18	2	0
Crizotinib	91	75	55	39	15	4	2

Lorlatinib FDA licensed: Nov 2018

Table 5 Efficacy Results in Study B7461001

Efficacy Parameter	Overall N=215
Overall response rate* (95% CI)†	48% (42, 55)
Complete response	4%
Partial response	44%
Duration of response	
Median, months‡ (95% CI)	12.5 (8.4, 23.7)



Table 6 Intracranial Response Rate in Patients with Measurable Intracranial Lesions in Study B7461001

Efficacy Parameter	Intracranial N=89
Intracranial response rate* (95% CI)†	60% (49, 70)
Complete response	21%
Partial response	38%
Duration of response	
Median, months‡ (95% CI)	19.5 (12.4, NR)



Prior crizotinib only (EXP2)	Prior crizotinib + CT (EXP3A)	Prior non- crizotinib ALK TKI ± CT (EXP3B)	2 prior ALK TKIs ± CT (EXP4)	3 prior ALK TKIs ± CT (EXP5)

Summary (Paraphrased)

- CNS metastases are common in NSCLC
 - They may differ in frequency by driver mutation
- Recent guidelines have clarified ‘appropriate’ CNS exclusion/inclusion to protect CNS if drug liability present (Scenario A in 2018 RANO guidelines)
- Capturing robust CNS efficacy data increasingly important as CNS active drugs emerge in NSCLC (cf RANO guidelines)
 - CNS differences in progression may read out sooner than extra-CNS PFS Some drugs SO CNS penetrant CNS efficacy in later lines can exceed extra-CNS efficacy – need for full 2 compartment efficacy readouts
 - High CNS activity prompts Drug vs (Radiation followed by drug) trial designs

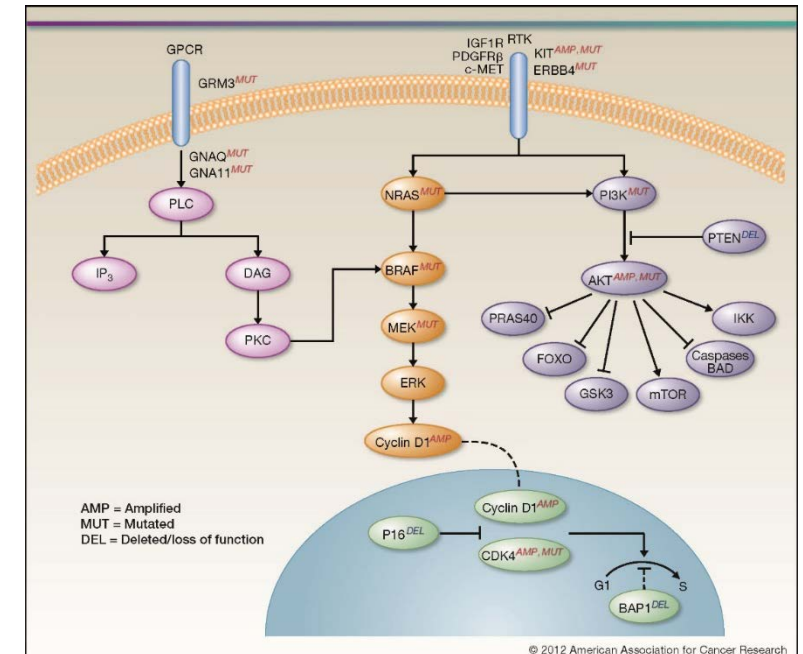
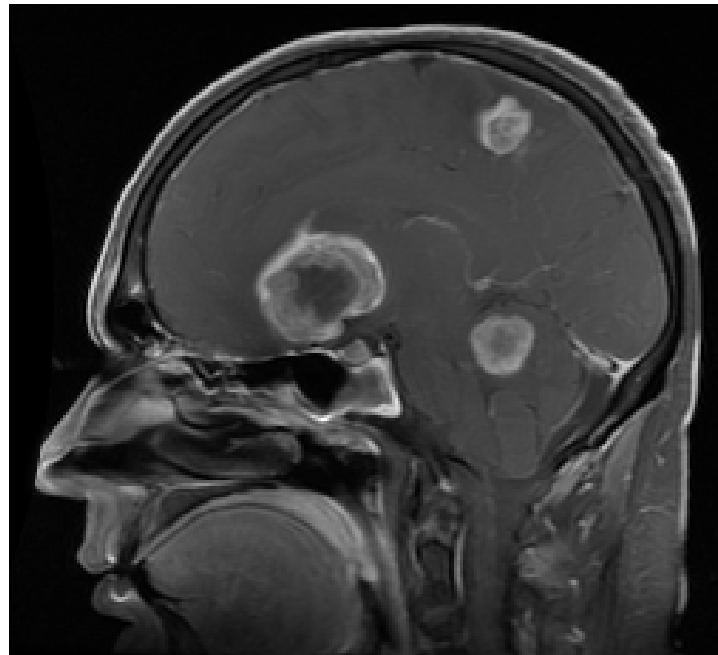
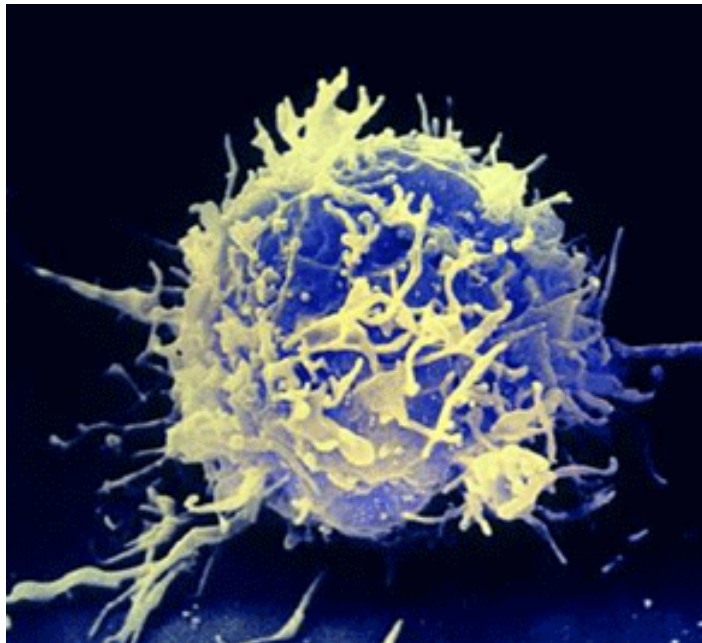
CNS Metastases from Melanoma: The Role of Systemic Therapy

Michael A. Davies, M.D., Ph.D.

Associate Professor, Deputy Chairman, Melanoma Medical Oncology
The University of Texas MD Anderson Cancer Center

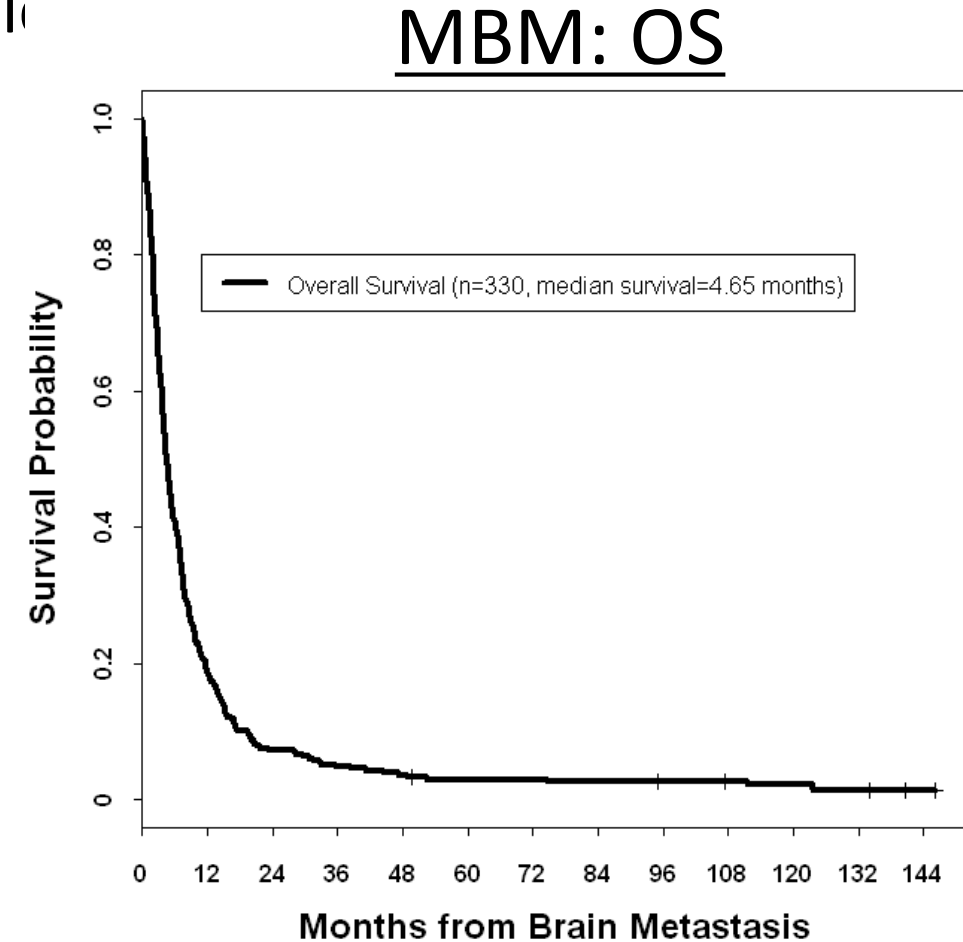


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Melanoma Brain Metastases (MBMs)

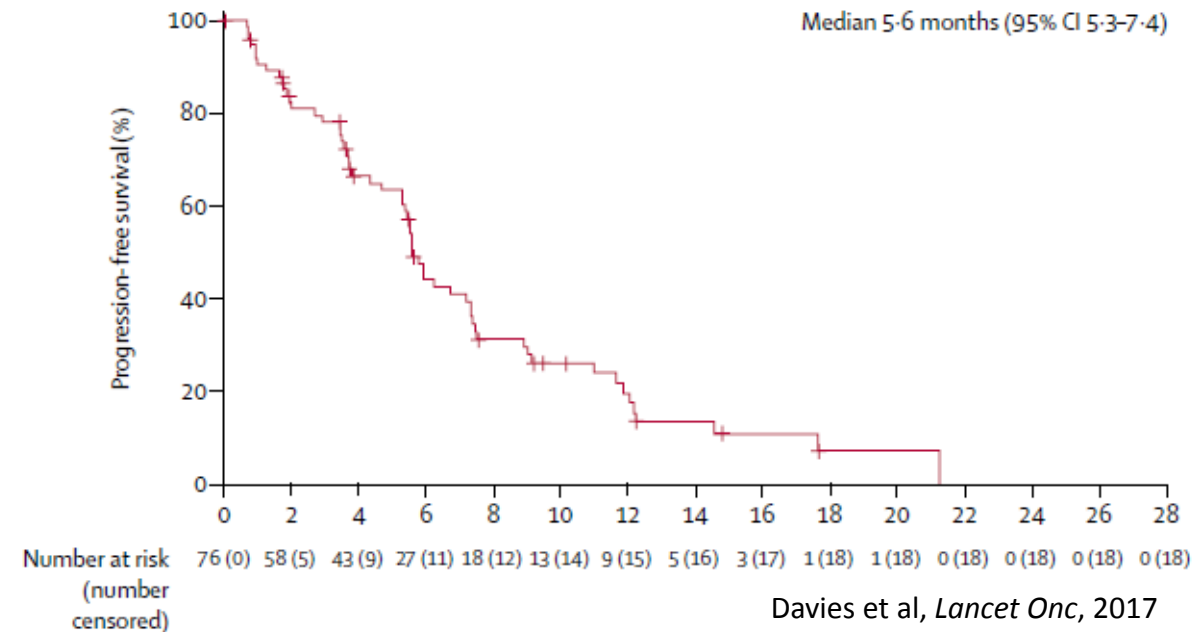
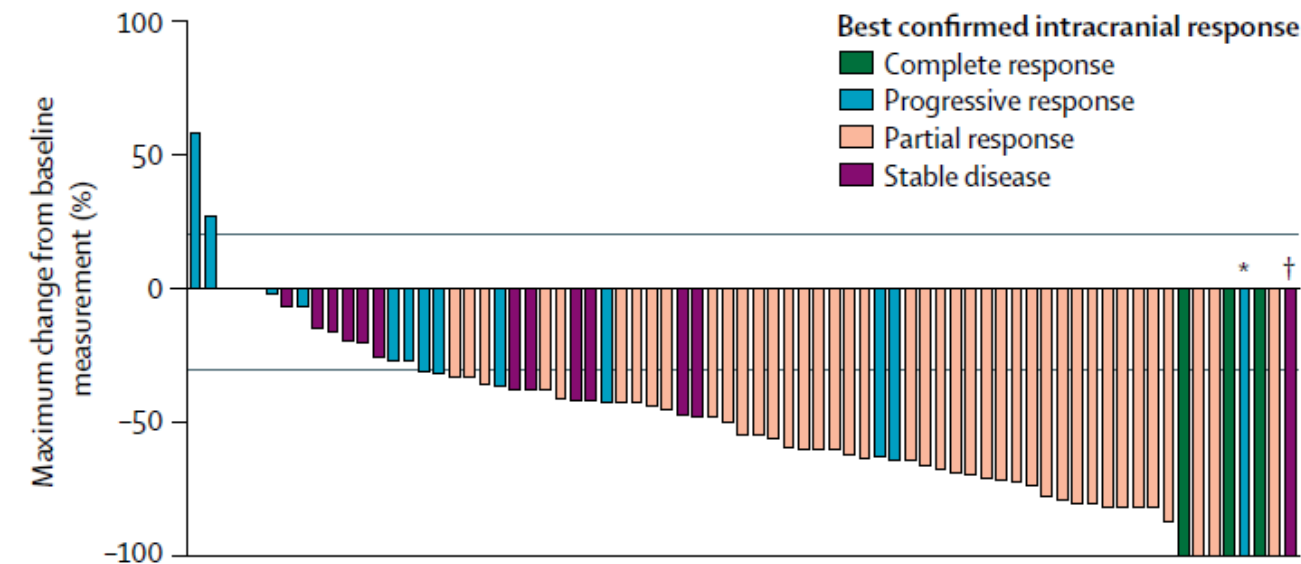
- Among highest risk of brain metastases among solid tumors
 - 10-20% at diagnosis of stage IV
 - Up to 50% over course of disease
 - Up to 70% in autopsy studies
 - Common initial site of treatment failure, especially for chemotherapy, biochemotherapy, and targeted therapy
- Historically median OS ~ 4 months
- BBB-penetrating chemotherapies achieve intracranial responses in $\leq 10\%$
- 11 Targeted & Immune therapies approved for stage IV melanoma 2011-2018
 - Pts with CNS disease excluded from all registration studies
 - \rightarrow Post-registration Phase II studies show safety/efficacy



BRAF^{V600} Targeted Therapy: BRAFi + MEKi

- COMBI-MB: 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%
 - **BUT** 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



Brain Metastases: Ipilimumab + Nivolumab

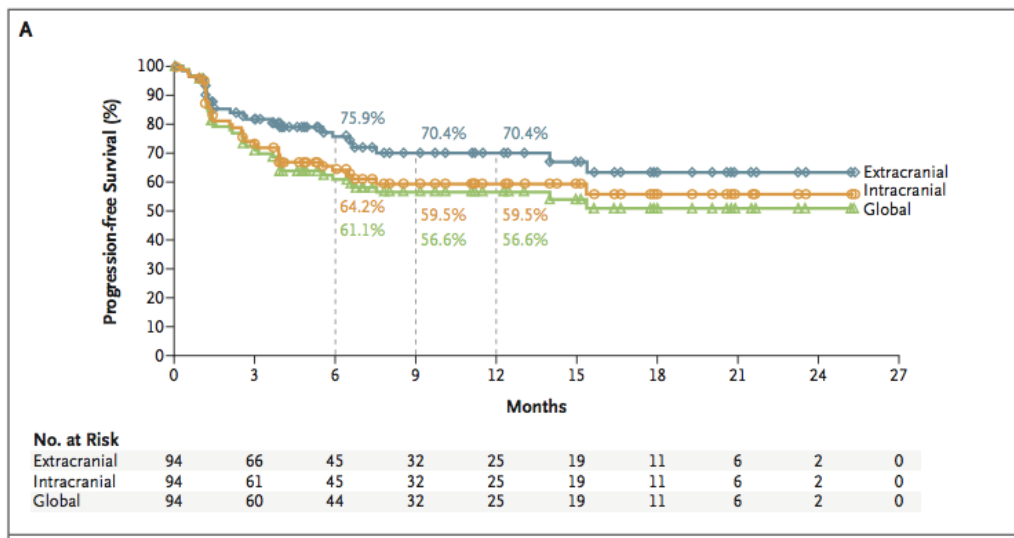
- Ipilimumab (ICr ORR 18% Cohort A, 5% Cohort B), Pembrolizumab (ICr ORR 22%)
Margolin et al, *Lancet Onc* 2012; Goldberg et al, *Lancet Onc* 2016

• 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

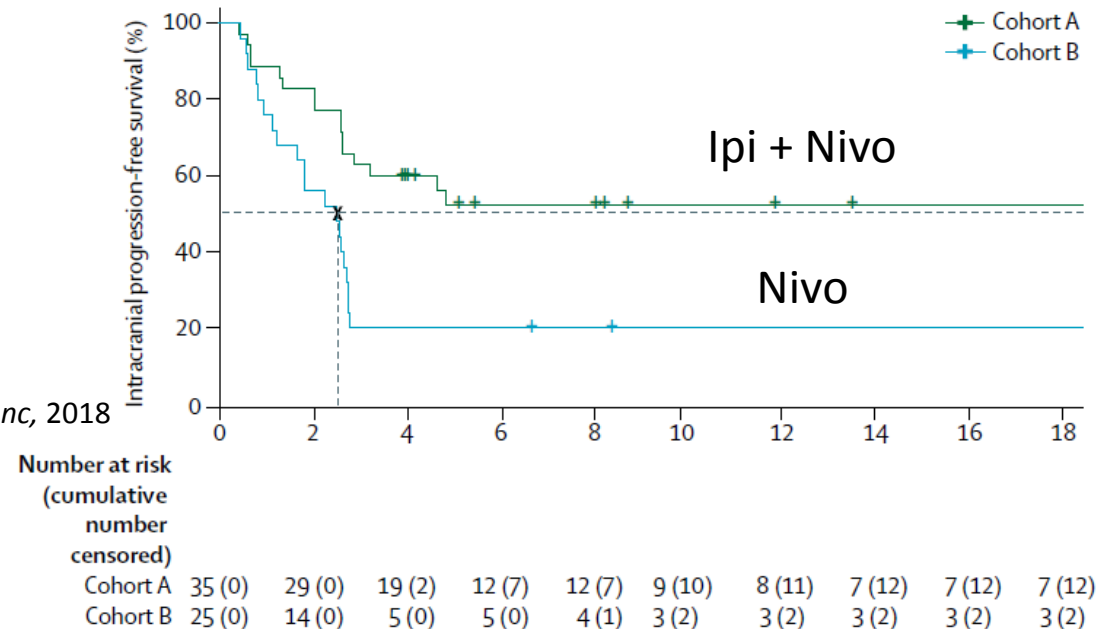
• ABC Trial: Nivo vs Ipi + Nivo (Ipi 3 + Nivo 1)

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



Tawbi et al, *NEJM*, 2018

Long et al, *Lancet Onc*, 2018



Systemic Therapy for Melanoma Brain Metastases: Current Status

- Immune Therapy: Ipilimumab + Nivolumab > Single-Agent PD-1
 - Strengths: ICRR ~50%, most responses to date have been durable, OS
 - Weaknesses: No data (yet) in pts on steroids; 35-40% PD best response; toxicity
- Targeted Therapy: BRAFi + MEKi- Dabrafenib and trametinib
 - Strengths: Rapid responses, initial disease control, including in pts on steroids
 - Weakness: Most responses are ≤ 6 months; CNS resistance mechanisms unknown
 - *No data yet for Vemurafenib + Cobimetinib, or Encorafenib + Binimetinib (dosing)*
- Current Investigations: **Combinatorial Approaches**
 - IMT + IMT; IMT + TTx; IMT +/-Sequencing SRS
 - Inclusion/Exclusion: Steroids, Prior Radiation, Prior Systemic Therapies
 - Endpoints: Response Rates, PFS, Clinical Benefit Rate, Safety (i.e., radiation necrosis)



UniversitätsSpital
Zürich

Leptomeningeal metastasis

Emilie Le Rhun

FDA Brain Metastasis Workshop:
Pre-Meeting Webinar

February 15, 2019



LMD: Incidence & Outcomes

- Affects up to 10% of patients with solid tumors
- LMD occurs:
 - In the context of progressive systemic disease in approximately 70% of solid cancer patients
 - In around 20% at the time of first progression after initial treatment
 - Present in up to 10% at the time of diagnosis
- Most patients with LMD also BM

The median survival is limited to 2-3 months, with a 1-year survival rate < 10%

- *Most previous studies of IT therapy evaluated agents without a significant role as single agent systemic therapy → Evaluation of active systemic agents administered intrathecally*

	Median overall survival
Breast cancer	3.5-4.4 months
Lung cancer	3-6 months
Melanoma	1.7-2.5 months

Yust Katz 2013, Le Rhun 2013, Abouharb 2014, Morkawa 2017, Niwinska 2018, Harstad 2008, Papadopoulos 2002, Geukes Foppen 2016, Grossman 1999, Hammerer 2005, Morris 2011, Park 2011, Gwak 2013, Lee 2013, Kuiper 2015

- No standards for:
 - Neurological examination
 - Neuro-imaging assessment
 - CSF cytological diagnosis
- No trial on systemic treatment
- No trial on radiotherapy
- Only 6 trials on IT therapy

Adapted from presentation by Emilie Le Rhun, MD

LMD: Clinical Trial Challenges & Considerations

ACCEPTED MANUSCRIPT

The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: lack of feasibility and clinical utility, and a revised proposal

Emilie Le Rhun, Patrick Devos, Thomas Boulanger, Marion Smits, Dieta Brandsma, Roberta Rudà, Julia Furtner, Johann-Martin Hempel, Tjeerd J Postma, Patrick Roth, Tom J Snijders, Frank Winkler, Sebastian Winklerhofer, Antonella Castellano, Elke Hattingen, Jaume Capellades, Thierry Gorlia, Martin van den Bent, Patrick Y Wen, Martin Bendzus, Michael Weller ✉,

European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group (BTG) Central Nervous System (CNS) Metastases Committee and the EORTC BTG Imaging Committee

Neuro-Oncology, noz024, <https://doi.org/10.1093/neuonc/noz024>

- Evolving systems & tools to evaluate response
 - Overall survival = historical standard
 - RANO-LM response criteria (2016)
 - Liquid biopsies (i.e. CSF ctDNA)
- Key Challenges
 - Defining LMD/Enrollment criteria
 - Impact of cancer type, concomitant tx, PS
 - Endpoints: OS vs LMD-specific, QOL, neurocognitive, safety, target inhibition
 - What is the control/SOC
- **Unmet need for disease-specific LMD trials**
 - Validated response criteria, adapted endpoints, evaluation of QOL & cognition

Summary

Therapeutic Landscape of CNS Metastasis, 2019

- Consistent under-representation or delay for patients with CNS disease in clinical trials/early therapeutic development
 - *Patients with LMD generally excluded from trials for brain metastases*
- Clear proof-of-concept for efficacy of systemic therapies
 - *Potential to identify effective regimens earlier, enhanced CNS activity*
 - *? Opportunities based on CNS-specific targets; ? Alternative dosing*
 - *Overall: high ORR, prolonged OS being seen in multiple tumor types*
- Key questions/challenges around trial design
 - *Defining patient characteristics; Inclusion/Exclusion criteria; Endpoints*
- Moving from single agents/modalities → Combinations (esp. SRS)



Thank you for your attention!

Michael Davies, M.D., Ph.D.
mdavies@mdanderson.org

Departments of Melanoma Medical Oncology, Translational Molecular Pathology and
Systems Biology
University of Texas M. D. Anderson Cancer Center

Research Support From:

*NIH/NCI and DoD
Cancer Prevention Research Institute of Texas (CPRIT)
Melanoma Research Alliance
Melanoma Research Foundation
Aim at Melanoma Foundation
Dr. Miriam and Sheldon Adelson Research Foundation*

*GlaxoSmithKline
AstraZeneca
Genentech
Merck
Myriad
Sanofi-Aventis
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