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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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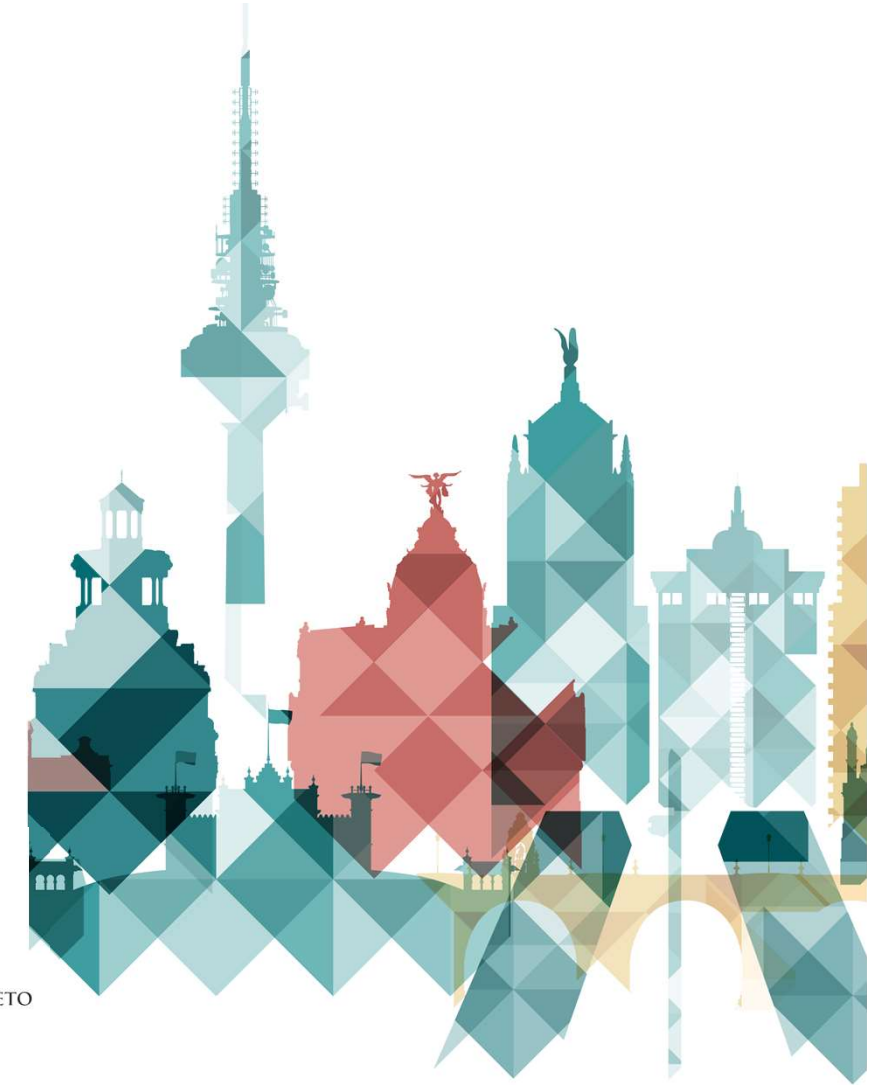


I.O.V. Istituto Oncologico Veneto

ESMO Designated Centers of Integrated Oncology and Palliative Care

OECI Comprehensive Cancer Centre

EURACAN

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**.

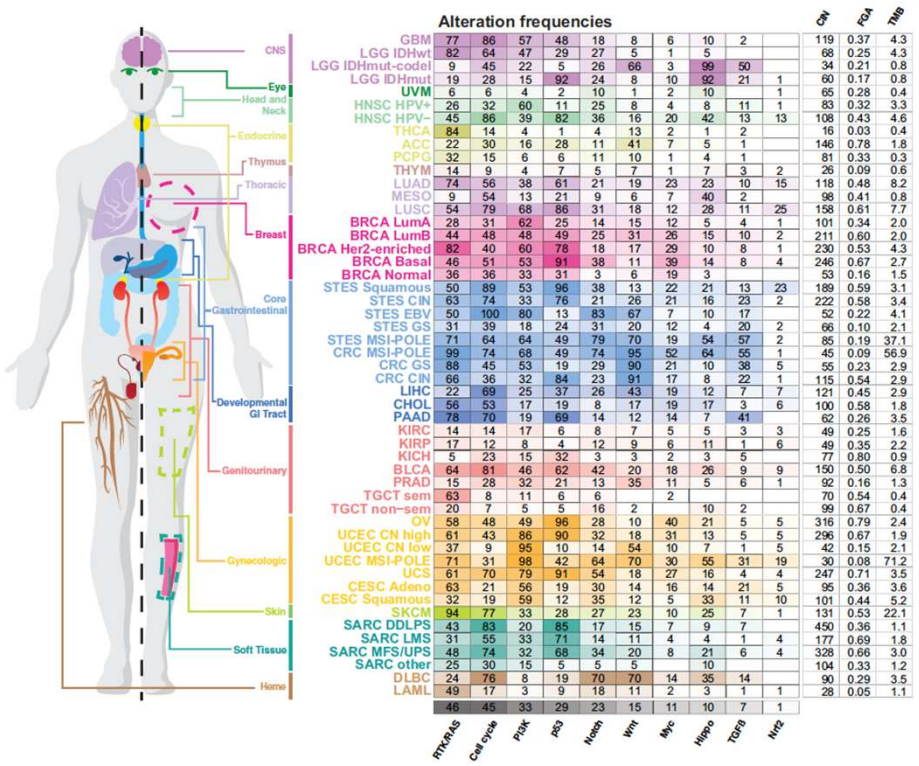


Image from Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell*. 2018;173(2):321-337.e10

Methods

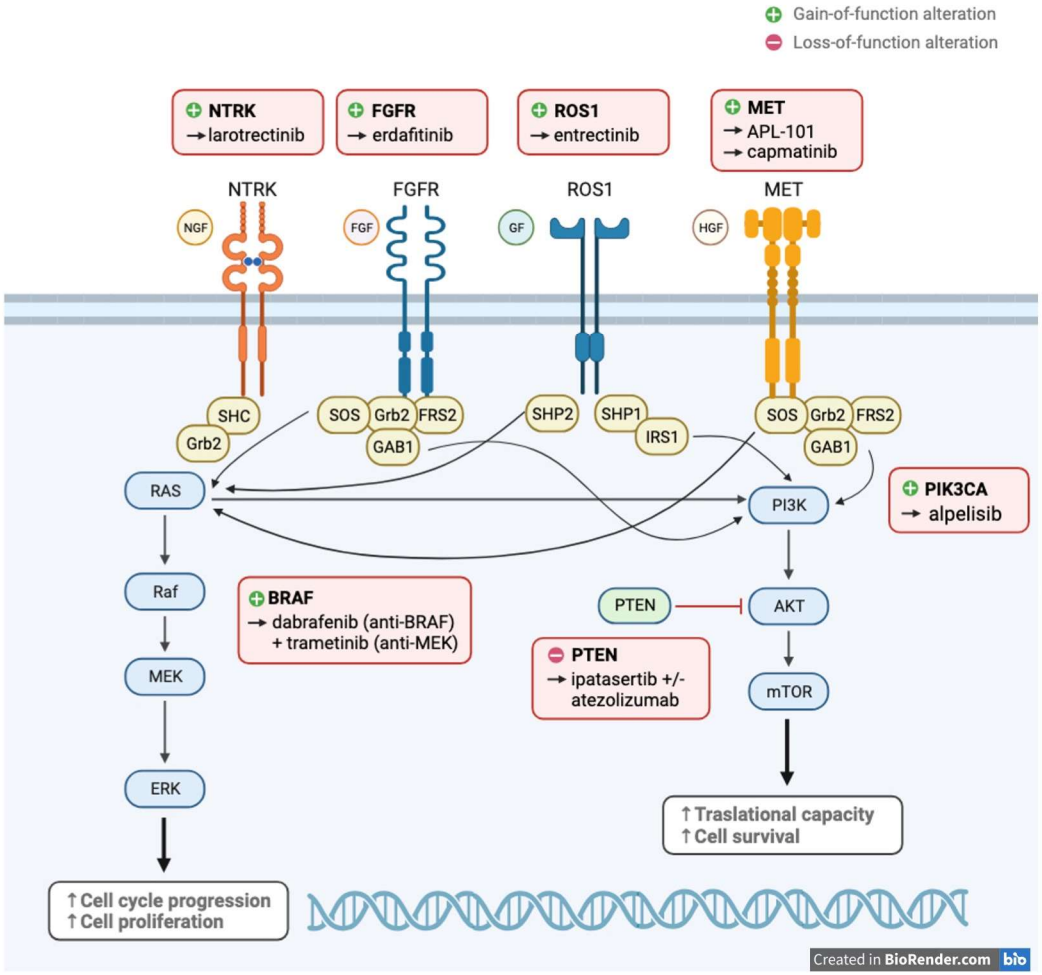
Nature of the study	Inclusion criteria	Targetable alteration	Treatment
Our **retrospective** study involved all patients with IDH wildtype GBM treated with target therapy between March 2020 and March 2023. A basal next-generation sequencing profiling was obtained from formalin-fixed paraffin-embedded tumor samples, using ***FoundationOne® CDx*** *or* ***Caris MI-Transcriptome®****.*	→ Newly diagnosed or recurrent **GBM** (according to *WHO 2021*); → Treatment with target therapy at relapse / progression.	**Molecular alterations** were classified into categories of targetability according with *ESCAT (ESMO Scale for Clinical Actionability of Molecular Targets).*	Target therapy was given as: → agnostic approval, or → in compassionate use programs, or → in clinical trials.

NGS=next-generation sequencing; GBM=glioblastoma

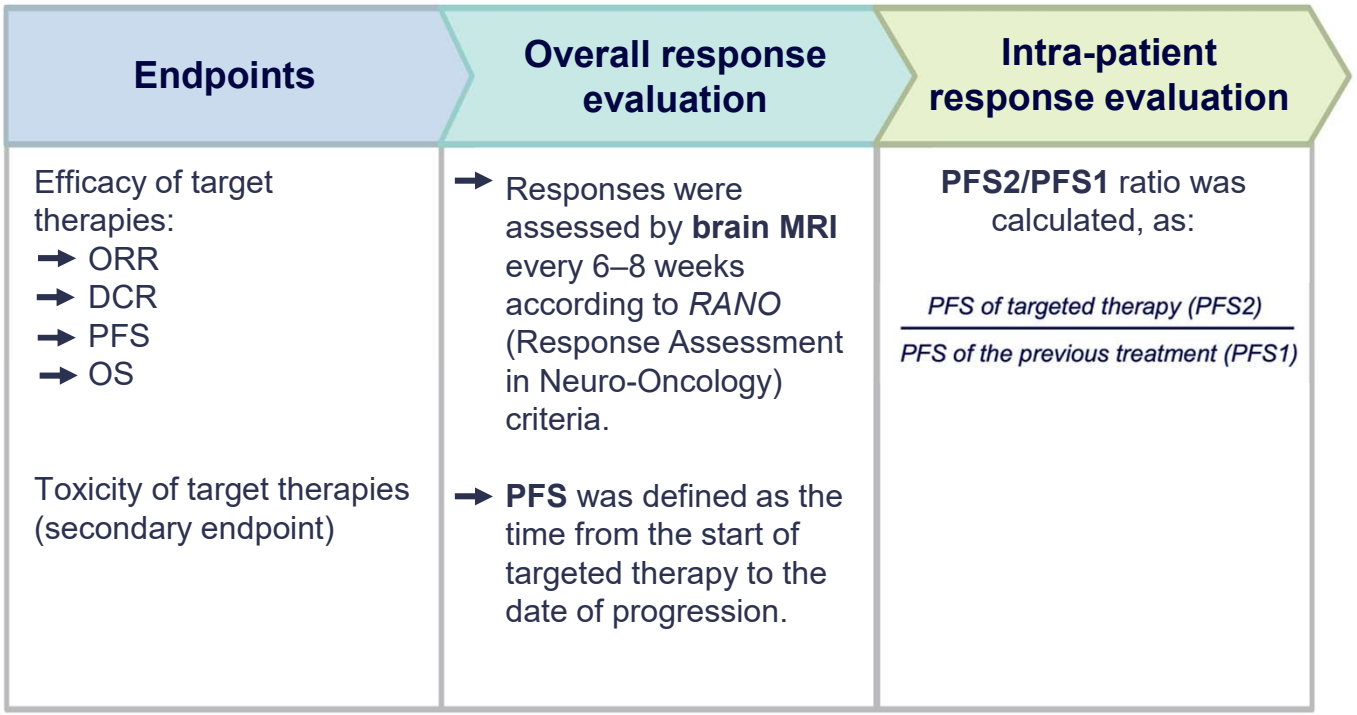
Methods

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



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ORR=objective response rate; DCR=disease control rate; PFS=progression-free survival; OS=overall survival

Results

- Out of the **37** patients who received TT, 21 were male; ECOG performance status was **≤ 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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- 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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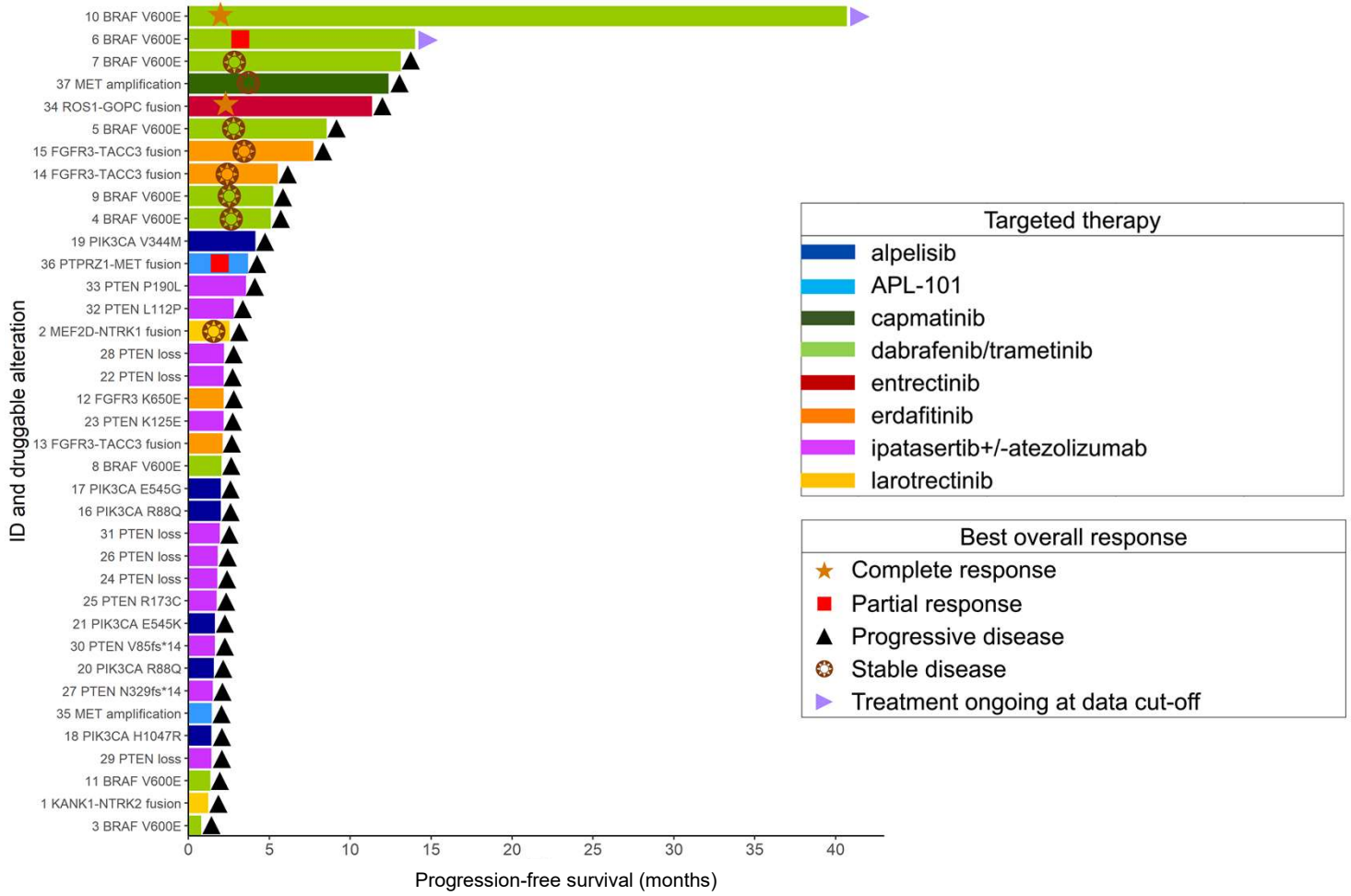
- The dabrafenib/trametinib subgroup had the **longest median PFS** (**5.23** months) and **OS** (**8.88** months), a disease control rate of 77%, an objective response rate of 22%, and a median duration of response of 27.35 months.
- Seven out of nine patients had died, and **two patients are continuing 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



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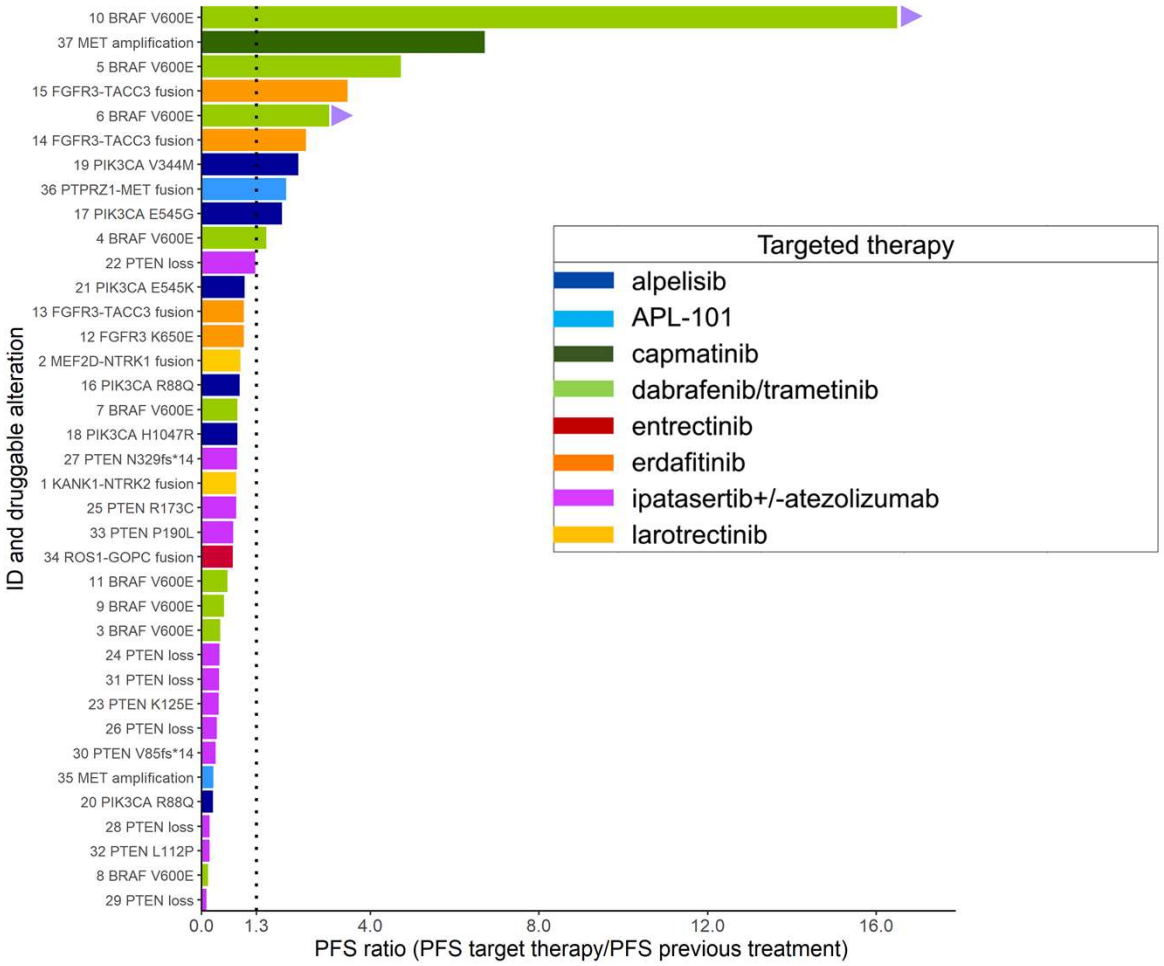
Results

$$\frac{\textit{PFS of targeted therapy (PFS2)}}{\textit{PFS of the previous treatment (PFS1)}}$$

- 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.



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Conclusions

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





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OECI Comprehensive Cancer Centre
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