Final Results of the KING trial: Phase 2 Study of Efficacy, Safety and Intratumoral Pharmacokinetics of Selinexor (KPT-330) Monotherapy in Recurrent Glioblastoma

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Virtually

COLUMBIA NewYork-Presbyterian

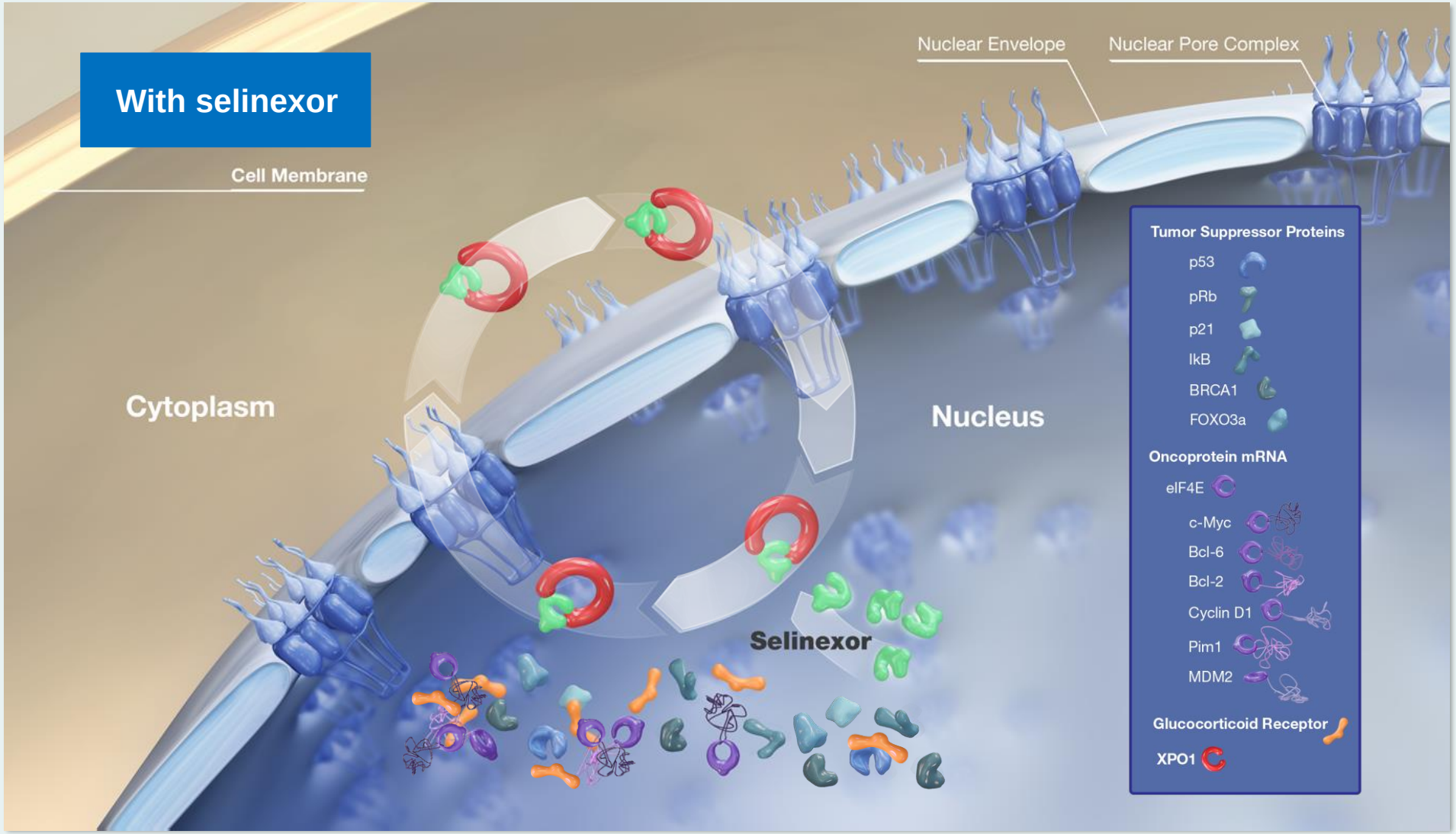
Disclosure

Last 12 months, commercial organization that produces, markets, re-sells or distributes health care goods or services consumed by, or used on, patients

- **Honoraria, Consulting, Advisory Board**: Abbott Molecular, AbbVie, Bayer, Bioclinica as an expert blinded independent reviewer for a BMS-sponsored trial, Forma, Karyopharm, Novocure, Orbus, QED, Sapience
- **Speakers' Bureau, Executive Positions**: None
- **Stock**: None
- **Funding** and drug supply for this clinical trial from Karopharm

Will discuss off-label use of selinexor for glioblastoma

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (**SINE**) Drug



Exportin 1 (XPO1) is the major nuclear export protein of:

1. Tumor suppressor proteins *(TSPs, e.g. p53, pRb, IκB, p27, p21, FOXOs)*
2. eIF4E-bound proto-oncogene mRNAs *(e.g. c-Myc, Bcl2, Bcl6, BclXL)*

Elevated XPO1 expression:

1. Inactivates TSP's by mislocalozation
2. Enhances proto-oncoprotein translation

Selinexor is an oral selective inhibitor of XPO1 that:

1. Reactivates TSP's and blocks proto-oncoprotein translation
2. Blocks DNA damage repair
3. Decreases gene translation efficacy in glioblastoma
4. Induces glioblastoma death
5. Synergies with temozolomide and radiation

Green et al., Neuro-Oncology, 2015; Argueta et al., Oncotarget, 2018; Shang et al., Sci Rep, 2018; Wahba et al., MCT, 2018

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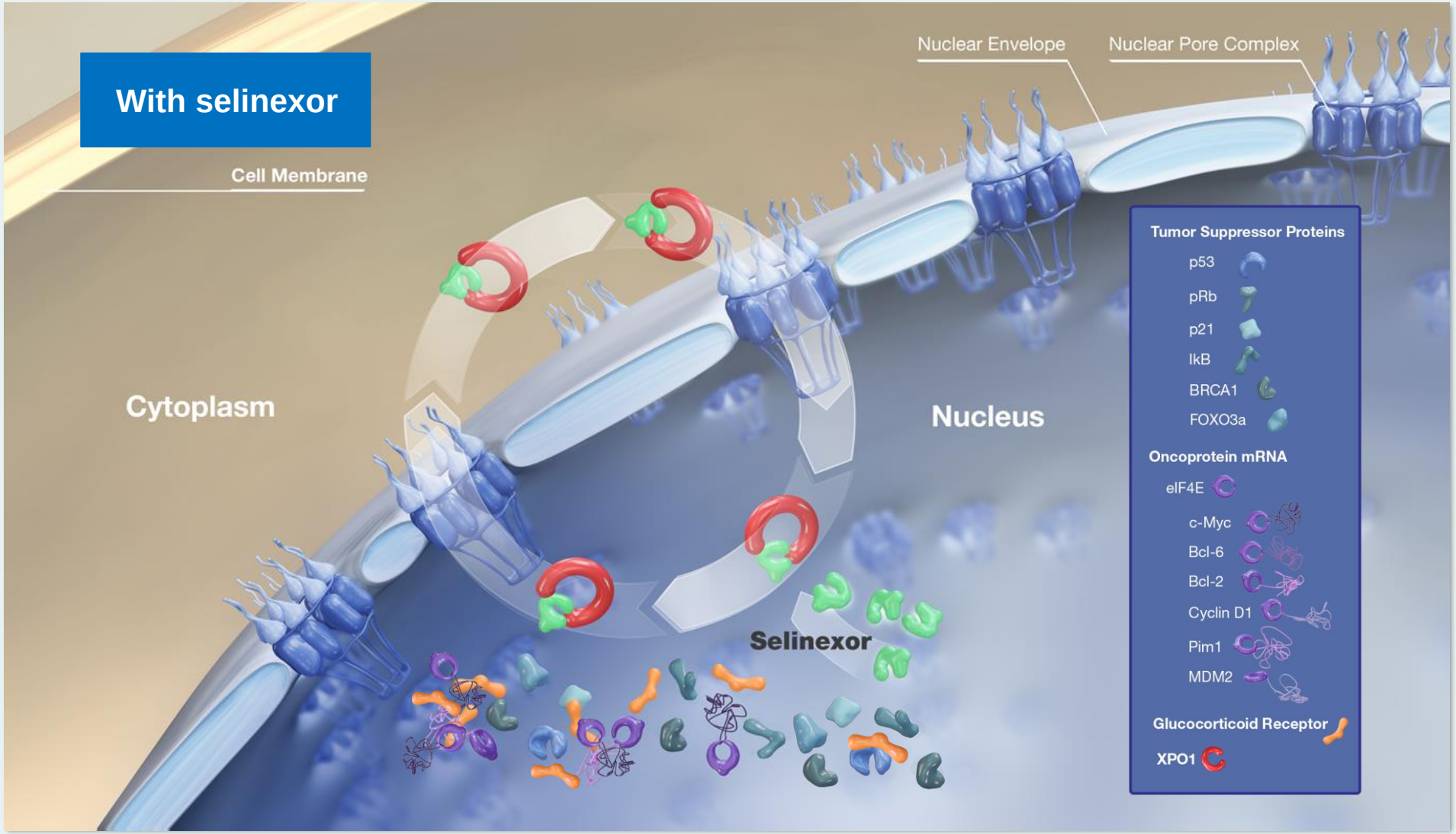

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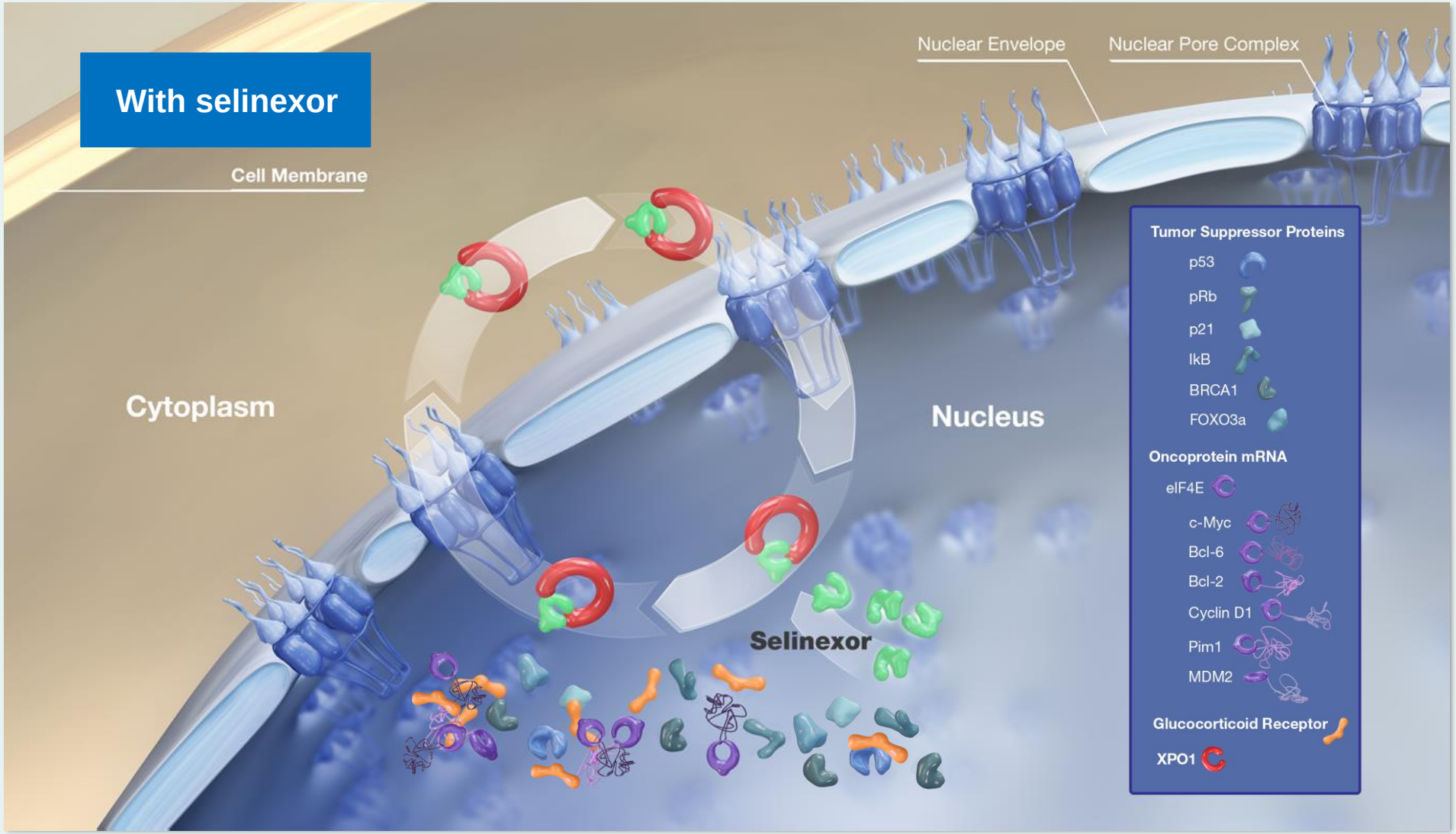

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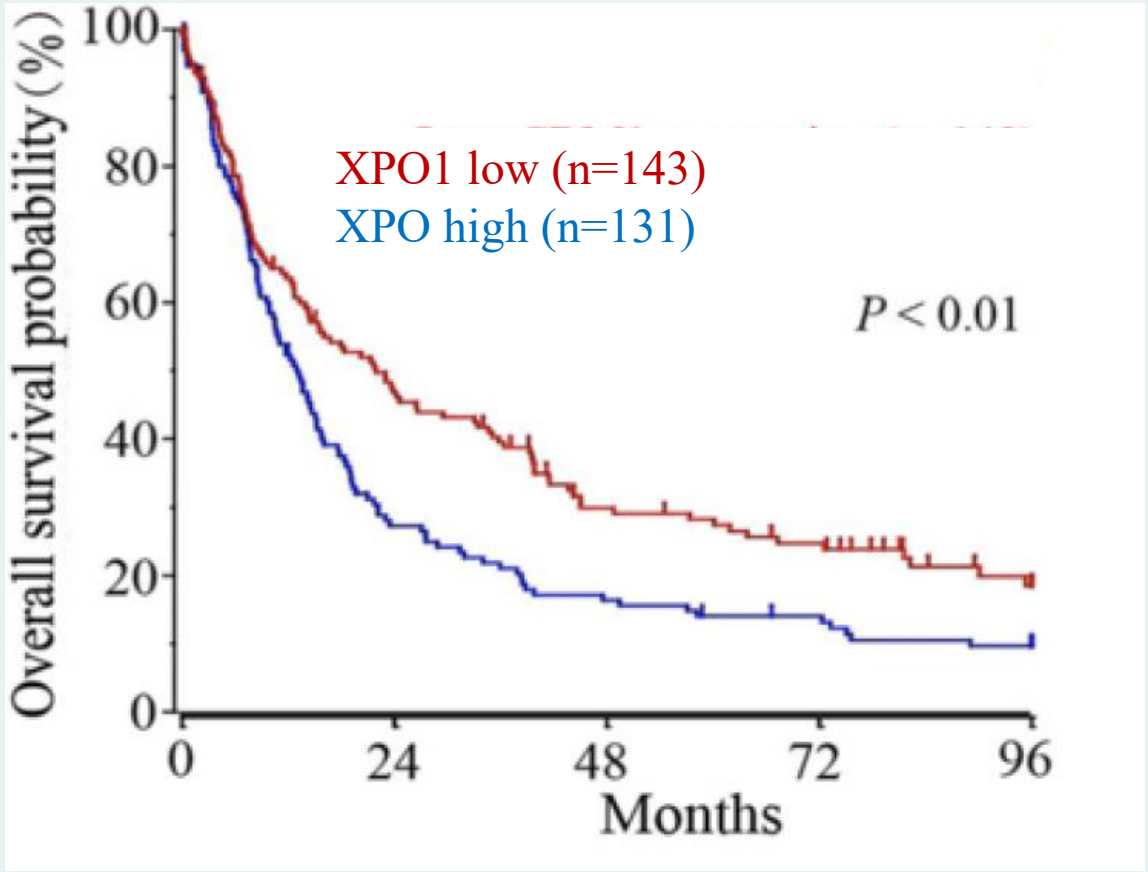
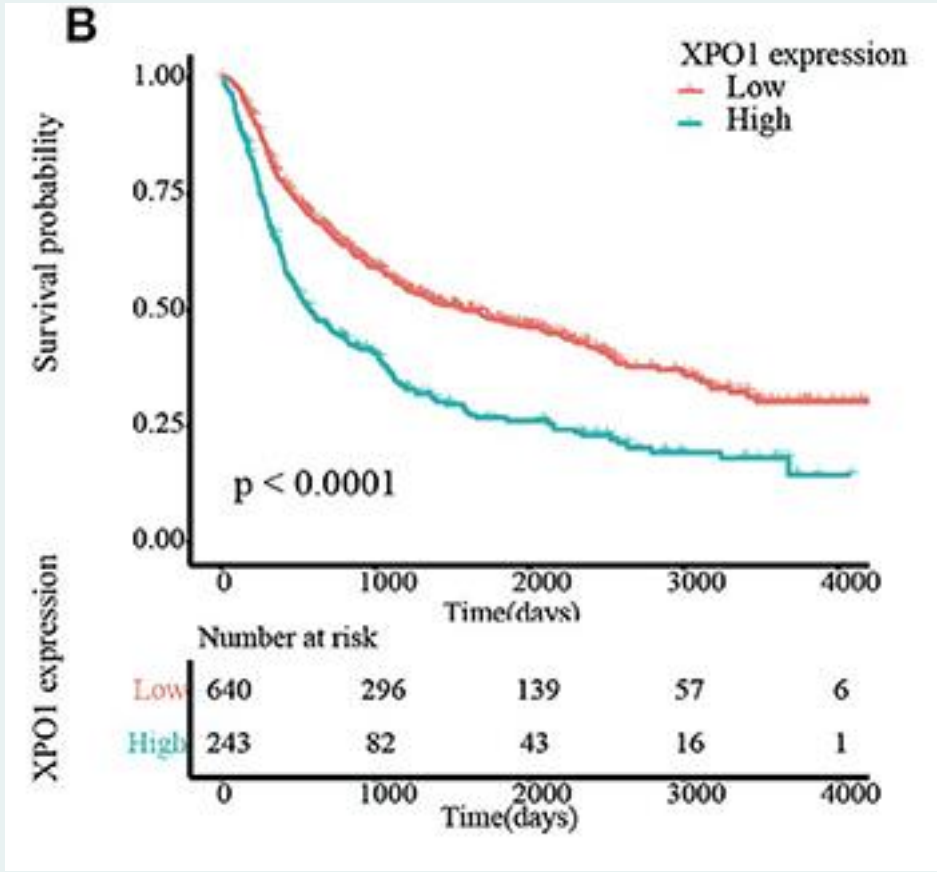
Green et al., Neuro-Oncology, 2015; Argueta et al., Oncotarget, 2018; Shang et al., Sci Rep, 2018; Wahba et al., MCT, 2018

Overexpression of XPO1 Correlates with Poor Prognosis in Glioma

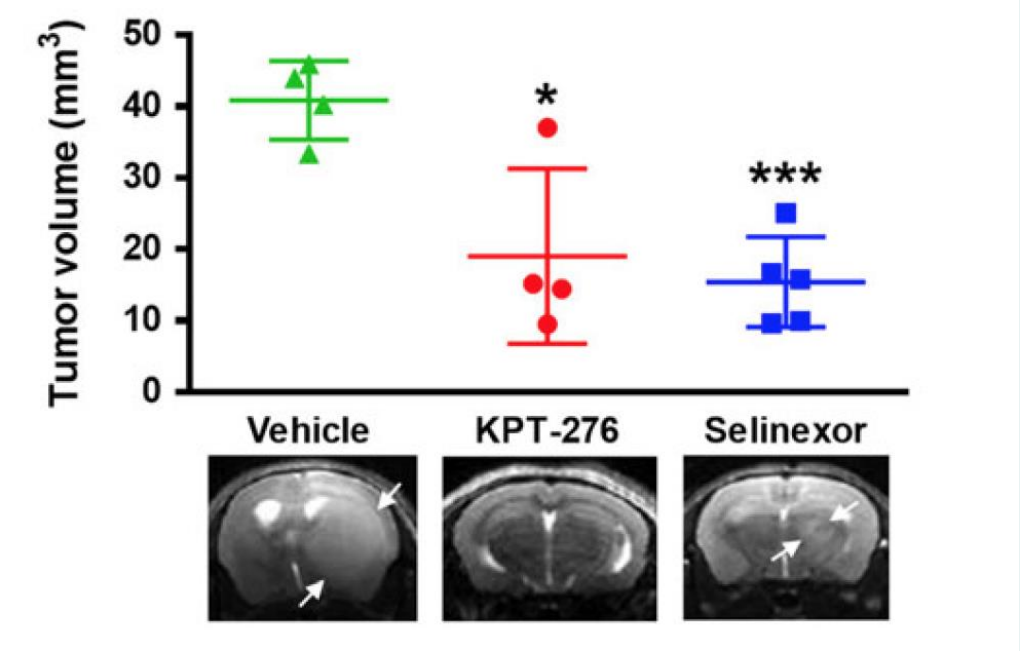


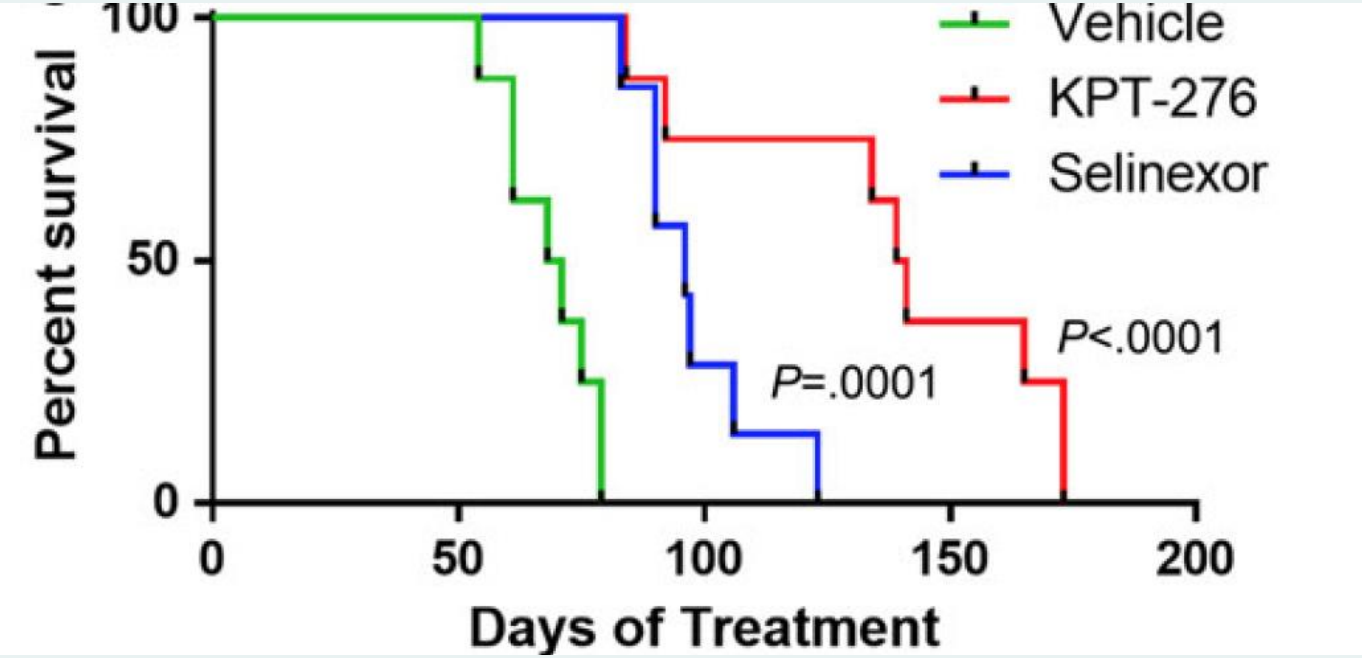
Liu X et al., J Hematol Oncol, 2016



Wu S et al., Front Oncol 2020

Selinexor Inhibits *In Vivo* Orthotopic GBM Patient-Derived-Tumors





Green et al., Neuro-Oncology, 2015

KING (KPT-330 in Recurrent Glioblastoma) Study Design

Primary Objectives:

- ARM A: Surgical arm to explore intra-tumoral pharmacokinetics (PK)
- ARMs B-D: 6mPFS rate

Patient Population:

- Recurrent/Progressive GBM (after RT and Temozolomide), no prior bev/VEGFRi
- Age ≥18 years, KPS ≥60, measurable disease (arms B-D)

Cycle = 4 w, treat until PD (RANO by local MD, MRI q 8 w)

Surgical Arm – PK Analysis	Medical Arms: Safety & Efficacy		
ARM A (n=8)	ARM B (n=24)	ARM C (n=14)	ARM D (n=30)
Selinexor: 50 mg/m^2 BIW ↓ **Resection** ↓ Resume Selinexor	**Selinexor**: 50 mg/m^2 BIW	**Selinexor**: 60 mg BIW	**Selinexor**: 80 mg QW

KING Study Results

Surgical Arm A – PK Analysis (*WFNOS 2017 Results*)

Pharmacokinetic results have demonstrated reasonable intra-tumor penetration with tumor concentration of SEL averaging 136 nM (~2h post dose, n=6) in a range of the mean *in vitro* IC_{50} of ~130 nM

Modified Intent to Treat (mITT) Population – Safety & Efficacy Analyses (ARMs B, C, D)

ARM B

Selinexor 50 mg/m^2 BIW
2 more arms added to explore dose/schedule

Randomized to ARM C or D (1:1)

ARM C

Selinexor 60 mg BIW
Tolerable but efficacy limited

ARM D

Selinexor 80 mg QW
WFNOS 2017: Tolerable and responses observed (WFNOS 2017)
→ Expanded

Patient Characteristics

	ARM A	ARM B	ARM C	ARM D
Patients Enrolled	8	24	14	30
Age: Years median (range)	58 (43-65)	50 (29-69)	52 (27-65)	56 (21-78)
Men (%) : Women (%)	88% : 12%	79% : 21%	64% : 36%	63% : 37%
Median Prior Therapies	2 (1-2)	1 (1-2)	1 (1-3)	2 (1-8)
Karnofsky Performance Score (KPS): Median	80%	90%	90%	80%
Patients KPS – 60%	--	2 (8%)	1 (7%)	1 (3%)
Patients KPS – 70% – 80%	5 (63%)	7 (29%)	4 (29%)	13 (43%)
Patients KPS – ≥90%	3 (37%)	15 (63%)	9 (64%)	16 (53%)

Treatment-Related non-Hematological Adverse Events in ≥10% of Patients (Safety)

AE Term	Arm B – 50 mg/m^2 BIW (n=24)		Arm C – 60 mg BIW (n=14)		Arm D – 80 mg QW (n=30)	
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
Nausea	**9 (37.5%)**	**1 (4.2%)**	**9 (64.3%)**	**--**	**20 (66.7%)**	**--**
Vomiting	7 (29.2%)	--	5 (35.7%)	--	10 (33.3%)	--
Decrease appetite	11 (45.8%)	--	10 (71.4%)	--	8 (26.7%)	
Diarrhea	3 (12.5%)	--	--	--	4 (13.3%)	--
Dysgeusia	9 (37.5%)	--	6 (42.9%)	--	4 (13.3%)	--
Constipation	2 (8.3%)	--	4 (28.6%)	--	5 (16.7%)	--
Constitutional						
Fatigue	**10 (41.7%)**	**7 (29.2%)**	**8 (57.1%)**	**2 (14.3%)**	**14 (46.7%)**	**1 (3.3%)**
Weight Loss	**4 (16.7%)**	**--**	**5 (35.7%)**	**1 (7.1%)**	**2 (6.7%)**	--
Malaise	--	--	3 (21.4%)	--	3 (10.0%)	--
Other						
Hyponatremia	**9 (37.5%)**	**1 (4.2%)**	**2 (14.3%)**	**--**	**1 (3.3%)**	--
Vision Blurred	5 (20.8%)	1 (7.1%)	2 (14.3%)	--	2 (6.7%)	--

- No Grade 4 treatment-related AEs were reported in ≥10% patients
- No Grade 5 treatment-related AEs were reported

Data cutoff 04-May-2020

Treatment-Related Hematological Adverse Events in ≥10% of Patients (Safety)

AE Term	Arm B – 50 mg/m^2 BIW (n=24)		Arm C – 60 mg BIW (n=14)		Arm D – 80 mg QW (n=30)		
Hematological	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**	**Grade 4**
Leukopenia	5 (20.8%)	2 (8.3%)	--	1 (7.1%)	12 (40.0%)	1 (3.3%)	--
Neutropenia	3 (12.5%)	4 (16.7%)	--	2 (14.3%)	8 (26.7%)	2 (6.7%)	--
Anemia	5 (20.8%)	--	1 (7.1%)	--	6 (20.0%)	--	--
Thrombocytopenia	**14 (58.3%)**	**2 (8.3%)**	**4 (28.6%)**	**--**	**6 (20.0%)**	**1 (3.3%)**	**--**
Lymphopenia	1 (4.2%)	1 (4.2%)	--	--	3 (10.0%)	--	1 (3.3%)

- No Grade 5 treatment-related hematological AEs were reported

Data cutoff 04-May-2020

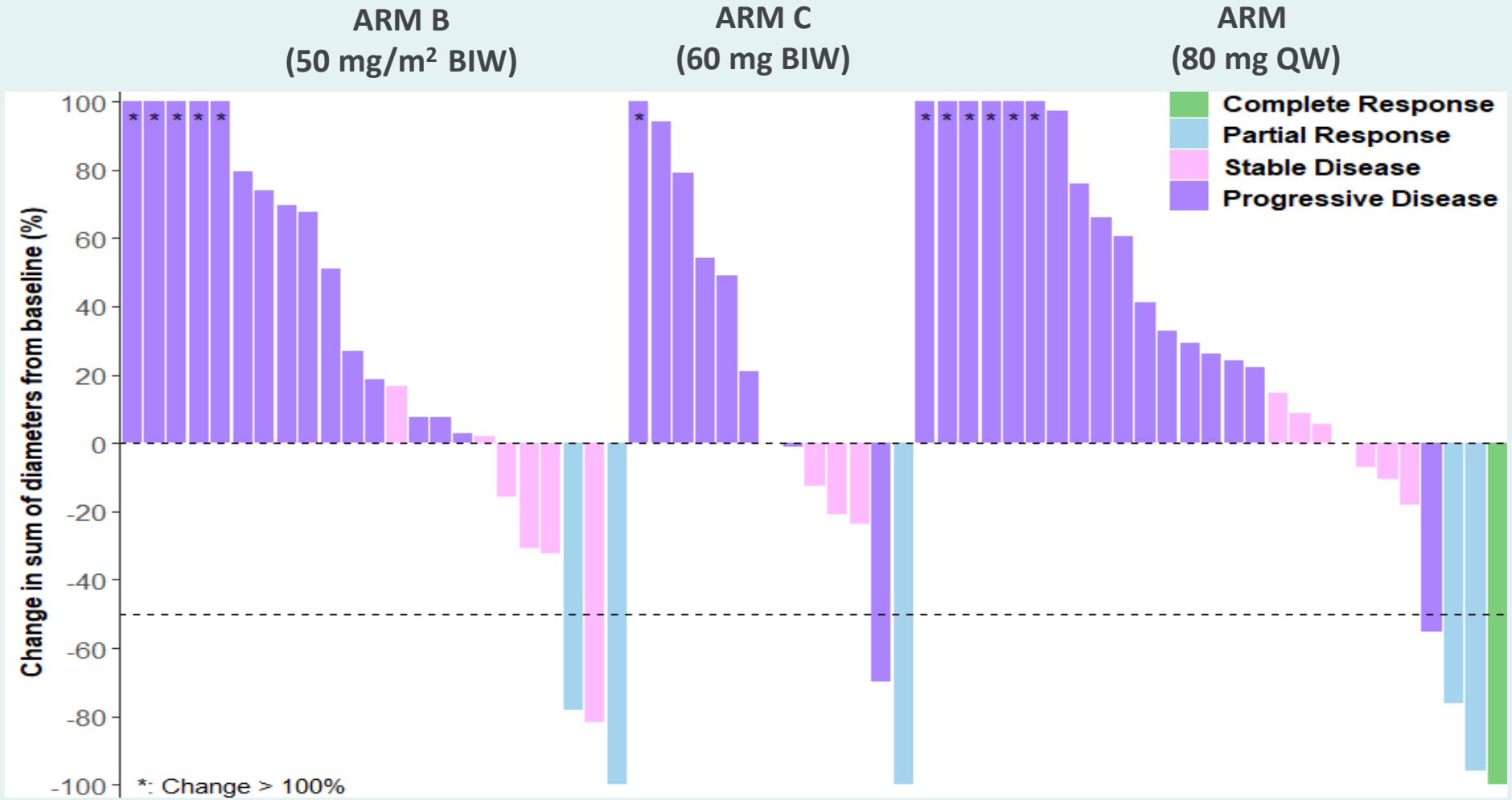
KING Efficacy

	ARM B – 50 mg/m^2 BIW	ARM C – 60 mg BIW	ARM D – 80 mg QW
N	**24**	**14**	**30**
6mPFS rate (95% CI)	10% (3 – 35)	7.69% (1 – 51)	**17% (8 – 38)**
6 cycle PFS rate (95% CI)	15% (5 – 40)	7.69% (1 – 51)	**28% (15– 50)**
Overall Response Rate (PR + CR)	8%	7%	**10%**
Median OS (95% CI) months	10.5 (4.9 – 17.0)	8.5 (7.8 – NE)	**10.2 (7.0-15.4)**

Data cutoff 04-May-2020, response by local investigators per Response Assessment in Neuro-Oncology (RANO). CR=Complete Response, PR=Partial Response, OS=Overall Survival, PFS=Progression Free Survival

- **17%** of patients on ARM D achieved 6-month PFS rate (180 days)
- **28%** of patients on ARM D achieved 6 cycle PFS rate (180 – 14 days)
- Median OS for ARM D: 10.2 months.

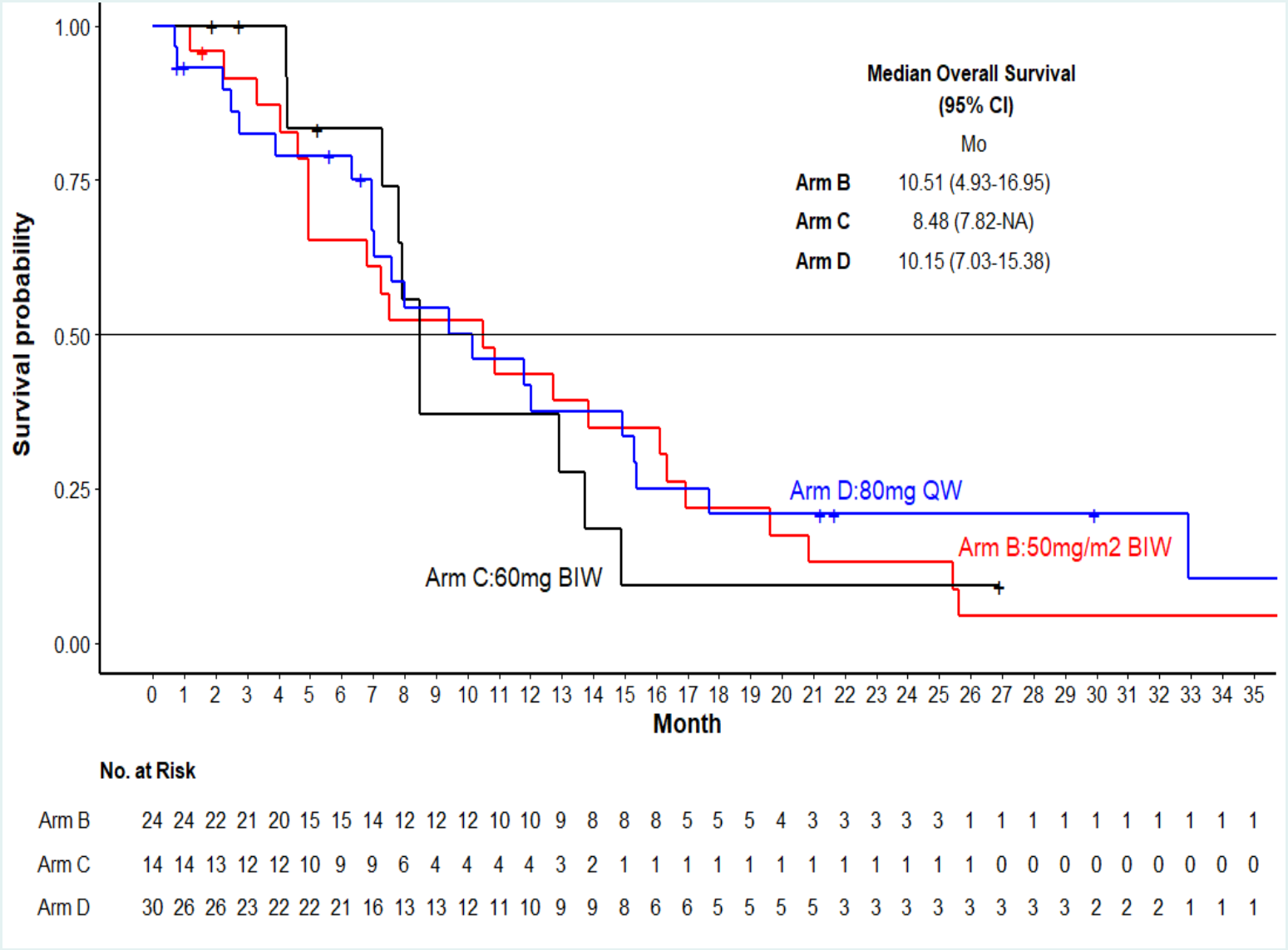
Selinexor Tumor Effect



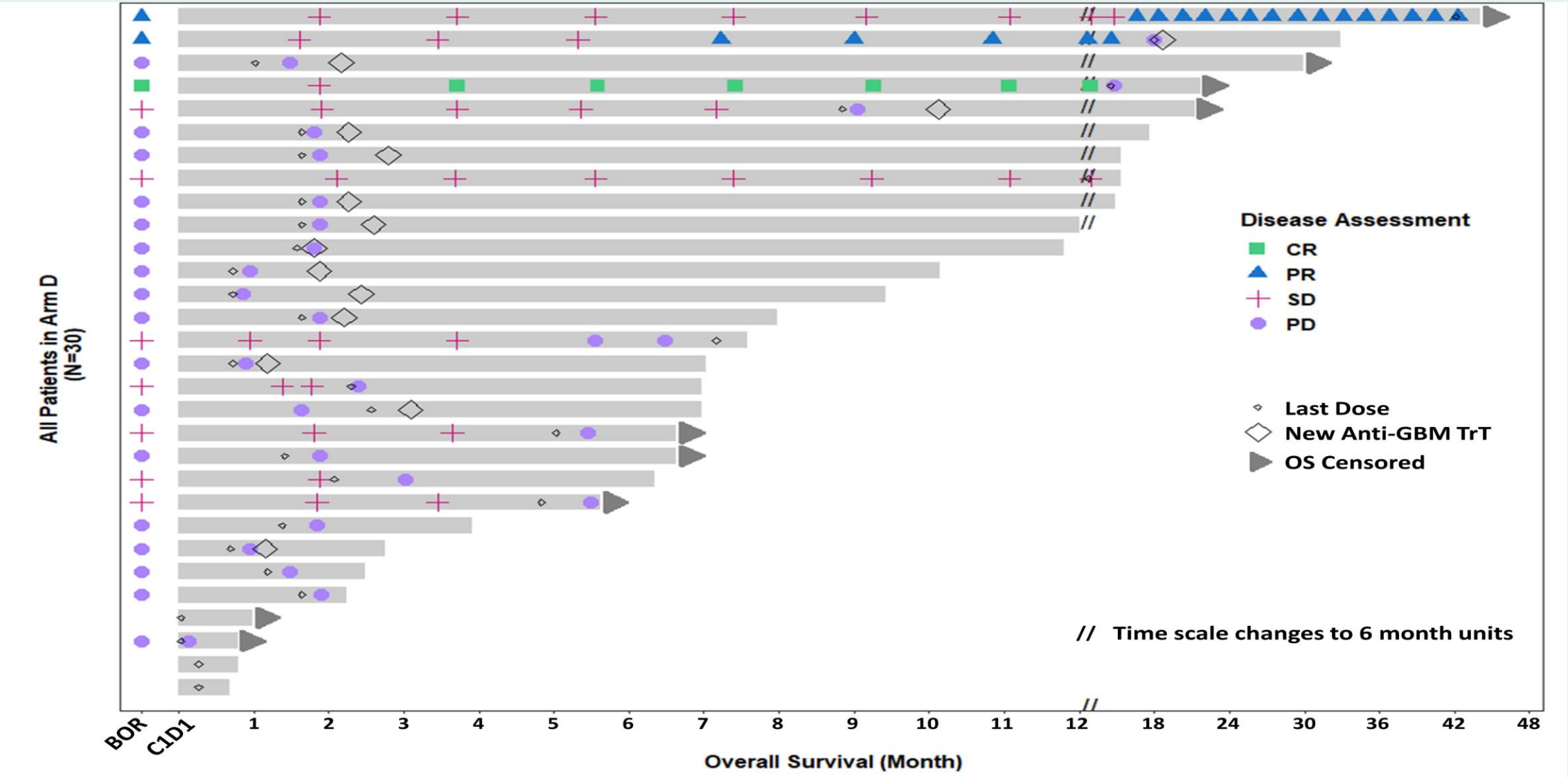
Arms B-D pooled

↓ tumor size
29% of patients

Overall Survival

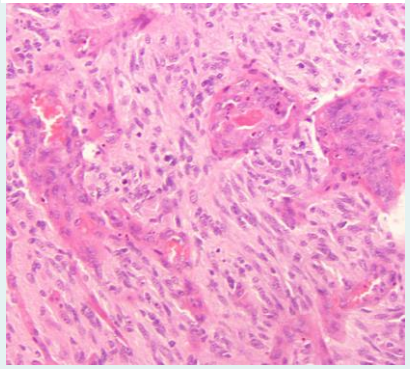


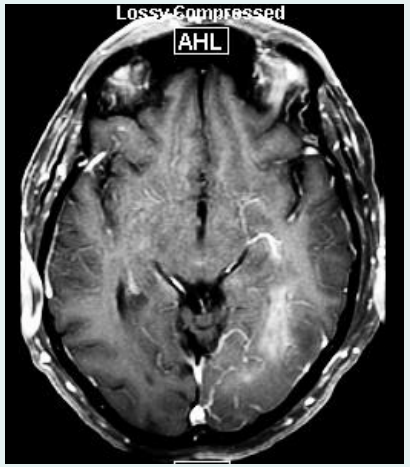
ARM D – Survival



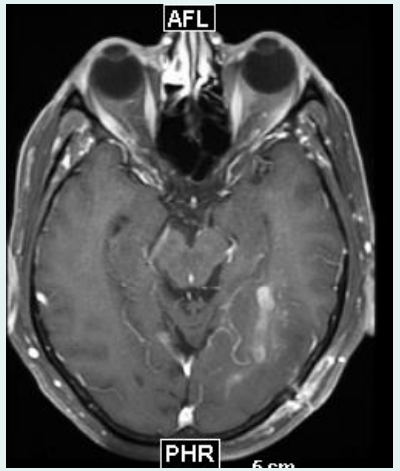
Patient 1: Durable PR 3L Therapy in Recurrent GBM

64 yo man
u*MGMT IDH*^{wt} (IHC & PCR)

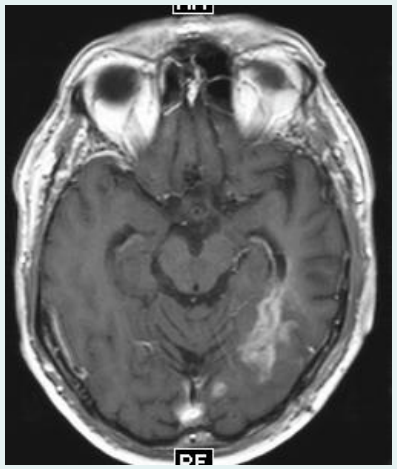




RT + TMZ

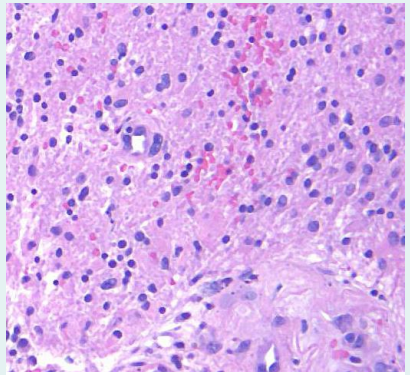


TMZ x 5

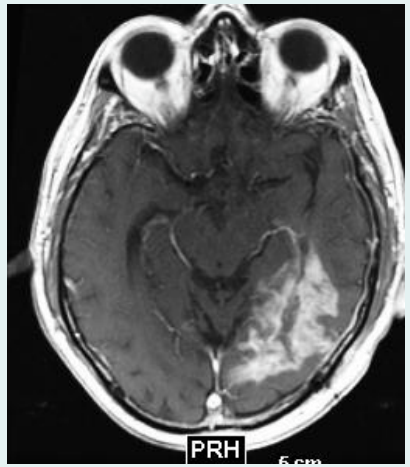


AKTi+mTORi

PD #1

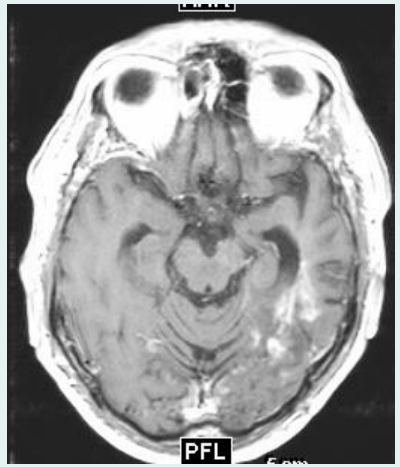


rGBM
(Subtotal resection)



PD #2 (post-op)

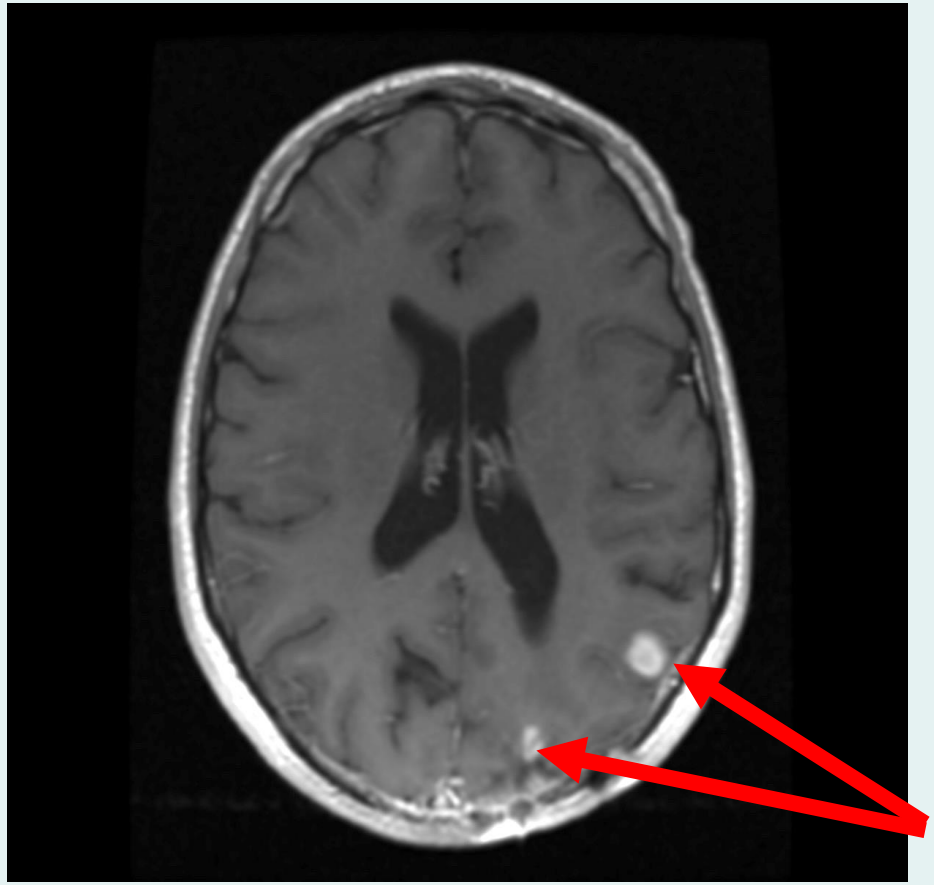
Selinexor



Durable PR

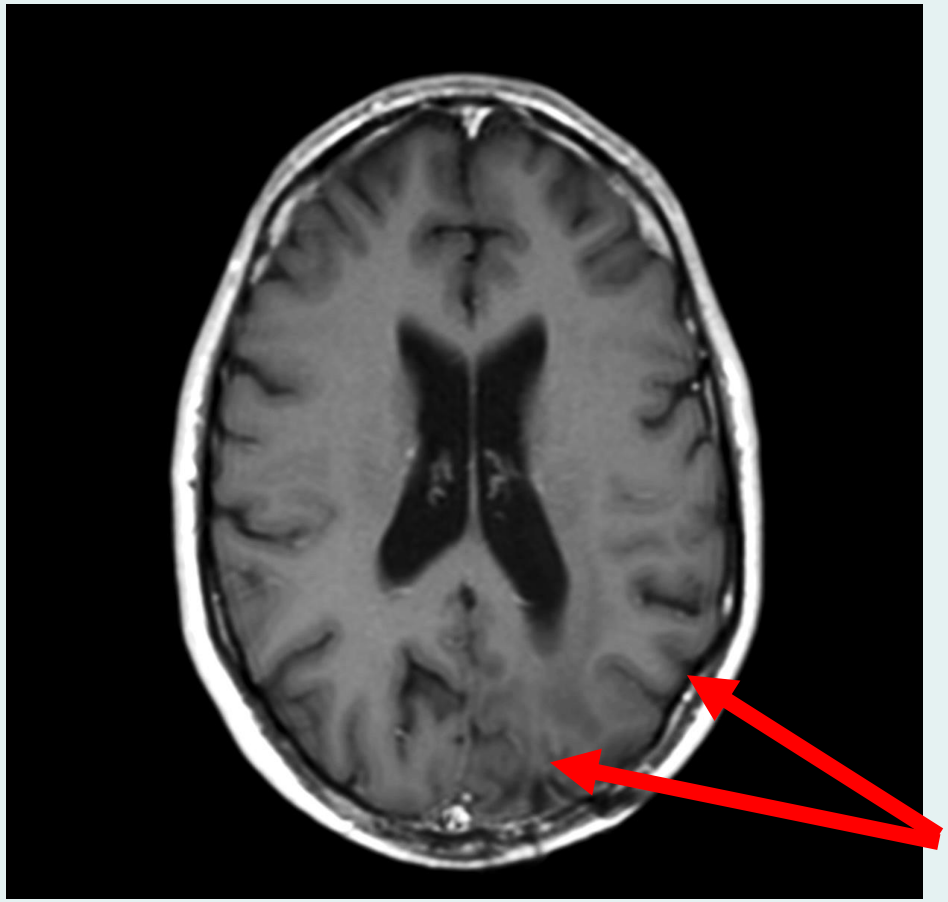
- Durable PR (↓72%)
- 80 mg QW
- > 3y

Patient 2: Complete Response Patient Profile



Selinexor

80 mg/w



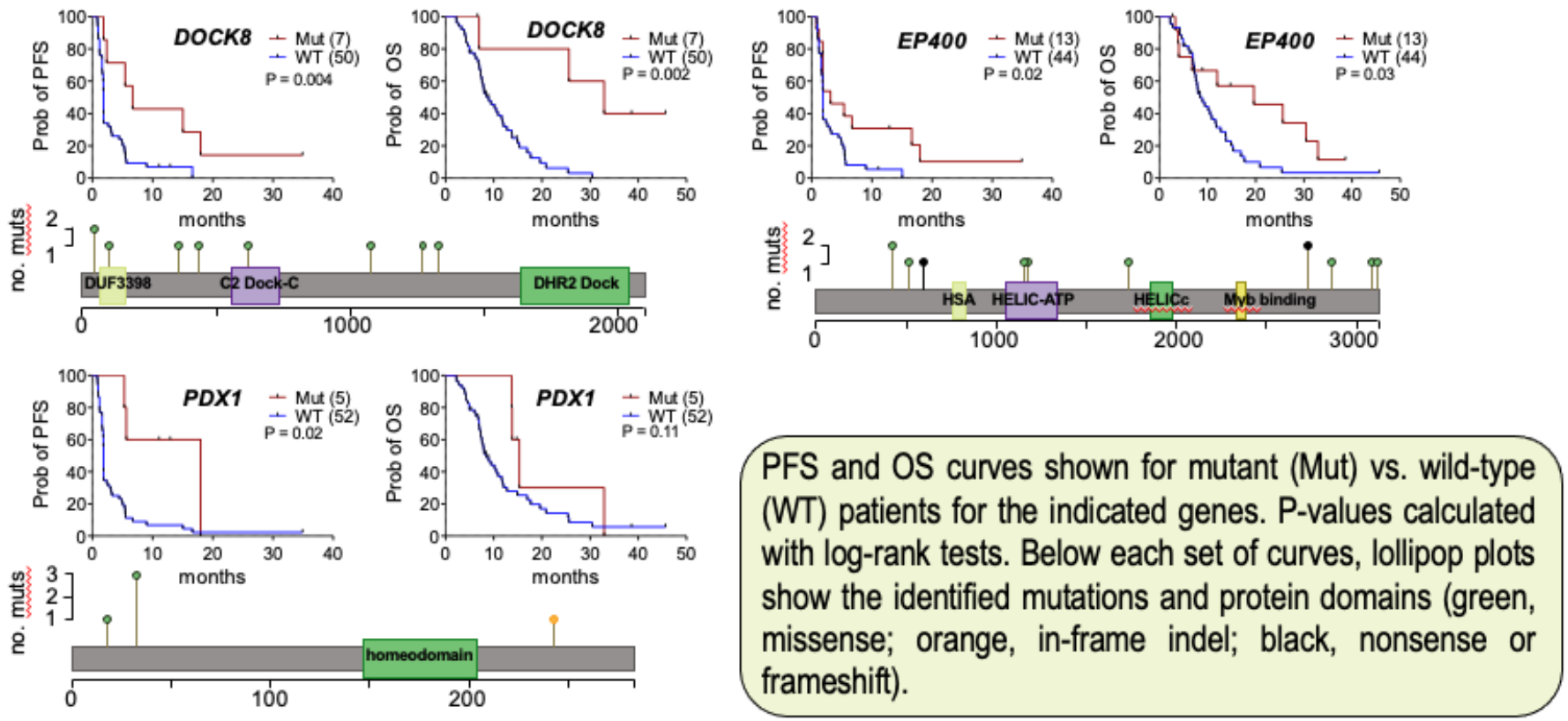
36 year old man, RT+TMZ+/-Deptux-m x 7 m

IDH^{wt} (IHC & PCR), m*MGMT*

CR, on treatment > 1y

Molecular Predictors of Response to Selinexor in Recurrent Glioblastoma (GBM)

Mutations Associated with Improved Survival in Selinexor-Treated Patients



PFS and OS curves shown for mutant (Mut) vs. wild-type (WT) patients for the indicated genes. P-values calculated with log-rank tests. Below each set of curves, lollipop plots show the identified mutations and protein domains (green, missense; orange, in-frame indel; black, nonsense or frameshift).

- Patients with adequate selinexor exposure (>21 days and > 3 doses) were exome and RNA sequenced.
- Three genes showed significant correlation between mutation and improved survival with selinexor treatment.
- Notably, the PDX1 transcription factor protein contains an XPO1 nuclear export sequence and the observed mutations have been shown to impact PDX1 mediated transcription of its target genes.

For more details please see Abstract #: BIOM-26
Abstract Title: **Molecular predictors of response to selinexor in recurrent glioblastoma (GBM)**

KING Conclusions

- Selinexor achieves adequate intra-tumor penetration
- 80 mg po QW is recommended dose for further evaluation
- Side effects expected and manageable
- Anti-tumor activity observed, supporting further development
- Molecular correlative analyses ongoing to identify enrichment biomarker(s)
  - Abstract #: BIOM-26: Molecular predictors of response to selinexor in recurrent GBM
- Ongoing phase I/II trial in newly diagnosed GBM (NCT04421378), enrolling
  - Abstract #: RTID-08: A Phase 1/2 study of Selinexor in combination with standard of care therapy for newly diagnosed or recurrent glioblastoma

Acknowledgments

Patients, their families, and caregivers

Investigators, co-investigators and study teams at each participating center:

- Columbia University Irving Medical Center and New York-Presbyterian Hospital, New York, NY
- Dana Farber Cancer Institute, Boston, MA
- Erasmus MC Cancer Center, Rotterdam, The Netherlands
- Massachusetts General Hospital, Boston, MA
- University of Groningen, Groningen, The Netherlands
- Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark