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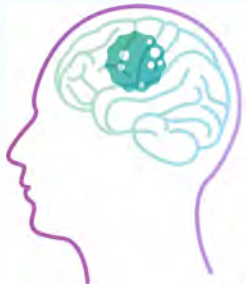
Clinical Case Study:

Using a Multi-pronged Approach to Treating Recurrent GBM – Overcoming the Tumor and its Microenvironment

Fahar Merchant, PhD

President & CEO, Medicenna Therapeutics



Glioblastoma Drug Development Summit

TSX: **MDNA**
OTCQB: **MDNAF**

Disclosure

Officer and Director of Medicenna
Shareholder of Medicenna (TSX: MDNA, OTCQB: MDNAF)

Therapeutic Challenges of GBM

- Blood Brain Barrier (BBB) blocks transport of therapy to tumor
- High doses are required to overcome BBB causing systemic toxicities
- GBM is very infiltrative
- Recurrent GBM patients have a compromised immune system following chemo-radiation which is further exacerbated by steroid use
- Tumor microenvironment (TME) comprises 40% of GBM tumor mass[1]
- GBM is heterogeneous with a highly complex tumor biology
  - IDH mutated vs. wild-type
  - MGMT promoter methylated vs. unmethylated

1) Kennedy B, et al (2013). J Oncol. Vo; 2013: 486912. 2) Hegi ME (2005). N Engl J Med;352:997-1003. 3) Yan H, et al (2009). N Engl J Med; 360:765-73.

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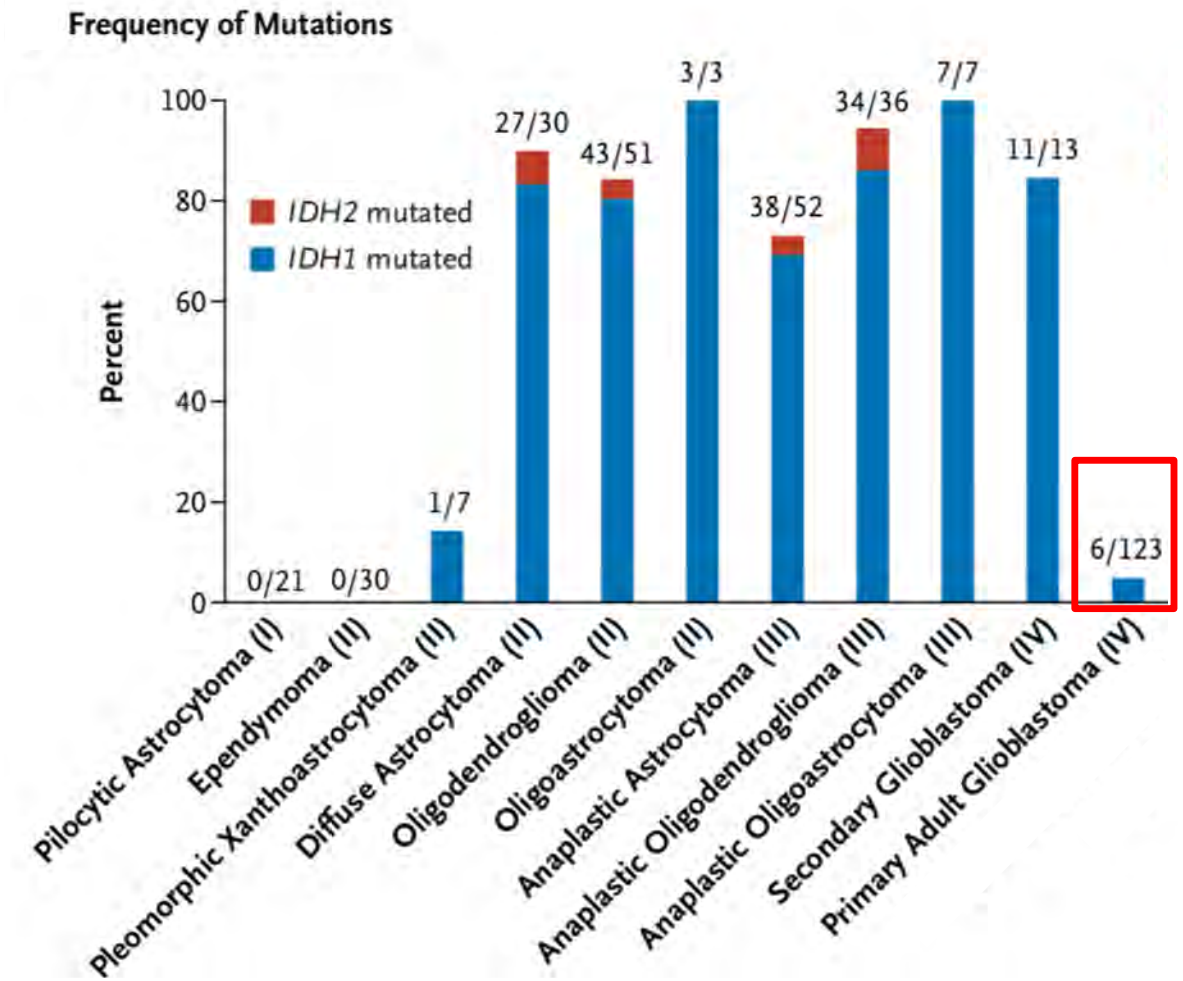
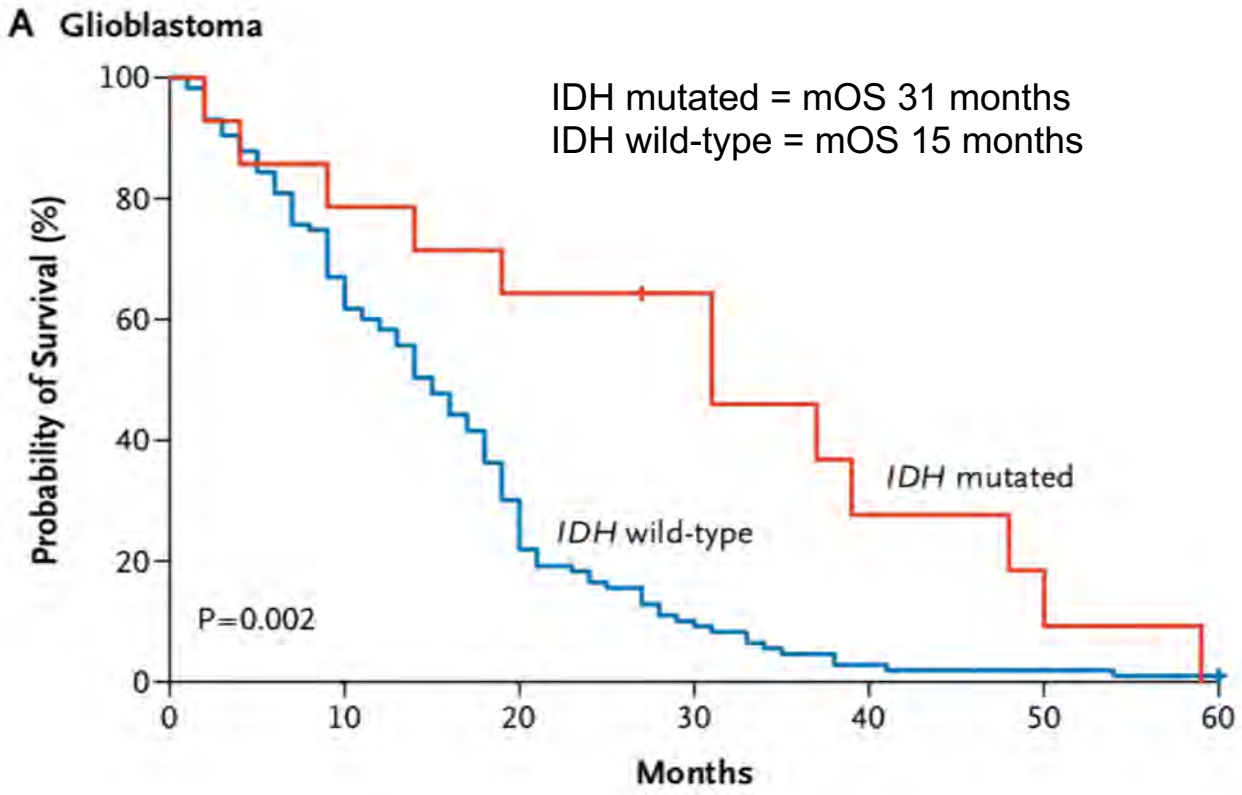
GBM with IDH Wild-Type is Associated with Poor Prognosis

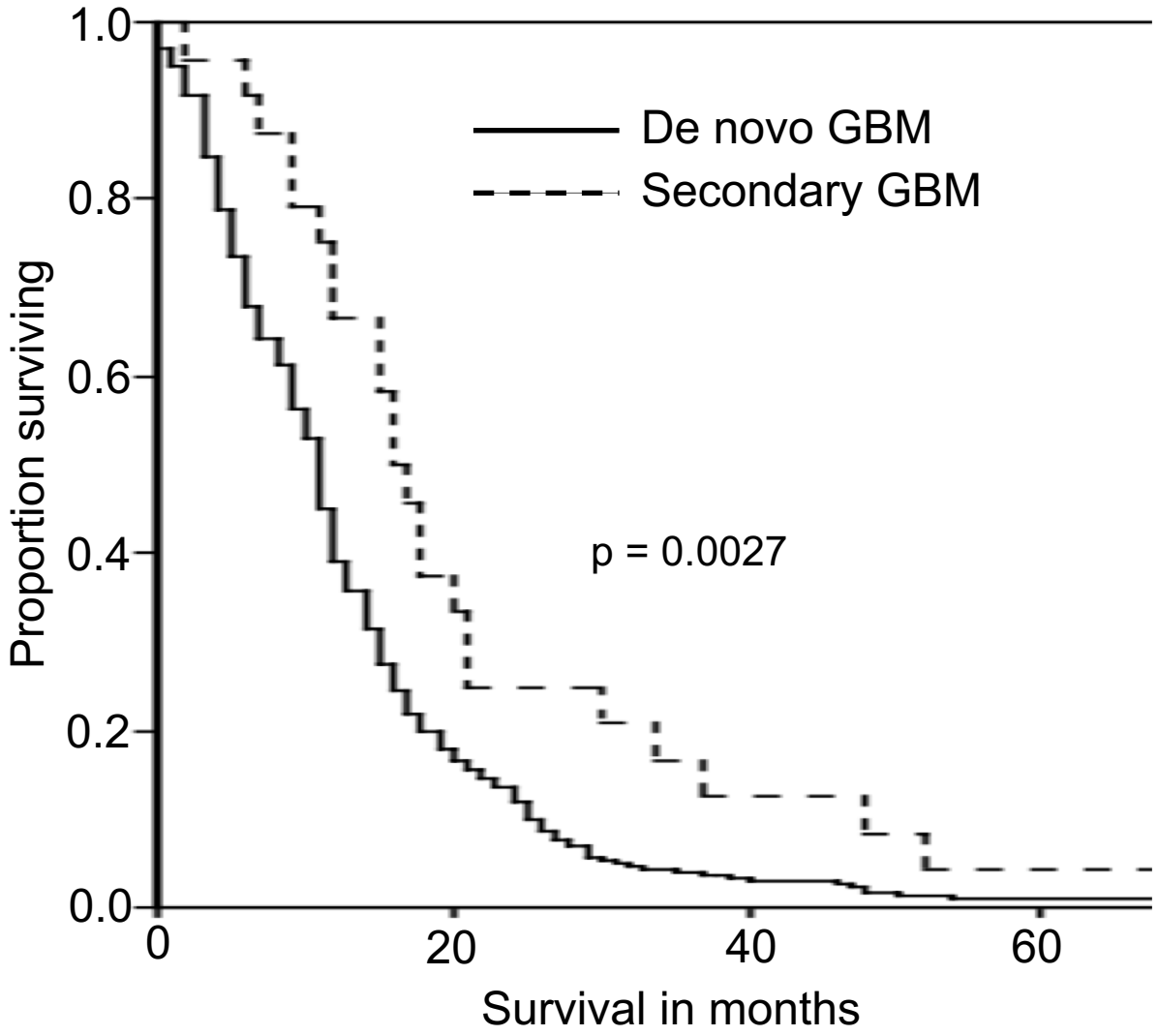




IDH mutated = mOS 31 months
IDH wild-type = mOS 15 months

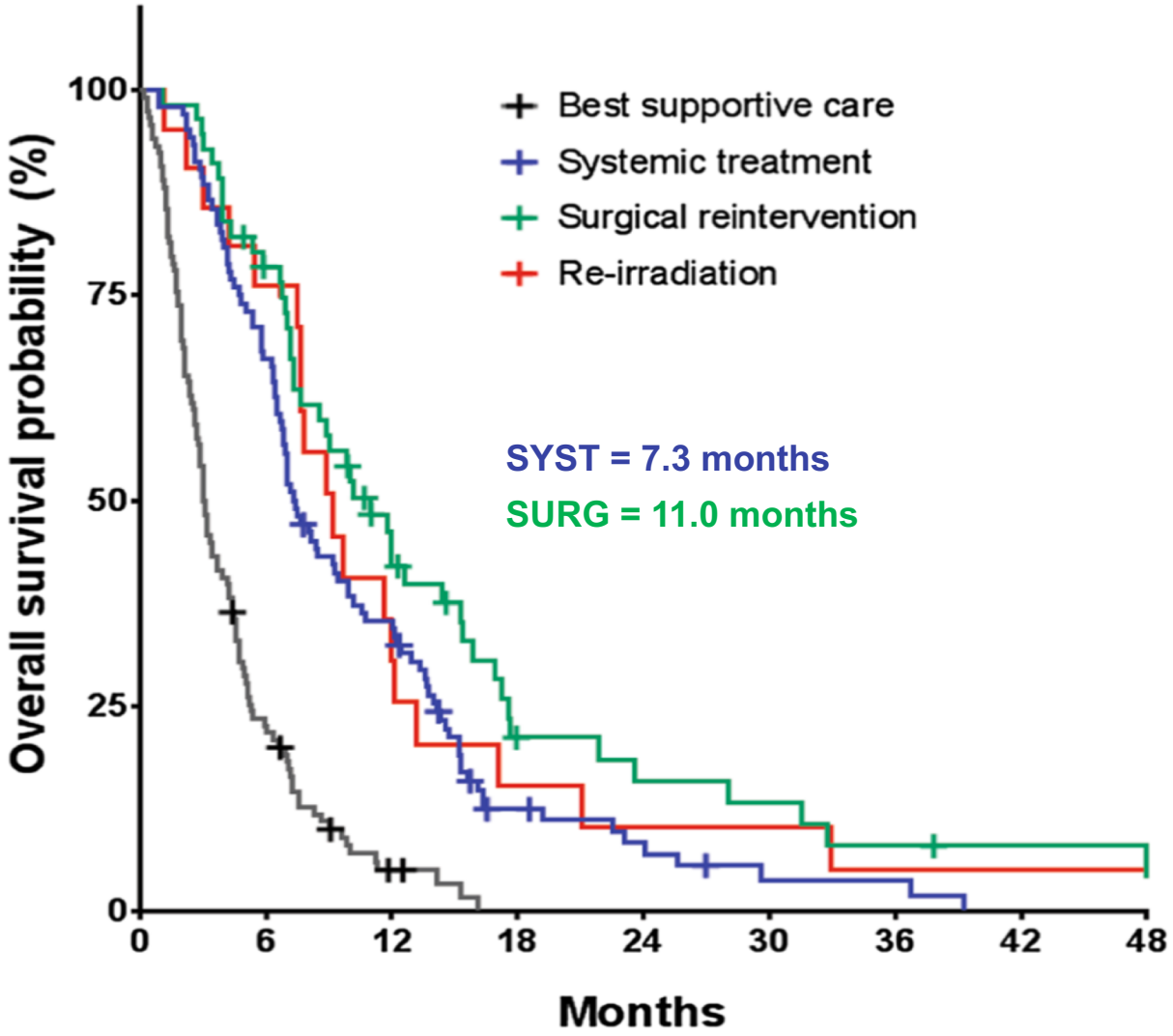
Yan et al. NEJM, 2009

De novo GBM and No Surgery at Relapse Lowers Survival



Data of 340 patients with newly-diagnosed GBM were retrospectively analyzed. GBM type (de novo or secondary) was suggested to influence survival by univariate analysis.

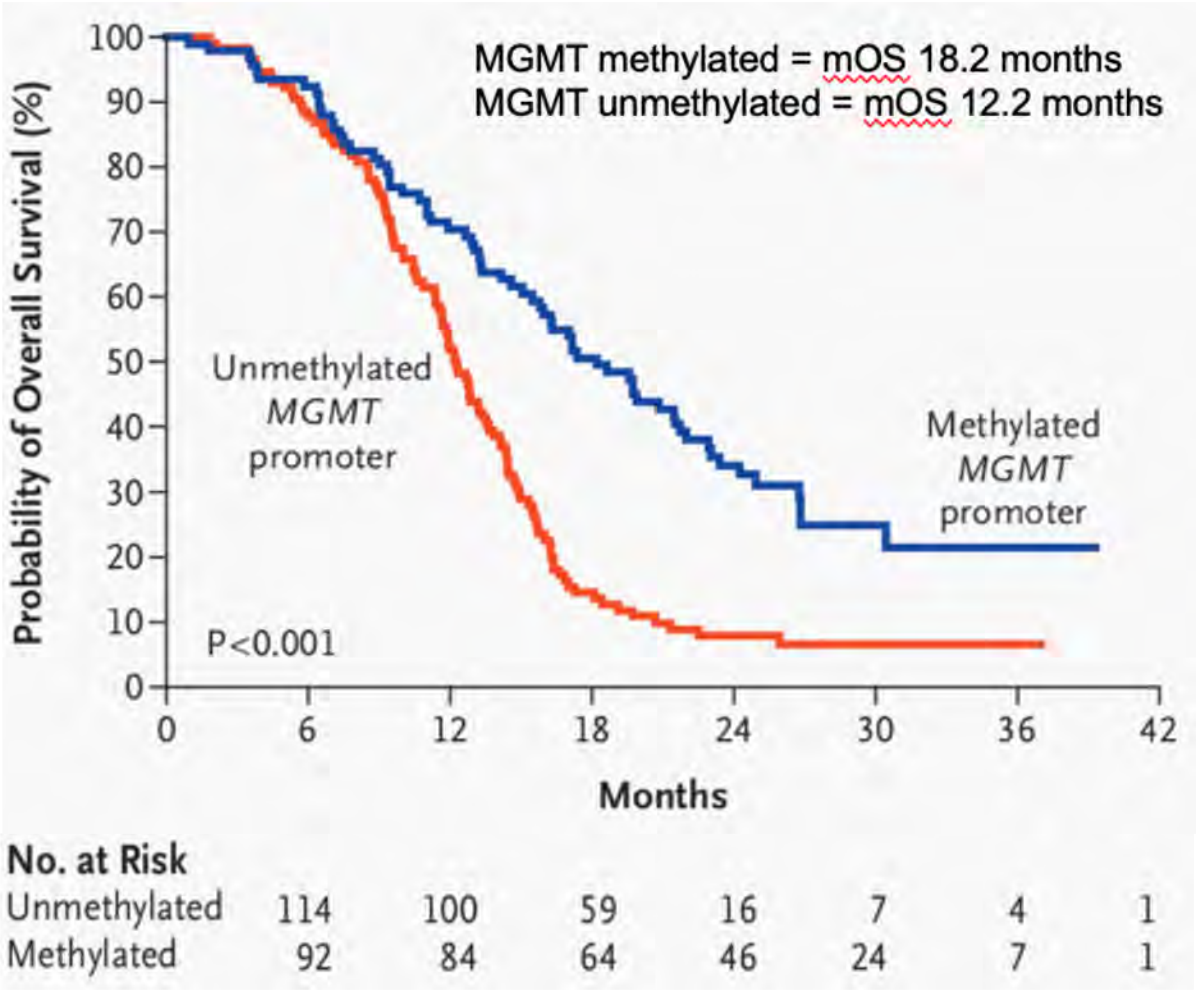
Mineo et al. Acta Neurochir, 2005



Data of 299 patients recurrent GBM were retrospectively analyzed. Different treatments were suggested to influence survival by univariate analysis.

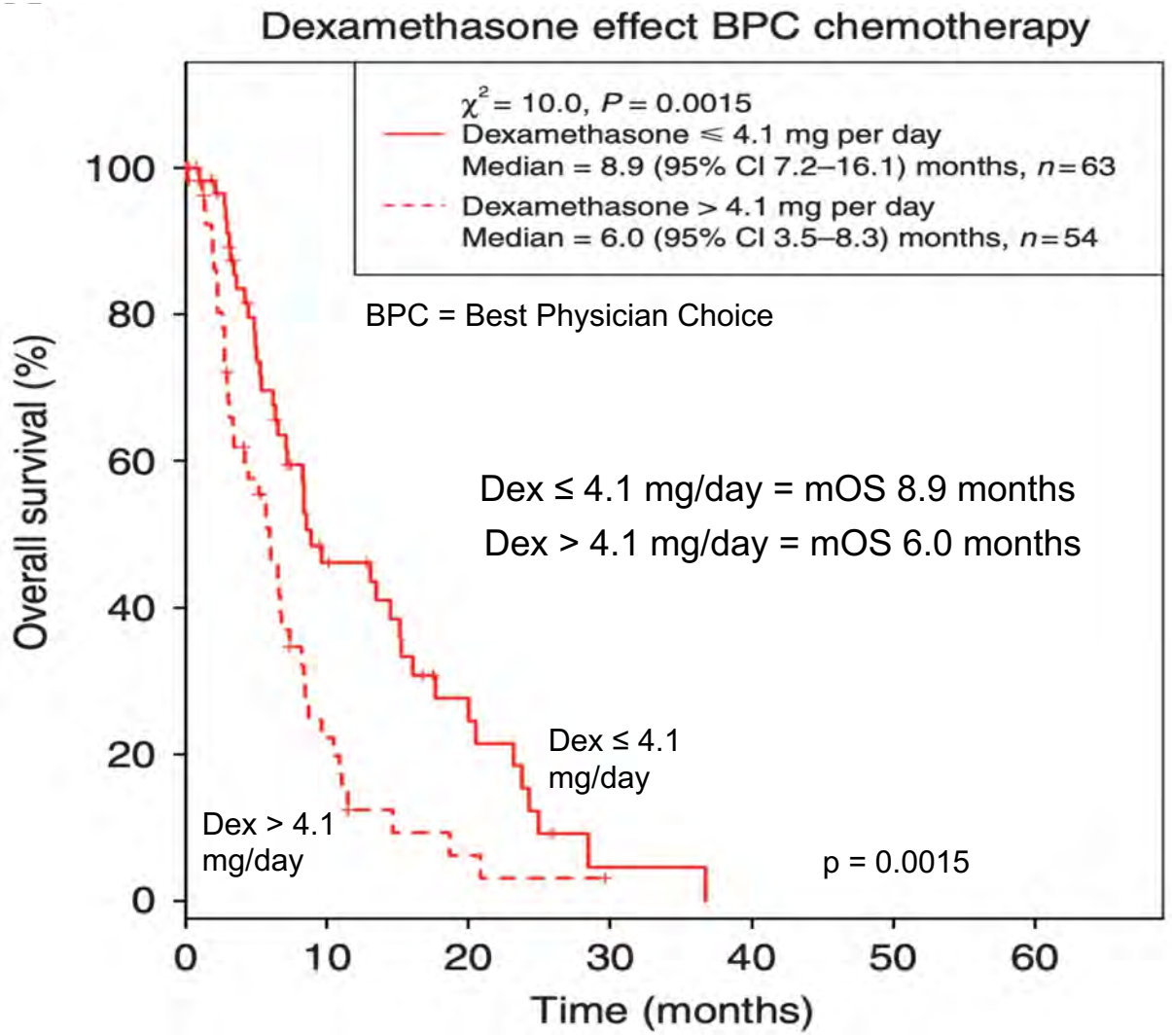
Van Linde et al. J. Neurooncol, 2017

Unmethylated MGMT Promoter and Steroid Use Negatively Impact Survival



Hegi et al. NEJM, 2005

Overall survival of 206 patients with newly diagnosed GBM for whom MGMT status could be evaluated irrespective of treatment assignment (RT or RT/TMZ).



Overall Survival with respect to dexamethasone requirement from recurrent GBM subjects enrolled in the phase III with BPC chemotherapy (NCT00379470).

Wong et al. BJC, 2015

IL4 Receptor

A New Prognostic Marker for Aggressive GBM

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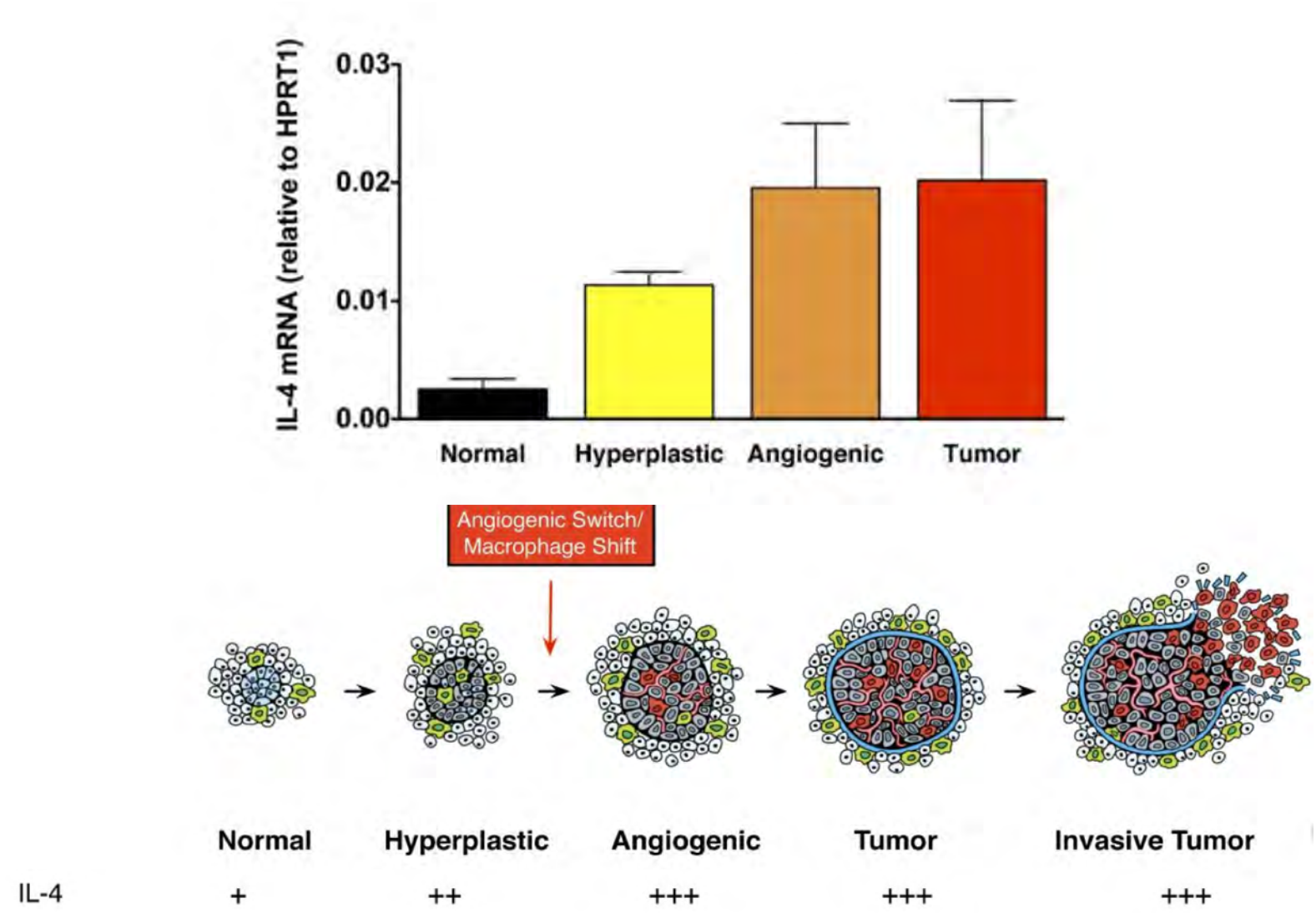
IL4 Levels Progressively Increase During Tumor Development



- IL4/IL4R Axis Responsible for Th2 Bias – Promotes Tumor Growth
- Induces cancer-promoting phenotypes in Tumor Associated Macrophages (TAMs)
- Boosts Myeloid Derived Suppressor Cells (MDSCs) in TME
- Enhances glucose and glutamine metabolism
- Up-regulates anti-apoptotic molecules (cFlip; Bcl-xL)

Adapted from: Gocheva et al, 2010 Genes Dev, 1;24(3):241-55.

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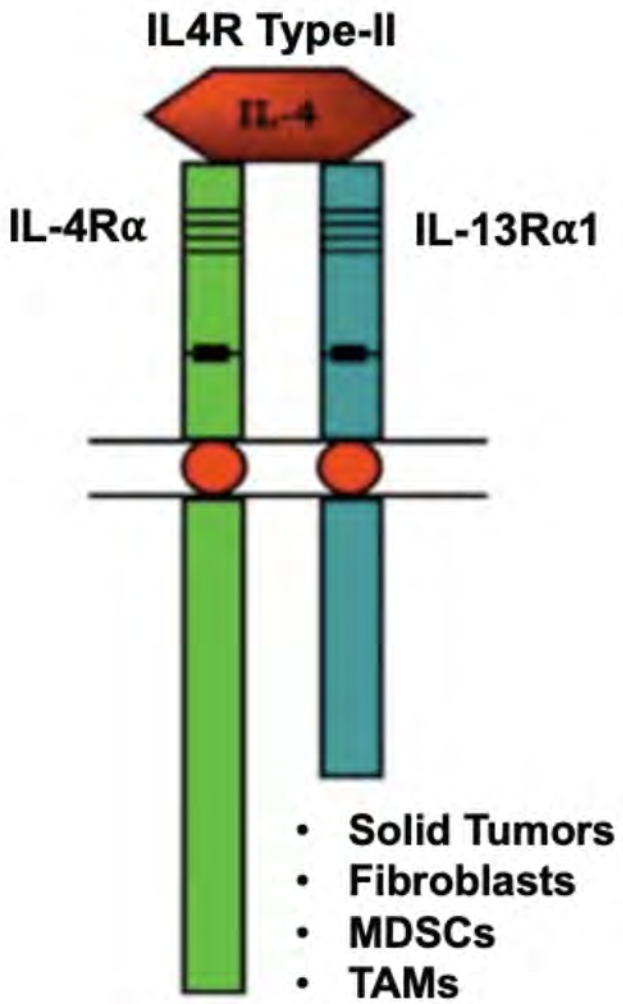
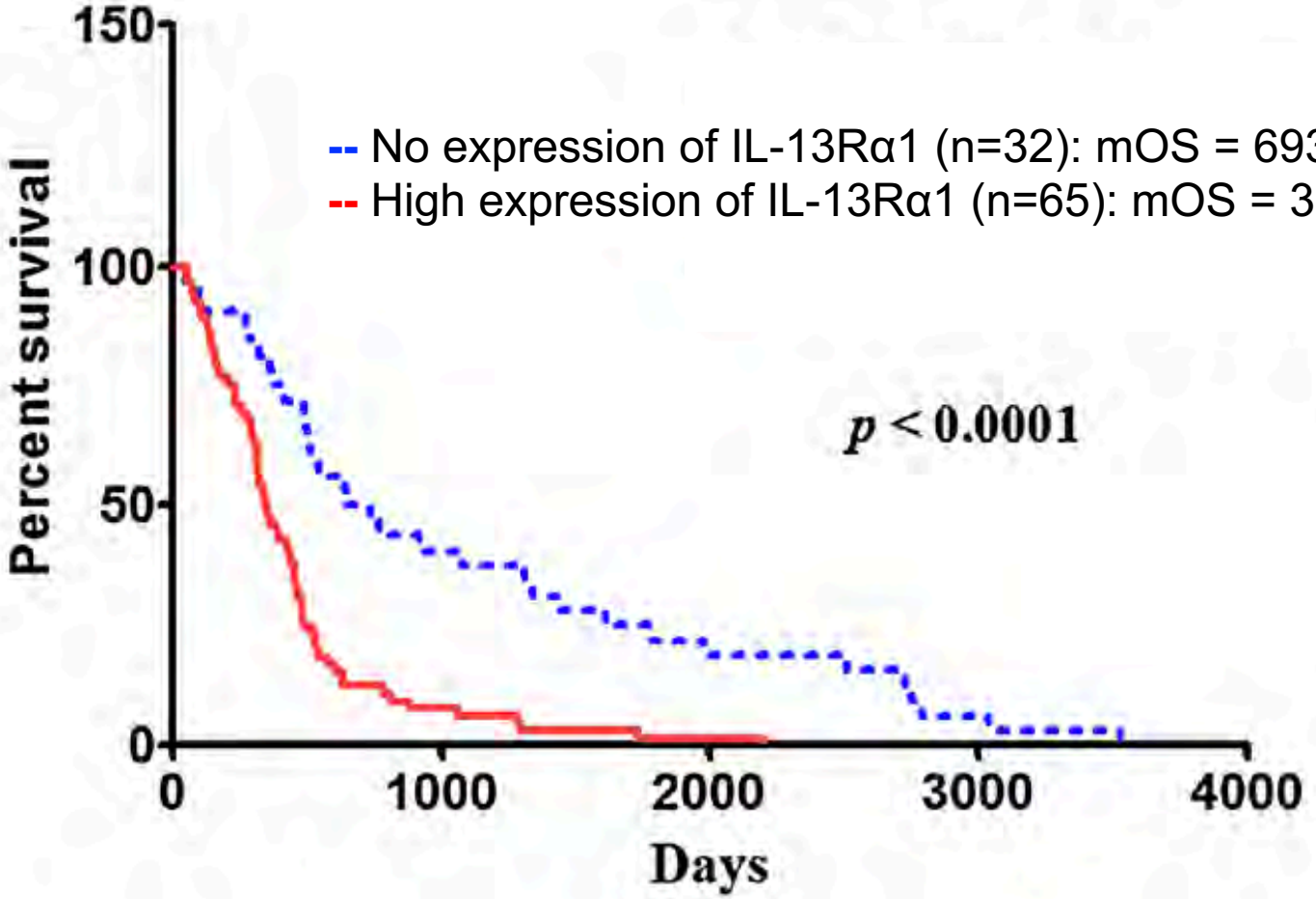
Type 2 IL4R Expression Predicts Poor Survival in GBM



Adapted from Puri et al., 2009

Survival in Subjects with GBM - TCGA



Han J. and Puri R. J of Neuro-Oncology (2018) 136:463–474

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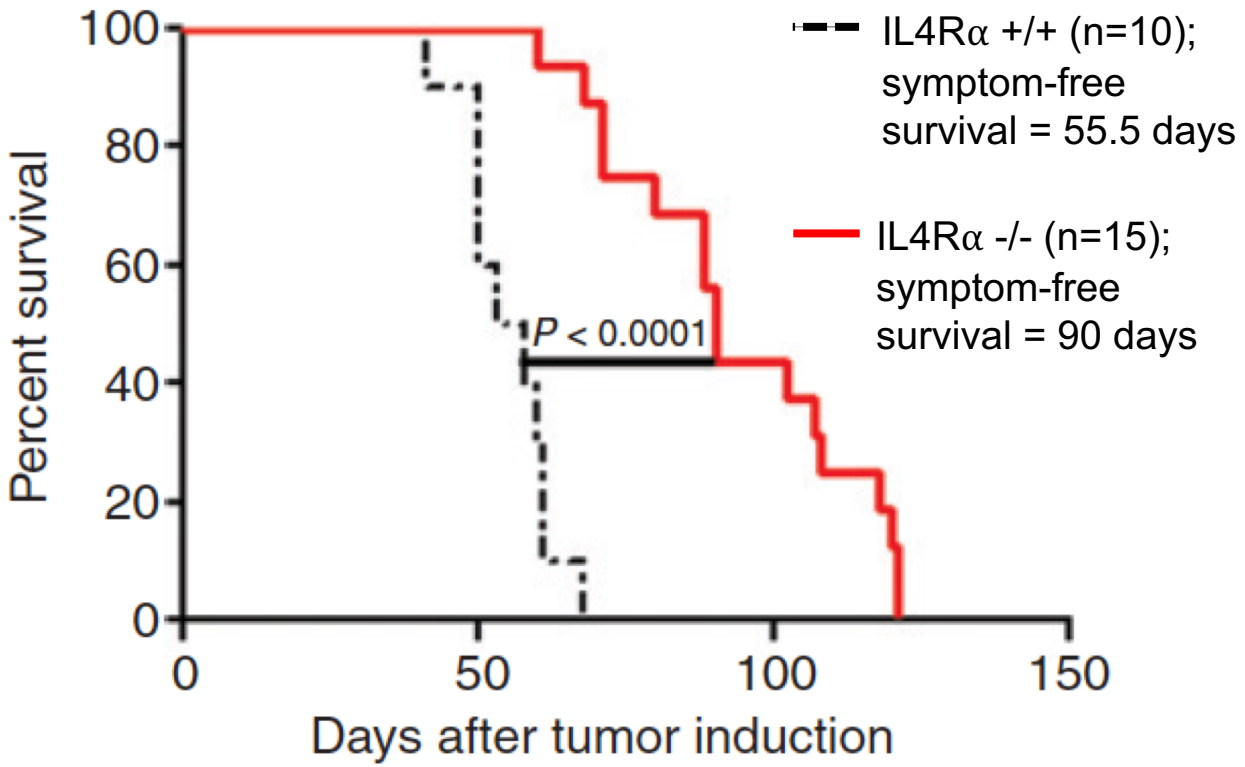
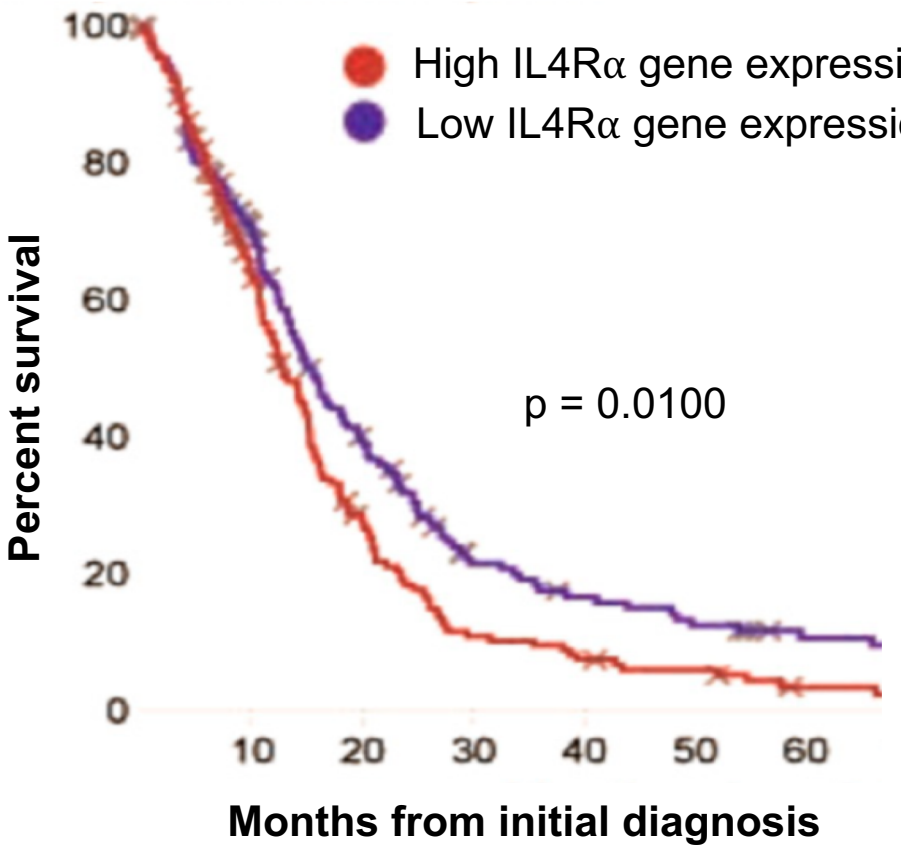
High IL4Rα Expression Predicts Poor Survival in GBM

Survival in BALB/c Glioma Mouse Model



Kohanbash G et al. Cancer Res 2013;73:6413-6423

Survival in GBM Patients - TCGA



Data Derived from TCGA GBM Database (https://tcga-data.nci.nih. gov/tcga/)

D'Alessandro G, et al. Cancers (Basel). 2019

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IL4Rα is Expressed in CNS Tumors But Not in Normal Brain

> 300 Patient Biopsies Analyzed Show IL-4R Over-Expression[1-7]

Glioblastoma **76%**	Mixed Adult Glioma **>83%**	Mixed Pediatric Glioma **76%**	Pediatric DIPG **71%**
Medulloblastoma **100%**	Adult Pituitary Adenoma **100%**	Meningioma **77%**	Normal Brain Tissue **0%**

1. Joshi BH, et. al. Cancer Res 2001;61:8058-8061.
2. Puri RK, et. al., Cancer Res 1996;56:5631-5637.
3. Kawakami M, et. al., Cancer. 2004 Sep 1; 101(5):1036-42.
4. Berlow NE, et al. PLoS One. 2018 Apr 5; 13(4):e0193565.
5. Joshi BH, et. al. British J of Cancer (2002) 86, 285 –291.
6. Chen L, et al. Neurosci Lett. 2007 Apr 24; 417 (1):30-5.
7. Puri S, et. al., Cancer. 2005 May 15; 103(10):2132-42.

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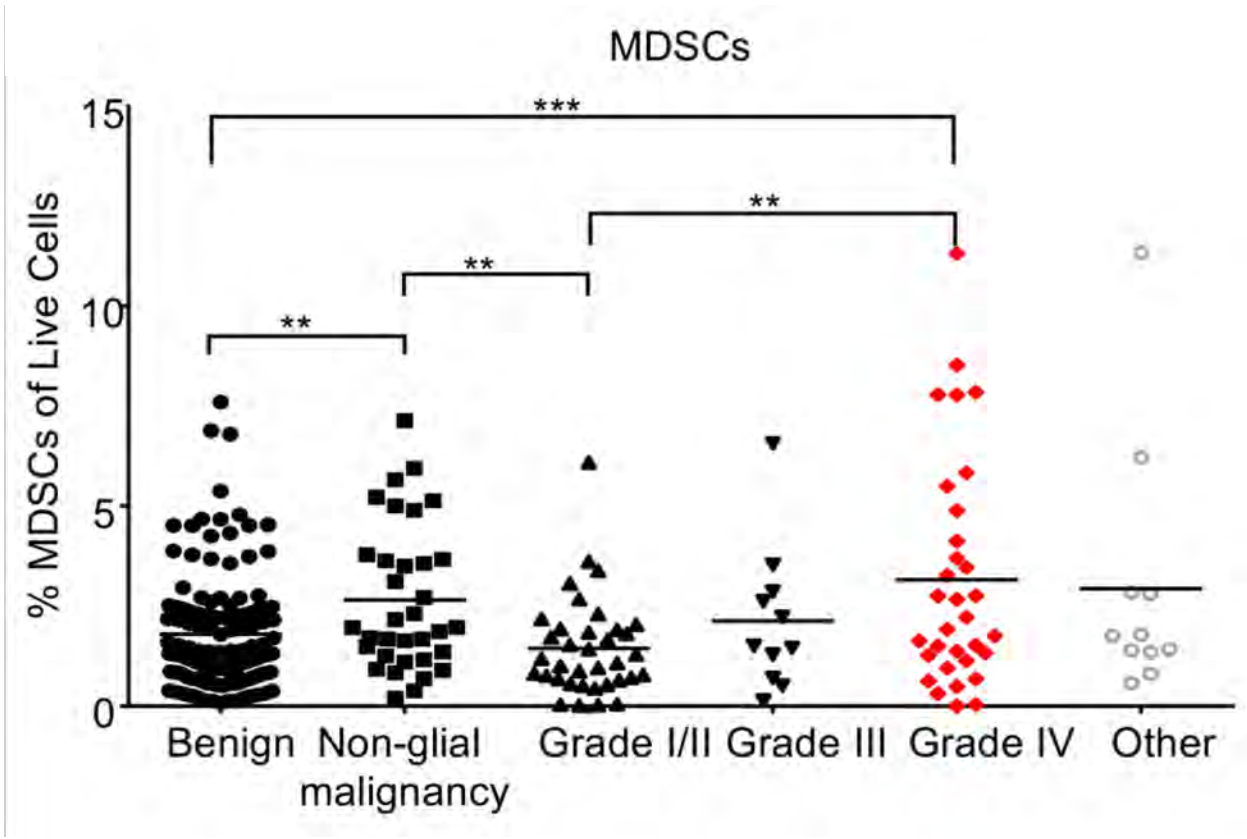
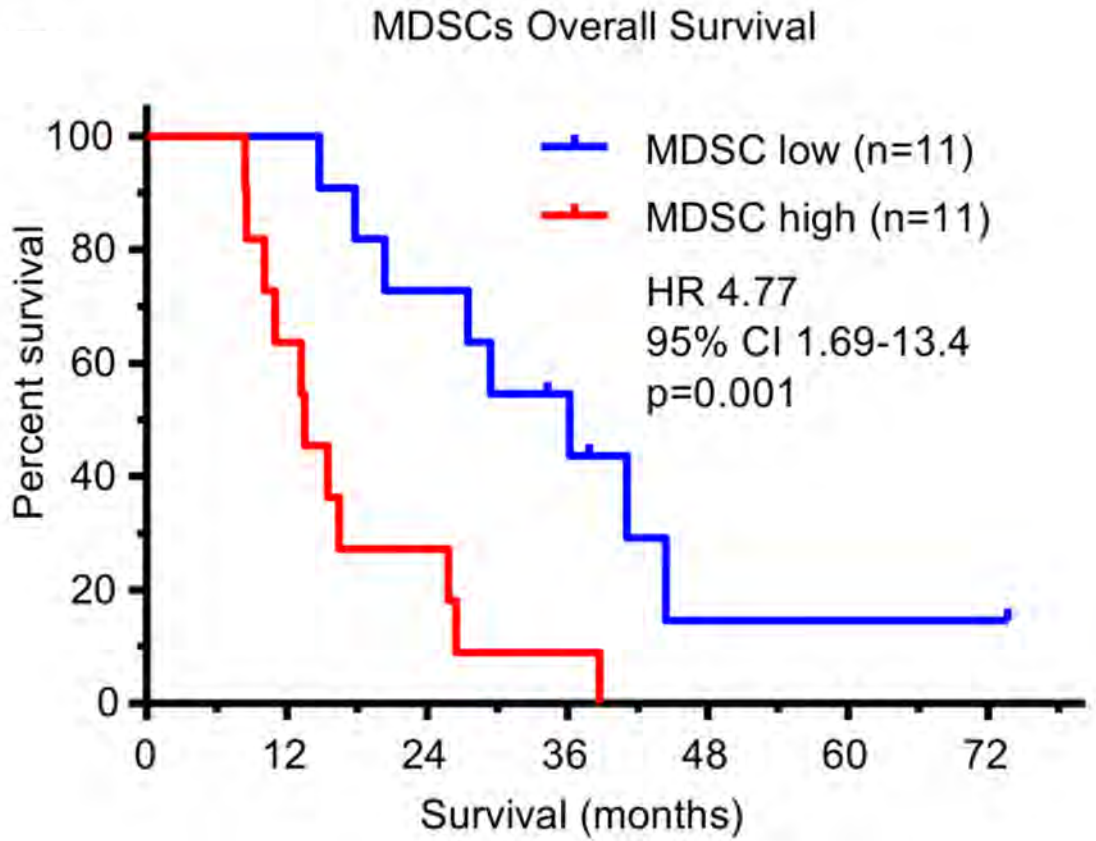
Increase in MDSCs Associated with Higher Grade Gliomas and Poor Survival





Peripheral blood MDSCs are increased in GBM patients compared with other brain tumor patients, and intratumoral MDSCs are predictive of patient prognosis

Alban et al., JCI Insight, 2018

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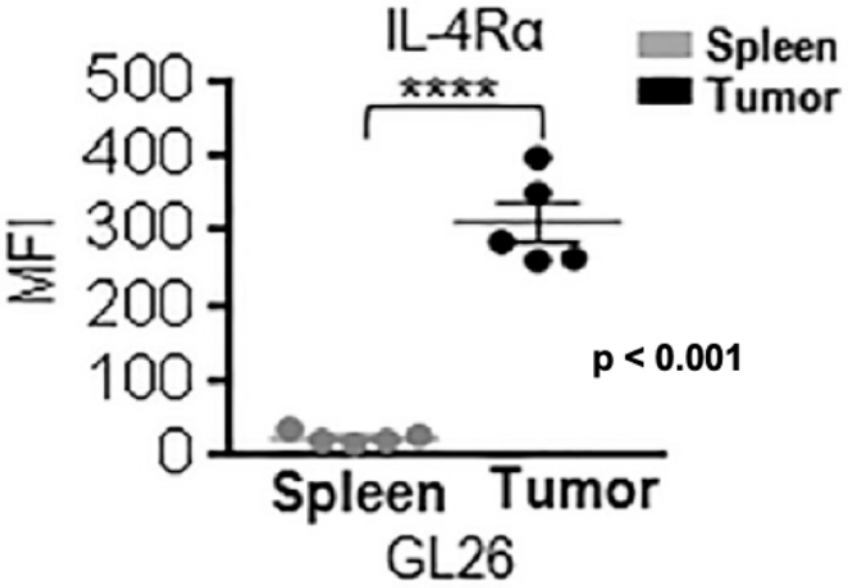
IL4Rα Expression Increases in GBM Infiltrating MDSCs

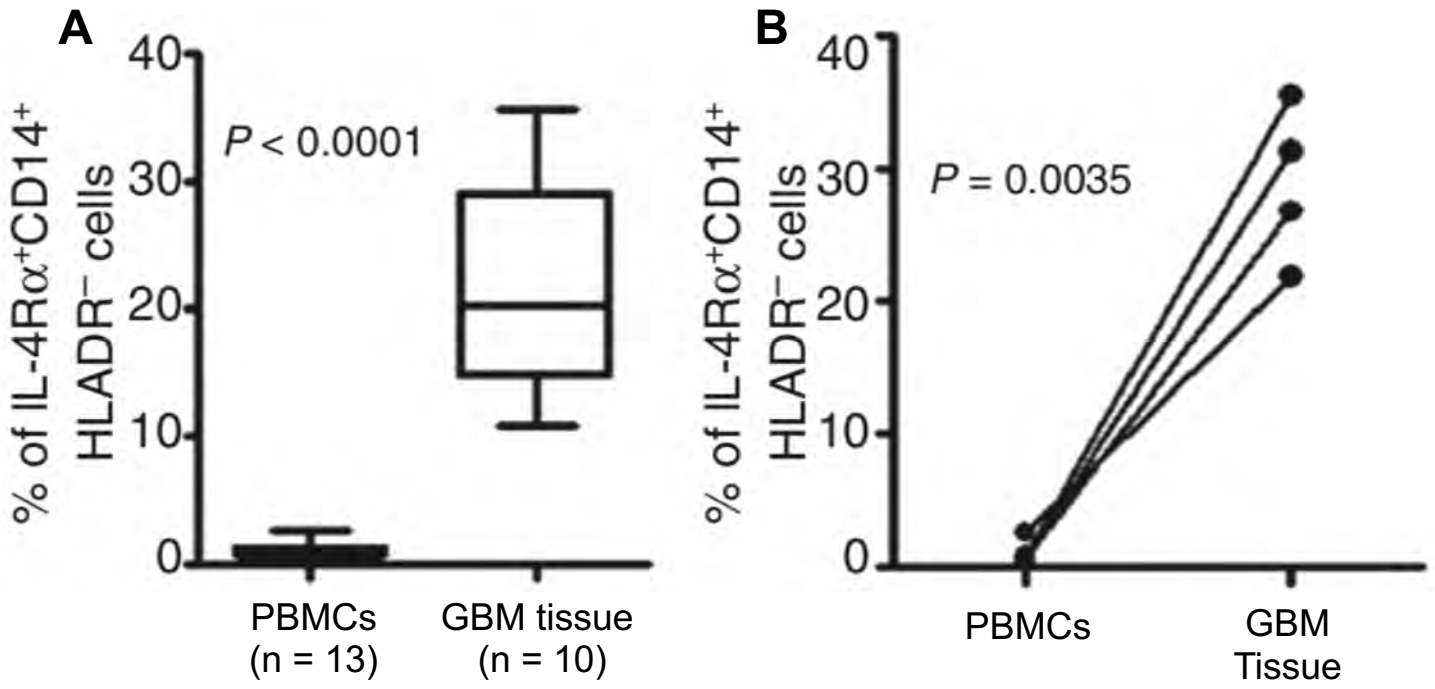
MDSCs from GL26 tumor-bearing mice



TME-MDSCs show 12-fold increase in IL-4Rα expression compared to splenic myeloid cells

Kamran N, et. al., (2017). Mol Ther 25:232-248

GBM patient-derived PBMCs and tumor tissues



IL-4Rα expression on human tumor-infiltrating monocytes isolated from glioblastoma patient-derived PBMCs and fresh glioblastoma tissues.

Adapted from Kohanbash G et al. Cancer Res 2013

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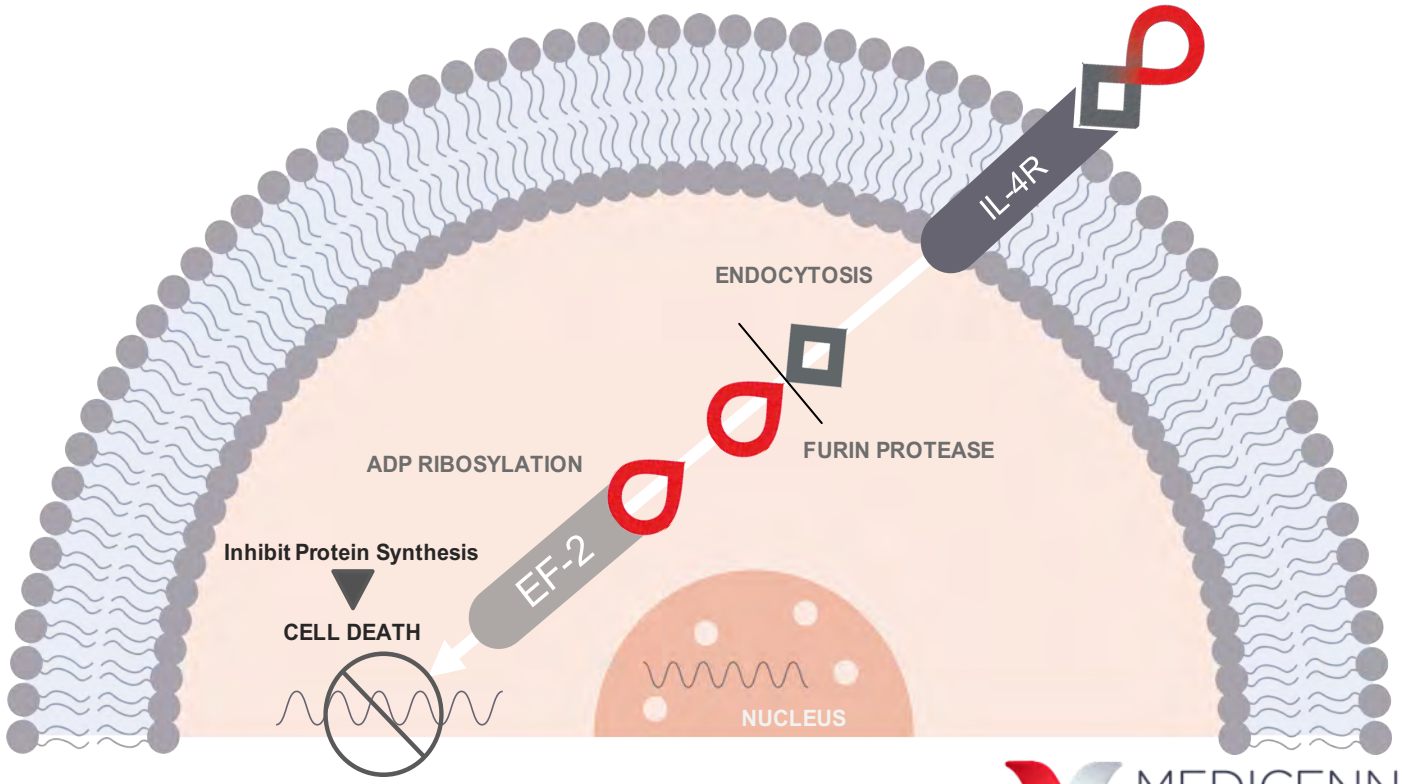
MDNA55: A Potent IL4R Targeted Molecular Trojan Horse

- **MDNA55:** Targets the IL4R expressed in CNS tumors but not healthy brain
- **Highly Selective:** Avoids collateral damage to healthy brain
- **Disrupts the Tumor Microenvironment (TME):** Targets IL4R positive MDSCs and reverses Th2 bias
- **Immunogenic Cell Death:** Anti-tumor immunity is initiated and remains active after MDNA55 is cleared

Targeting Domain
Circularly Permuted Interleukin-4 (cpIL-4)

Lethal Payload
Catalytic domain of *Pseudomonas* Exotoxin A
(FDA approved in 2018, Moxetumomab pasudotox)



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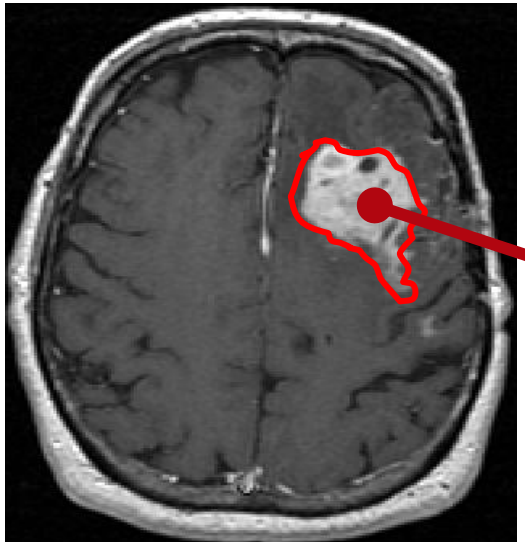
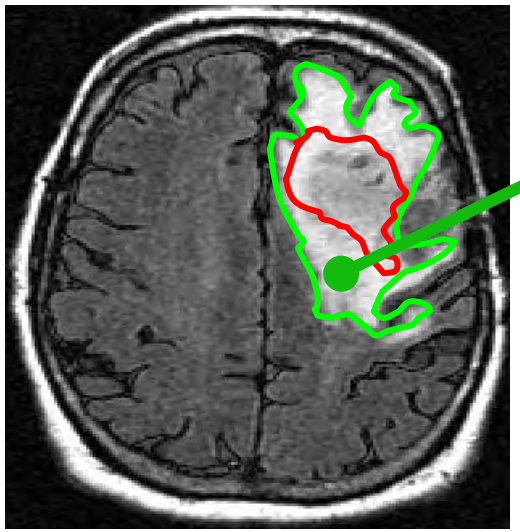
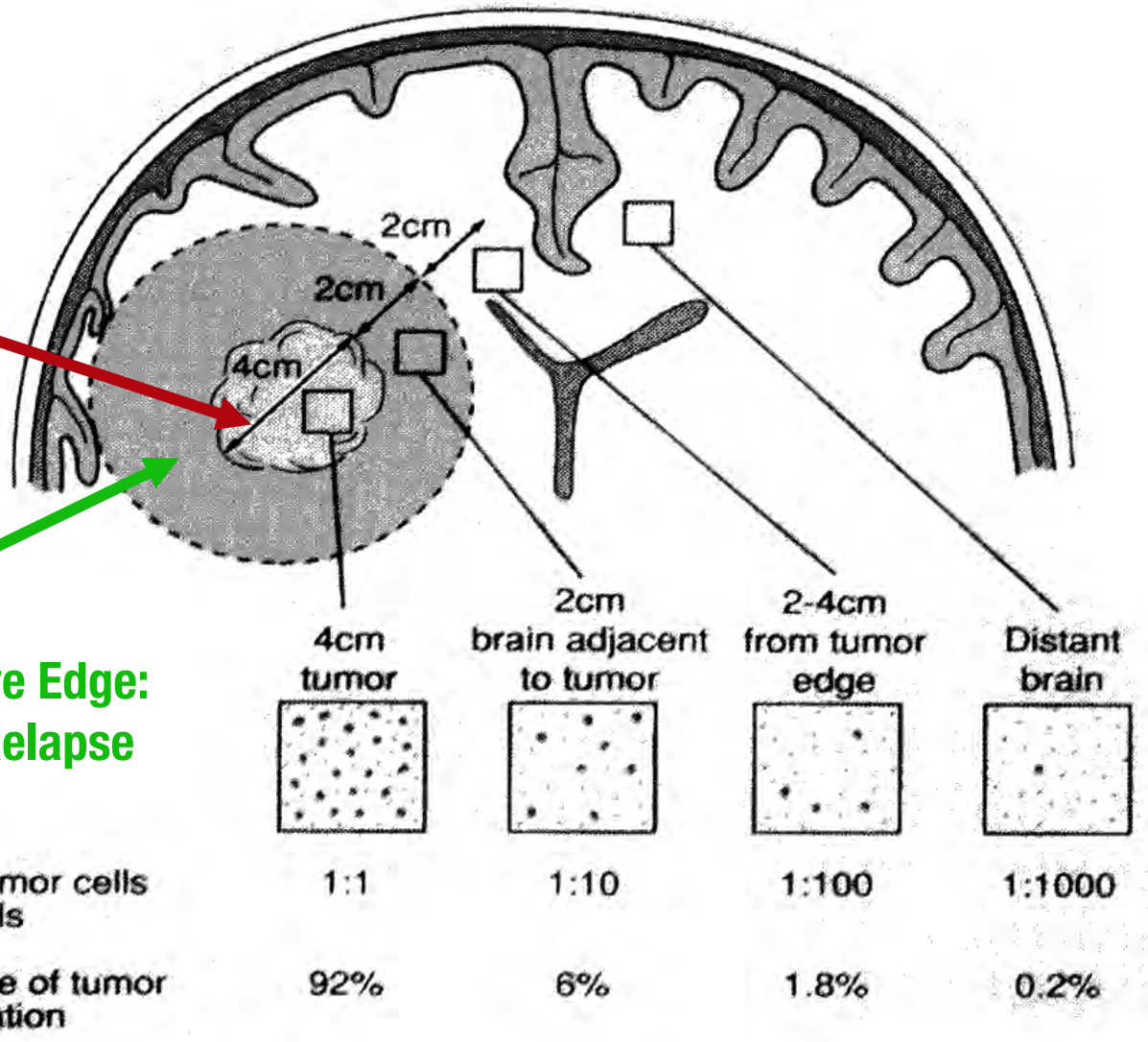
GBM Infiltrates Adjacent Normal Brain





Tumor

Infiltrative Edge:
Site of Relapse



courtesy of Dr Michael Vogelbaum

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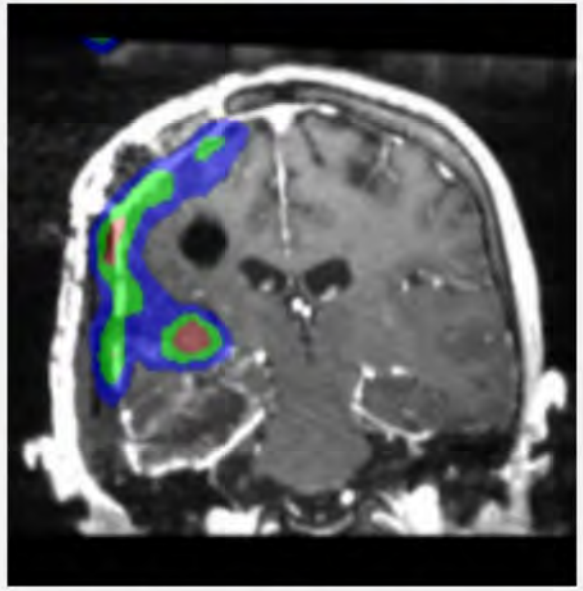
By-Passing the BBB: Single Local Administration of MDNA55

High-flow Image Guided Convection-Enhanced Delivery (CED) Improves Distribution

PAST STUDIES

1st Generation CED



Inaccurate catheter placement

Drug leakage due to backflow

Inadequate tumor coverage

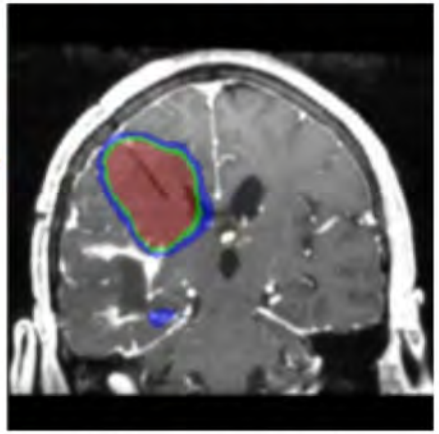
CURRENT STUDIES

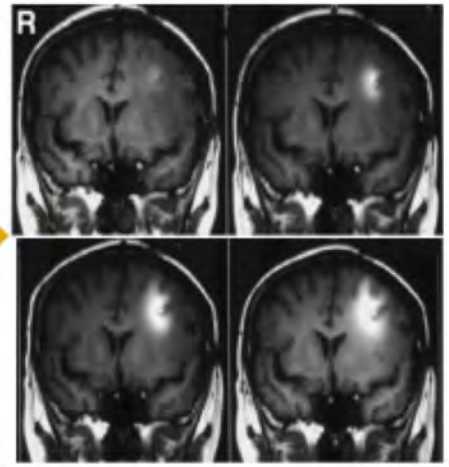
2nd Generation High-flow CED

Image-guided catheter placement

New catheters prevent backflow

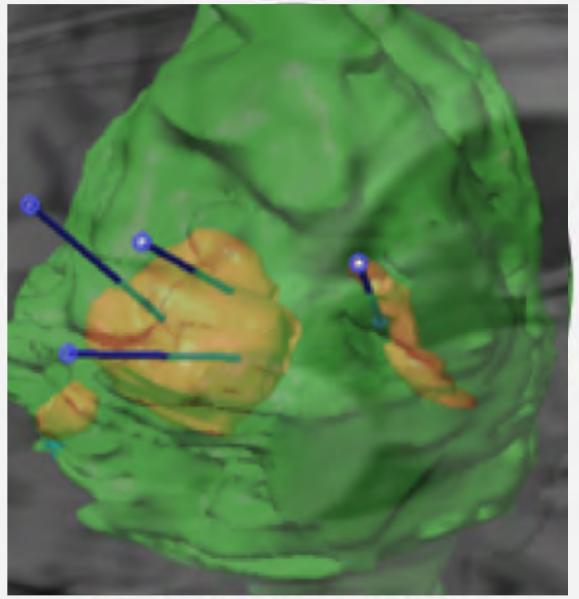
Real-time monitoring ensures tumor coverage





Saito and Tominaga (2012), Neurol Med Chir (Tokyo) 52, 531

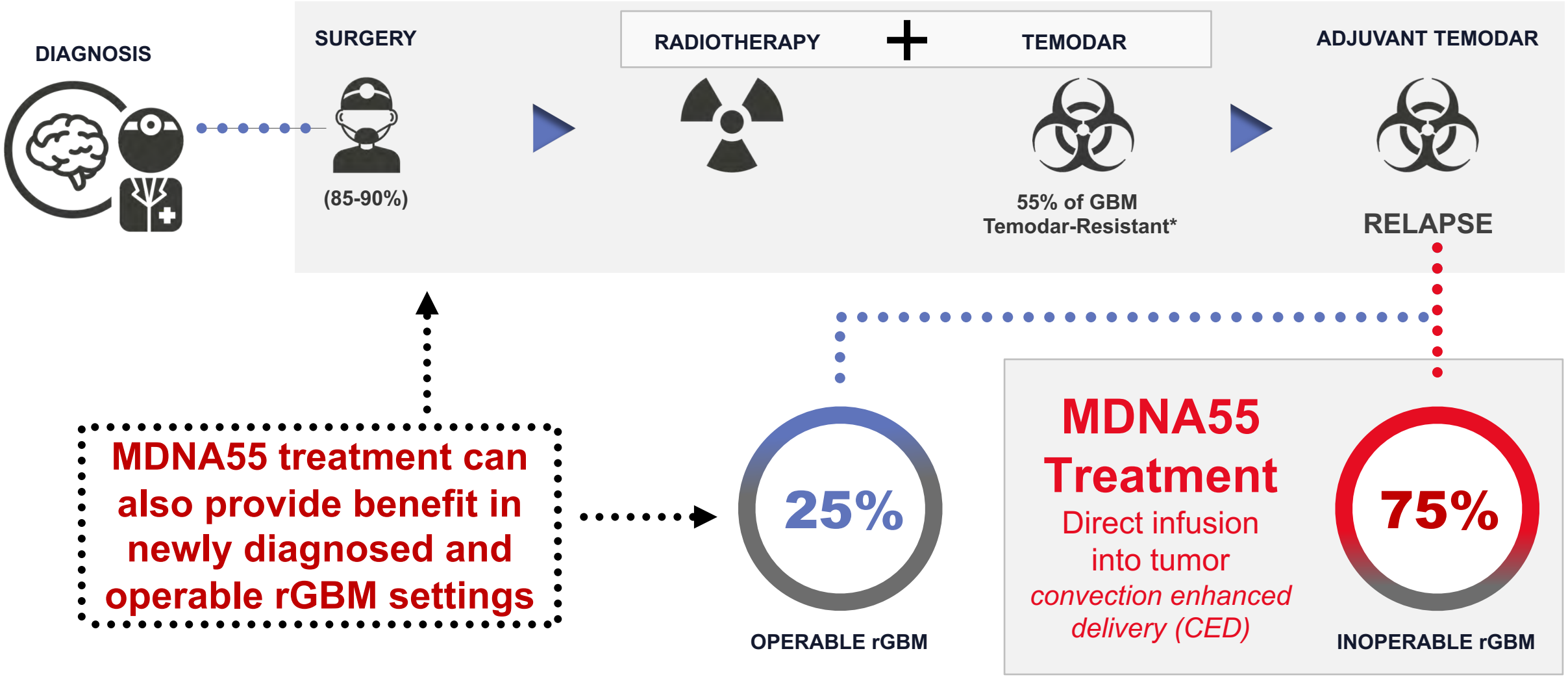
3D IMAGE FROM PATIENT IN CURRENT CLINICAL STUDY



Tumor Drug Coverage

Treatment Pathway for GBM

GBM IS UNIFORMLY FATAL – VIRTUALLY ALL TUMORS WILL RECUR (rGBM)



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* Expression of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) is responsible for resistance to Temodar used in GBM treatment.

MDNA55: Clinical Use in 118 Patients

Summary of 4 Clinical Trials (rGBM = 112; rAA =6)

STUDY	PATIENT	MDNA55 DOSE (µg)
NIH-sponsored Investigator Initiated (U.S.)	Recurrent GBM (n=9)	6 - 720
Multi-Center (U.S./Germany) Phase 1	Recurrent HGG **No Resection** (n=31; 25 rGBM + 6 AA)	240 - 900
Multi-Center (U.S./Germany) Phase 2	Recurrent GBM **+ Resection** (n=32)	90 - 300
Multi-Center (U.S./Poland) Phase 2b	Recurrent *de novo* GBM IDH wild-type only **No Resection** (n=46)	18 - 240

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MDNA55-05 Phase 2b Study Design Summary

Open-Label Single Arm Study in Recurrent GBM Patients (n=46) (NCT02858895)

DIAGNOSIS

- Retrospective IL4R analysis from initial Dx
- *De novo* GBM at initial diagnosis
- IDH wild-type only
- 1st or 2nd relapse
- No resection
- KPS ≥ 70

PLANNING

- MRI - tumor size and location
- Optimal catheter trajectory

TREATMENT

- Image-guided catheter placement
- Monitor MDNA55 distribution in real-time with co-infusion of Magnevist ®
- Single infusion lasting 24 to 48 hrs

FOLLOW UP

1º Endpoint

- mOS

2º Endpoint

- ORR
- PFS
- mOS vs. IL4R expression
- Safety

Duke University · Penn · Cleveland Clinic · UT Medicine CTRC Health Science Center San Antonio · UCSF University of California San Francisco · John Wayne Cancer Institute at Providence Saint John's Health Center · Boca Raton Regional Hospital · Mazowiecki Szpital Bródnowski · Oregon Health & Science University OHSU · MEDICENNA

MDNA55-05 Demographics

Variable	Value
Total Patients	**46**
Age	56 years (35 – 78)
Sex (Male)	29 / 46 (63%)
KPS at Enrolment : 70, 80 90, 100	22 / 46 (48%) 24 / 46 (52%)
De novo GBM	46 / 46 (100%)
Poor candidates for repeat surgery	46 / 46 (100%)
IDH Wild-type	37 / 37 (100%)
Unmethylated MGMT	24 / 42 (57%)
IL4R over-expression	23 / 42 (55%)
Steroid use during study > 4mg/day	25 / 45 (56%)
Max Tumor Diameter	28 mm (10 – 64)
# Prior Relapse: 1 , 2	37 (80%) , 9 (20%)

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MDNA55 Safety Profile (n=118)

- No deaths attributed to MDNA55
- No systemic toxicity
- No clinically significant laboratory abnormalities
- Drug-related adverse events were primarily neurological/aggravation of pre-existing neurological deficits characteristic with GBM and had generally been manageable with standard measures.
- Maximum Tolerated Dose established at 240 µg
- No evidence of a differential rate of neurological toxicities between doses of MDNA55 used in the current study (up to 240 µg) and a range of higher doses explored in previous studies (up to 900 µg)

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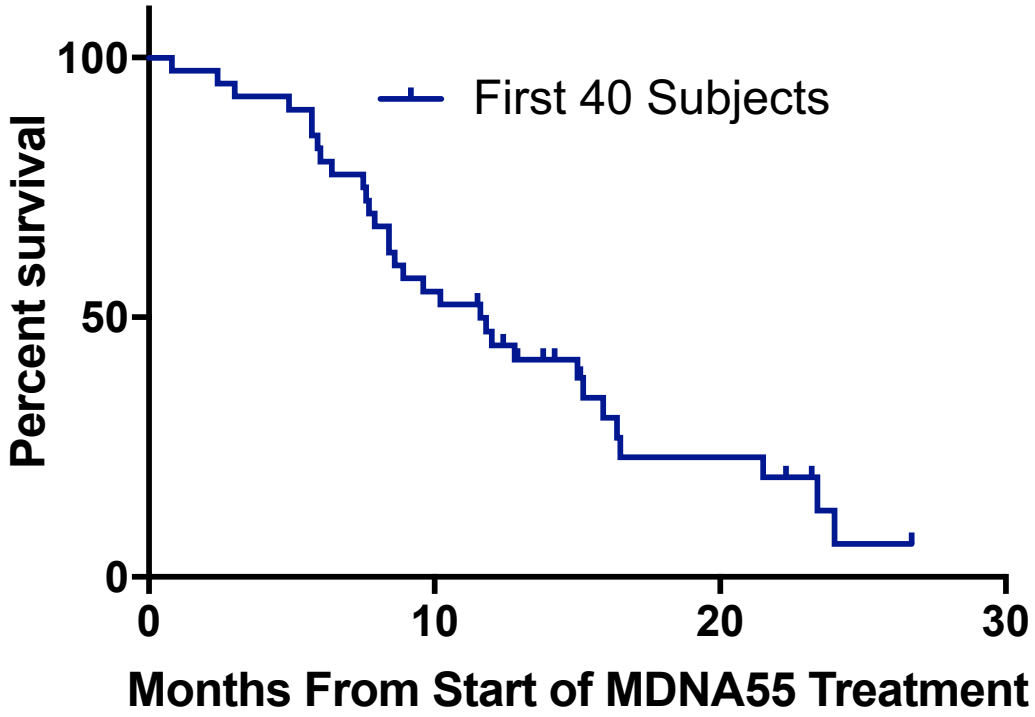
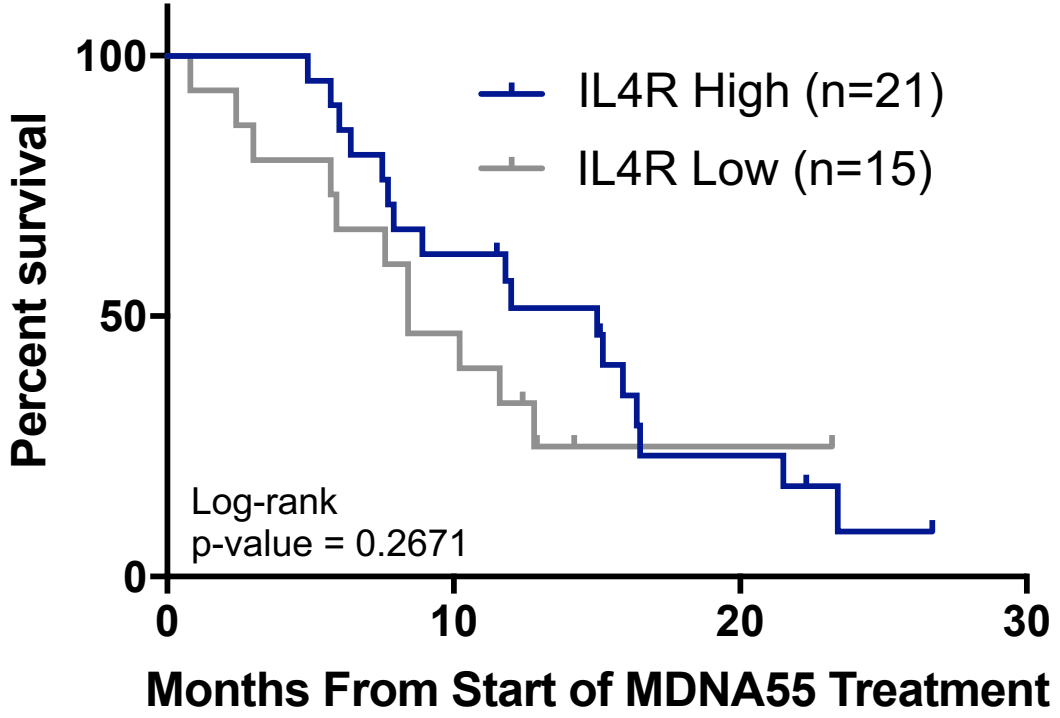
Improved Survival Seen with MDNA55 Particularly in IL4R High Patients

First 40 Subjects (36 of 40 Subjects Evaluable for IL4R)





Group	N	mOS (months)	OS-12
MDNA55	N=40	11.6	45%

Group	N	mOS (months)	OS-12
IL4R High	N=21	15.0	52%
IL4R Low	N=15	8.4	33%

Data cut-of 31Oct2019

MDNA55 is Potent Irrespective of MGMT Status

MDNA55 is Potent in Cancer Cell Lines (MGMT methylated or unmethylated) but Not Normal Cells

Cell Line	Cell Type	IC_{50} (ng/mL)
Normal Cell Lines		
NT-2	Human Neuronal cell line[1]	>1000
NHA	Normal Brain astrocyte cell line[1]	350
H9	T cells, resting[2]	>1000
Tumor Cell Lines		
U251	GBM[2]	6.5
UW-228-3	Medulloblastoma[3]	0.9
HN12	Head and Neck Cancer[4]	0.4
T98G*	GBM[2]	**1.2**
HT-29*	Colon Cancer[5]	**0.4**
MIA-PaCa-2*	Pancreatic cancer[6]	**0.065**

(*Cell lines with unmethylated MGMT Promoter)

1) Joshi et al., 2001
2) Puri et al., 1996
3) Joshi et al., 2002
4) Kawakami et al., 2000
3) Kreitman et al., 1995
4) Shimamura et al., 2007

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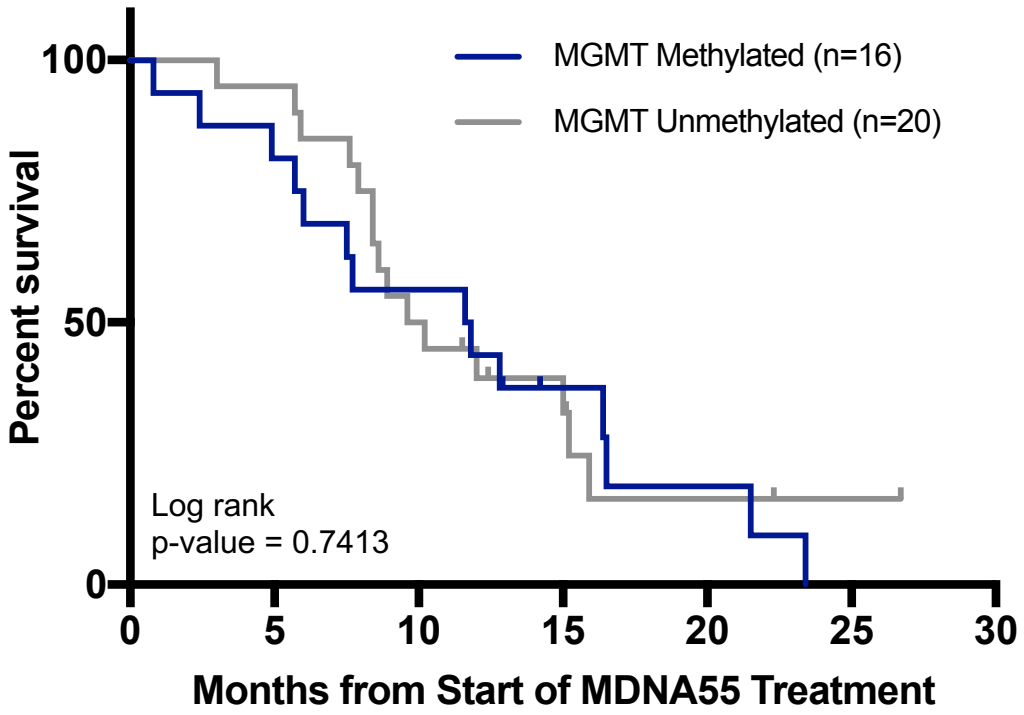
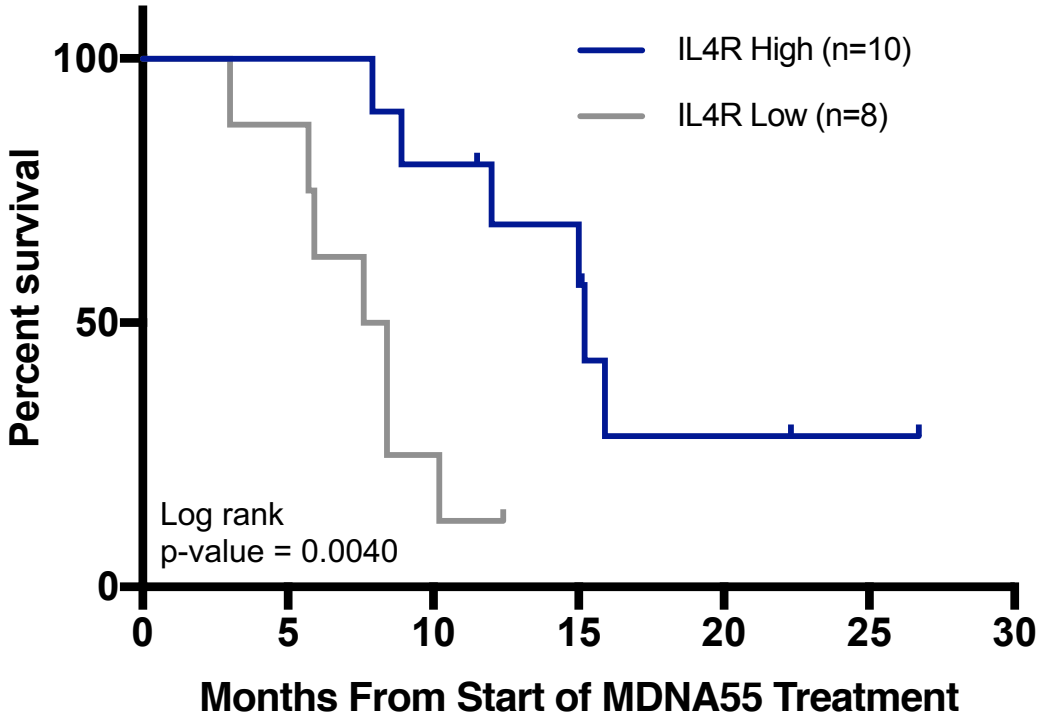
IL4R High Subjects Show Improved Survival Despite Having Unmethylated MGMT

First 40 Subjects (36 Evaluable for MGMT)



Group	N	mOS (months)	OS-12
MGMT Methyl	16	11.7	44%
MGMT Unmethyl	20	9.9	39%

MGMT Unmethylated Group n=20 (18 Evaluable for IL4R)



Group	N	mOS (months)	OS-12
MGMT Unmethyl / IL4R High	10	15.2	69%
MGMT Unmethyl / IL4R Low	8	8.0	13%

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Steroid Use is Restricted in Immunotherapy Trials

Sponser / NCT#	Agent	Phase	Patient Segment	Treatment	Steroid Use
Ziopharm NCT03679754	Ad-RTS-hIL-12 (IL12-expressing Ad-vector)	Phase 1 (20 mg Veledimex cohort n=51)	rHGG	Resection + Ad-RTS-hIL-12 + 20 mg veledimex	Expansion Sub-study (n=36): ≤ 20 mg during Days 0-14 **(≤ 1.5 mg/day)**
BMS CheckMate 143 NCT02017717	Nivolumab (PD-1 inhibitor)	Phase 3 (n=369)	rGBM	No resection Nivolumab	Nivo arm (n=184): **101 subjects = no steroid use** **73 subjects = < 4 mg/day** 10 subjects = ≥ 4 mg/day
Istari Oncology NCT02986178	PVSRIPO (Oncolytic recombinant polio/rhinovirus)	Phase 1 (n=61)	rGBM	No resection PVSRIPO	Expansion Cohort: **≤ 4 mg/day**
MDNA55-05 NCT02858895	IL4R-targeting immunotoxin	Phase 2b (n=46)	rGBM	No resection MDNA55	**20 subjects = ≤ 4 mg/day** 25 subjects = > 4 mg/day

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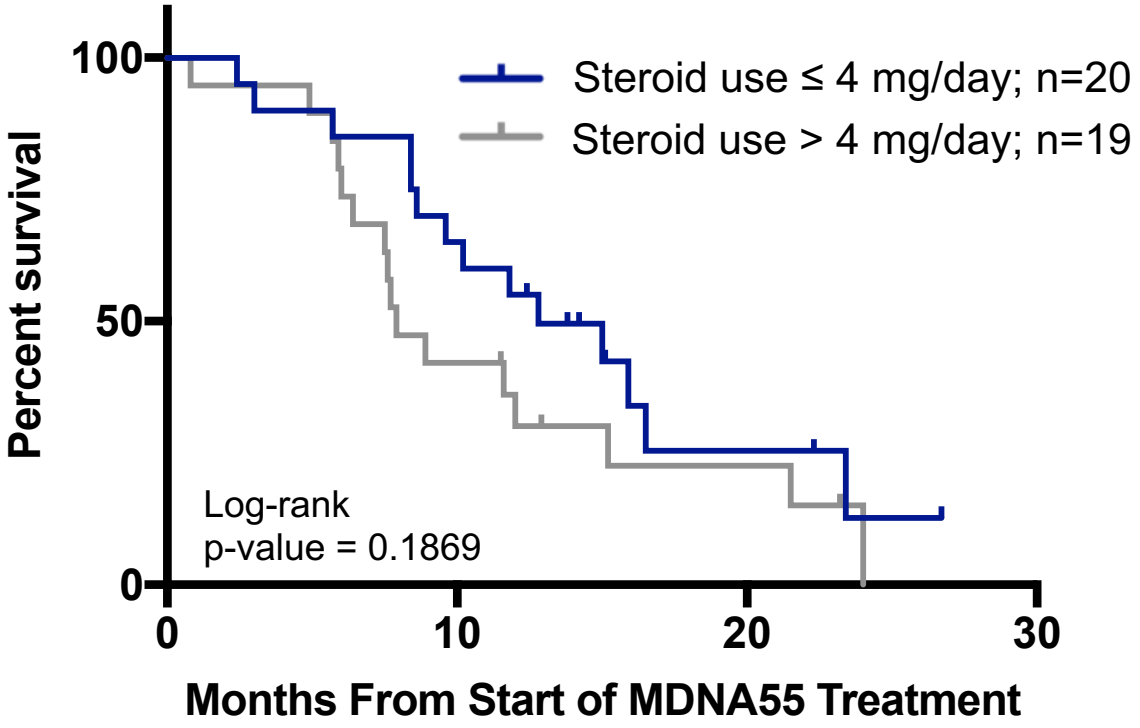
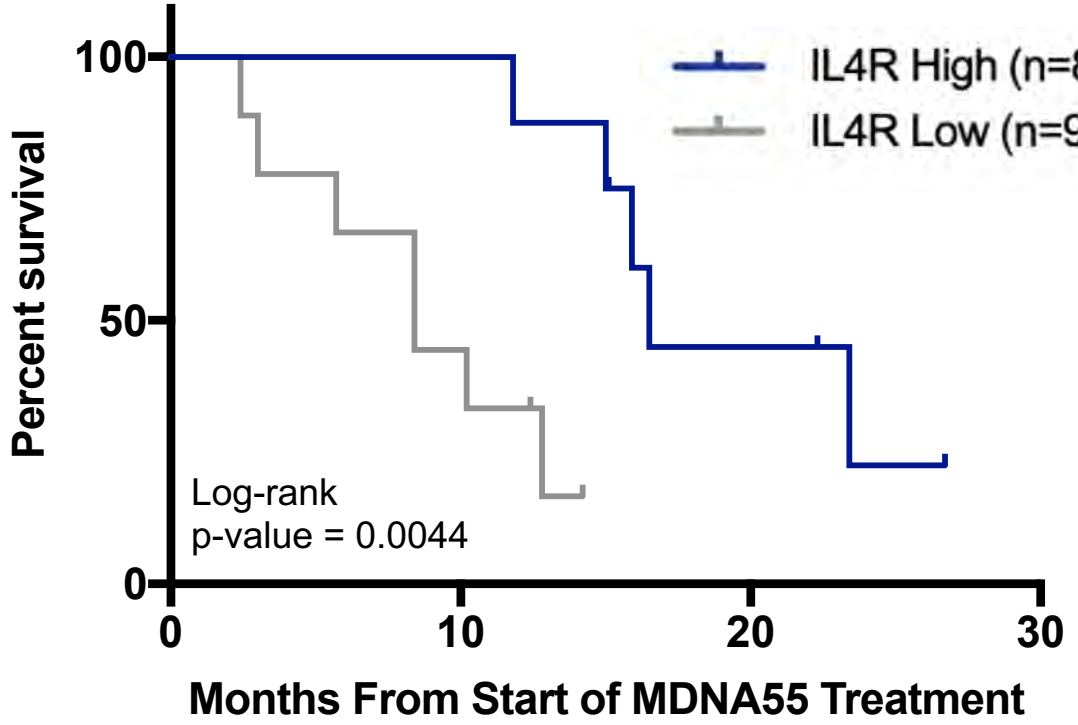
Longer Survival Associated with Low Steroid Use

First 40 Subjects (39 Evaluable for Steroid Use)



Group	N	mOS (months)	OS-12
≤ 4 mg/day	n=20	12.8	55%
> 4 mg/day	n=19	7.9	30%

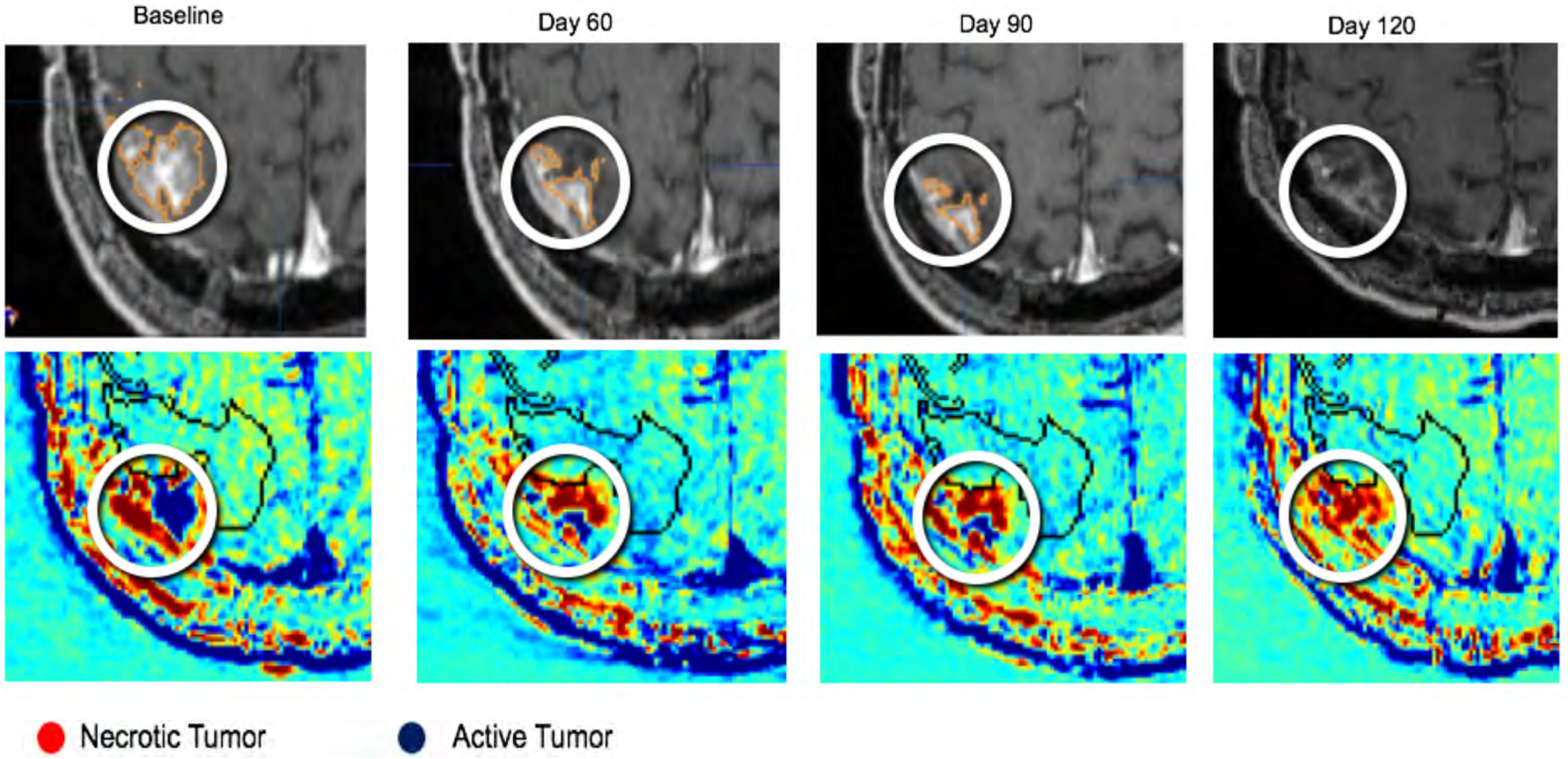
Subjects Using ≤ 4 mg/day (n=20; 17 evaluable for IL4R)



Group	N	mOS (months)	OS-12
IL4R High	n=8	16.5	88%
IL4R Low	n=9	8.4	33%

Case 1: Early Onset Response After MDNA55 Treatment

IDH Status = Wild-Type
MGMT Status = Unmethyl
IL4R Status = High
 # Prior Relapses = 2



1. Zach L, et al. Neuro Oncol., 2015

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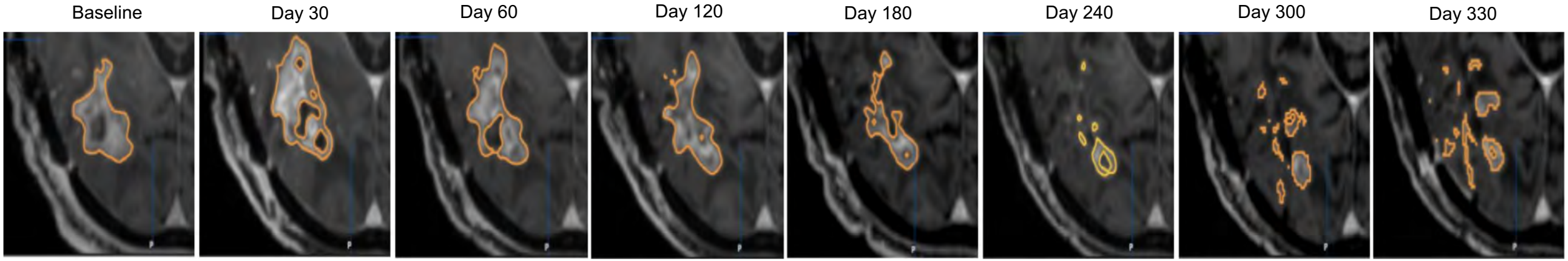
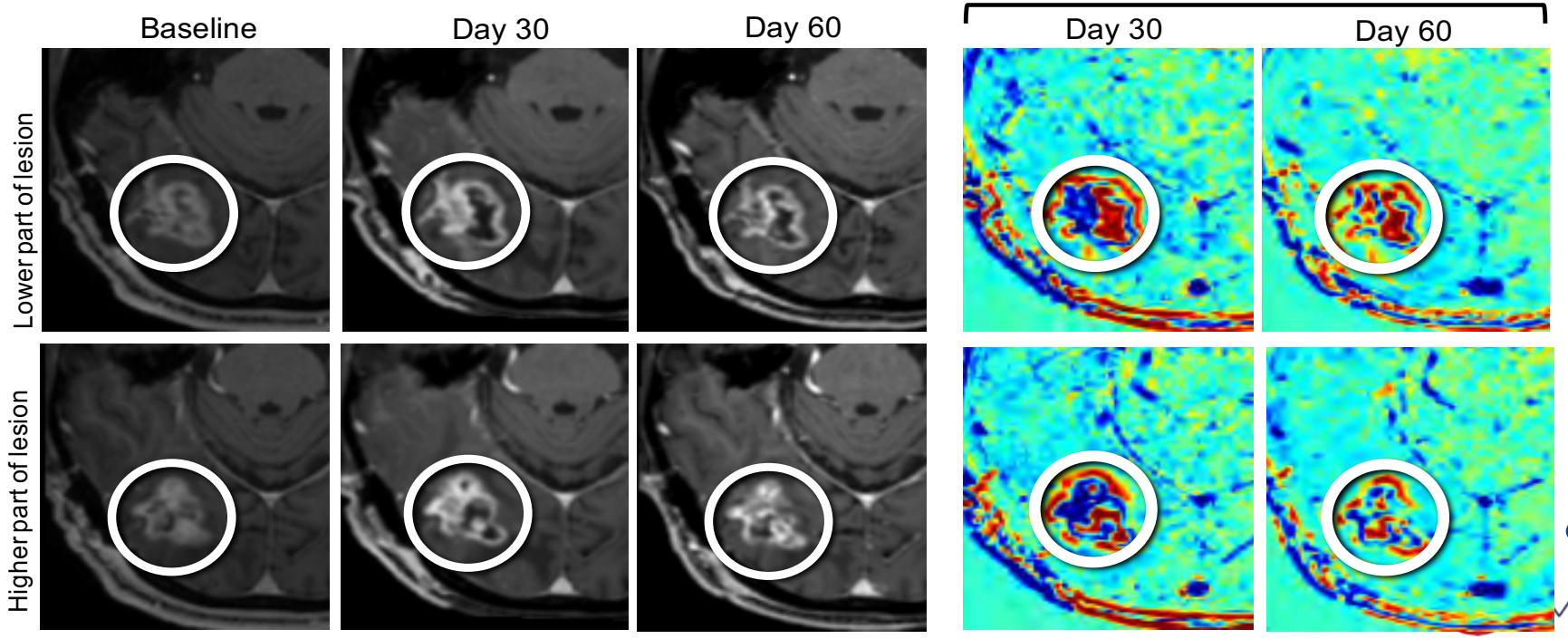
Case 2: Delayed Onset Response After Pseudo-Progression



IDH Status = Wild-Type
MGMT Status = Methylated
IL4R Status = High
 # Prior Relapses = 1



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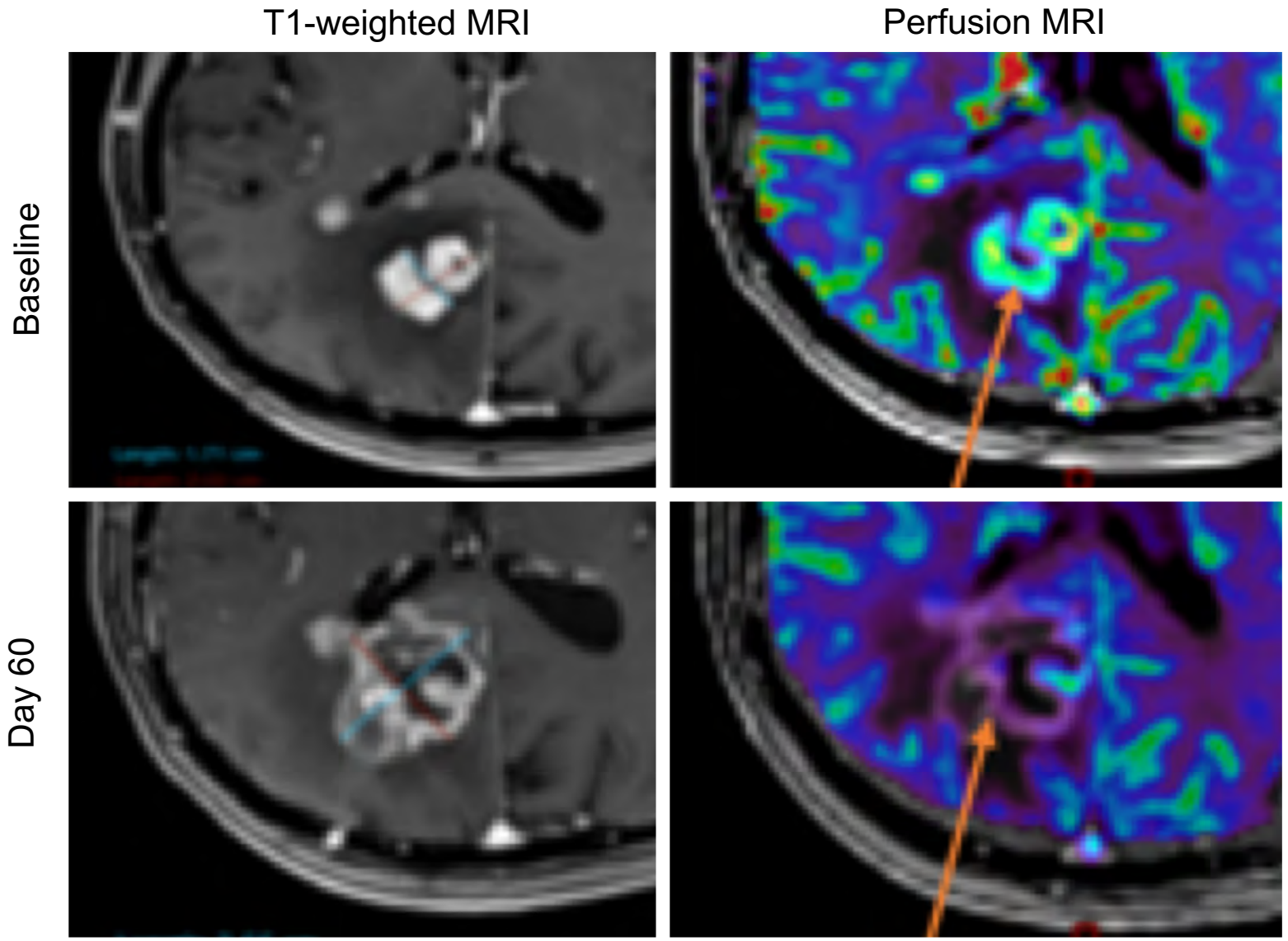
Case 3: Delayed Onset Response After Pseudo-Progression

IDH Status = Wild-Type
MGMT Status = Methylated
IL4R Status = High
 # Prior Relapses = 1



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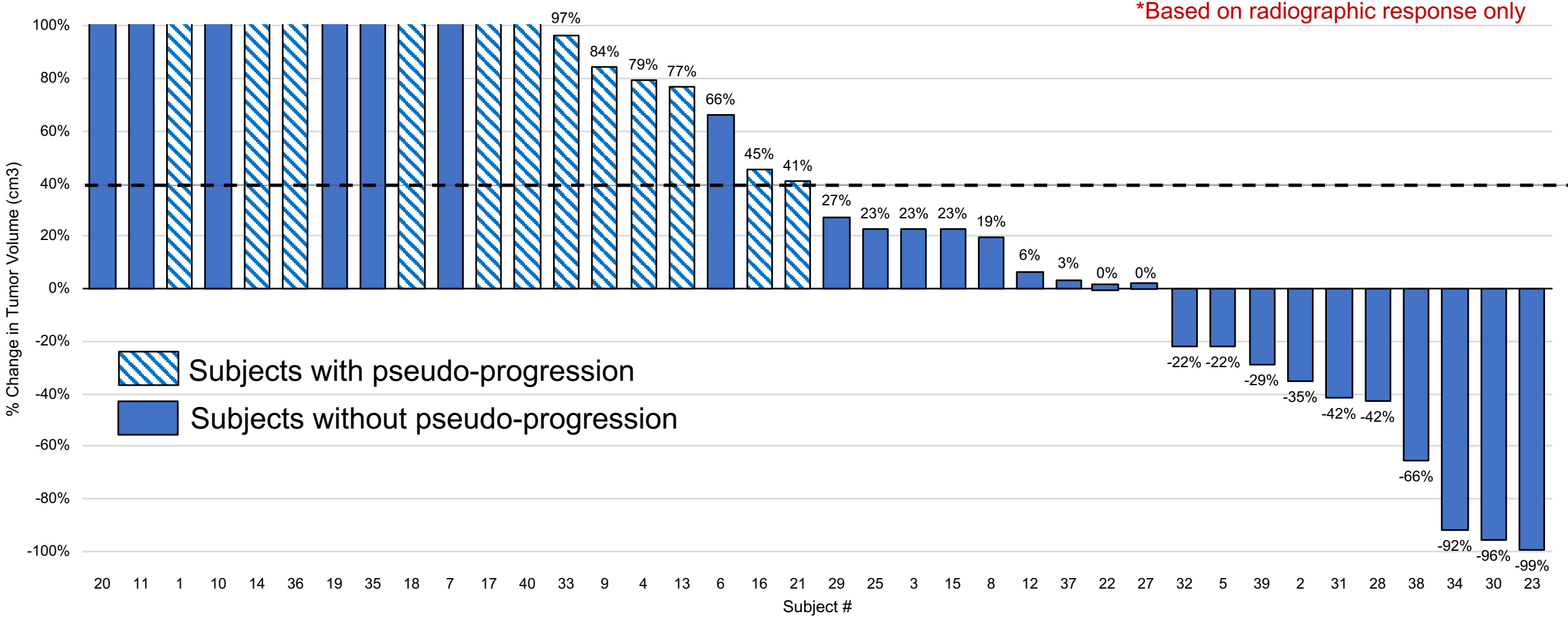
Tumor Control Seen from Baseline: Preliminary Results

Tumor shrinkage or stabilization seen in 19 of 38 evaluable subjects = Tumor control rate of 50%*

*Based on radiographic response only



Data is based on preliminary volumetric assessments from all on-study scans and is subject to change during formal assessment performed by independent central review.

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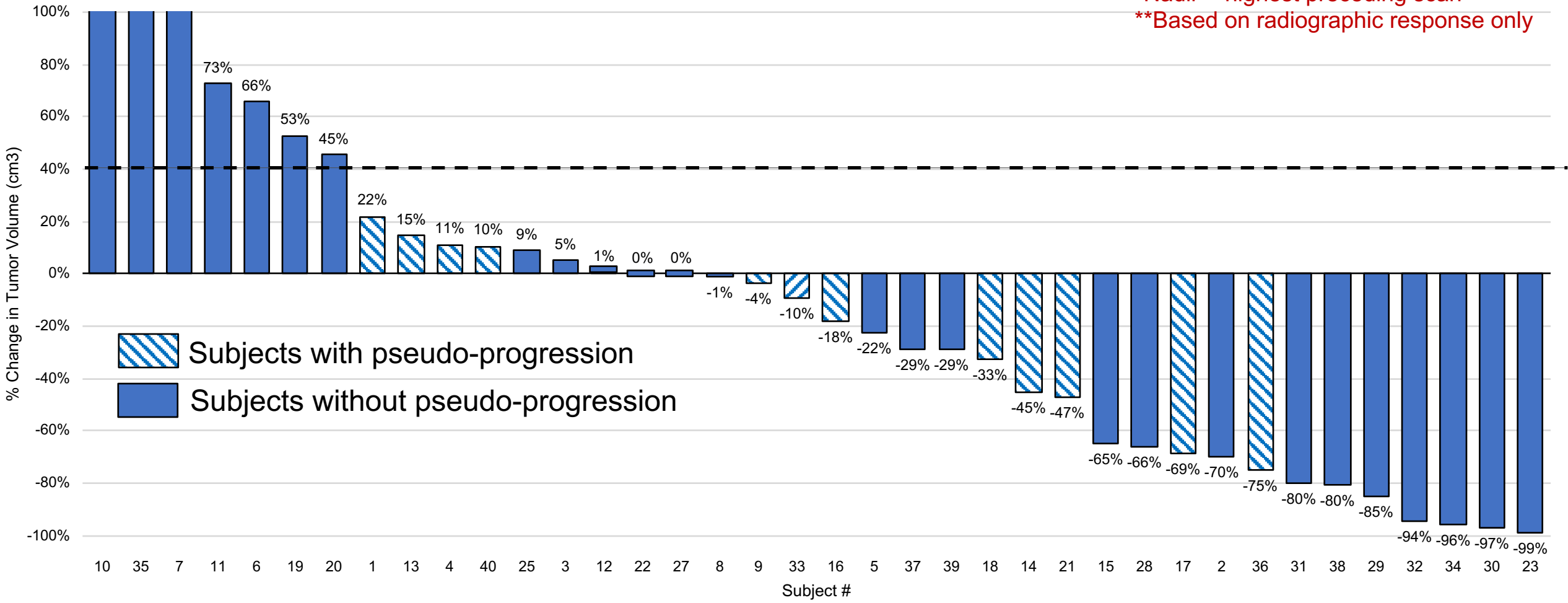
Tumor Control Seen from Nadir*: Preliminary Results

Tumor shrinkage or stabilization seen in 31 of 38 evaluable subjects = Tumor control rate of 82%**

*Nadir = highest preceding scan
**Based on radiographic response only



Data is based on preliminary volumetric assessments from all on-study scans and is subject to change during formal assessment performed by independent central review.

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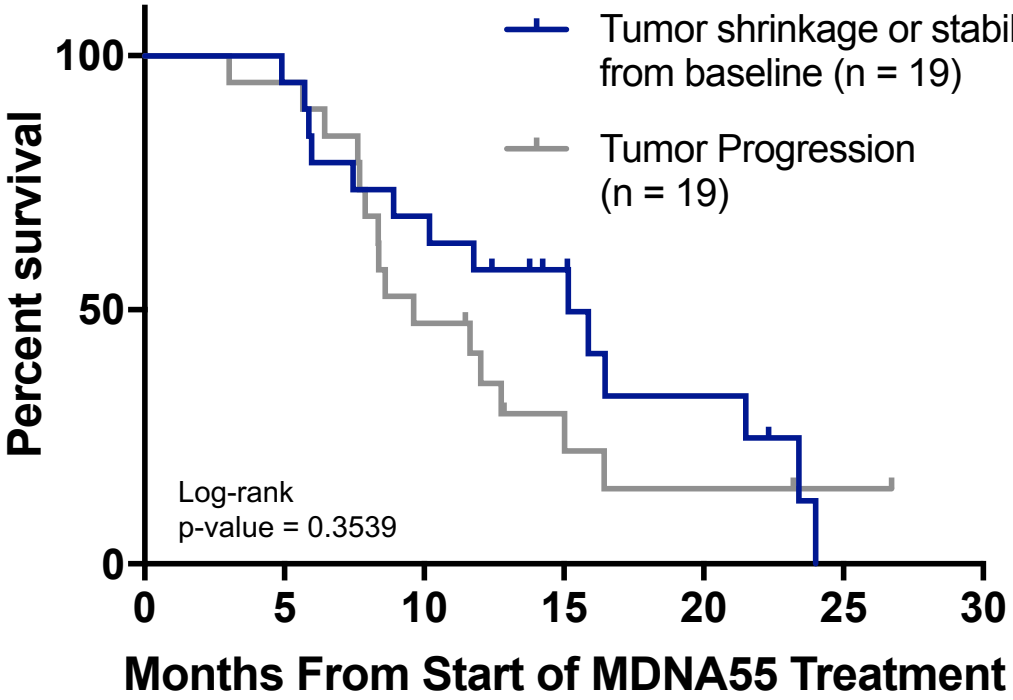
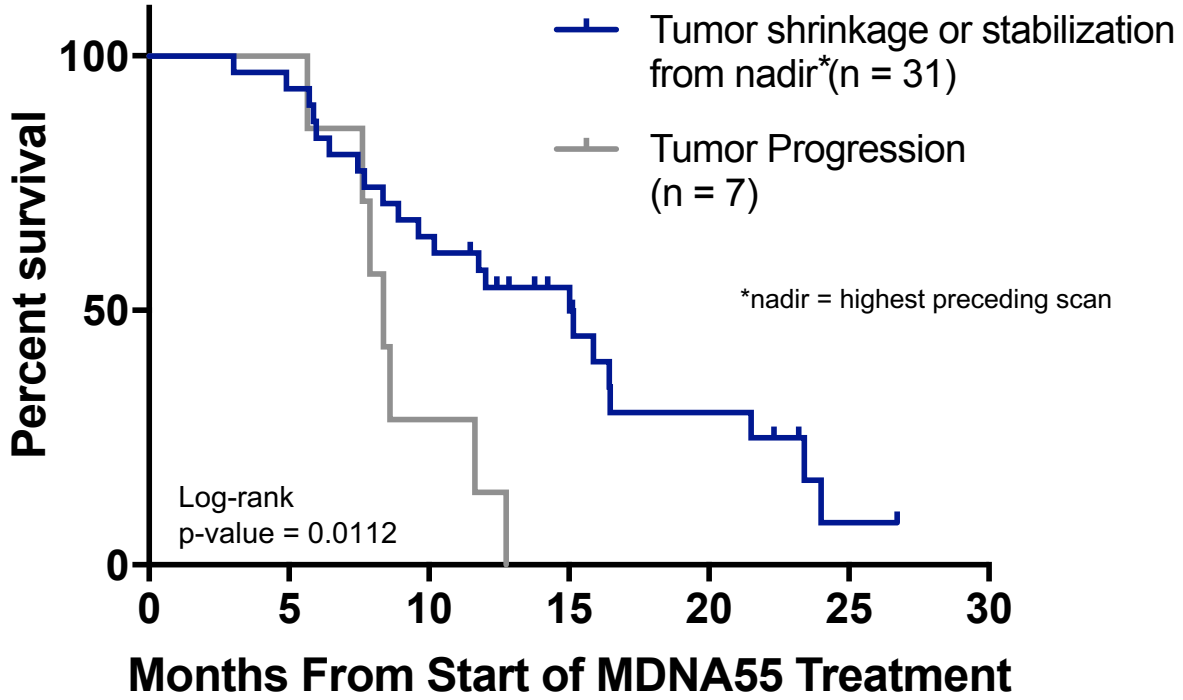
Longer Survival is Associated with Tumor Control

First 40 Subjects (38 Evaluable for Tumor Response)



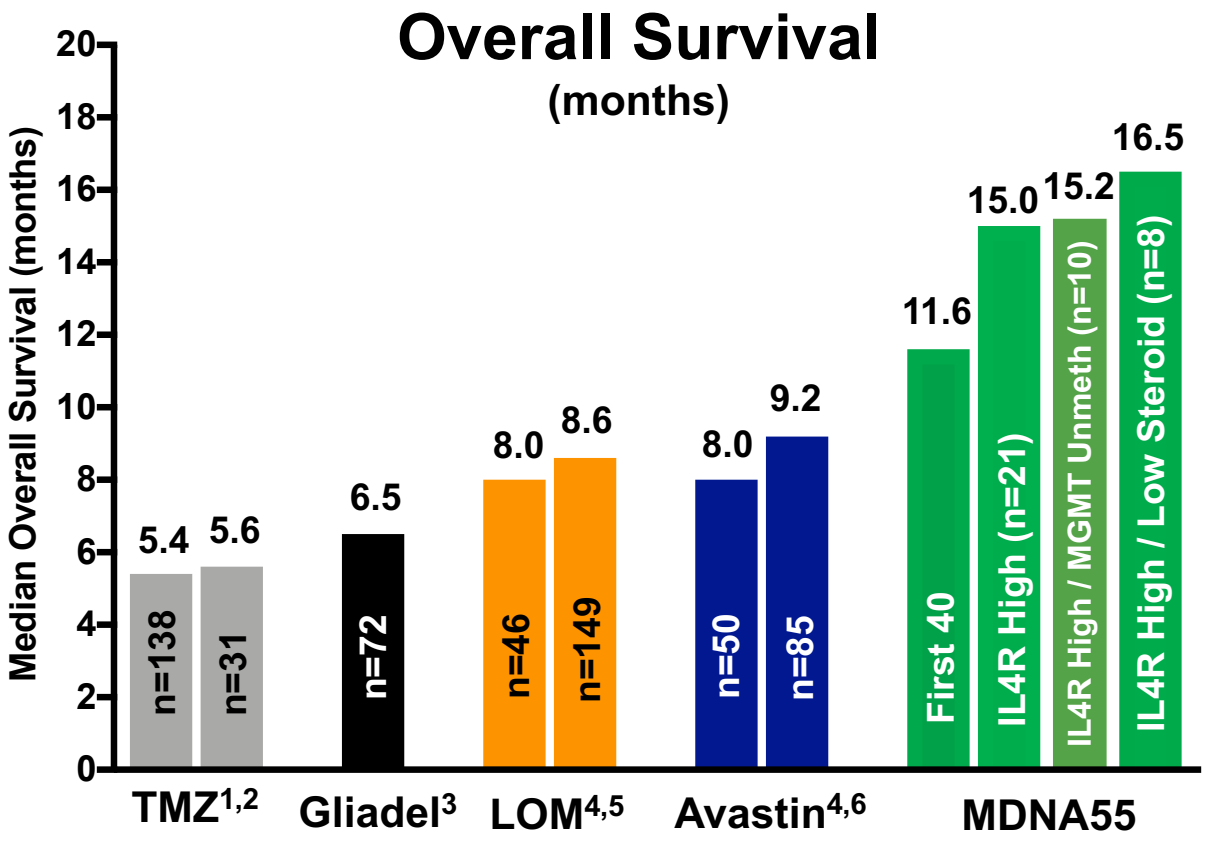


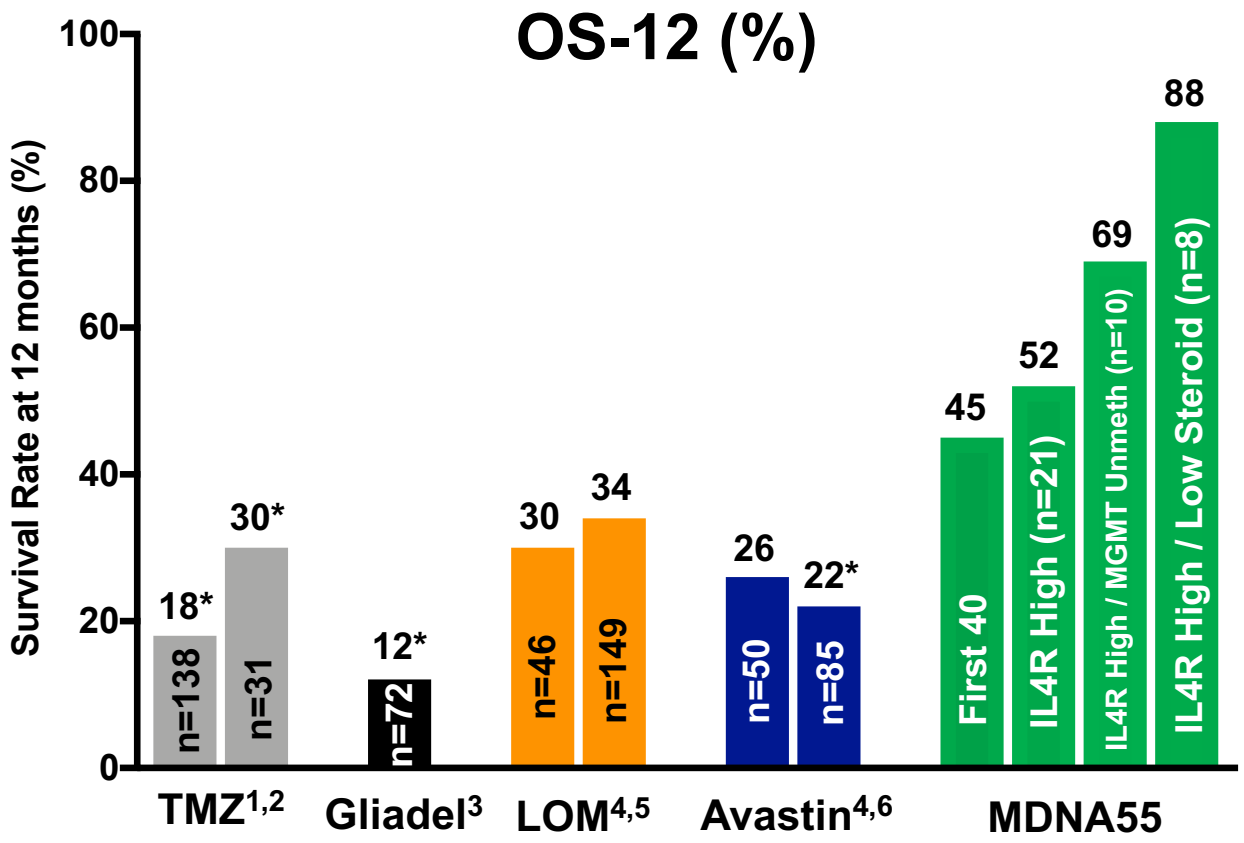
Best Response from Baseline	mOS (months)	OS-12
Tumor shrinkage or stabilization	15.2	58%
Tumor progression	9.6	42%

Data cut-of 31Oct2019

Best Response from Nadir	mOS (months)	OS-12
Tumor shrinkage or stabilization	15.0	58%
Tumor progression	8.4	14%

Promising Efficacy of MDNA55 Compared to Approved Therapies for rGBM





*Approximations based on Kaplan-Meier curve.

1 Brada et al., Ann Oncol. 2001;12(2):259–266.
2 Kim et al., J Clin Neuroscience 22 (2015) 468–473, 2015.
3 Gliadel FDA Label 2018
4 Taal et al., Lancet Oncol 2014 Aug;15(9):943-53.
5 Wick et al., N Engl J Med. 2017 Nov 16;377(20):1954-1963.
6 Friedman et al., J Clin Oncol. 2009 Oct 1;27(28):4733-40.

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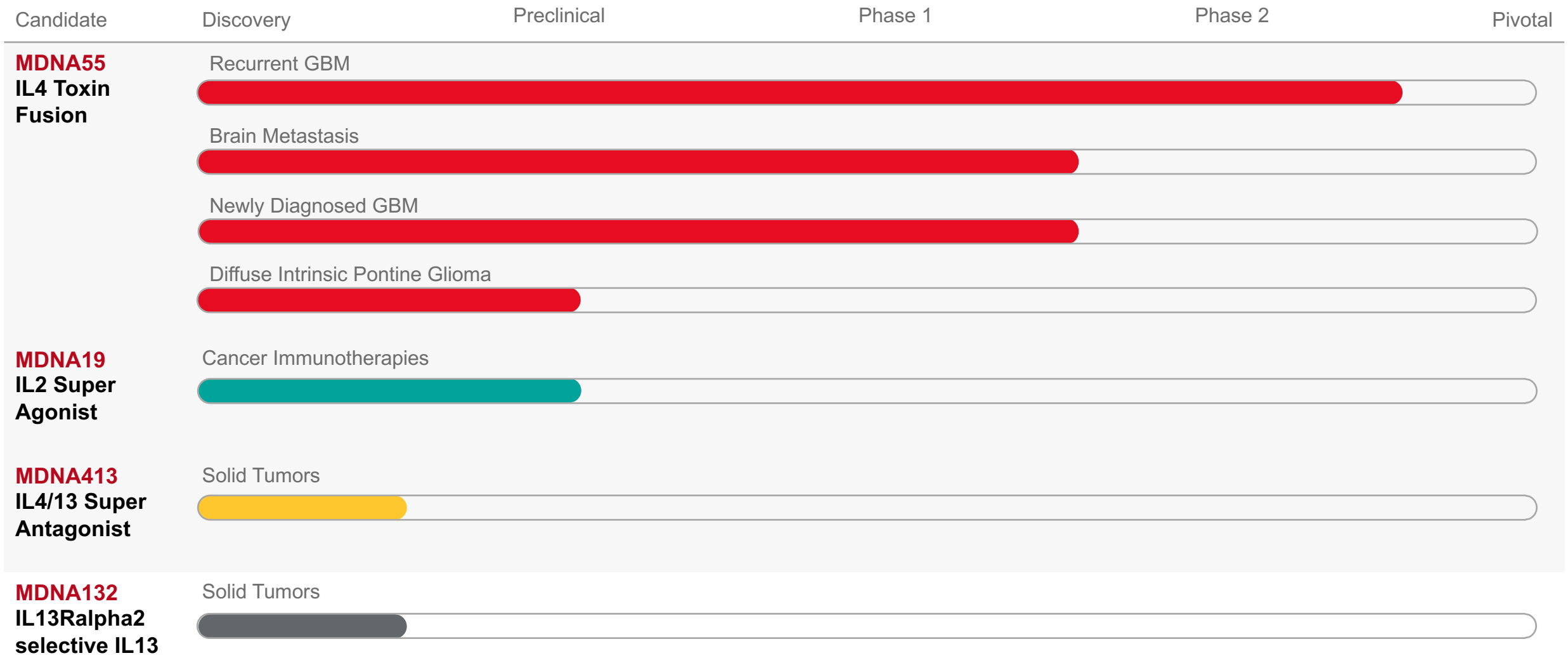
MDNA55 Supported by a Pipeline of Superkines



MDNA55 By The Numbers

1

TREATMENT

15

Months of Median Overall Survival in IL4R High Patients

>50%

Improvement in Median Survival compared to Standard of Care

4,000

Brain Tumor Patients that can be treated with 1 Gram of MDNA55

10,000

Number of Patients Annually Diagnosed with rGBM in NA

250,000

Annual Incidence of Primary and Metastatic Brain Cancers

20

Number of Cancers Known to Over-Express the IL4R

1 Million

Annual Incidence of IL4R Positive Cancers

∞

HOPE

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Summary

- Treatment options for patients with recurrent GBM are **very limited** and positive outcomes remain very rare.
- IL4R is frequently and intensely expressed on a variety of human carcinomas, including GBM, and is associated with aggressive disease and **poor survival outcomes**.
- MDNA55 is a novel IL4R targeted fusion toxin, administered intratumorally via MRI-guided convection enhanced delivery as a **single treatment** for recurrent GBM.
- There is strong evidence of **clinical benefit** and improved survival with MDNA55.
- $IL4R^{High}$ subjects show **promising survival** outcomes following MDNA55 treatment.
- IL4R may serve as a rational biomarker and **immunotherapeutic target** for recurrent GBM.

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…..And most of all, to the patients & their families

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CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

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Thank You!

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