

# Oncogene addicted brain metastases

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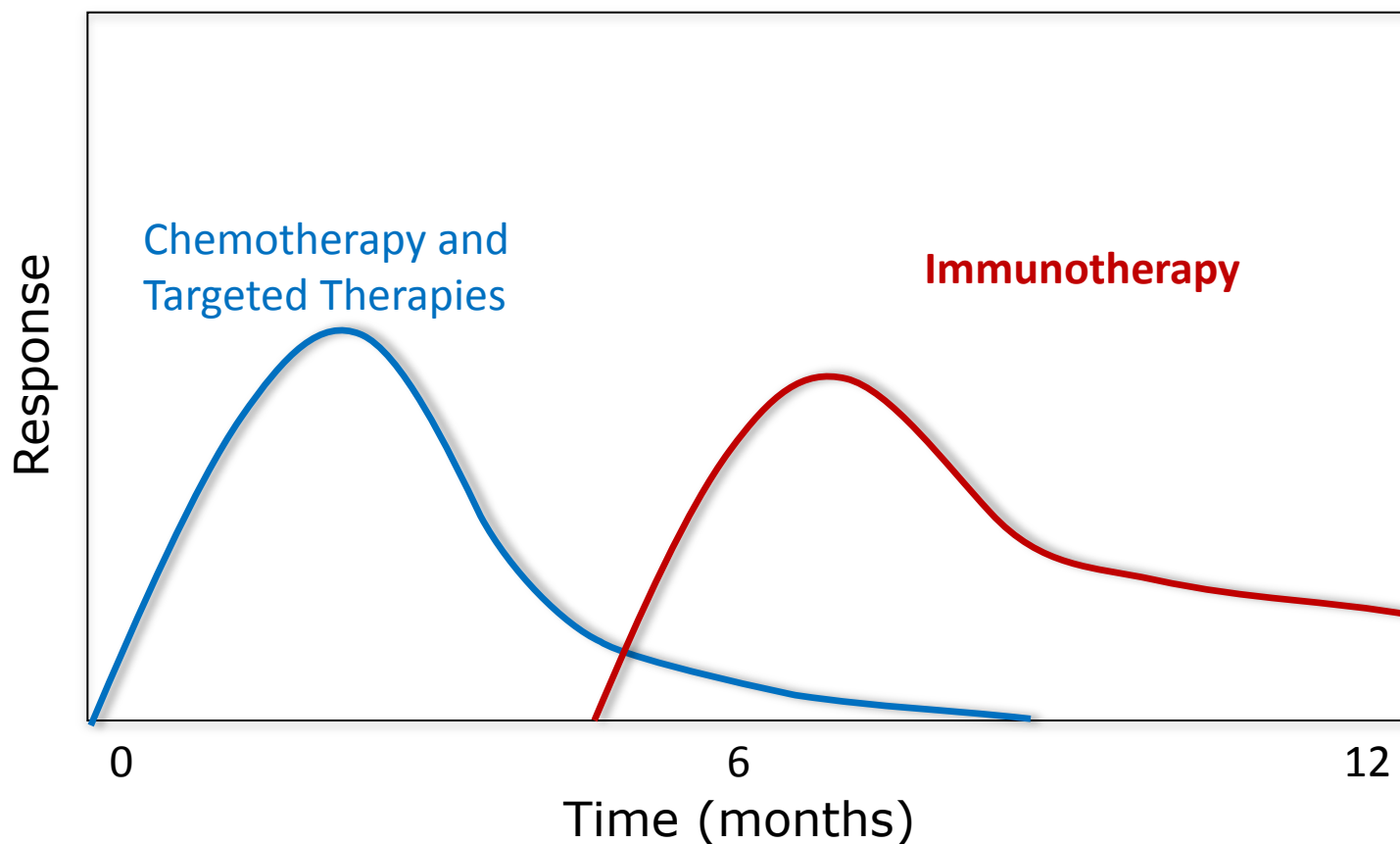
## Disclosure slide

- Compensated educational activities:  
BMS, Roche

# Melanoma Brain Metastases (MBM)

- **Brain metastases develop in ~ 50% of advanced melanoma patients**
- **Life expectancy of patients with MBM is 3–5 months**
- **Limited activity of chemotherapy and radiotherapy on MBM**
- **Generally excluded from clinical trials**
- **Upcoming evidences of activity in MBM anti-CTLA-4 mAb and BRAFi**
- **MBM represent an active focus of clinical research**

# Chemotherapy/Targeted Agents and Immuno-therapy Differ in Action and Outcome



# BRAF inhibitors in MBM

| <b>DABRAFENIB</b><br><i>Long GV, Lancet Oncol 2012</i> | <b>N</b> | <b>DCR</b> | <b>OS (wks)</b> | <b>PFS (wks)</b> |
|--|----------|------------|-----------------|------------------|
| Untreated  |          |            |                 |                  |
| V600E  | 74       | 39%        | 33.1            | 16.1             |
| V600K  | 15       | 7%         | 16.3            | 8.1              |
| Pretreated   |          |            |                 |                  |
| V600E  | 65       | 31%        | 31.4            | 16.6             |
| V600K  | 18       | 22%        | 21.9            | 15.9             |

| <b>VEMURAFENIB</b><br><i>Dummer R, Eur J Cancer 2014</i> | <b>N</b> | <b>DCR</b> | <b>OS (m)</b> | <b>PFS (m)</b> |
|--|----------|------------|---------------|----------------|
| Pretreated   | 24       | 42%        | 5.3           | 3.9            |

| <b>VEMURAFENIB</b><br><i>Kefford RR, SMR 2013</i> | <b>N</b> | <b>DCR</b> | <b>OS (m)</b> | <b>PFS (m)</b> |
|---|----------|------------|---------------|----------------|
| Untreated   | 90       | 61%        | 7.06          | 3.7            |
| Pretreated  | 56       | -          | 9.53          | 3.94           |

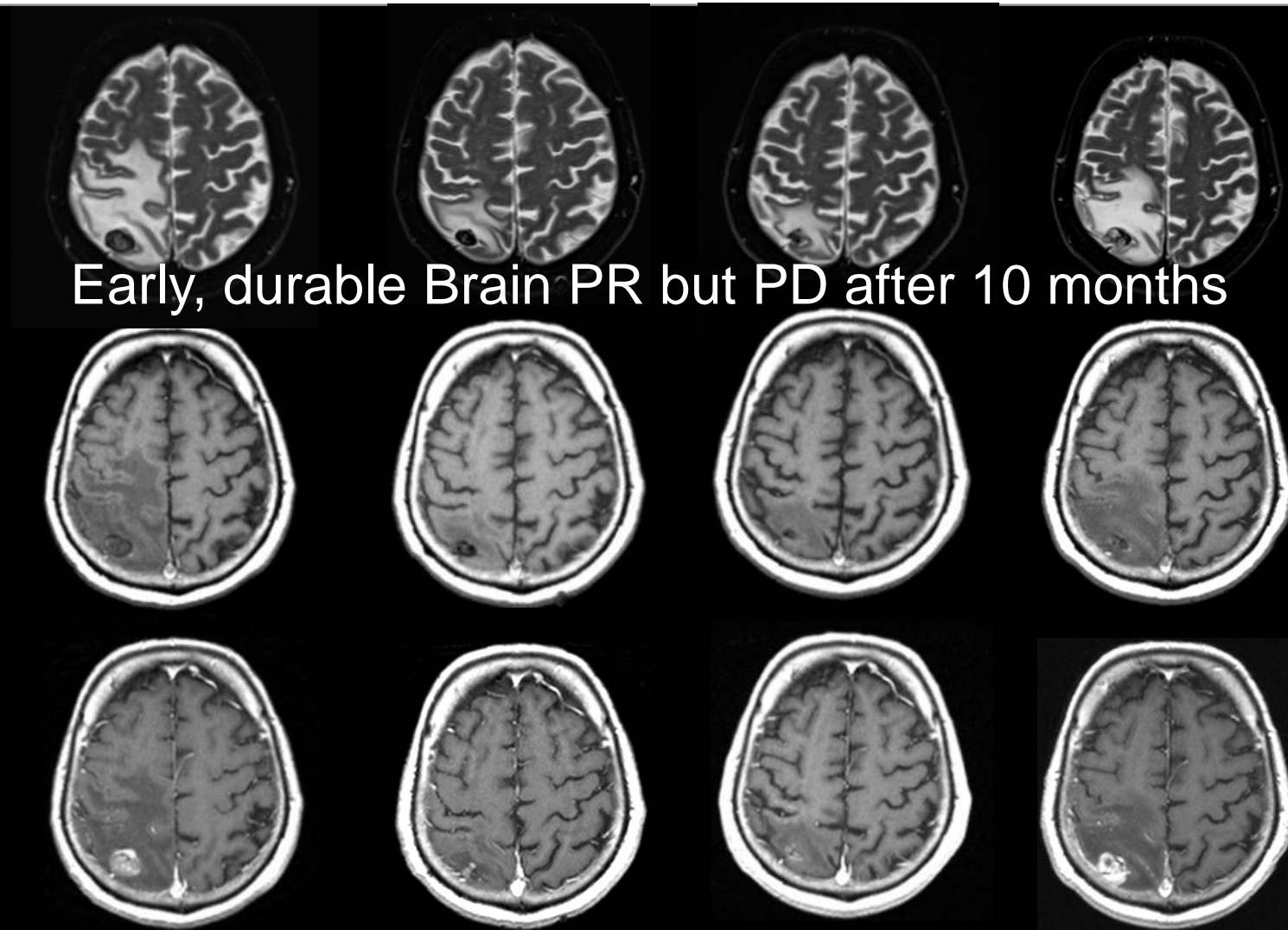
# Patient Case 1

**Male, 64 y.o.**

- **May 1999:** cutaneous melanoma, Breslow 0.8 mm
- **August 2010:** axillary lymph node dissection (+2/25 nodes)
- **August 2011:** stereotactic RT for MBM - no extracranial disease
- **September 2011:** CDDP+DTIC+Fotemustine → PD
- **January 2012:** second-line treatment with vemurafenib

# Patient Case 1

VEMURAFENIB 960 mg BID os



Early, durable Brain PR but PD after 10 months

Baseline

W 4

W 36

W 44

# CTLA-4 blockade in MBM

| <b>IPIILIMUMAB</b><br><i>Margolin K, Lancet Oncol 2012</i> | <b>N</b> | <b>DCR</b> | <b>OS (m)</b> | <b>PSF (m)</b> |
|--|----------|------------|---------------|----------------|
| Asymptomatic   | 51       | 24%        | 7.0           | 1.5            |
| Symptomatic  | 21       | 10%        | 4.0           | 1.2            |

| <b>IPIILIMUMAB + FTM<br/>NIBIT M1</b><br><i>Di Giacomo AM, ESMO 2013</i> | <b>N</b> | <b>DCR</b> | <b>OS (m)</b> | <b>PSF (m)</b> |
|--|----------|------------|---------------|----------------|
| Asymptomatic   | 20       | 50%        | 12.7          | 3.4            |

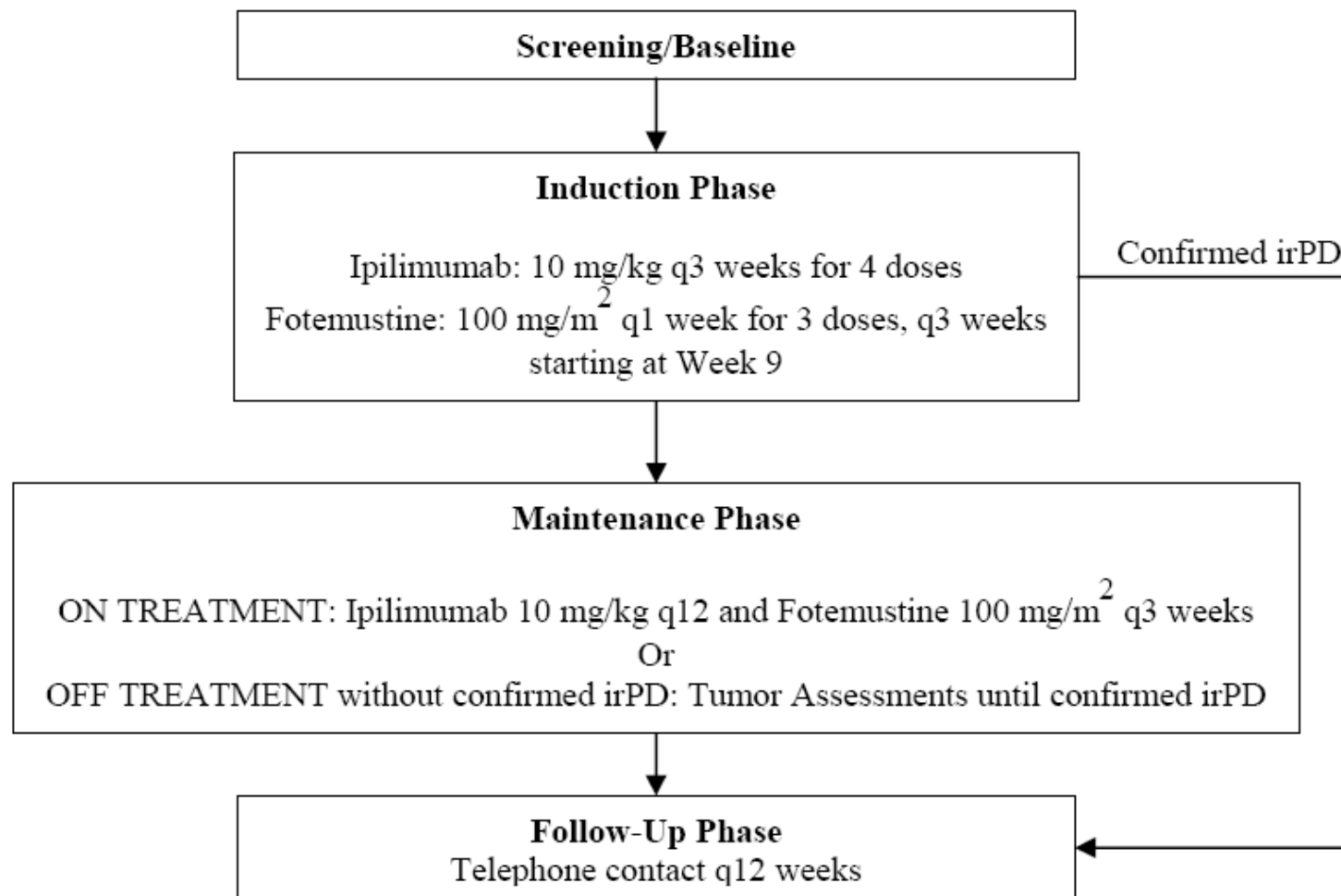


## Patient Case 2

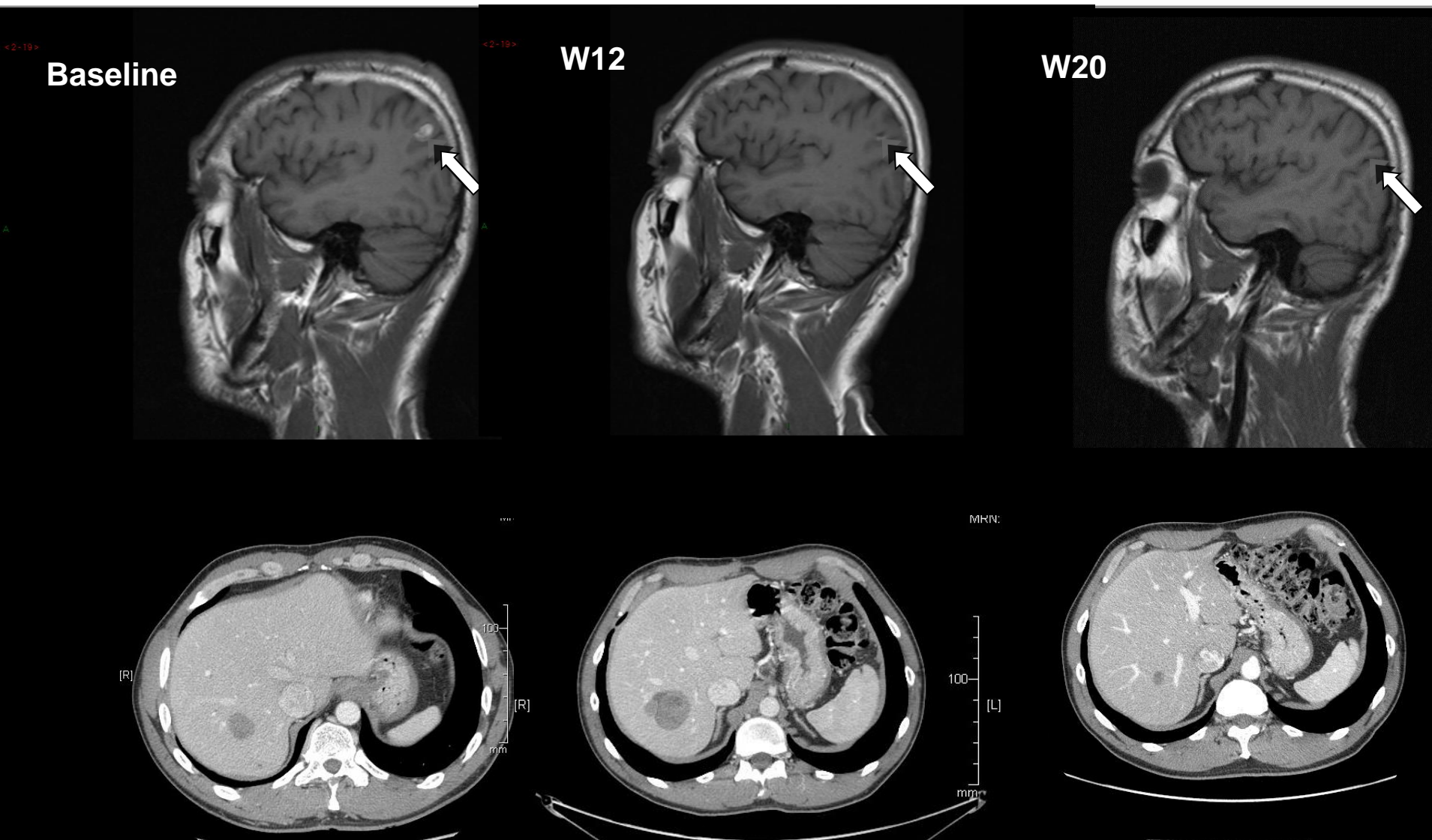
**Male, 45 y.o.**

- **June 2006:** cutaneous melanoma, Breslow 3.4 mm, SLNB -, BRAF<sup>V600E</sup> mutant
- **May 2010:** liver and brain metastases
- **June 2010:** ipilimumab *plus* fotemustine in NIBIT-M1 study

# The NIBIT-M1 study design

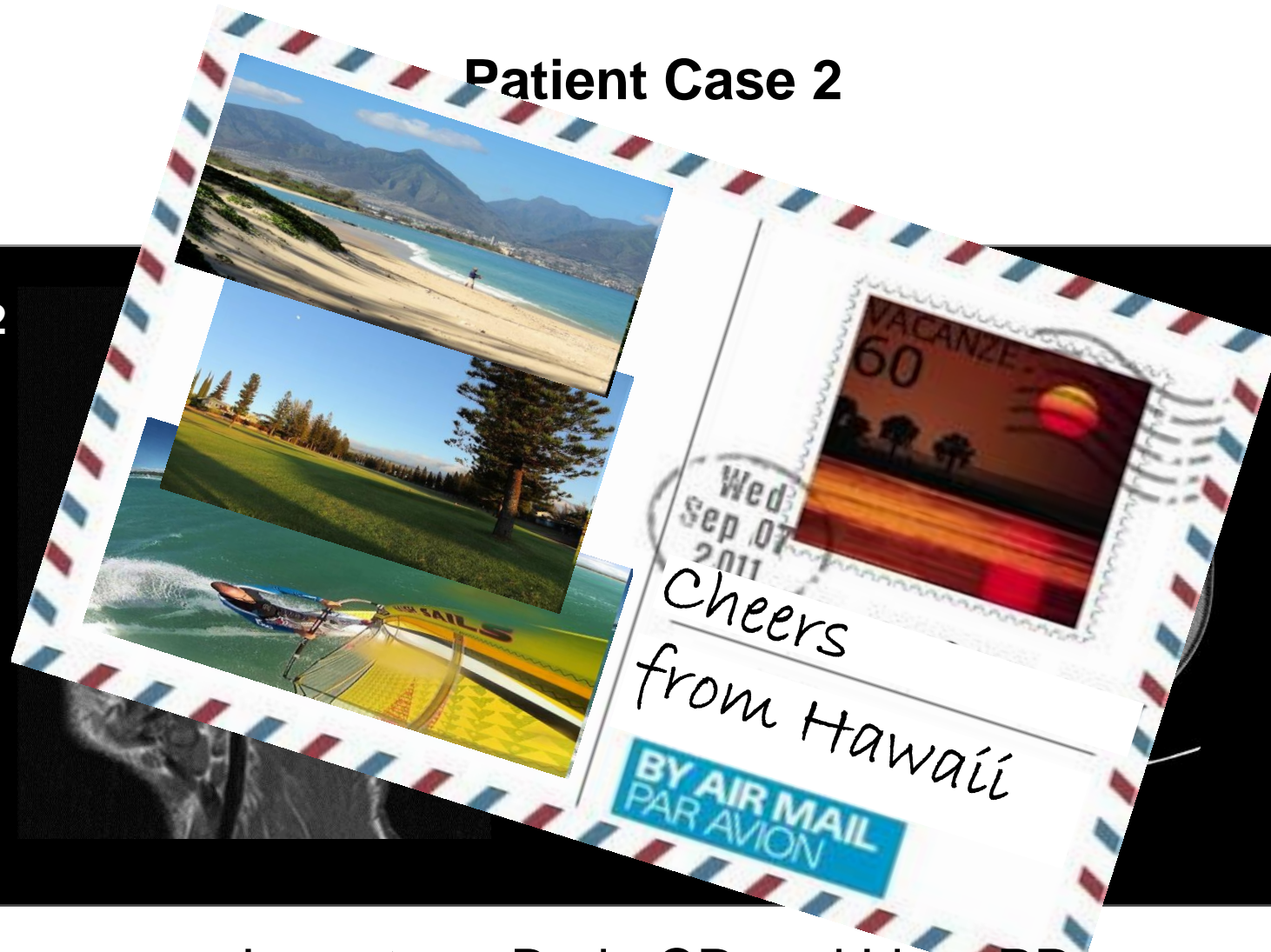


## Patient Case 2



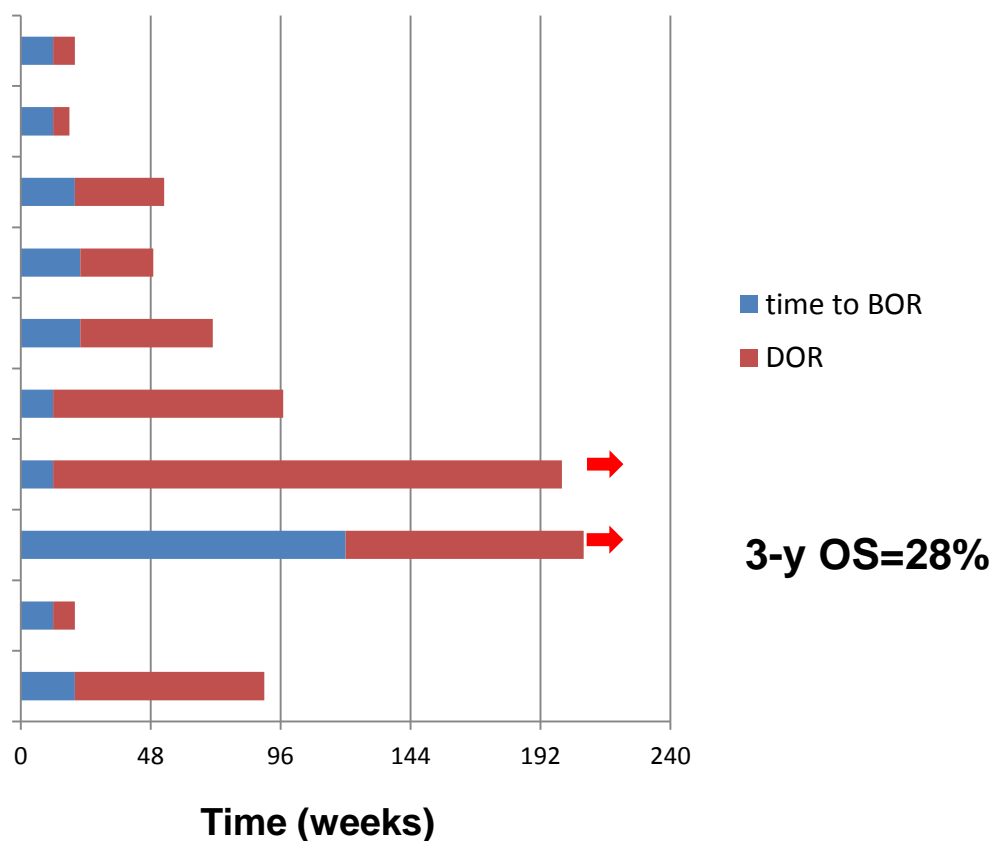
## Patient Case 2

W 192

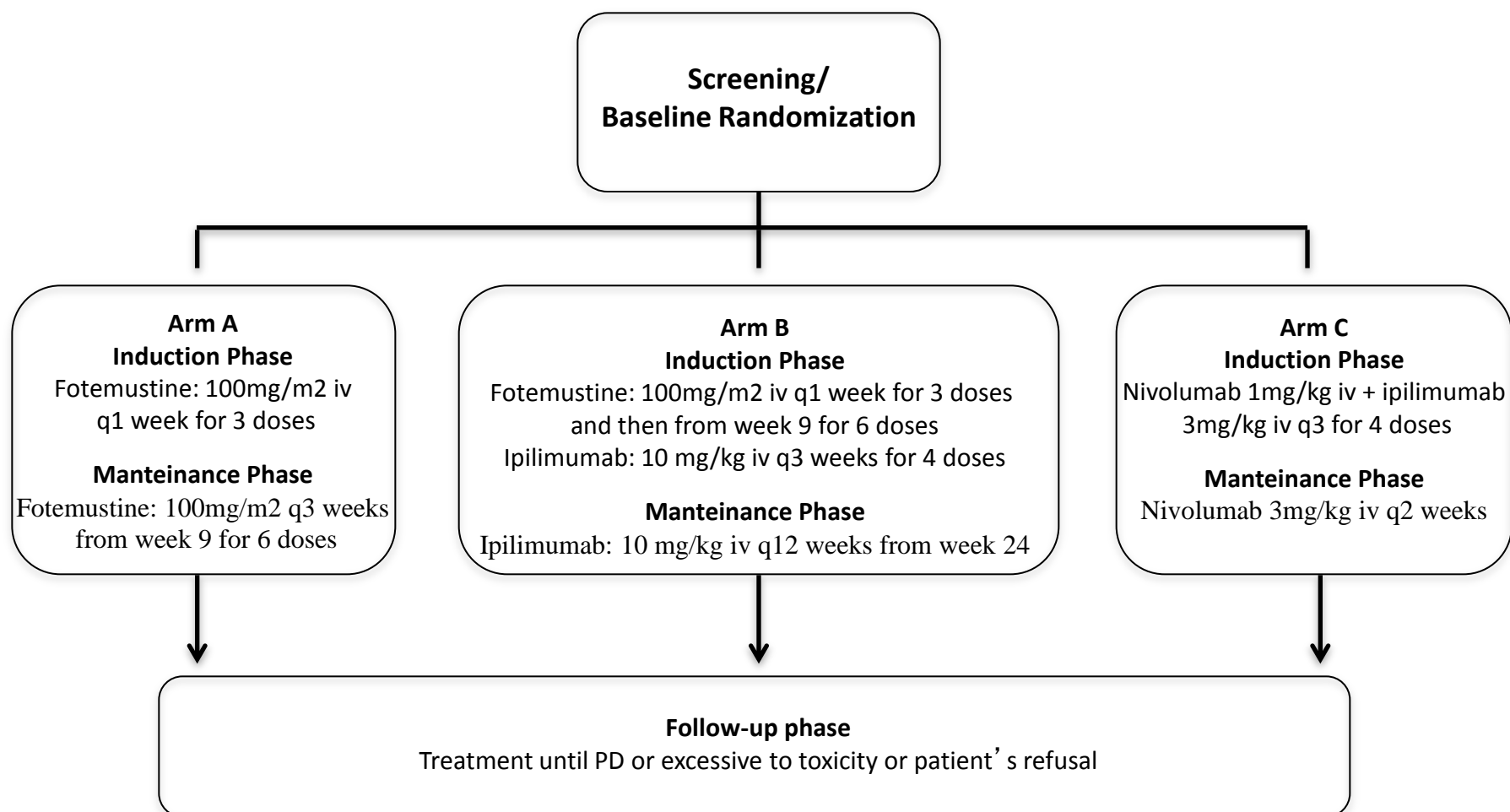


Long-term Brain CR and Liver PR

# Ir-DOR of MBM patients in the NIBIT-M1 study



# The NIBIT-M2 study design





# The future of oncogene addicted MBM

- Long-term efficacy check-point or assessment
- Overexpression of oncogenes/sequences of interest
- Address the role of neurosurgery in the treatment of MBM
- Clinical Trials
- Address the role of neurosurgery in the treatment of MBM

Thanks God, I can party tonight, no MBM in the operating theater!



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Thank you for your attention!

