SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9–13, 2016

Society for Immunotherapy of Cancer

SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9–13, 2016

Incidence and Outcomes of Central Nervous System Metastasis in Metastatic Melanoma Patients Treated with Anti-PD1 Therapy

Gustavo Schvartsman, MD

Division of Cancer Medicine

The University of Texas MD Anderson Cancer Center

sitc

Society for Immunotherapy of Cancer

#SITC2016

Presenter Disclosure Information

Gustavo Schvartsman, MD

No Relationships to Disclose

Melanoma Brain Metastases (MBM) Background

- Highest propensity for brain metastases among solid tumors
- Third in incidence after lung and breast cancer
- Up to 40% of metastatic patients at the time of presentation
- Up to 75% at the time of death
- Treatment: Surgery, radiation or systemic therapy
- Systematically excluded from clinical trials - stability for 4-12 weeks

Gorantla, Kirkwood, Tawbi- Current Oncology Reports- 2013 Oct;15(5):483-91.

Trials Excluding MBM vs MBM-Specific

Ipi+gp100	676
Ipi + DTIC	502
BRIM-3	645
BREAK-3	250
COMBI-v	704
COMBI-d	423
coBRIM	495
KEYNOTE-002	540
KEYNOTE-006	834
CheckMate-037	631
CheckMate-067	945
TOTAL	**6,134**

Ipi- CWG	72
BREAK-MB	172
NIBIT-M1	20
Pembro	18
TOTAL **283**	

MBM <5% pts enrolled on clinical trials

Cohen et al. Pigment Cell Melanoma Res, 2016

BREAK-MB: Cohort A BRAF^{V600E} maximal intracranial target lesion reduction

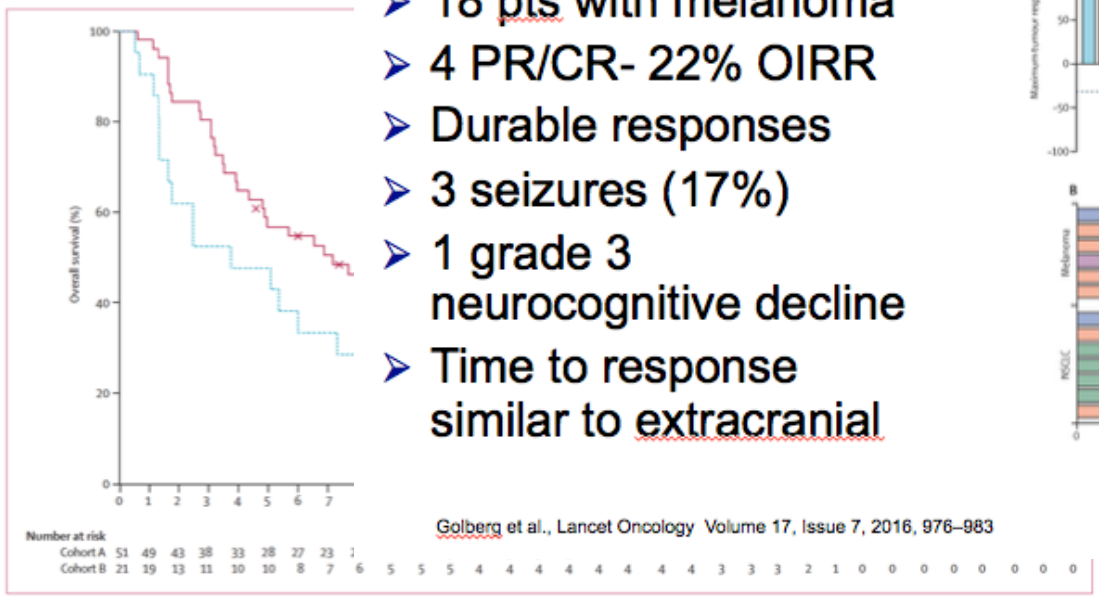
Vemurafenib in Metastatic Melanoma Patients With Brain Metastases: Case 2, Multicenter Study

Single agent Pembrolizumab in MBM

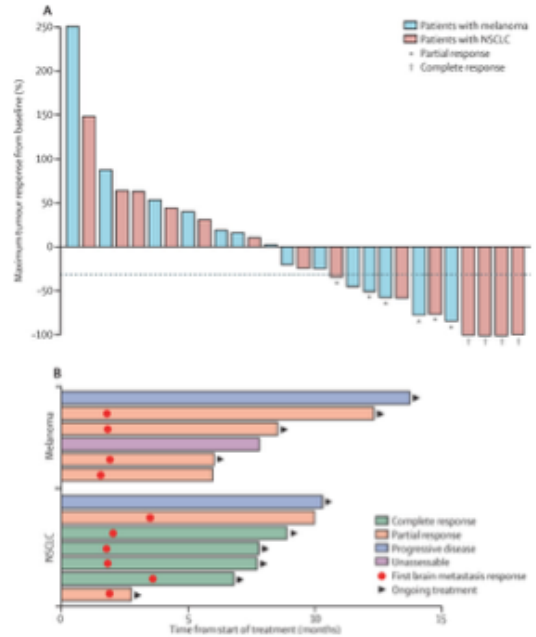
100

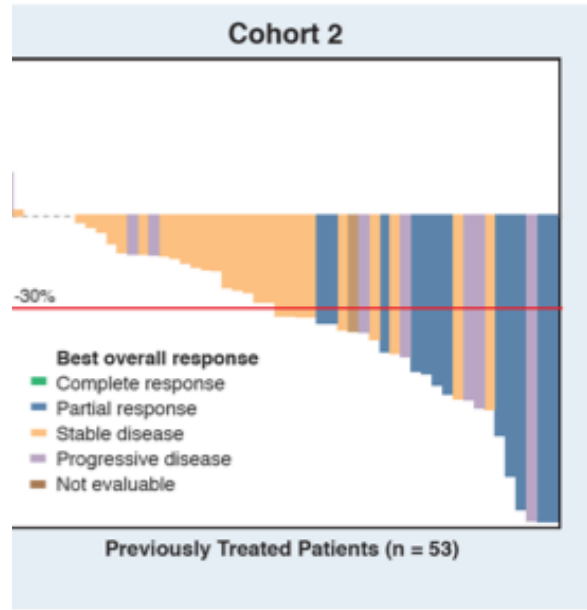
Ipilimu

- Both lung and melanoma
- 18 pts with melanoma
- 4 PR/CR- 22% OIRR
- Durable responses
- 3 seizures (17%)
- 1 grade 3 neurocognitive decline
- Time to response similar to extracranial



Golberg et al., Lancet Oncology Volume 17, Issue 7, 2016, 976–983





Margolin, et al. Lancet Oncology 2011

esented at SMR; November 17-20, 2013; Philadelphia, Pennsylvania, USA

Objectives

- Determine the incidence of new MBM in patients being treated with PD1 inhibitors
- Determine the impact of MBM on survival outcomes in the modern era
- Identify risk factors for development of MBM and death

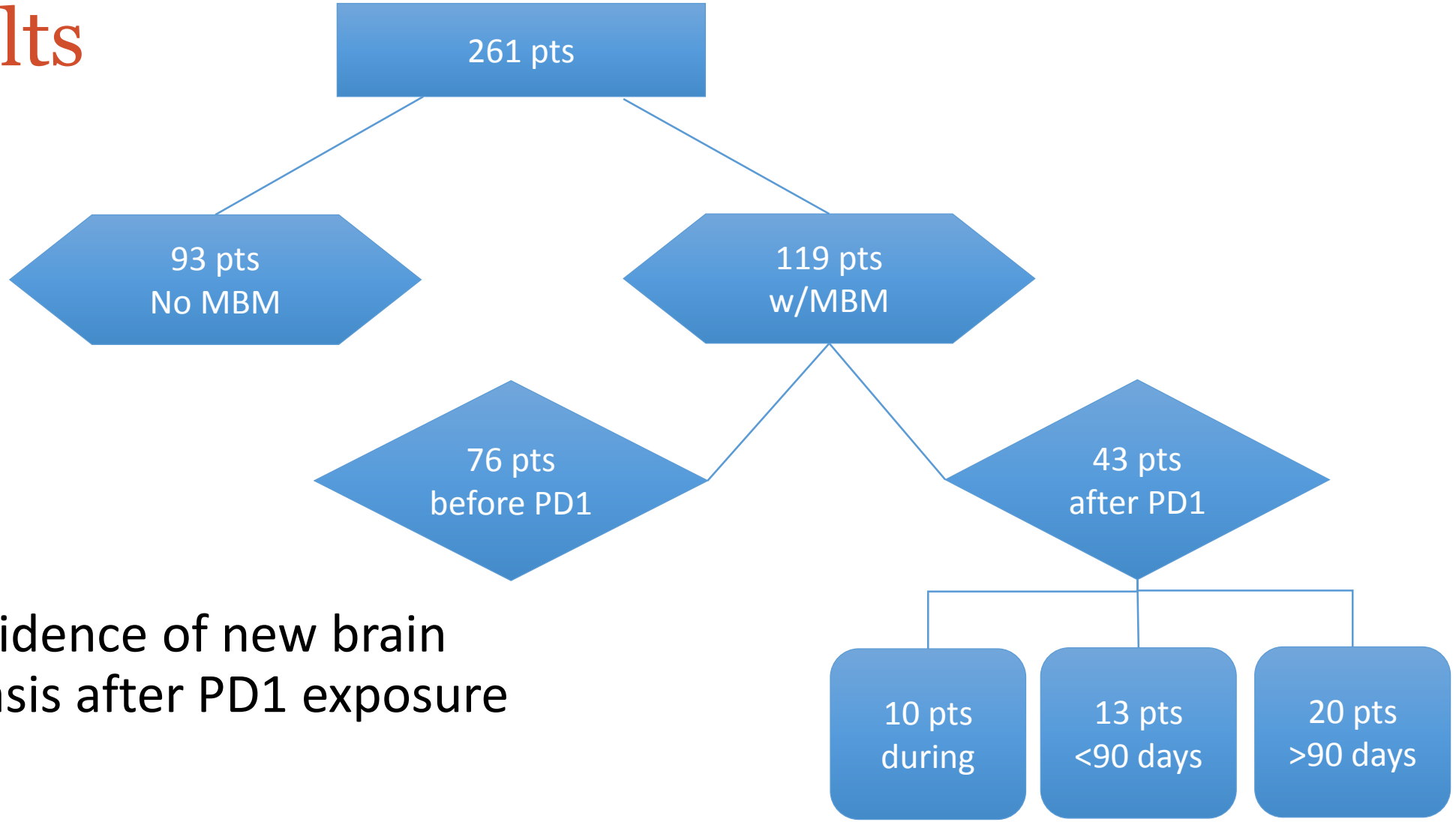
Methods

- MDACC pharmacy queried for metastatic melanoma patients that received anti-PD1 single-agent therapy from Jan/12 to Feb/16
- Patients classified into three groups:
  - No MBM
  - MBM diagnosed prior to initiation of PD1 therapy (BEFORE PD1)
  - MBM diagnosed after initiation of PD1 therapy (AFTER PD1)

Statistical Analysis

- **Logistic regression** was used to model the association between the development of brain metastases and factors of interest.
- The method of **Kaplan and Meier** was used to estimate the distributions of survival times. The **log-rank test** was used to com- pare groups, and **Cox proportional hazards regression** was used to model the association between OS and factors of interest.

Results



- 23% incidence of new brain metastasis after PD1 exposure

Results - Baseline Patient Characteristics

Variable	Levels	No MBM (n)	Before PD1 (n)	After PD1 (n)
Age	**Median (IQR)**	66 (54 – 86)	57 (50 – 66)	62 (54 – 66)
Gender	**Female**	41 (29%)	28 (37%)	15 (40%)
Race	**White**	136 (96%)	73 (96%)	39 (91%)
Pathology	**Cutaneous, non acral**	76 (65%)	21 (89%)	27 (72%)
	Cutaneous, acral	3 (3%)	1 (2%)	1 (3%)
	Mucosal	11 (9%)	3 (5%)	4 (11%)
	Uveal	12 (10%)	1 (2%)	1 (3%)
	No information	15 (13%)	1 (2%)	4 (11%)
Ulceration	**Present**	32 (43%)	16 (43%)	11 (44%)
Location	**H&N**	42 (36%)	13 (23%)	9 (24%)
LDH	**Elevated**	39 (27%)	20 (26%)	12 (30%)
BMI	**<18**	0 (0%)	0 (0%)	0 (0%)
	≥ 18, <25	23 (17%)	24 (35%)	8 (20%)
	≥25, <30	52 (39%)	18 (27%)	17 (40%)
	≥30	58 (44%)	26 (38%)	17 (40%)

Results- Baseline Patient Characteristics – Mutation Profile

Mutated Gene	No MBM (n)	Before PD1 (n)	After PD1 (n)
BRAF	30 (25%)	24 (37%)	12 (30%)
NRAS	23 (19%)	20 (30%)	8 (20%)
KIT	13 (11%)	12 (18%)	7 (18%)
PTEN	1 (1%)	3 (5%)	1 (2%)
TP53	14 (12%)	13 (20%)	2 (5%)

Results- Brain directed therapy for patients with MBM

Variable	Before PD1 (n)	After PD1 (n)	All (n)
SRS	56 (74%)	26 (60%)	82 (69%)
Whole-Brain XRT	31 (41%)	11 (25%)	42 (35%)
Craniotomy	24 (32%)	9 (21%)	33 (28%)
At least 1 modality	68 (90%)	34 (79%)	102 (86%)
2+ modalities	36 (47%)	10 (25%)	46 (39%)

Results

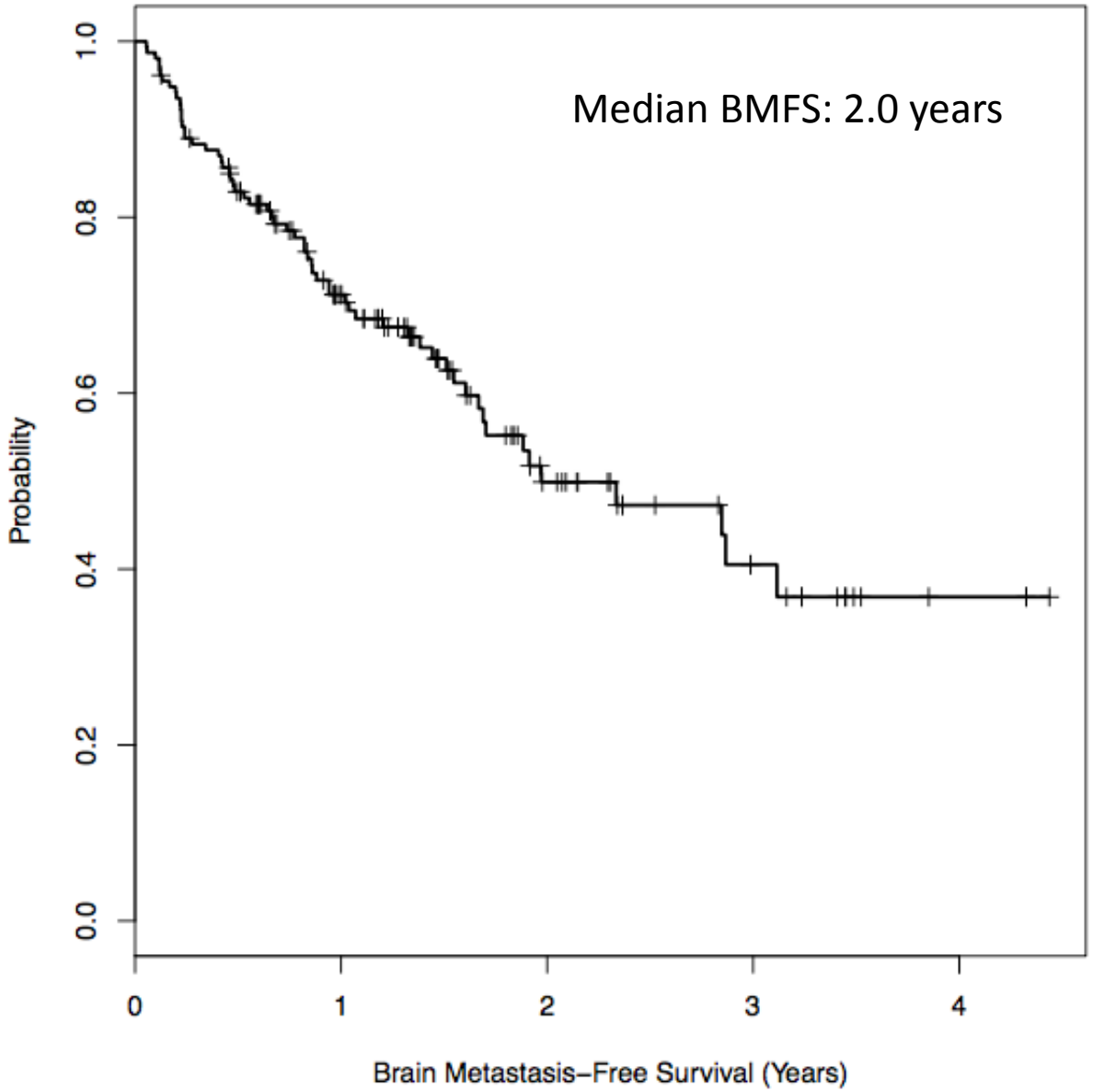


Figure 1. Brain-metastases free survival

Results- Risk factors for the development of MBM

Parameter	Level	Total N	N w/ Brain Mets	OR	Lower CI	Upper CI
Age	Continuous	261	119	**0.970*** **	0.951	0.988
Pathology	Cutaneous, non acral	154	78	**1.539**	0.250	9.742
	Mucosal	18	7	**0.955**	0.126	7.230
	Uveal	14	2	**0.250**	0.024	2.577
Race	White	248	112	**0.824**	0.258	2.624
Ulceration	Present	59	27	**1.012**	0.513	2.000
Location	Non-H&N	145	71	**1.832***	0.995	3.371
LDH	Elevated	71	32	**0.971**	0.562	1.680
BMI	>30	101	43	**0.818**	0.489	1.366
BRAF	Wildtype	158	70	**0.663***	0.372	1.181
NRAS	Wildtype	173	78	**0.674**	0.360	1.263
KIT	Wildtype	181	83	**0.579***	0.270	1.244
PTEN	Wildtype	218	102	**0.220**	0.024	1.999
TP53	Wildtype	194	91	**0.825**	0.378	1.801

Table Univariate Regression for Development of Brain Metastases – Risk Factors. ***P<0.01; *trend, non-significant

Results

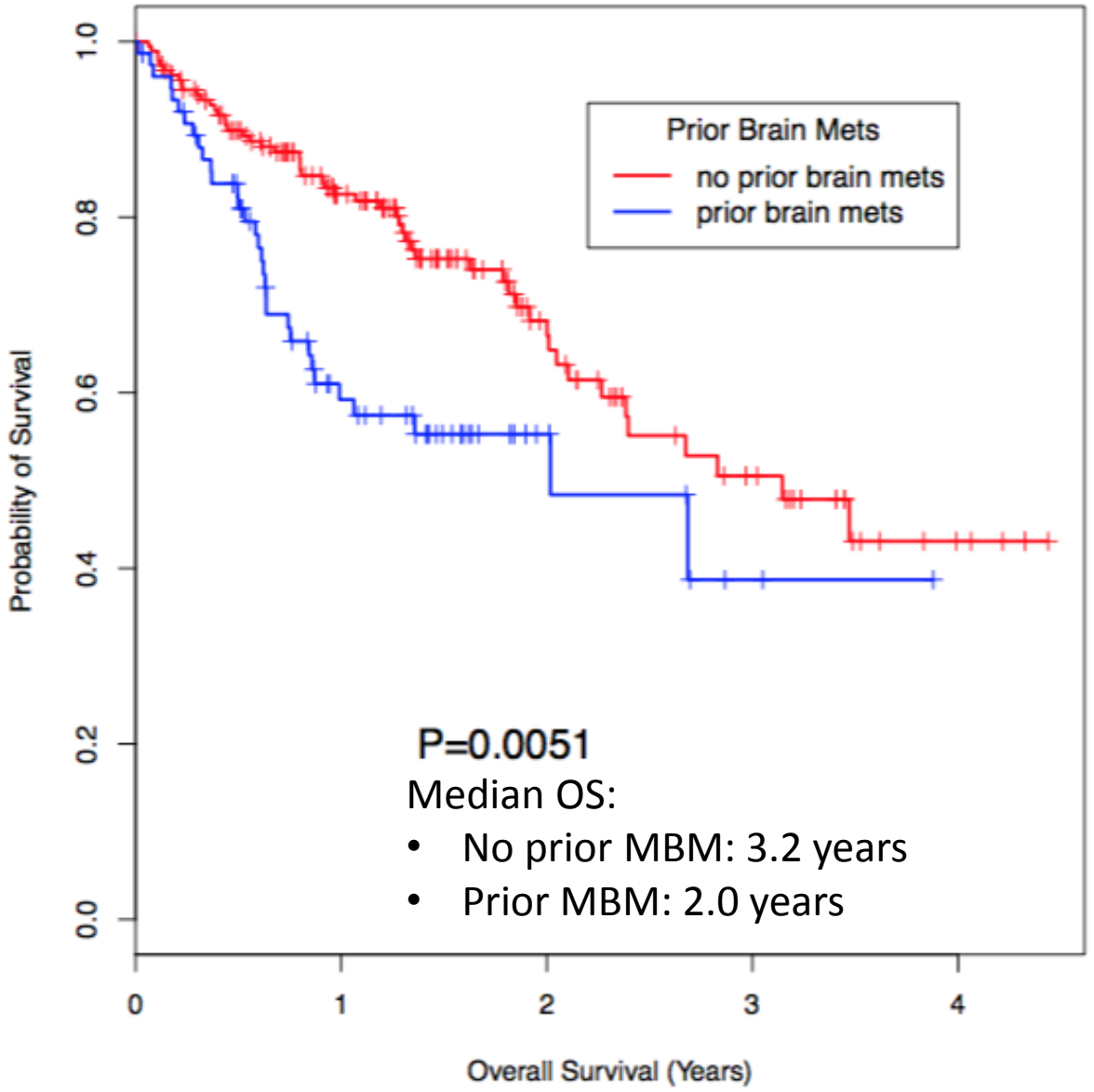


Figure 2. Overall survival from start of PD1 therapy by presence of MBM

Results- Overall survival

Parameter	Level	Total N	N w/ Brain Mets	HR	Lower CI	Upper CI
Age	Continuous	261	85	**1.000**	0.985	1.016
Pathology	Cutaneous, non acral	154	52	**0.576**	0.179	1.853
	Mucosal	18	5	**0.558**	0.133	2.346
	Uveal	14	2	**0.378**	0.063	2.280
Race	White	248	81	**1.545**	0.488	4.897
Ulceration	Present	59	27	**2.047*** **	1.137	3.688
Location	Non-H&N	145	51	**1.250**	0.729	2.142
LDH	Elevated	71	35	**2.676*** **	1.731	4.138
Prior Brain Mets	Present	76	32	**1.865*** **	1.198	2.903
BMI	>30	101	43	**1.665*** **	1.075	2.578
BRAF	Wildtype	158	52	**1.019**	0.619	1.678
NRAS	Wildtype	173	52	**0.688**	0.418	1.134
KIT	Wildtype	181	57	**0.754**	0.374	1.442
PTEN	Wildtype	218	73	**1.900**	0.264	13.677
TP53	Wildtype	194	64	**1.020**	0.524	1.988

Table Univariate Regression for Overall Survival - Risk Factors; ***P<0.05

Conclusions

- 23% incidence of new brain metastasis in patients being treated with PD1 inhibitors
- High risk of death if CNS disease, despite aggressive local therapy
- Systemic therapy approaches are still needed for this poor prognosis population

Future Directions

- Ongoing Clinical Trials
  - CheckMate 204: Ipilimumab + Nivolumab
  - BEAT-MBM: Atezolizumab + Bevacizumab
  - Pembrolizumab + Bevacizumab
  - NIBIT-M2: Fotemustine vs Fotemustine +Ipi vs Ipi+Nivo
  - Pembrolizumab + SRS
  - Ipilimumab + SRS
  - COMBI-MB: Dabrafenib + Trametinib
  - CONVERCE: Vemurafenib + Cobimetinib

www.ClinicalTrials.gov, accessed on 11/6/16

Acknowledgements

Collaborators

- Dr. Isabella Glitza
- Dr. Hussein Tawbi
- Dr. Michael Davies
- Dr. JenniferMcQuade

Melcore Database

- Lauren Haydu

Biostatics Department

- Rolland Bassett

Fellowship Leadership

- Dr. Patrick Hwu
- Dr. Robert Wolff
- Dr. Michael Kroll
- Kary Garnica
- Crystal Franzese
- Camillia Moses
- Catherine Bulter-Gunn

Patients and their families

Thank You!