Efficacy and Safety of Selinexor (KPT-330) in Recurrent Glioblastoma (KING)

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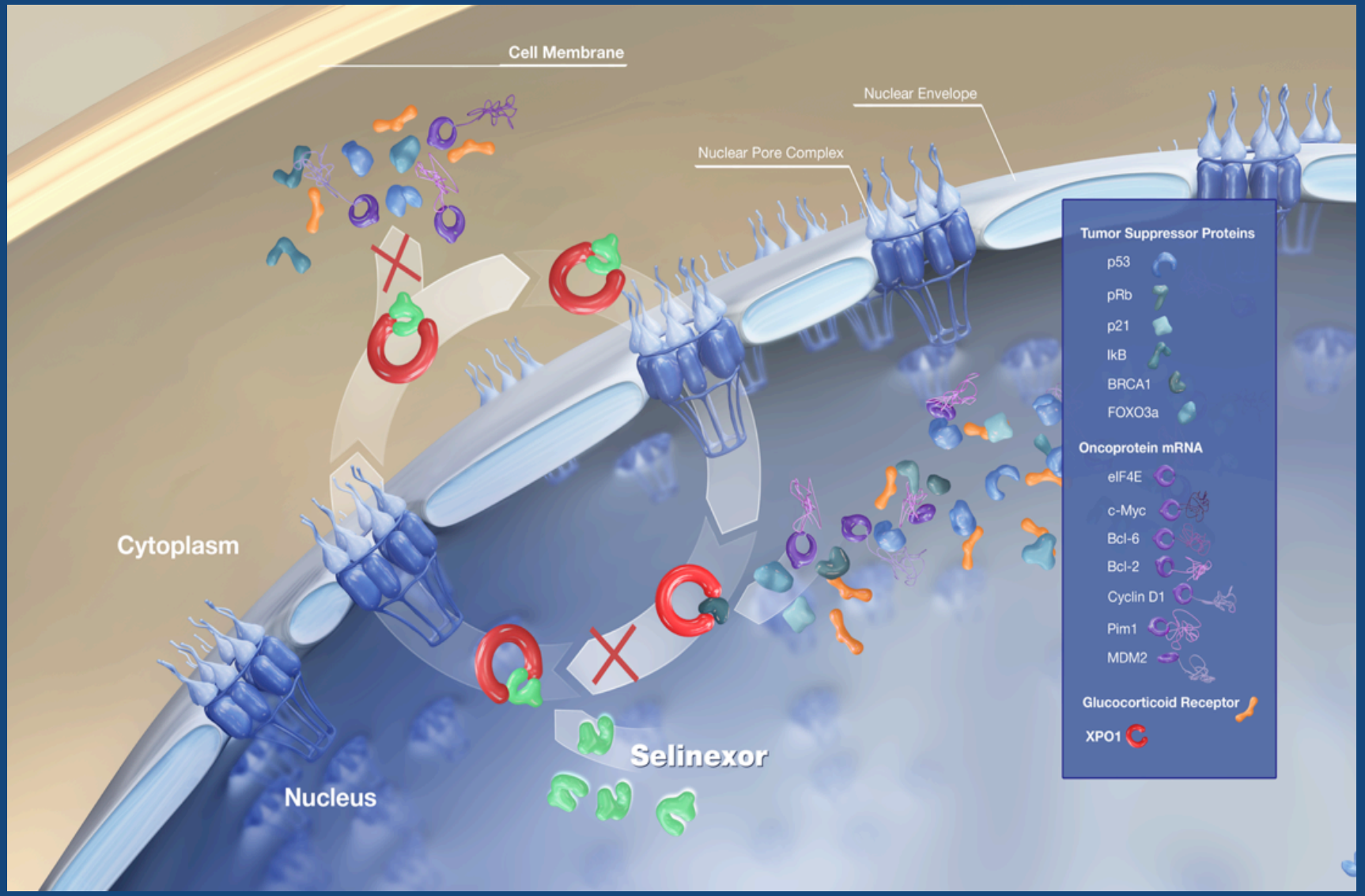
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]



- Exportin 1 (XPO1) is a major nuclear exporter.
- Increased XPO1 inactivates tumors suppressor proteins by mislocalization
- Selinexor: selective XPO1 inhibitor

[1]Green et al., Neuro-Oncology, 2014, [2]Argueta et al., Oncotarget, 2018, [3]Shang et al., Sci Rep, 2018, [4]Wahba et al, MCT 2018

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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 136nM (~2h post dose, n =6) in a range of the mean in vitro IC_{50} of 133 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 as of 1-May-2019	**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 (1-3)	1 (1-3)	1 (1-3)	2 (1-7)
Karnofsky Performance Score (KPS): Median	**80%**	**90%**	**90%**	**80%**
Patients KPS – 60%	--	2 (8%)	1 (7%)	2 (6%)
Patients KPS – 70% – 80%	5 (63%)	8 (33%)	4 (29%)	14 (47%)
Patients KPS – ≥90%	3 (37%)	14 (58%)	9 (64%)	14 (47%)

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

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%)**	**--**	**19 (63.3%)**	**--**
Anorexia	**11 (45.8%)**	**--**	**10 (71.4%)**	**--**	**8 (26.7%)**	--
Vomiting	8 (33.3%)	--	5 (35.7%)	--	10 (33.3%)	--
Diarrhea	3 (12.5%)	--	--	--	4 (13.3%)	--
Altered Taste	9 (37.5%)	--	6 (42.9%)	--	7 (23.3%)	--
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%)**	--
Weight Loss	**5 (20.8%)**	**--**	**5 (35.7%)**	**1 (7.1%)**	**2 (6.7%)**	--
Confusional State	1 (4.2%)	--	--	--	4 (13.3%)	--
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 01-May-2019;

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

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	8 (33.3%)	1 (4.2%)	--	1 (7.1%)	12 (40.0%)	1 (3.3%)	--
Neutropenia	4 (16.7%)	3 (12.5%)	--	2 (14.3%)	7 (23.3%)	3 (10.0%)	--
Anemia	5 (20.8%)	--	1 (7.1%)	--	7 (23.3%)	--	--
Thrombocytopenia	**14 (58.3%)**	**2 (8.3%)**	**4 (28.6%)**	**--**	**7 (23.3%)**	**--**	**--**
Lymphopenia	2 (8.3%)	1 (4.2%)	--	--	3 (10.0%)	1 (3.3%)	1 (3.3%)

- No Grade 5 treatment-related AEs were reported

Data cutoff 01-May-2019

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KING Efficacy

	ARM B – 50 mg/m² BIW	ARM C – 60 mg BIW	ARM D – 80 mg QW
N	**24**	**14**	**30**
6mPFS rate (95% CI)	10% (3 – 35)	NE	**19% (9 – 41)**
6 cycle PFS rate (95% CI)	15% (5 – 40)	11% (2 – 68)	**30% (17 – 54)**
Overall Response Rate (PR + CR)	8%	7%	**10%**
Median OS (95% CI) months	9.0 (4.9 – 16.4)	8.5 (7.8 – NE)	**9.4 (7.0-NE)**

- **19%** of patients on ARM D achieved 6 month PFS rate (180 days)
- **30%** of patients on ARM D achieved 6 cycle PFS rate (180 – 14 days)

Data cutoff as of May 1, 2019, response by local investigators per Response Assessment in Neuro-Oncology (RANO).
CR=Complete Response, PR=Partial Response, OS=Overall Survival, PFS=Progression Free Survival

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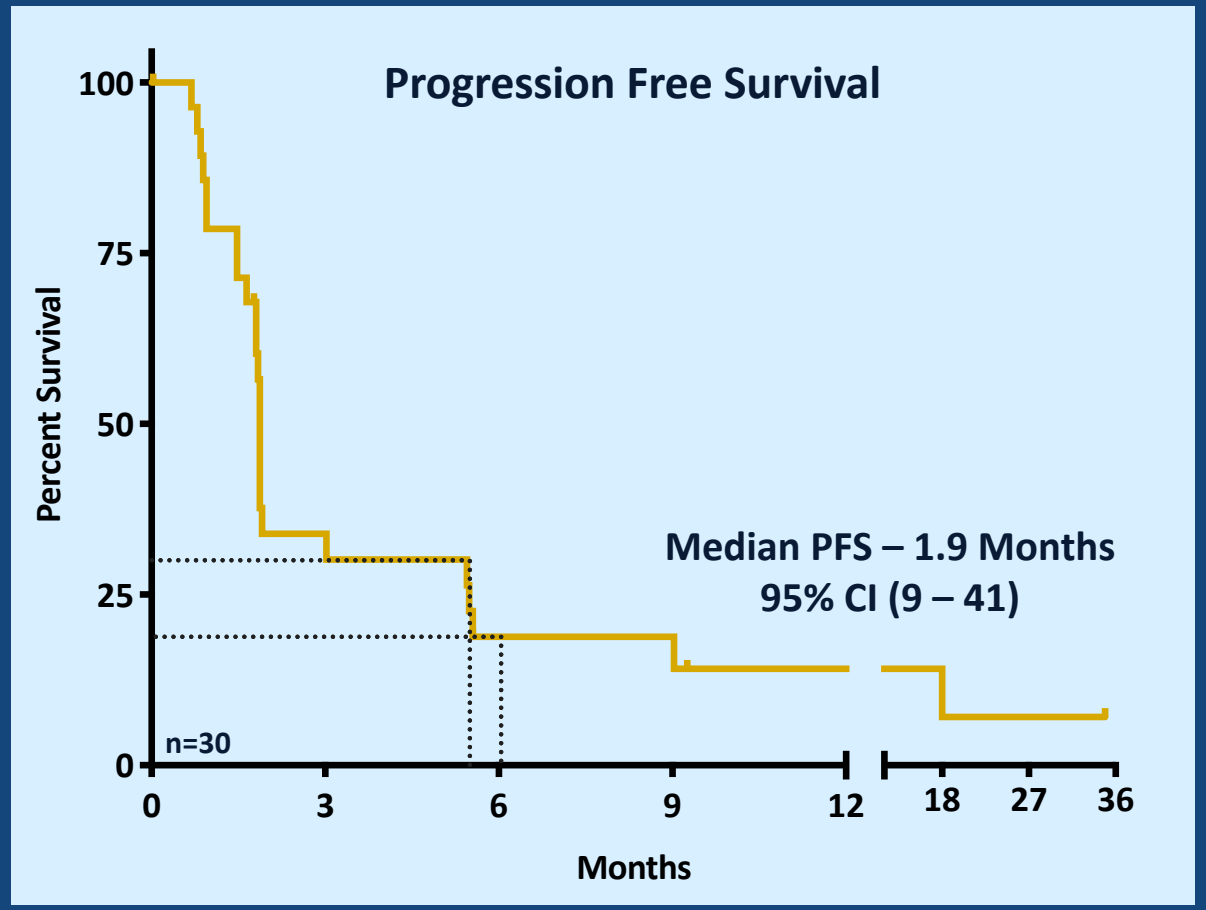
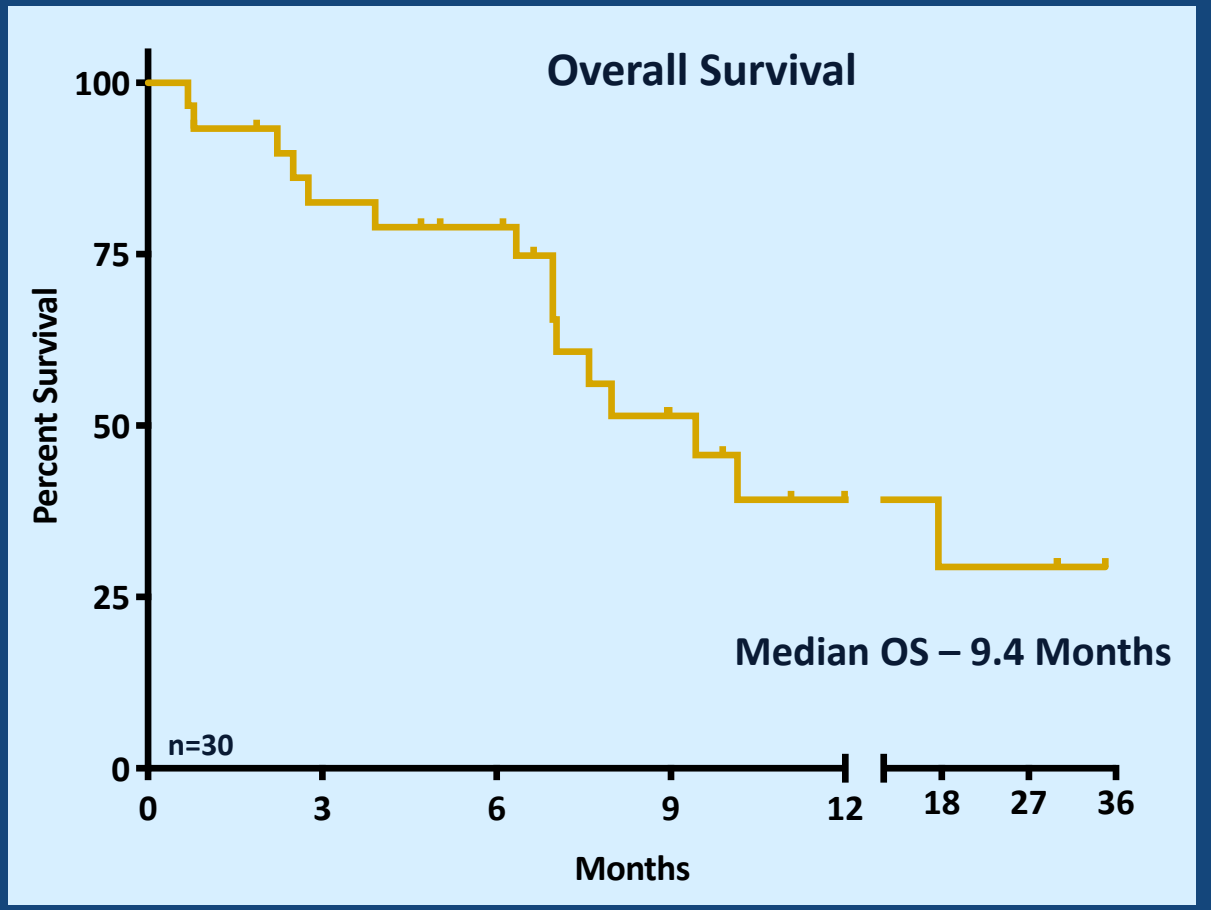
ARM D Results – PFS and OS

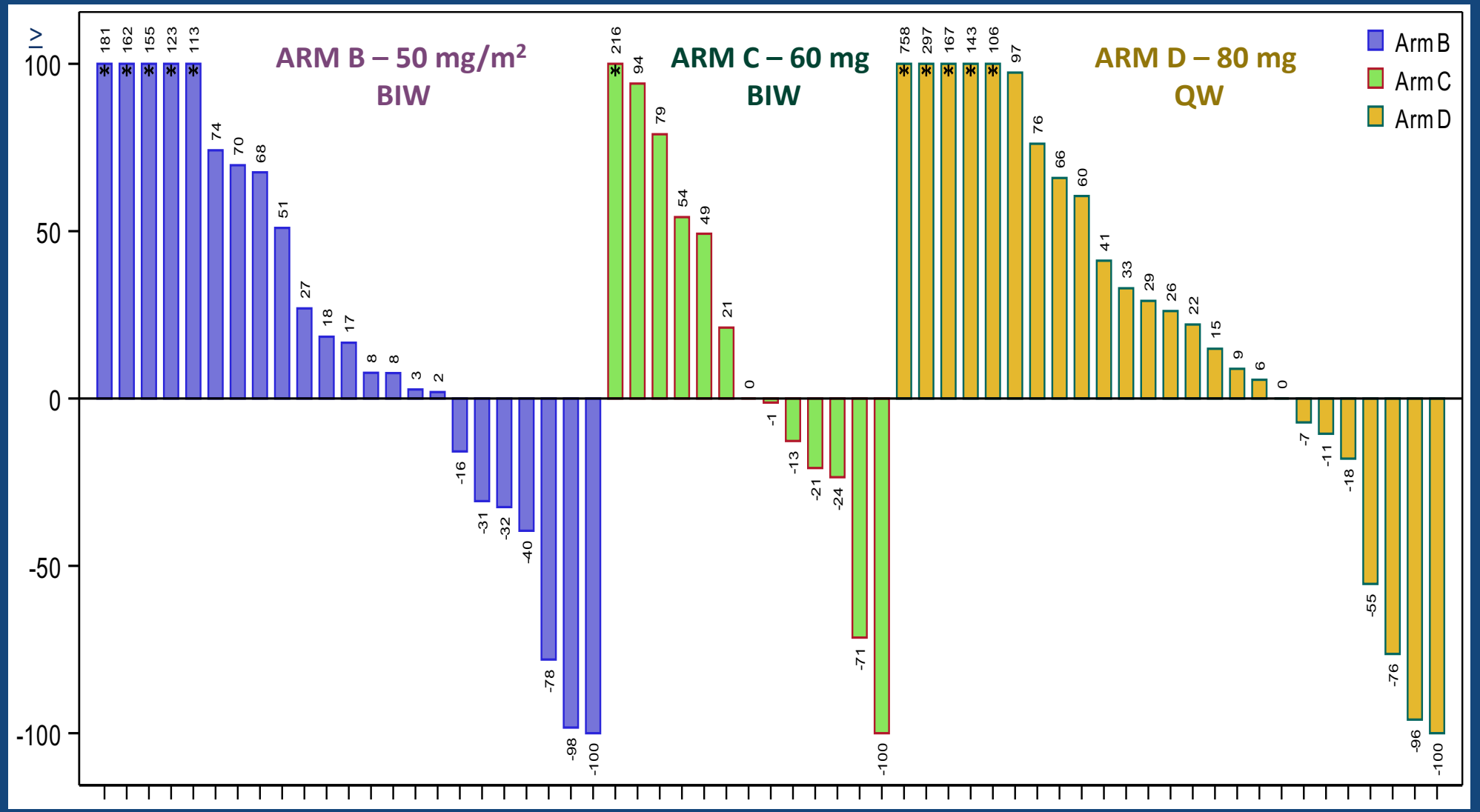




Months	0	1.5	3.0	5.6	9.0	18.0	34.9
Patients at Risk	30	22	9	6	4	2	1

Months	0	2.8	6.1	9.0	12.0	17.7	29.9	30.0	34.9
Patients at Risk	30	24	20	10	5	4	3	2	1

Selinexor Tumor Effect



* Denotes patient with increases beyond 100%

Arms B-D pooled

↓ tumor size in 29%

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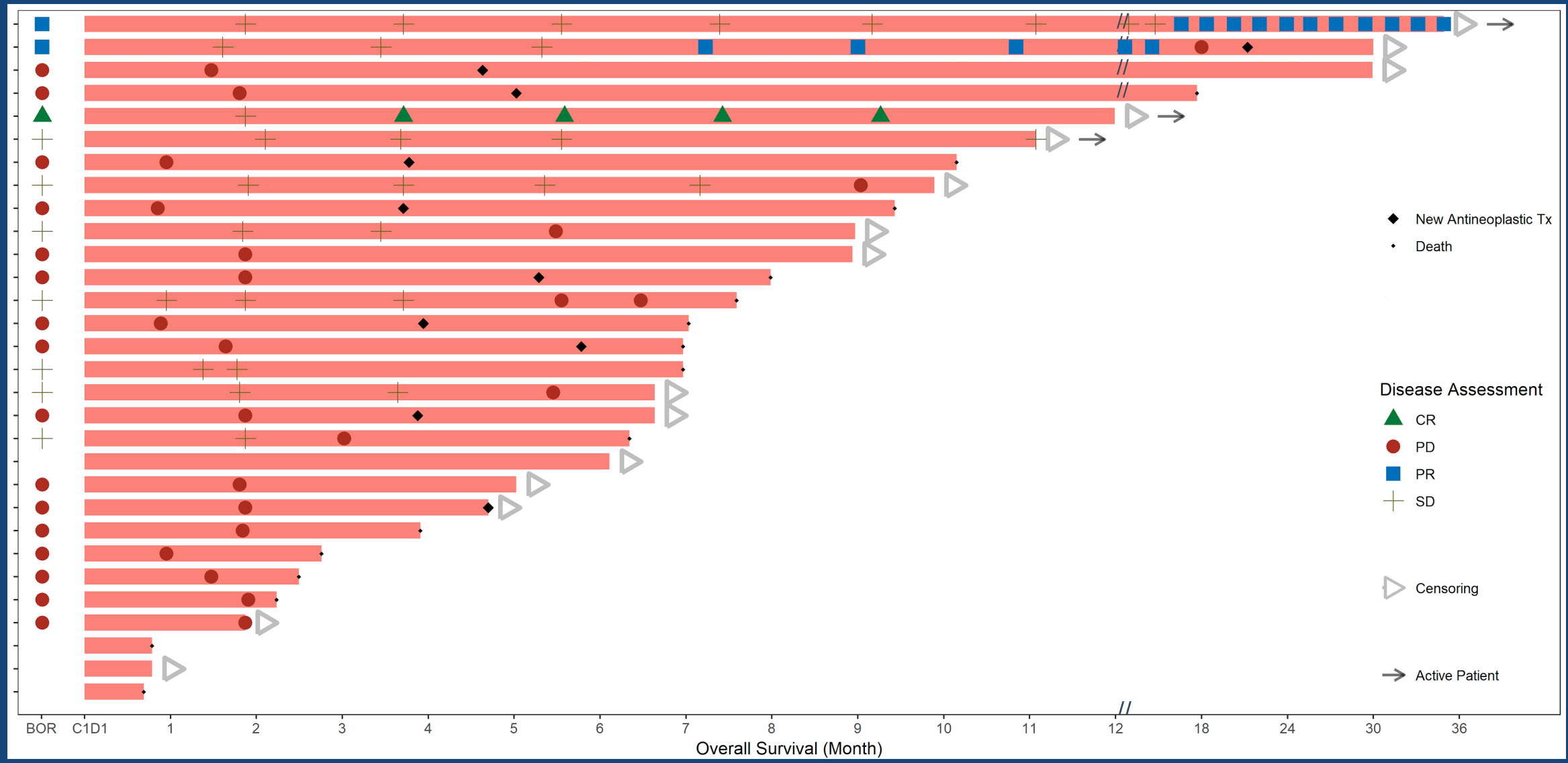
ARM D – Survival



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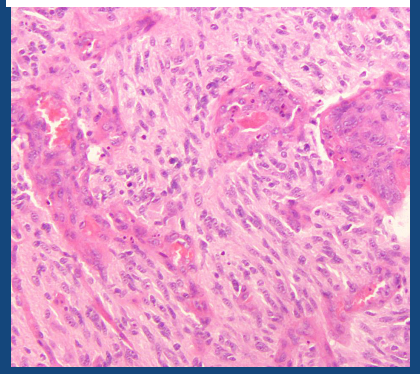
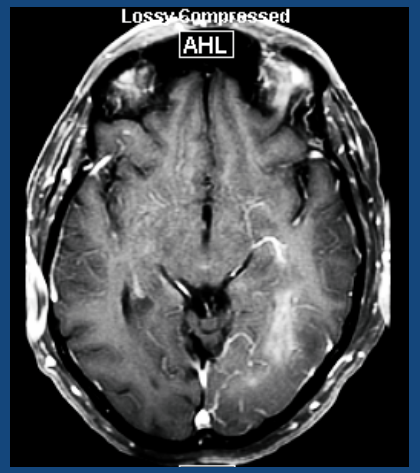
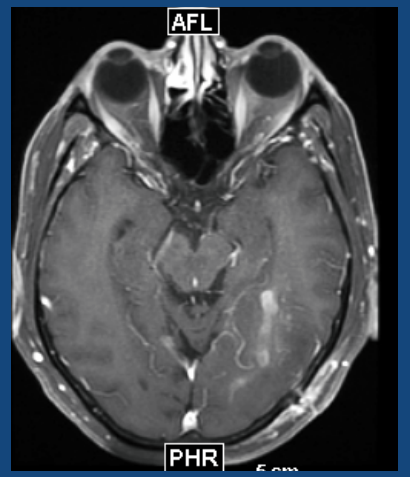
Patient 1: Durable PR 3L Therapy in Recurrent GBM

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

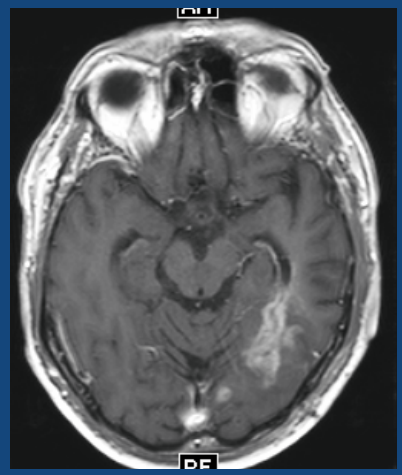




RT + TMZ

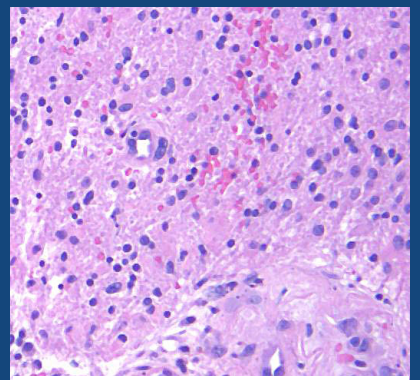


TMZ x 5

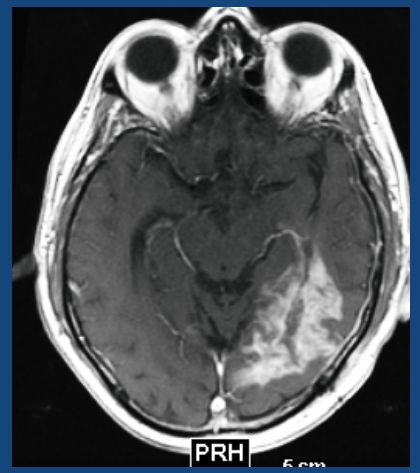


PD #1

AKTi+mTORi

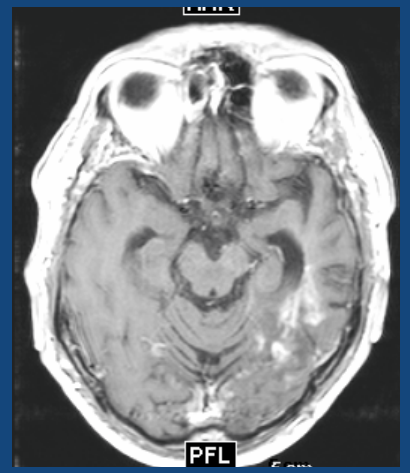


rGBM
(Subtotal resection)



PD #2 (post-op)

Selinexor



Ongoing PR

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

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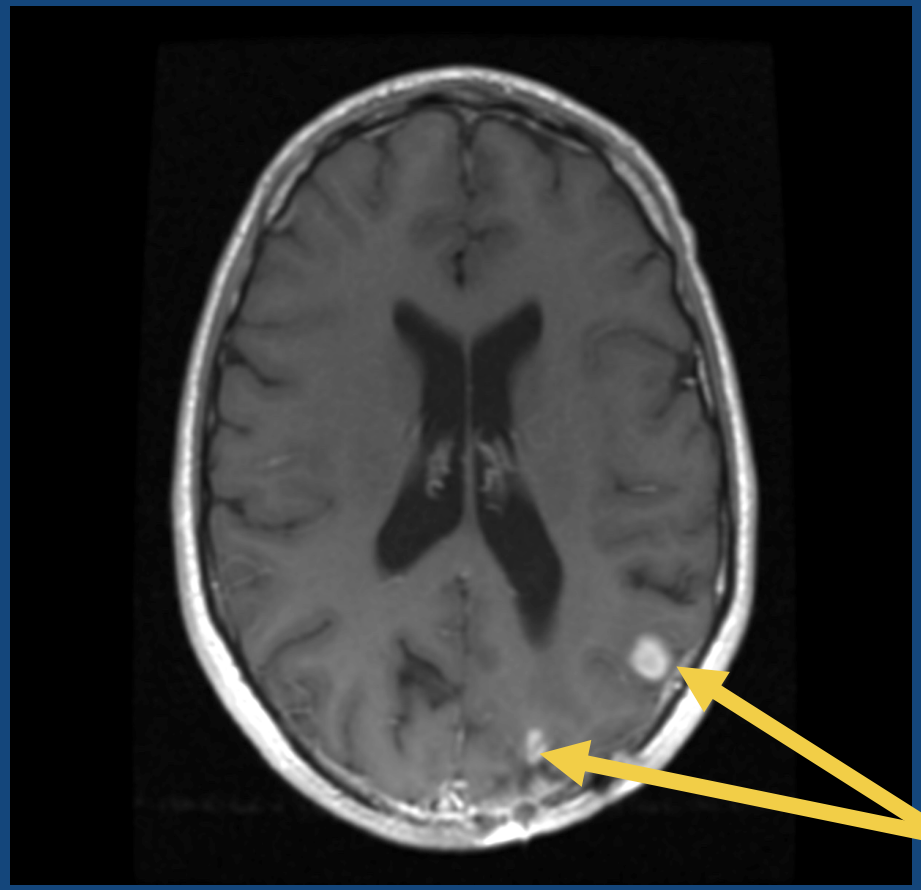
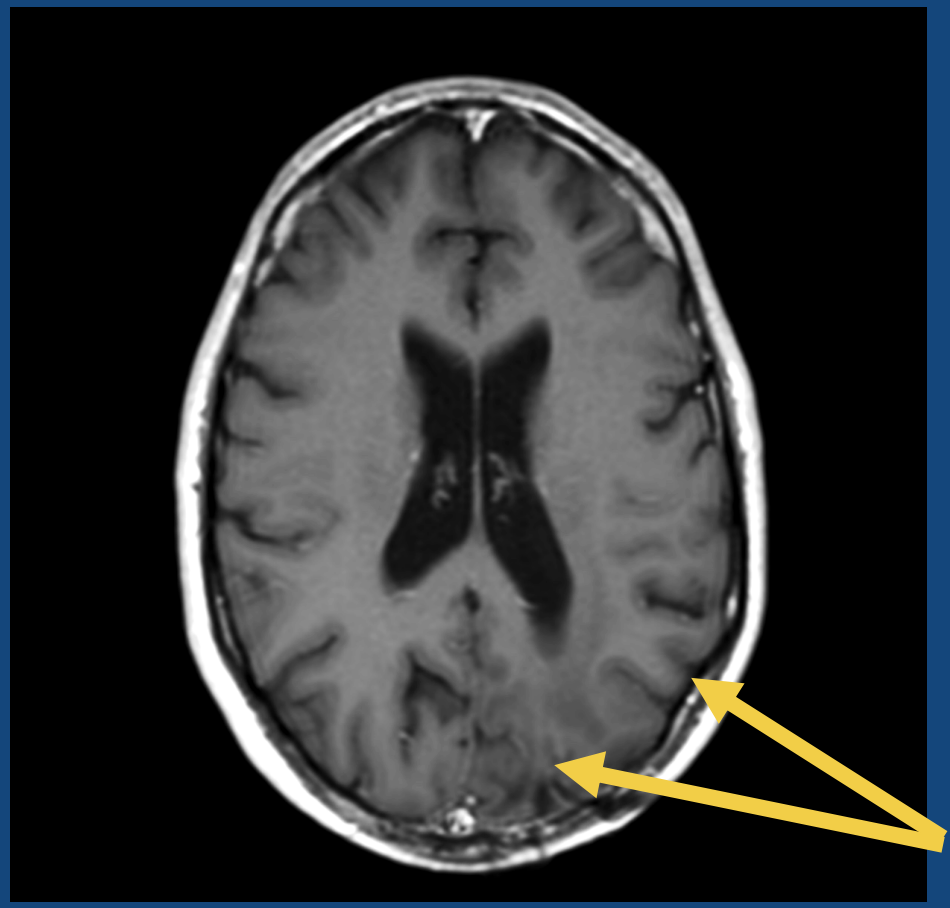
Patient 2: Complete Response Patient Profile



Selinexor

80 mg/w



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

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

Ongoing CR, on treatment > 1y

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, supporting further development
- Molecular correlative analyses ongoing to identify enrichment biomarker(s)

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- University of Groningen, Groningen, The Netherlands
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