2024 ASCO® ANNUAL MEETING

Efficacy and safety of the vebreltinib in previously treated, IDH mutant high-grade glioma patients with *PTPRZ1-MET* FUsion GENe (FUGEN): a randomized, multicentre, open-label, phase II/III trial

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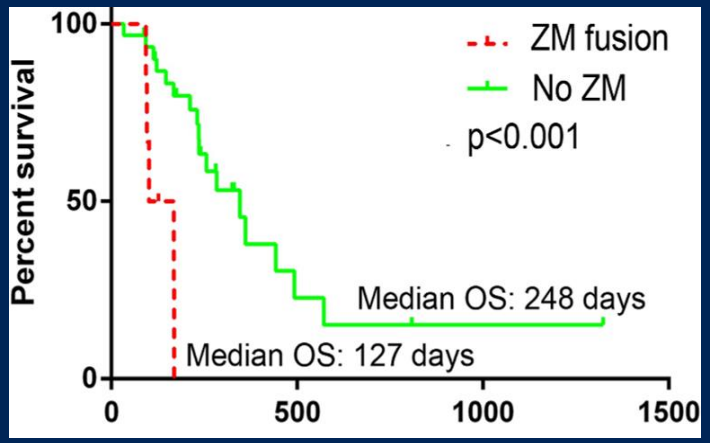
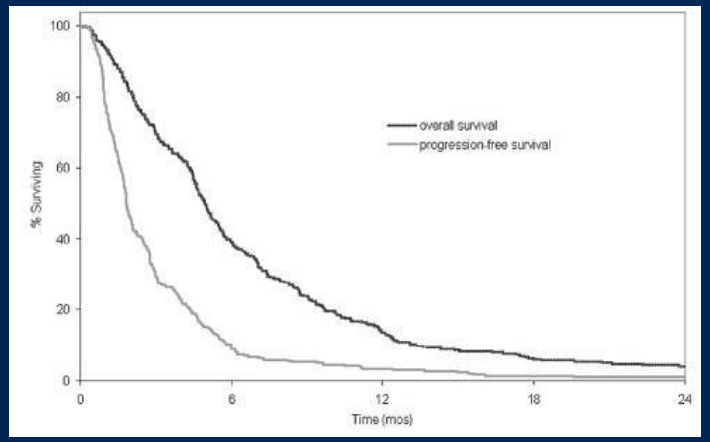
FUGEN trial_Take-home Messages

- A randomized, multicentre, open-label, phase II/III trial;
- A total of 84 patients were enrolled and randomized 1:1 to **Vebreltinib** or control (temozolomide or cisplatin with etoposide)
- The median **OS** in the vebreltinib and control group was **6.31 months** (95% CI, 4.44-8.77) and **3.38 months** (95% CI, 2.37-4.27), respectively($p<0.05$)
- The **HR** for OS was **0.52** (95% CI, 0.32-0.85, $p<0.05$)
- The FUGEN trial sheds light on a novel therapeutic pathway in the landscape of IDH mutant high-grade glioma

Background_*PTPRZ1-MET（ZM）* Fusion Gene has Independent Prognostic Value for Glioma Patients

- The ZM fusion gene was discovered in 15% of patients with IDHmut astrocytoma WHO grade 4;
- Survival analyses demonstrated that IDHmut astrocytoma WHO grade 4 patients with ZM fusion had poorer OS than those without this fusion.
- Median OS in patients with ZM fusion was 4.2 month (ZM fusion vs. without ZM fusion: 127 d vs. 248 d, P < 0.001, log-rank test) (top graph) 1;
- Even worse than the OS of 5.0 month in recurrent GBM (bottom graph) 2.

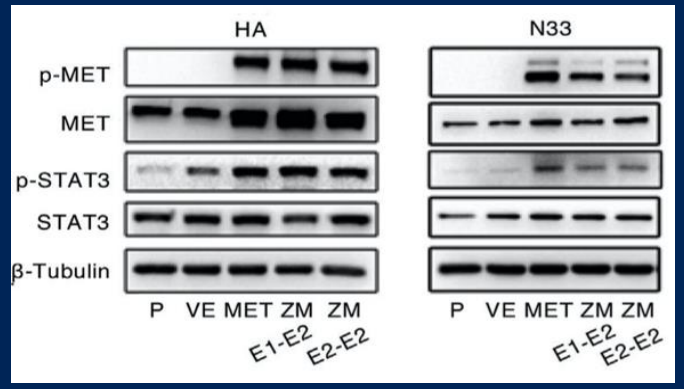


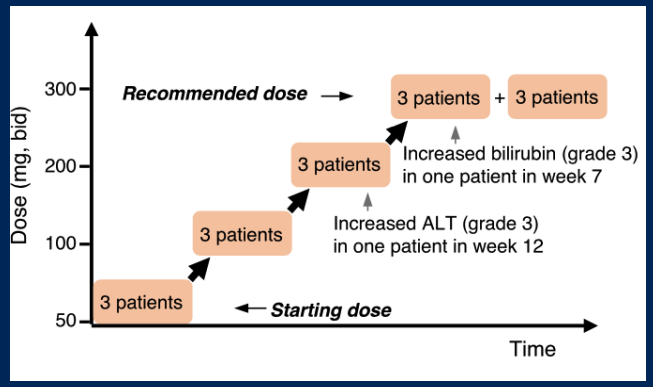


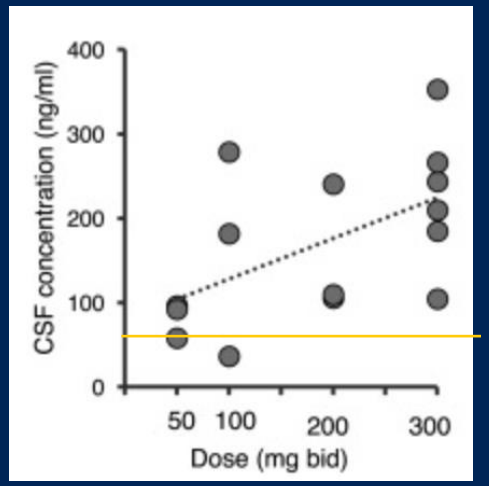
1. Bao, Zhao-Shi et al. “RNA-seq of 272 gliomas revealed a novel, recurrent PTPRZ1-MET fusion transcript in secondary glioblastomas.” *Genome research* vol. 24,11 (2014): 1765-73. doi:10.1101/gr.165126.113
2. Ballman, Karla V., et al. "The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme." *Neuro-oncology* 9.1 (2007): 29-38.

Background_Vebreltinib is a BBB-permeable, Efficient and Safe MET Inhibitor

- Expression of ZM fusions resulted in hyper-activation of MET and STAT3 signaling;
- Phase I to identify RP2D: 300mg BID;
- Vebreltinib was well tolerated and demonstrated preliminary anti-tumor activity in IDH mutant high-grade glioma;
- The drug concentration in the cerebrospinal fluid increased with the dose;
- The CSF concentration in patients treated with 300 mg dosage had reached the corresponding 90% effective dose (ED90) in ZM-positive U87 cell line-derived xenograft models.







Hu, Huimin, et al. "Mutational landscape of secondary glioblastoma guides MET-targeted trial in brain tumor." Cell 175.6 (2018): 1665-1678.

FUGEN trial：Phase II/III Study Design

Key eligibility criteria

- Age: 18-65
- Histologically confirmed astrocytoma IDH^{mut} WHO grade 4 or GBM with LGG history (IHC for IDH^{mut} test)
- ZM fusion gene positive
- KPS≥60
- Previous treatment with radiotherapy and/or temozolomide

Stratification

KPS(60-79 vs ≥80）

N=84

R 1:1

Vebreltinib 300mg BID, 28-day/cycle

Temozolomide dose-dense regimen: 100-150 mg/m^2/d of temozolomide orally for 7 days followed by a 7-day interval, 28-day/cycle

or

Cisplatin combined with Etoposide: 80-100 mg/m^2 of cis-platinum combined with 100 mg/m2/d of etoposide intravenously for 3 days in continuous 28-day cycles

Primary endpoint:

- Overall survival

secondary endpoint:

- Investigator-assessed PFS
- ORR by Investigator (RANO)
- KPS scores
- EORTC Quality of Life Questionnaires QLQ-C30 and QLQ-BN20

- Samples assessed for ZM fusion variants (*PTPRZ1* exon1-*MET* exon2, *PTPRZ1* exon2- *MET* exon2, *PTPRZ1* exon8- *MET* exon2) using Adx-ARMS-PTPRZ1-MET Test (Amoydx Medical Institute)

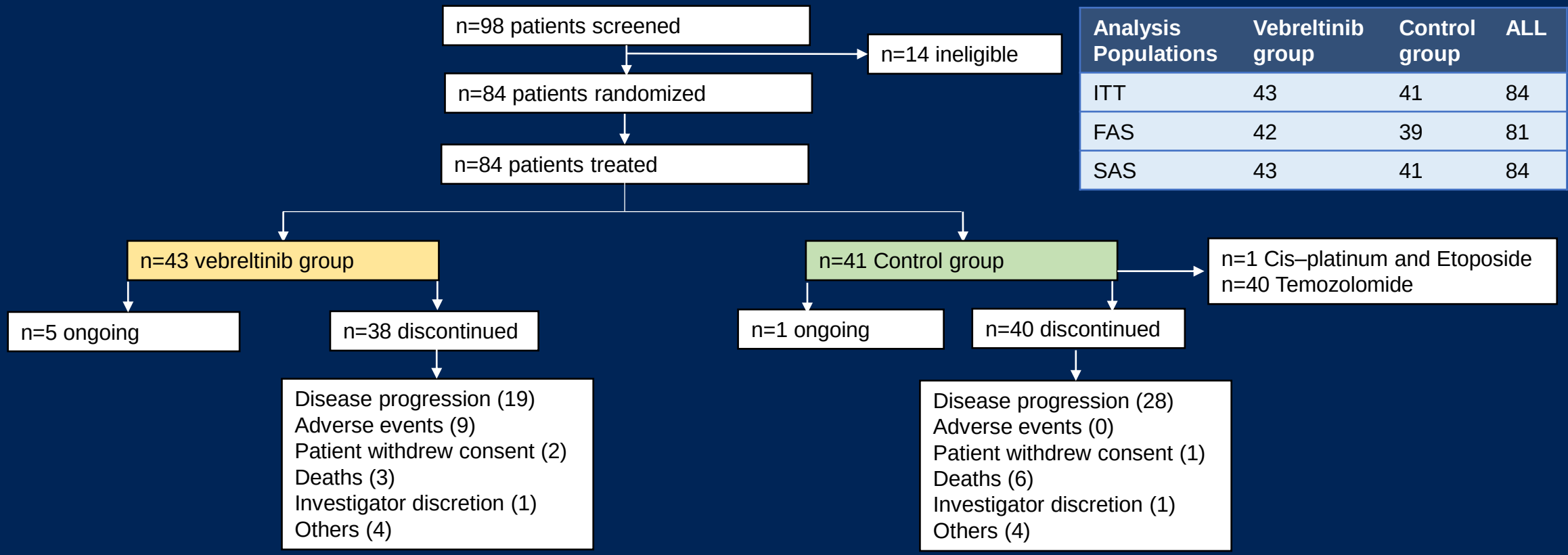
Statistical considerations

- To achieve a power of 80, with the assumption of the median OS for 4 months for the control group, a total sample size of 74 subjects (with 70 death events) is required. Therefore, an enrollment of 84 subjects was planned, allowing for a 10% dropout.

ZM: *PTPRZ1-MET*, PFS: progression-free survival , ORR:objective response rate， RANO: Response Assessment for Neuro-oncology.

FUGEN trial：Patient Disposition

- From July 2018 to September 2022



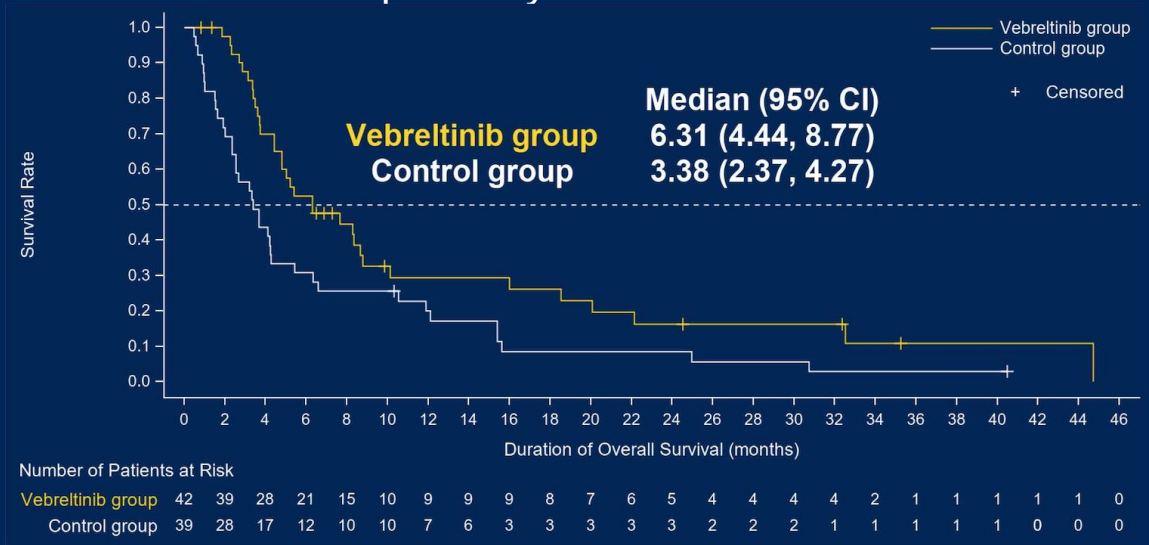
Analysis Populations	Vebreltinib group	Control group	ALL
ITT	43	41	84
FAS	42	39	81
SAS	43	41	84

Results_Baseline Demographics and Disease Characteristics

	Vebreltinib group (N=42)	Control group (N=39)	All (N=81)
Age (years)			
Mean (SD)	41.6 (9.47)	41.1 (9.58)	41.4 (9.47)
Median [Min, Max]	41.0	40.0	41.0
Gender , n (%)			
Male	22 (52.4)	22 (56.4)	44 (54.3)
Female	20 (47.6)	17 (43.6)	37 (45.7)
KPS			
Mean (SD)	71.4 (9.77)	71.0 (12.73)	71.2 (11.22)
Median [Min, Max]	70.0	70.0	70.0
KPS，n(%)			
60≤KPS＜80	29 (69.0)	27 (69.2)	56 (69.1)
KPS≥80	13 (31.0)	12 (30.8)	25 (30.9)
Max lesion diameter at baseline, n(%)			
n	39	35	74
≤3cm	8 (20.5)	9 (25.7)	17 (23.0)
>3cm	31 (79.5)	26 (74.3)	57 (77.0)
Missing	3	4	7
Time from initial diagnosis to randomization （months）			
n (missing）	42 (0)	37 (2)	79 (2)
Mean (SD)	45.77 (35.011)	50.32 (31.300)	47.90 (33.192)
Median	35.45	51.09	43.93
Prior antitumor surgery			
Yes	42 (100)	38 (97.4)	80 (98.8)
No	0	1 (2.6)	1 (1.2)
Prior antitumor radiotherapy			
Yes	42 (100)	39 (100)	81 (100)
No	0	0	0
Prior antitumor chemotherapy			
Yes	42 (100)	39 (100)	81 (100)
No	0	0	0
Prior other therapy			
Yes	6 (14.3)	4 (10.3)	10 (12.3)
No	36 (85.7)	35 (89.7)	71 (87.7)
Astrocytoma IDH mutant WHO grade 4, n (%)	39 (92.9)	34 (87.2)	73 (90.1)
IDH wildtype Glioblastoma, n (%)	3 (7.1)	5 (12.8)	8 (9.9)

Results_Primary Endpoint: Overall Survival (FAS)

- As of April 1st, 2023, the average follow-up was 9.9 months in the vebreltinib group and 6.8 months in the control group;
- Based on Full Analysis Set (FAS): Vebreltinib treatment group extended mOS from 3.38 months to 6.31 months, with HR value of 0.52 and P value of 0.009;
- The 3-month improvement in OS with Vebreltinib treatment is both statistically and clinically significant;
- Since 1996, the three drugs approved by the FDA for the treatment of glioblastoma have improved overall survival by 1.8, 2.1 and 2.5 months respectively [1-3].



FAS	Vebreltinib group (N=42)	Control group (N=39)
HR（95% CI）	0.52 (0.32, 0.85)	
	P=0.009	

Reduce the risk of death by 48%

Control group: Temozolomide group or Cisplatin combined with Etoposide group CI: Confidence interval; FAS: **Full Analysis Set** HR: Hazard ratio; ITT: intention to treat; mo: Months; mOS: median Overall survival.

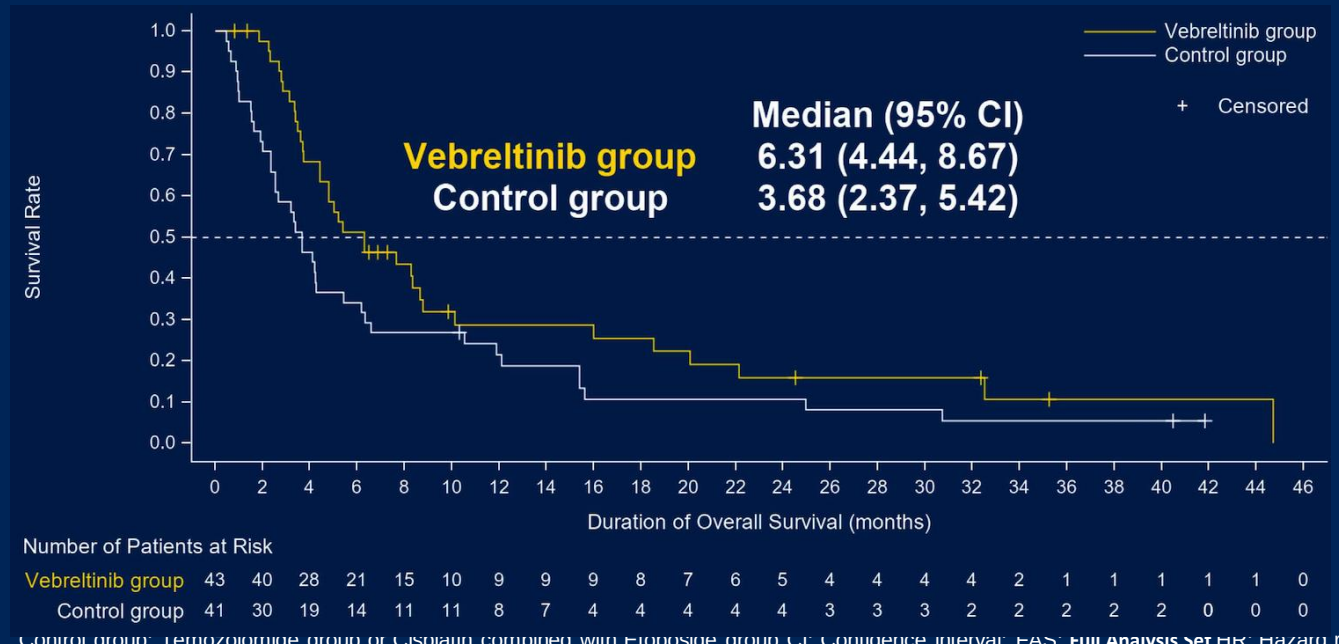
[1]:Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, et al. (1995) Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 345: 1008–1012

[2]:Westphal, Manfred et al. "A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma." *Neuro-oncology* vol. 5,2 (2003): 79-88. doi:10.1093/neuonc/5.2.79

[3]:Cohen, Martin H et al. "Food and Drug Administration Drug approval summary: temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme." *Clinical cancer research : an official journal of the American Association for Cancer Research* vol. 11,19 Pt 1 (2005): 6767-71. doi:10.1158/1078-0432.CCR-05-0722

Results_Primary Endpoint: Overall Survival (ITT)

- As of April 1st, 2023, the average follow-up was 9.9 months in the vebreltinib group and 6.8 months in the control group
- Vebreltinib demonstrated the capacity to extend the median survival period from 3.68 months to 6.31 months, compared with the control group
- Vebreltinib was associated with a 40% reduction in the risk of mortality for the patients in ITT population, imparting both statistical and clinical significance to the observed survival benefit



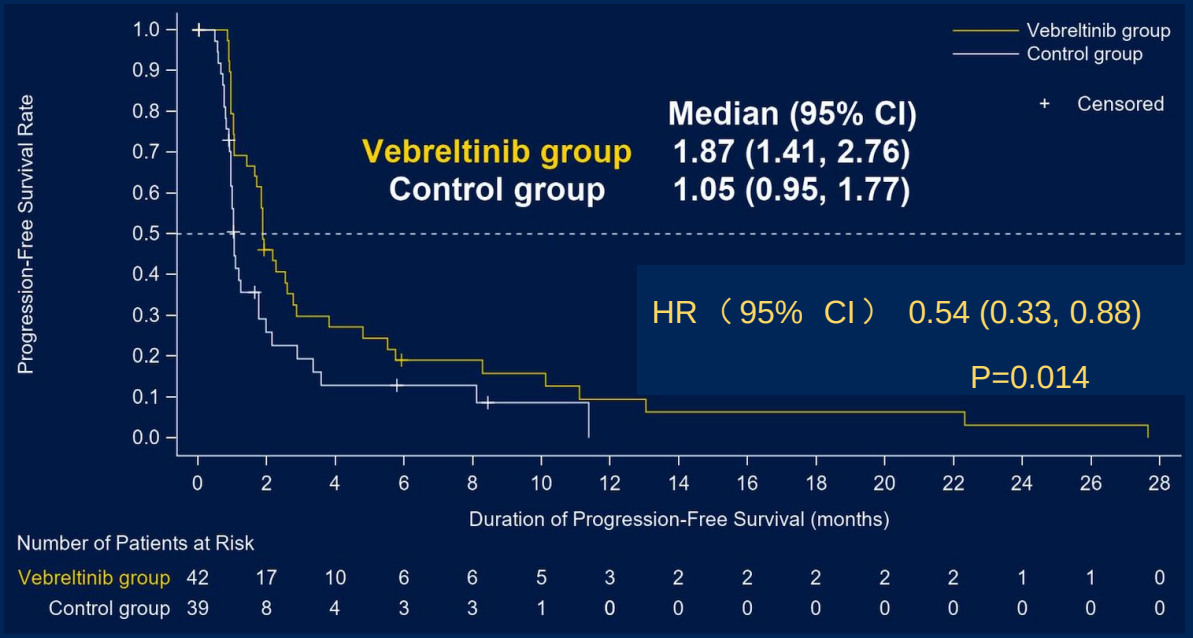
ITT	Vebreltinib group (N=43)	Control group (N=41)
HR（95% CI）	0.60 (0.37, 0.97）	
	P=0.036	

Reduce the risk of death by 40%

Control group: Temozolomide group or Cisplatin combined with Etoposide group CI: Confidence interval; FAS: Full Analysis Set HR: Hazard ratio; ITT: intention to treat; mo: Months; mOS: median Overall survival.

Results_Secondary Endpoint PFS and ORR (FAS)

PFS

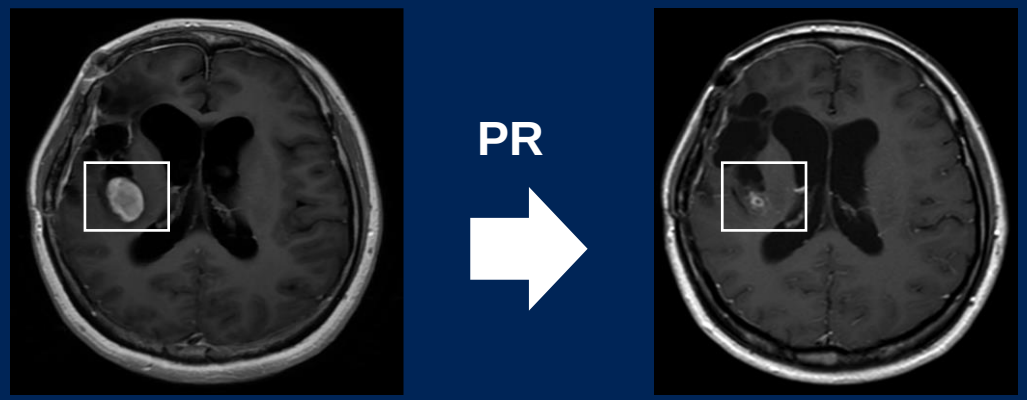


Control group: Temozolomide group or Cisplatin combined with Etoposide group

CI: Confidence interval; FAS: **Full Analysis Set** HR: Hazard ratio; mPFS: median Progression Free survival.

ORR

	Vebreltinib group (N=42)	Control group (N=39)
The objective response rate, n (%)	**4 (9.5)**	**1 (2.6)**
95% CI	(2.66, 22.62)	(0.06, 13.48)
Complete Response, n (%)	1 (2.4)	1 (2.6)
Partial Response, n (%)	3 (7.1)	0
Stable Disease, n (%)	20 (47.6)	12 (30.8)
Progressive Disease, n (%)	14 (33.3)	18 (46.2)
Not Available*, n (%)	4 (9.5)	8 (20.5)
	P=0.361	

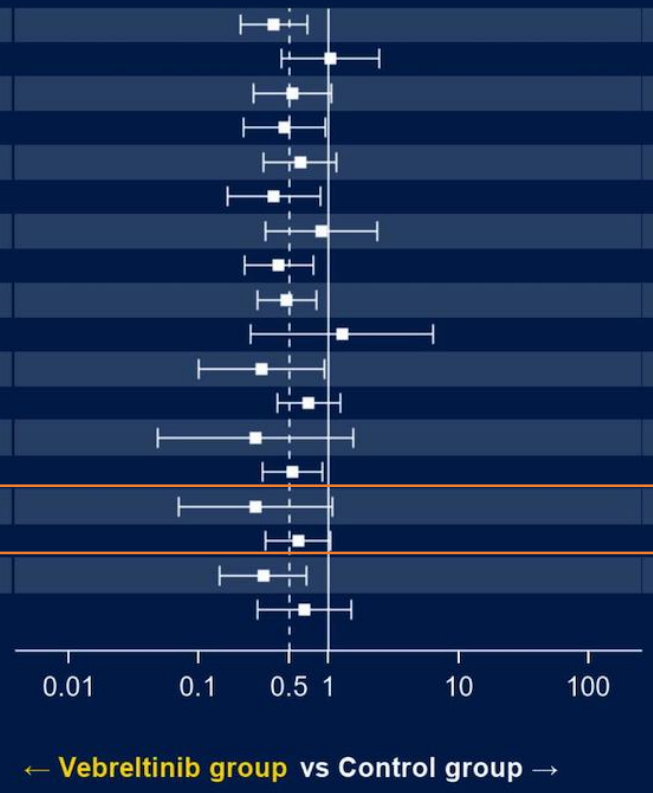


Baseline

2C with vebreltinib

Results_Notable Reduction in the Risk of Mortality Observed across Various Subgroups in Vebreltinib Group

Subgroup	Vebreltinib group (Death/n)	Control group (Death/n)	HR (95% CI)
60≤KPS<80	22/29	26/27	0.38 (0.21, 0.68)
KPS≥80	11/13	11/12	1.03 (0.43, 2.44)
Age≤40	17/20	20/20	0.53 (0.26, 1.05)
Age>40	16/22	17/19	0.46 (0.22, 0.94)
Male	20/22	21/22	0.60 (0.31, 1.15)
Female	13/20	16/17	0.38 (0.16, 0.85)
Concomitant antitumor therapy*	11/12	9/9	0.88 (0.33, 2.35)
No concomitant antitumor therapy	22/30	28/30	0.41 (0.23, 0.75)
Astrocytoma IDH mutant WHO grade 4	30/39	32/34	0.48 (0.28, 0.80)
GBM with LGG history	3/3	5/5	1.26 (0.25, 6.32)
1 Prior antitumor surgery history	8/13	8/9	0.30 (0.10, 0.92)
≥2 Prior antitumor surgery history	25/29	28/29	0.70 (0.40, 1.23)
Prior Bevacizumab	5/7	5/5	0.27 (0.05, 1.54)
Prior without Bevacizumab	28/35	32/34	0.52 (0.31, 0.89)
Max lesion diameter at baseline≤3cm	4/8	9/9	0.27 (0.07, 1.06)
Max lesion diameter at baseline>3cm	28/31	25/26	0.58 (0.33, 1.03)
Max lesion diameter at baseline≤4.285cm	12/16	21/21	0.31 (0.14, 0.67)
Max lesion diameter at baseline>4.285cm	20/23	13/14	0.64 (0.28, 1.48)

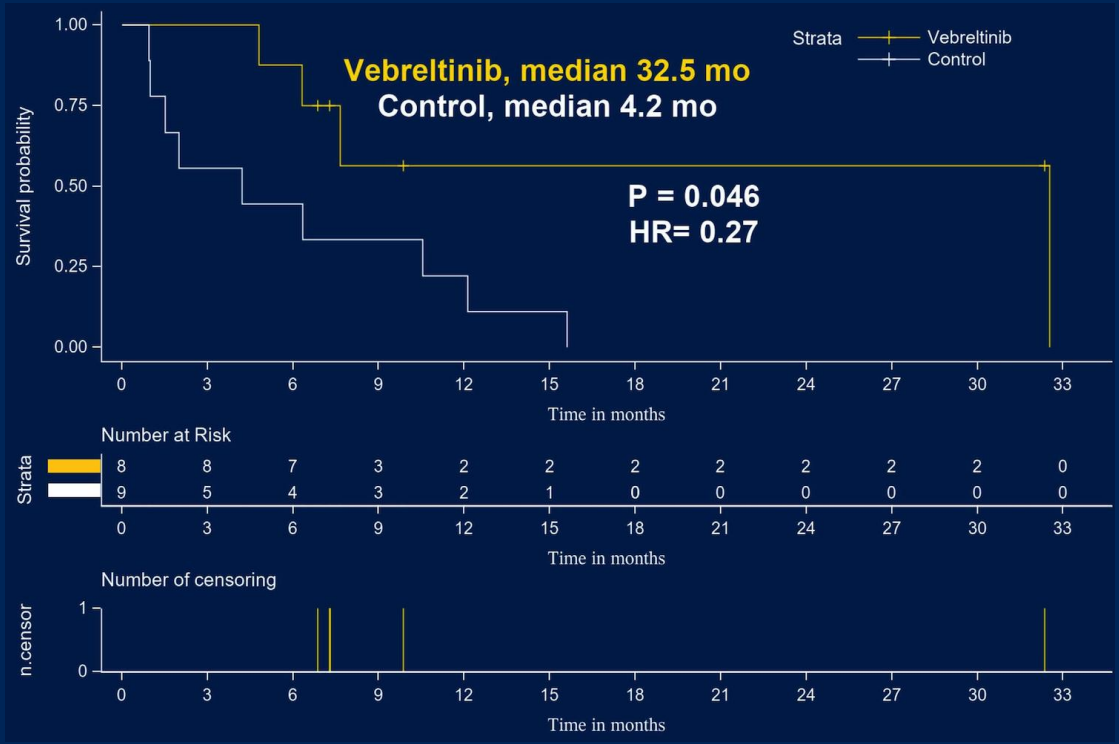


Control group: Temozolomide group or Cisplatin combined with Etoposide group

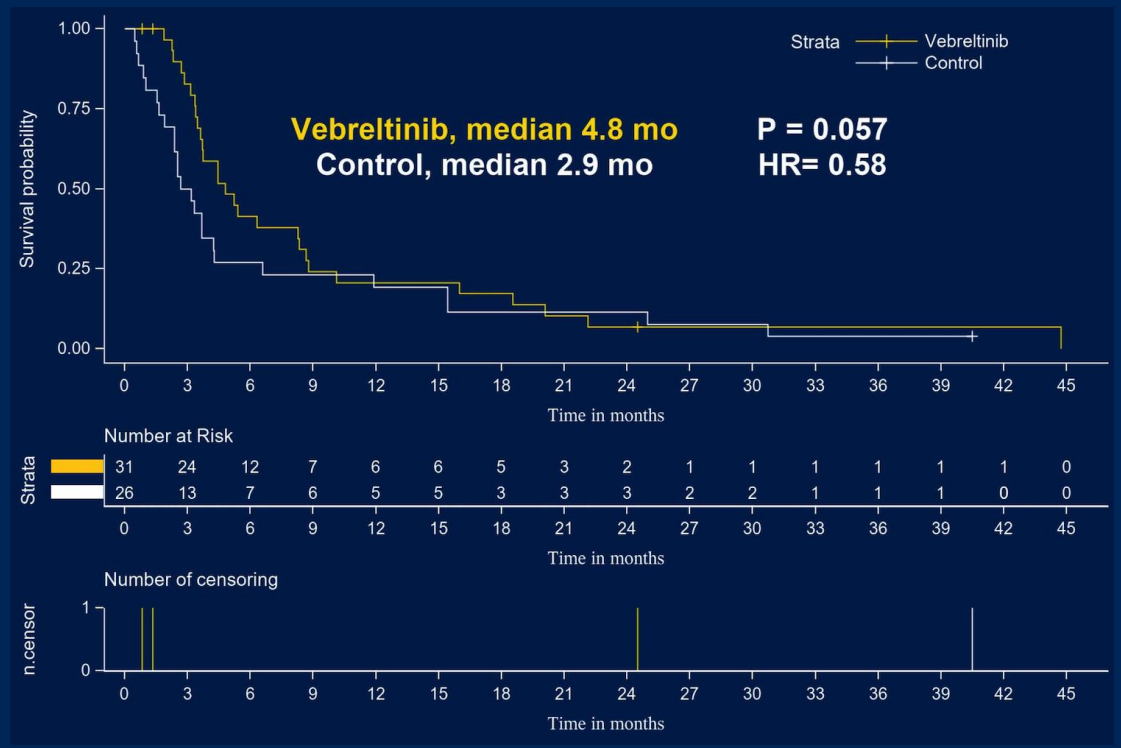
* Concomitant antitumor therapy is defined as of those were received non-investigational antitumor therapy during survival follow-up.

Results_Subgroup Analysis of the Impact of Tumor Size at Baseline ≤ 3cm

OS_ Tumor Size at Baseline ≤ 3cm



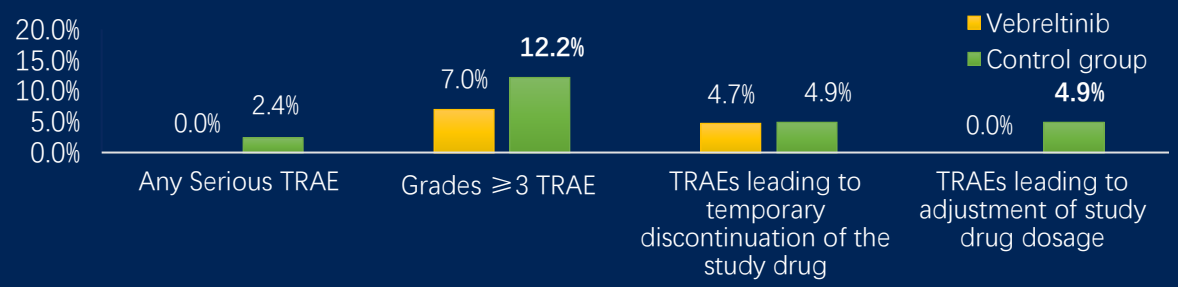
OS_ Tumor Size at Baseline > 3cm



Results_Safety summary

	Vebreltinib group (N=43)	Control group（N=41）			Total (N=84)
		Temozolomide（N=40）	Cisplatin combined with etoposide（N=1）	Control group total (N=41)	
TEAEs*, n(%)	43 (100)	36 (90.0)	1 (100)	37 (90.2)	80 (95.2)
Grades ≥3 TEAE	27 (62.8)	23 (57.5)	1 (100)	24 (58.5)	51 (60.7)
SAE	23 (53.5)	18 (45.0)	0	18 (43.9)	41 (48.8)
TEAEs leading to temporary discontinuation of the study drug	13 (30.2)	7 (17.5)	0	7 (17.1)	20 (23.8)
TEAEs leading to adjustment of study drug dosage	3 (7.0)	1 (2.5)	1 (100)	2 (4.9)	5 (6.0)
TEAEs leading to permanent discontinuation of study drug	8 (18.6)	0	0	0	8 (9.5)
TEAEs leading to study discontinuation	0	0	0	0	0
TEAEs leading to death	12 (27.9)	10 (25.0)	0	10 (24.4)	22 (26.2)
TRAEs, n(%)	26 (60.5)	19 (47.5)	1 (100)	20 (48.8)	46 (54.8)
Grades ≥3 TRAE	3 (7.0)	4 (10.0)	1 (100)	5 (12.2)	8 (9.5)
Any treatment-related SAE	0	1 (2.5)	0	1 (2.4)	1 (1.2)
TRAEs leading to temporary discontinuation of the study drug	2 (4.7)	2 (5.0)	0	2 (4.9)	4 (4.8)
TRAEs leading to adjustment of study drug dosage	0	1 (2.5)	1 (100)	2 (4.9)	2 (2.4)
TRAEs leading to permanent discontinuation of study drug	0	0	0	0	0
TRAEs leading to study discontinuation	0	0	0	0	0
TRAEs leading to death	0	0	0	0	0

- Vebreltinib showed favorable safety profile: most TRAEs are grade 1-2 and recoverable with clinical management;
- TRAEs of grade 3 or more were reported in 7% of the patients in the vebreltinib group, as compared with 12.2% of those in the control group;
- No serious TRAEs were reported in the vebreltinib group, while only 2.4% was observed in the control group;
- No deaths were attributed to the study treatment in either the vebreltinib group or the control group.



*Adverse events related to study drugs include adverse events whose study relevance in CRF is definitely related, probably related, or possibly related. Missing correlations were treated as if they were related to the study drug.
AE: adverse event

Results_TRAEs and SAE (Safety Analysis)

Event	Vebreltinib group (N=43[a])				
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade ≥3 n (%)	Any Grade n (%)
Any TRAEs[b]	2 (4.7)	1 (2.3)	0	3 (7.0)	26 (60.5)
Rash	0	0	0	0	11 (25.6)
Peripheral Edema	0	0	0	0	6 (14.0)
Alanine Aminotransferase Increased	1 (2.3)	1 (2.3)	0	2 (4.7)	5 (11.6)
Aspartate Aminotransferase Increased	1 (2.3)	0	0	1 (2.3)	5 (11.6)
Vomiting	0	0	0	0	4 (9.3)
Lymphocyte Count Decreased	1 (2.3)	0	0	1 (2.3)	3 (7.0)
Blood Bilirubin Increased	0	0	0	0	3 (7.0)
Serious AE[b]	13 (30.2)	2 (4.7)	3 (7.0)	18 (41.9)	18 (41.9)
Epilepsy Seizure	3 (7.0)	0	0	3 (7.0)	4 (9.3)
Headache	4 (9.3)	0	0	4 (9.3)	4 (9.3)
Brain Edema	2 (4.7)	0	0	2 (4.7)	3 (7.0)
Serious TRAE[b]	0	0	0	0	0

Event	Control group (N=41[a])				
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade ≥3 n (%)	Any Grade n (%)
Any TRAEs[b]	3 (7.3)	2 (4.9)	0	5 (12.2)	20 (48.8)
Vomiting	0	0	0	0	12 (29.3)
Nausea	0	0	0	0	7 (17.1)
White Blood Cell Count Decreased	3 (7.3)	0	0	3 (7.3)	6 (14.6)
Constipation	0	0	0	0	6 (14.6)
Appetite Decreased	0	0	0	0	4 (9.8)
Neutrophil Count Decreased	2 (4.9)	0	0	2 (4.9)	4 (9.8)
Serious AE[b]	9 (22.0)	2 (4.9)	2 (4.9)	13 (31.7)	13 (31.7)
Headache	5 (12.2)	0	0	5 (12.2)	5 (12.2)
Epilepsy Seizure	3 (7.3)	0	0	3 (7.3)	3 (7.3)
Serious TRAE[b]	1 (2.4)	0	0	1 (2.4)	1 (2.4)

The Most Commonly Observed TRAEs

[a]Patients who received ≥ 1 dose of study treatment
[b]AEs occurring between the start date of administration of the product and 28 days after the last dose or the start dose of subsequent anti-cancer therapy after the last dose whichever comes first.

Abbreviations: AEs, adverse events; TRAEs, treatment-related adverse events

Summary

- The FUGEN study resulted in statistical and clinical improvement in OS, and PFS in patients diagnosed with IDH mutant high-grade glioma bearing ZM fusion，when compared to the control group (Temozolomide or Cisplatin combined with Etoposide);
- These findings highlight the substantial and meaningful therapeutic benefits of vebreltinib, supporting its potential as an effective treatment option for a subset of IDH mutant high-grade glioma;
- FUGEN trial sheds light on a novel therapeutic pathway in the landscape of IDH mutant high-grade glioma;
- In April 2024, vebreltinib has received the full approval by NMPA in China for the adult patients with astrocytoma IDH mutant (WHO grade 4) with the *ZM* fusion or glioblastoma with LGG history and harboring the *ZM* fusion gene, who have experienced treatment failure in prior therapies.

NMPA: National Medical Products Administration

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