

## Target therapy matched to genomic alterations in patients with recurrent IDH wildtype glioblastoma

A real-life cohort analysis from Veneto Institute of Oncology, Padua (Italy)

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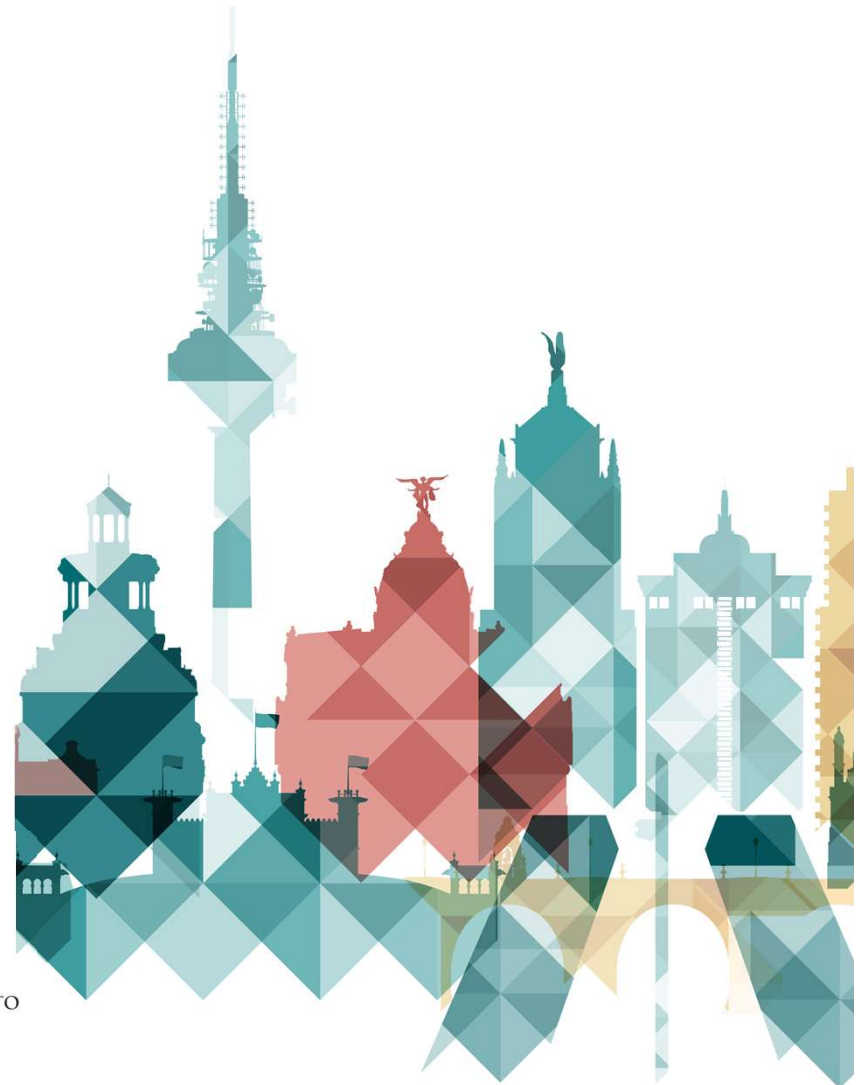


**ESMO**

Designated Centers of Integrated Oncology and Palliative Care



REGIONE DEL VENETO

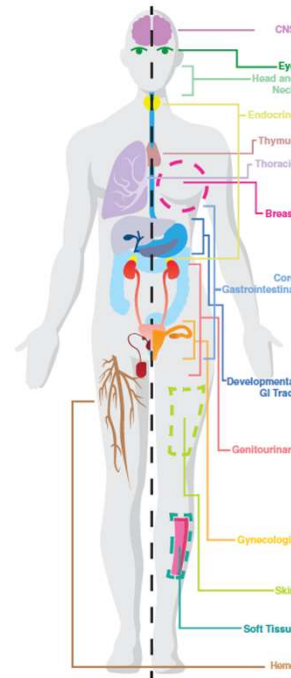


# DECLARATION OF INTERESTS

Nothing to declare

# Background

- New molecular technologies allow the identification of alterations within hundreds of cancer-related genes and can guide a **personalized strategy** in cancer treatment.
- There are only few data available regarding target therapy efficacy and feasibility for patients with **glioblastoma**.



Alteration frequencies										Cy	PC	Thp	
GBM	77	86	57	48	18	8	6	10	2	119	0.37	4.3	
LGG IDHwt	82	64	47	29	27	5	1	5		68	0.25	4.3	
LGG IDHmut-codel	9	45	22	5	26	66	3	99	50	34	0.21	0.8	
LGG IDHmut	19	28	15	92	24	8	10	92	21	60	0.17	0.8	
LVM	6	6	4	2	10	1	2	10	1	65	0.28	0.4	
HNSC HPV+	26	32	60	11	25	8	4	8	11	83	0.32	3.3	
HNSC HPV-	45	86	39	82	36	16	20	42	13	108	0.43	4.6	
THCA	84	14	4	1	4	13	2	1	2	16	0.03	0.4	
ACC	22	30	16	28	11	41	7	5	1	146	0.78	1.8	
PCPG	32	15	6	6	11	10	1	4	1	81	0.33	0.3	
THYM	14	9	4	7	5	7	1	7	3	26	0.09	0.6	
LUAD	74	56	38	61	21	19	23	23	10	118	0.48	8.2	
MESO	9	54	13	21	9	6	7	40	2	98	0.41	0.8	
LUSC	54	79	68	86	31	18	12	28	11	158	0.61	7.7	
BRCA LumA	28	31	62	25	14	15	12	5	4	101	0.34	2.0	
BRCA LumB	44	48	46	49	25	31	26	15	10	211	0.60	2.0	
BRCA Her2-enriched	82	40	60	78	18	17	29	10	8	230	0.53	4.3	
BRCA Basal	46	51	53	91	38	11	39	14	8	246	0.67	2.7	
BRCA Normal	36	36	33	31	3	6	19	3		53	0.16	1.5	
STES Squamous	50	89	53	96	38	13	22	21	13	23	189	0.59	3.1
STES CIN	63	74	33	76	21	26	21	16	23	2	222	0.58	3.4
STES EBV	50	100	80	13	83	67	7	10	17		52	0.22	4.1
STES GS	31	39	18	24	31	20	12	4	20	2	66	0.10	2.1
STES MSI-POLE	71	64	64	49	79	70	19	54	57	2	85	0.19	37.1
CRC	99	74	68	49	74	95	52	64	55	1	45	0.09	56.9
CRC GS	88	45	53	19	29	90	21	10	38	5	55	0.23	2.9
CRC CIN	66	36	32	84	23	91	17	8	22	1	115	0.54	2.9
LIHC	22	89	25	37	26	43	19	12	7	7	121	0.45	2.9
CHOL	56	53	17	19	8	17	19	17	3	6	100	0.58	1.8
PAAD	78	70	19	69	14	12	14	7	41		62	0.26	3.5
KIRC	14	14	17	6	8	7	5	5	3	3	49	0.25	1.6
KIRP	17	12	8	4	12	9	6	11	1	6	49	0.35	2.2
KICH	5	23	15	32	3	3	2	3	5		77	0.80	0.9
BLCA	64	81	46	62	42	20	18	26	9	9	150	0.50	6.8
PRAD	15	28	32	21	13	35	11	5	6	1	92	0.16	1.3
TGCT sem	63	8	11	6	6		2				70	0.54	0.4
TGCT non-sem	20	7	5	5	16	2		10	2		99	0.67	0.4
OV	58	48	49	98	28	10	40	21	5	5	316	0.79	2.4
UCEC CN high	61	43	86	90	32	18	31	13	5	5	296	0.67	1.9
UCEC CN low	37	9	95	10	14	54	10	7	1	5	42	0.15	2.1
UCEC MSI-POLE	71	31	98	42	64	70	30	55	31	19	30	0.08	71.2
UCS	61	70	79	91	54	18	27	16	4	4	247	0.71	3.5
CESC Adeno	63	21	56	19	30	14	16	14	21	5	95	0.36	3.6
CESC Squamous	32	19	59	12	35	12	5	33	11	10	101	0.44	5.2
SKCM	94	77	33	28	27	23	10	25	7	1	131	0.53	22.1
SARC DDLPS	43	83	20	85	17	15	7	9	7		450	0.36	1.1
SARC LMS	31	55	33	71	14	11	4	4	1	4	177	0.69	1.8
SARC MFS/UPS	48	74	32	68	34	20	8	21	6	4	328	0.66	3.0
SARC other	25	30	15	5	5	5	10				104	0.33	1.2
DLBC	24	76	8	19	70	70	14	35	14		90	0.29	3.5
LAML	49	17	3	9	18	11	2	3	1	1	28	0.05	1.1
	46	45	33	29	23	15	11	10	7	1			

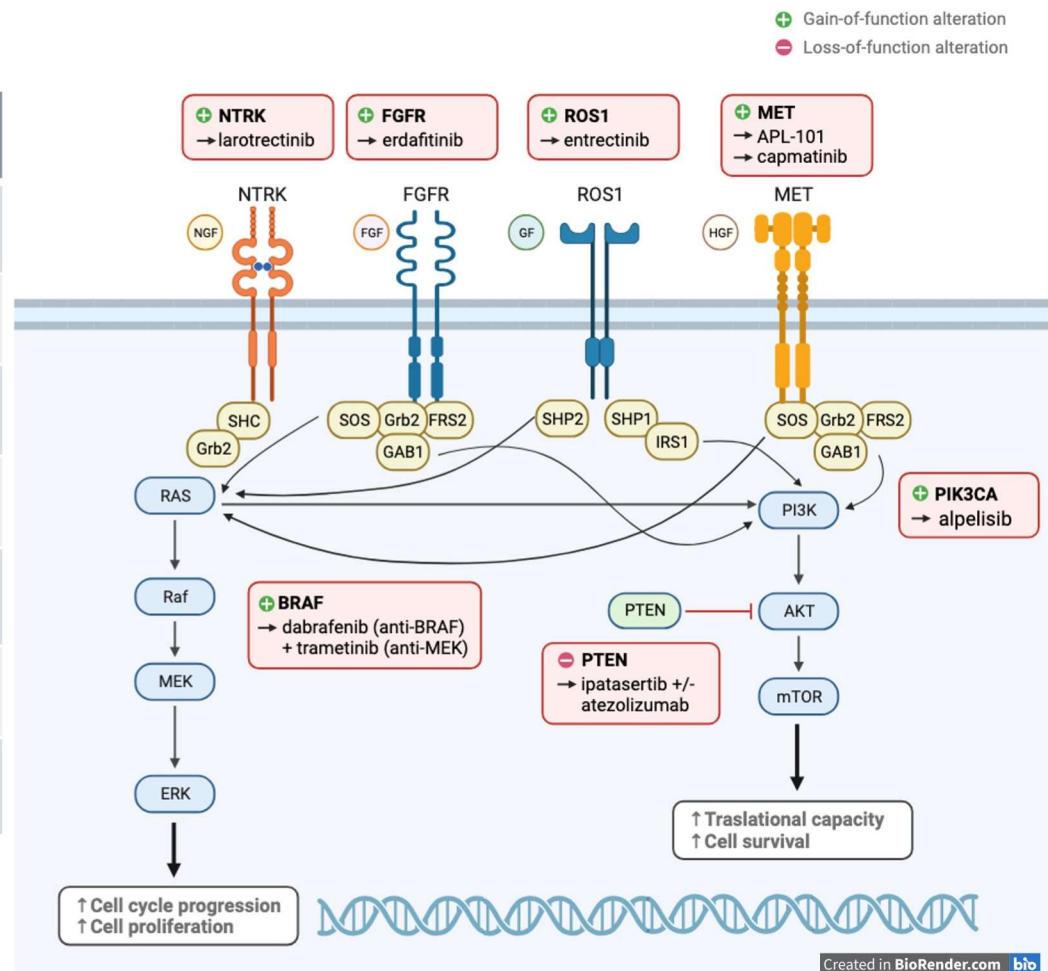
# Methods

Nature of the study	Inclusion criteria	Targetable alteration	Treatment
<p>Our <b>retrospective</b> study involved all patients with IDH wildtype GBM treated with target therapy between March 2020 and March 2023.</p> <p>A basal next-generation sequencing profiling was obtained from formalin-fixed paraffin-embedded tumor samples, using <b>FoundationOne® CDx</b> or <b>Caris MI-Transcriptome®</b>.</p>	<ul style="list-style-type: none"> <li>➔ Newly diagnosed or recurrent <b>GBM</b> (according to <i>WHO 2021</i>);</li> <li>➔ Treatment with target therapy at relapse / progression.</li> </ul>	<p><b>Molecular alterations</b> were classified into categories of targetability according with <i>ESCAT (ESMO Scale for Clinical Actionability of Molecular Targets)</i>.</p>	<p>Target therapy was given as:</p> <ul style="list-style-type: none"> <li>➔ <u>agnostic approval</u>, or</li> <li>➔ in <u>compassionate use programs</u>, or</li> <li>➔ in <u>clinical trials</u>.</li> </ul>

# Methods

Target	ESCAT	Therapy
<b>BRAF V600E</b>	IB	dabrafenib/trametinib
<b>NTRK 1-2-3 fusion</b>	IC	larotrectinib
<b>FGFR 1-2-3 alteration</b>	IIB	erdafitinib
<b>ROS1 fusion</b>	IIIA	entrectinib
<b>MET fusion - amplification</b>	IIIA	capmatinib; APL-101
<b>PIK3CA mutation</b>	IIIA	alpelisib
<b>PTEN loss - mutation</b>	IIIA	ipatasertib +/- atezolizumab

ESCAT Scale is from: Mateo J, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol.* 2018;29(9):1895-1902



# Methods

Endpoints	Overall response evaluation	Intra-patient response evaluation
<p>Efficacy of target therapies:</p> <ul style="list-style-type: none"> <li>→ ORR</li> <li>→ DCR</li> <li>→ PFS</li> <li>→ OS</li> </ul> <p>Toxicity of target therapies (secondary endpoint)</p>	<p>→ Responses were assessed by <b>brain MRI</b> every 6–8 weeks according to <i>RANO</i> (Response Assessment in Neuro-Oncology) criteria.</p> <p>→ <b>PFS</b> was defined as the time from the start of targeted therapy to the date of progression.</p>	<p><b>PFS2/PFS1</b> ratio was calculated, as:</p> $\frac{\text{PFS of targeted therapy (PFS2)}}{\text{PFS of the previous treatment (PFS1)}}$

# Results

- Out of the **37** patients who received TT, 21 were male; ECOG performance status was  $\leq 1$  in **31** patients.
- Median line of treatment was **3** (2 – 7).

Gene alteration	Patients treated with targeted therapy	Targeted therapy	Best Response (RANO criteria)				ORR	DCR
			CR	PR	SD	PD		
BRAF V600E	9	dabrafenib/trametinib	1	1	5	2	22%	77%
NTRK 1-2-3 fusion	2	larotrectinib			1	1	0%	50%
FGFR1-3 alteration	4	erdafitinib			2	2	0%	50%
ROS1 fusion	1	entrectinib	1				100%	100%
MET fusion – amplification	1	capmatinib			1		33%	67%
	2	APL-101		1		1		
PIK3CA mutation	6	alpelisib				6	0%	0%
PTEN loss – mutation	6	ipatasertib			1	5	0%	8.3%
	6	ipatasertib +/- atezolizumab				6		

14/37 patients (37.8%) obtained a disease control

TT=targeted therapy; ECOG=Eastern Cooperative Oncology Group; CR=complete response; PR=partial response; SD=stable disease; PD=progression disease; ORR=objective response rate; DCR=disease control rate

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ROS1 fusion	1	entrectinib	1				100%	100%
MET fusion – amplification	1	capmatinib			1		33%	67%
	2	APL-101		1		1		
PIK3CA mutation	6	alpelisib				6	0%	0%
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- At the cut-off date (Aug 2023), **26 patients had died**, and **35** patients had a **progressive disease**.
- In the entire cohort, the median **overall survival** after starting TT was **8.06** months (95% CI: 6.48-15.92) and **progression-free survival** after starting TT was **2.17** months (95% CI: 1.94-3.68).

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# Results

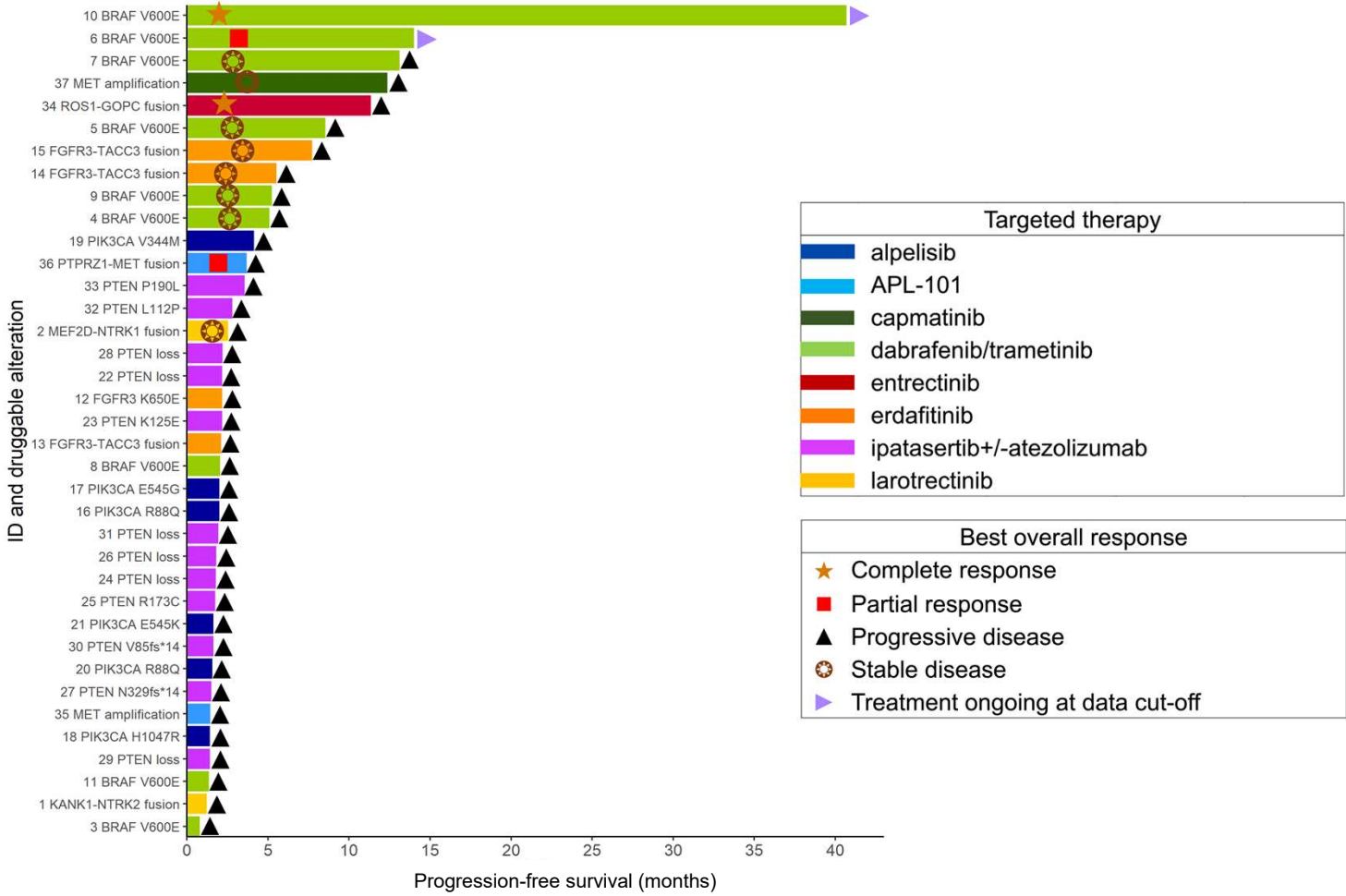
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			CR	PR	SD	PD		
BRAF V600E	9	dabrafenib/trametinib	1	1	5	2	22%	77%

- The dabrafenib/trametinib subgroup had the **longest median PFS (5.23 months)** and **OS (8.88 months)**, a disease control rate of 77%, an objective response rate of 22%, and a median duration of response of 27.35 months.
- Seven out of nine patients had died, and **two patients are continuing dabrafenib/trametinib**.
- No toxicities were reported with patients treated with dabrafenib/trametinib.
- Among all patients, no grade 4 adverse events were observed and in no case target therapy was interrupted for toxicity.

CR=complete response; PR=partial response; SD=stable disease; PD=progression disease; ORR=objective response rate; DCR=disease control rate; PFS=progression-free survival; OS=overall survival

# Results

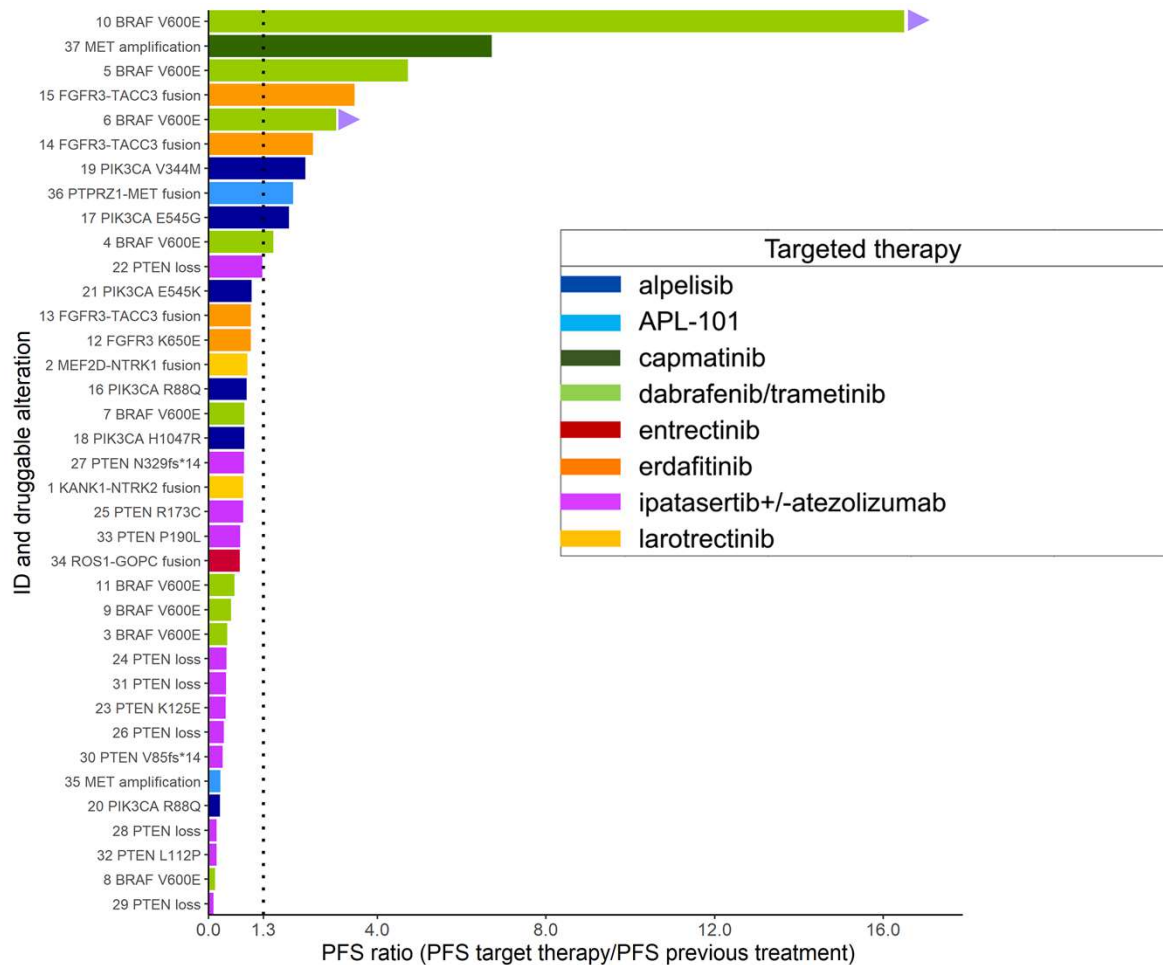


# Results

*PFS of targeted therapy (PFS2)*

*PFS of the previous treatment (PFS1)*

- ❑ PFS-ratio > 1.3 might suggest a clinical benefit, according to previous literature.
- ❑ PFS-ratio > 1.3 was achieved in 27% of overall cohort and in 44% of patients treated with dabrafenib/trametinib.



# Conclusions

Target therapy	Present perspectives	Future trends
<p>In selected cases of patients with recurrent glioblastoma, target therapy is a <b>viable option</b> that can have <b>activity</b> and improve <b>overall survival</b>. In our cohort, target therapy was well tolerated.</p>	<p>Our findings endorsed the efficacy of <b>anti-BRAF / anti-MEK</b> treatment for BRAF V600E mutant glioblastomas.</p>	<p>We reported interesting results targeting MET, ROS1, NTRK and FGFR, but a better definition of the level of evidence will derive from <b>basket trials, prospective studies, and registries</b>.</p>



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