CDK4 Amplification Associated with Longer Term Response to Bevacizumab in Glioblastoma

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Background

- Bevacizumab remains the standard second line therapy in glioblastoma (GBM) with improved progression free survival (PFS), but not overall survival
- This improvement in PFS is meaningful to GBM patients and led to full FDA approval
- We investigated a large clinico-genomic database of GBM patients treated with bevacizumab for molecular alterations associated with treatment outcome, including survival differences

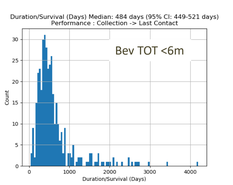
Methods

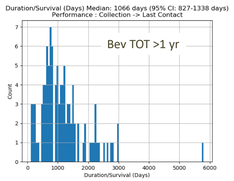
- Molecular profiles of GBM were tested by next-generation sequencing (NGS) of DNA (592 genes, NextSeq or whole-exome sequencing, Novaseq) and RNA (whole transcriptome sequencing, NovaSeq) at Caris Life Sciences (Phoenix, AZ)
- Gene amplification was determined by NGS with a threshold of > = 6 copies. Real-world survival information was obtained from insurance claims data
- Time-on-treatment (TOT) of bevacizumab was calculated from start to finish of treatment while post-bevacizumab overall survival (bevOS) from start of bevacizumab to last day of contact; overall survival from tissue collection to last day of contact
- Short-term (ST) and long-term (LT) responders were defined as those with TOT ≤6 months and ≥1 year, respectively
- Kaplan-Meier estimates were calculated, and significance was determined as p values of < 0.05. For molecular comparisons, Fisher's exact tests and Mann-Whiney U were used when appropriate

Results

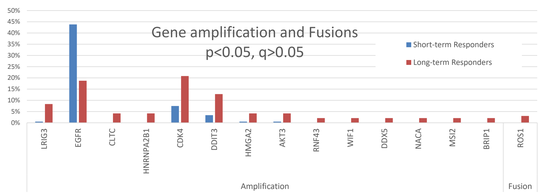
1. Patient characteristics (left) and patient overall survival (right)

	Cancer type	Bev TOT <6 mon	Bev TOT >1 yr
	High Grade Glioma	383	107
Histology	Glioblastoma, IDH wildtype	75	19
	Glioblastoma, NOS	220	64
	Glioblastoma multiforme	93	24
	Gliosarcoma	1	0
	Astrocytoma, NOS	2	0
Gender	Female	132	44
	Male	251	63
Age	< 25	6	4
	25-29	8	4
	30-34	16	3
	35-39	12	5
	40-44	17	7
	45-49	32	13
	50-54	46	19
	55-59	64	12
	60-64	81	17
	65-69	45	11
	70+	56	12
Therapy	TTFields	106	29
	Radiation Treatment (External)	259	67
	Radiation Treatment (All)	269	68
	Radiation Treatment (Internal)	5	0





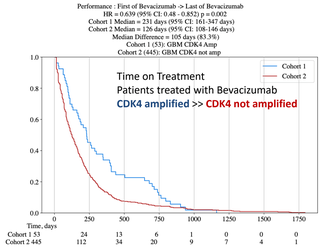
2. Molecular differences between long-term responders vs. short-term responders – amplifications and fusions

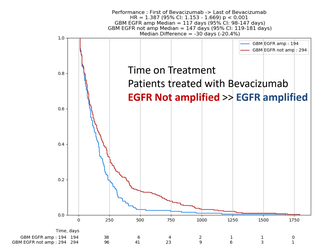


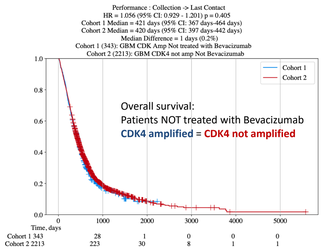
	Feature	q-value	p-value	Positive N in GBM Bev <6m	Total N - GBM Bev <6m	Short-term Responders	Positive N in GBM Bev > 1 year	Total N - GBM Bev > 1 year	Long-term Responders
Amplification	LRIG3	0.9548	8.00E-04	1	187	1%	4	48	8%
	EGFR	0.9548	0.0014	82	187	44%	9	48	19%
	CLTC	0.9548	0.0051	0	187	0%	2	48	4%
	HNRNPA2B1	0.9548	0.0051	0	187	0%	2	48	4%
	CDK4	0.9548	0.0065	14	187	7%	10	48	21%
	DDIT3	0.9548	0.0108	6	178	3%	6	47	13%
	HMGA2	0.9548	0.0456	1	187	1%	2	48	4%
	AKT3	0.9548	0.0456	1	187	1%	2	48	4%
	RNF43	0.9548	0.0479	0	187	0%	1	48	2%
	WIF1	0.9548	0.0479	0	187	0%	1	48	2%
	DDX5	0.9548	0.0479	0	187	0%	1	48	2%
	NACA	0.9548	0.0479	0	187	0%	1	48	2%
	MSI2	0.9548	0.0479	0	187	0%	1	48	2%
	BRIP1	0.9548	0.0479	0	187	0%	1	48	2%
Fusion	ROS1	0.9548	0.0433	0	134	0%	1	33	3%

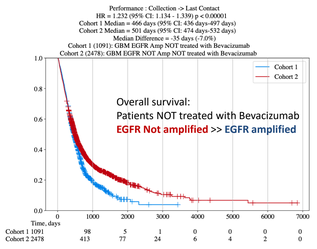
Results

3. CDK4 and EGFR amplification in high grade glioma tumors treated and not treated with bevacizumab

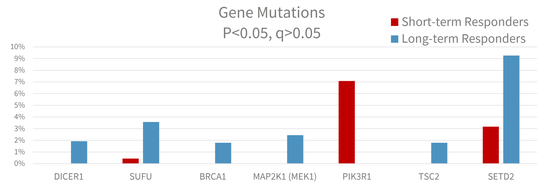








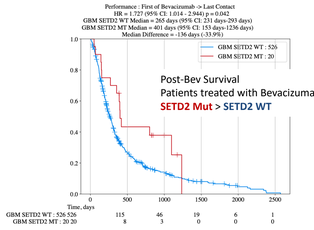
4. Molecular differences between long-term responders vs. short-term responders – Gene mutations

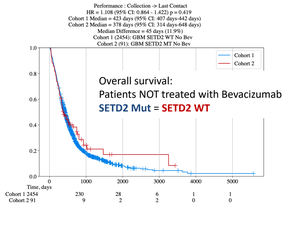


Feature	q-value	p-value	Positive N in GBM Bev <6m	Total N - GBM Bev <6m	Short-term Responders	Positive N in GBM Bev > 1 year	Total N - GBM Bev > 1 year	Long-term Responders
DICER1	0.9548	0.038	0	223	0%	1	52	2%
SUFU	0.9548	0.0394	1	229	0%	2	56	4%
BRCA1	0.9548	0.041	0	233	0%	1	56	2%
MAP2K1 (MEK1)	0.9548	0.0418	0	169	0%	1	41	2%
PIK3R1	0.9548	0.0422	16	226	7%	0	55	0%
TSC2	0.9548	0.0486	0	217	0%	1	56	2%
SETD2	0.9548	0.0495	7	221	3%	5	54	9%

Results

5. SETD2 mutation in high grade glioma tumors treated and not treated with bevacizumab





Conclusions

- Using a large clinical genomic database with GBM subjected to comprehensive molecular profiling, we demonstrated that amplification of CDK4 and EGFR were associated with long-term and short-term responses to bevacizumab, respectively
- Investigation into the tumors not treated with bevacizumab suggests that CDK4 amplification may be a predictive marker for bevacizumab while EGFR amplification may be prognostic of poor survival
- SETD2 mutations and PIK3R1 mutations are suggested to be predictive of bevacizumab benefit and prognostic of poor survival, respectively
- This warrants further investigation in independent cohorts controlled for age and other prognostic factors. If confirmed, a genetic basis for treatment optimization may provide meaningful clinical outcomes

References

1. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, et al. (2014) A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 370: 699-708.
2. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, et al. (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 370: 709-722.
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