AINO Giovani Meeting
30/05/2023

Two different stories targeting MET: Rome was not built in a day

Marta Padovan

Associazione Italiana di Neuro-Oncologia

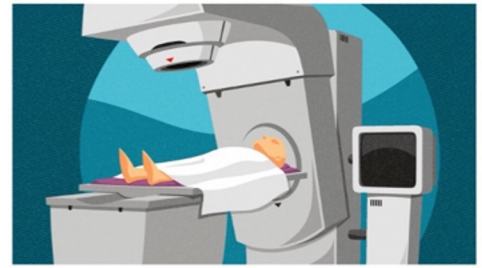
Male, 40
Mental confusion followed by a generalized seizure

Left temporal lesion

March 2016

Radical surgical resection
Anaplastic astrocytoma [grade 3 WHO 2016] IDH wildtype, MGMT methylated

April 2016



Radiotherapy
[60 Gy/30 fractions] and concomitant Temozolomide

May – June 2016

Temozolomide
12 cycles

July 2016 – July 2017

Follow up

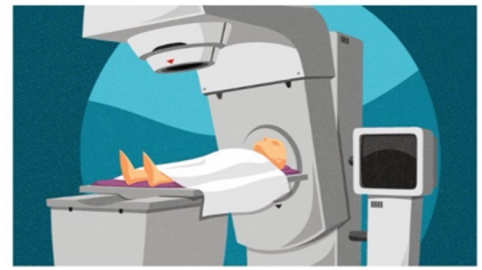
Good seizure control with levetiracetam, acceptable quality of life

Radiological progression in temporal region

April 2021

2nd surgery
Glioblastoma IDH wildtype **[grade 4 WHO 2021], MGMT methylated**

May 2021



Radiotherapy on temporal region [30 Gy/5 fractions]

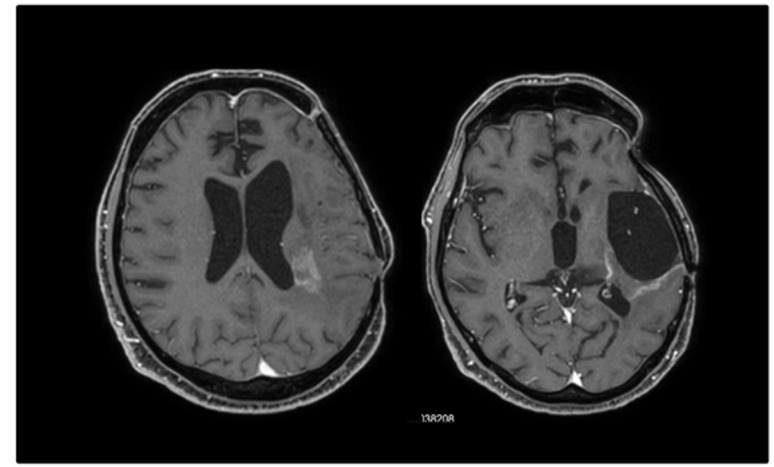
June 2021

Regorafenib 6 cycles

June – December 2021

Radiological progression in left posterior horn of lateral ventricle

January 2022



Introduction of dexamethasone for right-sided hemiparesis and aphasia

FOUNDATION MEDICINE®

GENE	ALTERATION
RAD21	amplification
MYC	amplification
CDKN2A	loss
CDKN2B	loss
MTAP	loss
MET	amplification
TP53	Q144P

gene copy number = 10

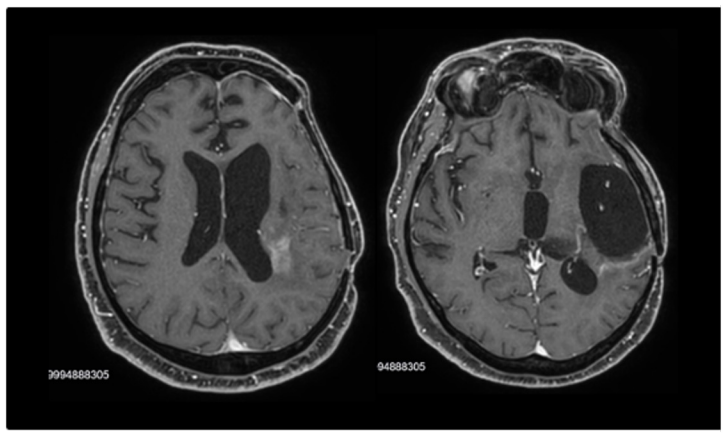
Capmatinib [compassionate use] 400 mg BID

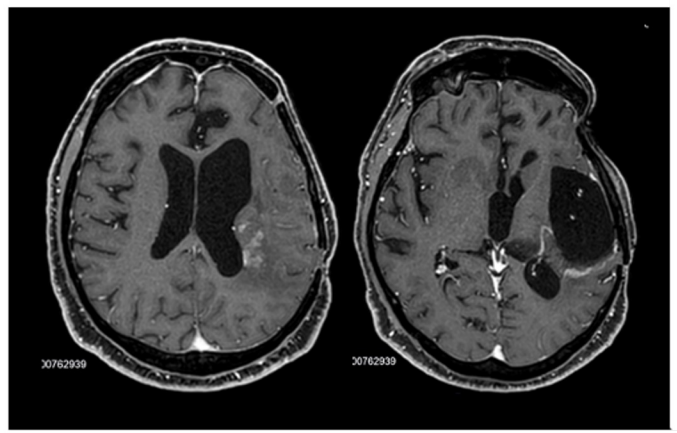
Best response: SD

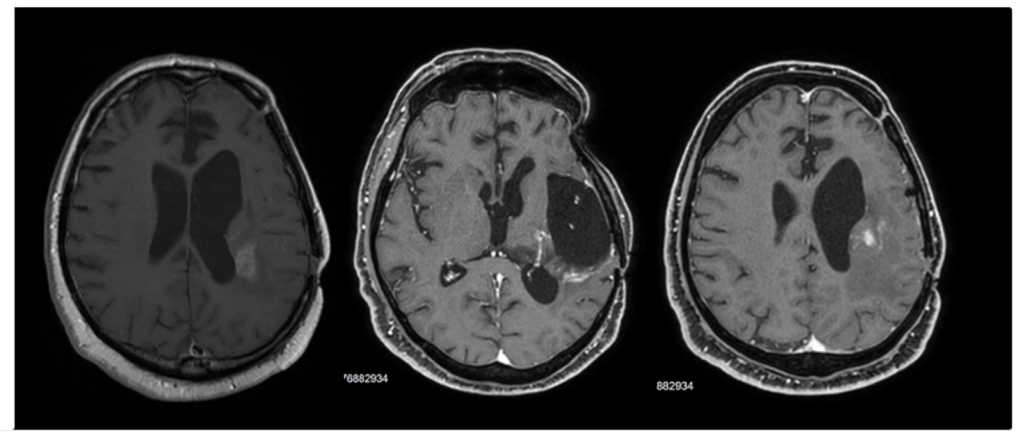
No AEs

Major extension of the lesion to left centrum semiovale

NGS | January – August 2022 | August 2022







Clinically stable (right-sided hemiparesis and mild aphasia)

Radiotherapy on
left centrum semiovale
[25 Gy/5 fractions]

August 2022

Capmatinib
[compassionate use]
400 mg BID

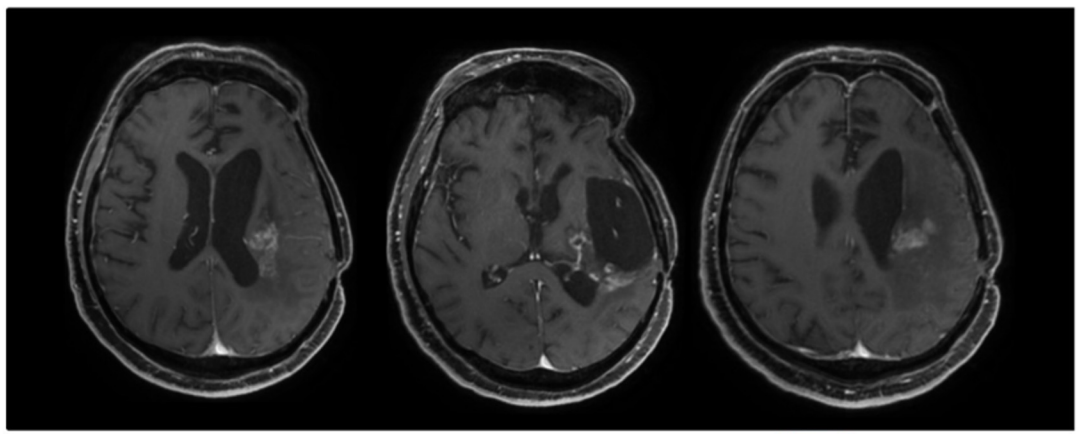
August 2022 – January 2023

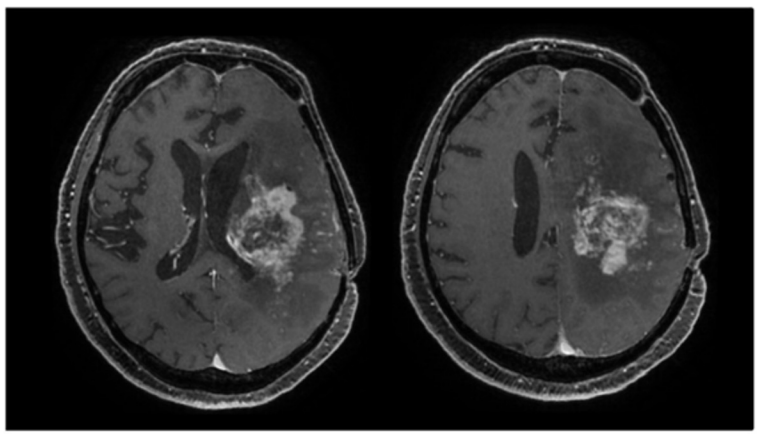
Radiological
progression

February 2023

Best
supportive
care

March 2023 – ongoing…





Clinical worsening, dependence in instrumental activities of daily living

AINO Giovani Meeting

30/05/2023

Two different stories targeting MET: Rome was built in a day

Mario Caccese

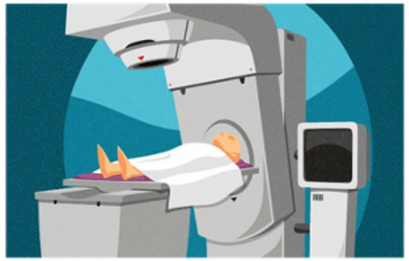
Associazione Italiana di Neuro-Oncologia

Female, 51
Headache and Seizures

Pellucid Septum lesion

Radical surgical resection
Neurocytoma

July 2007



Radiotherapy alone [45 Gy] and subsequent Follow-up

Aug - Sep 2007

Progression Disease
Temozolomide 150-200 mg/mq (24 cycles)

Sep 2017 - July 2021

2nd Surgical Resection
Glioblastoma (Grade 4 WHO 2021) IDH wt

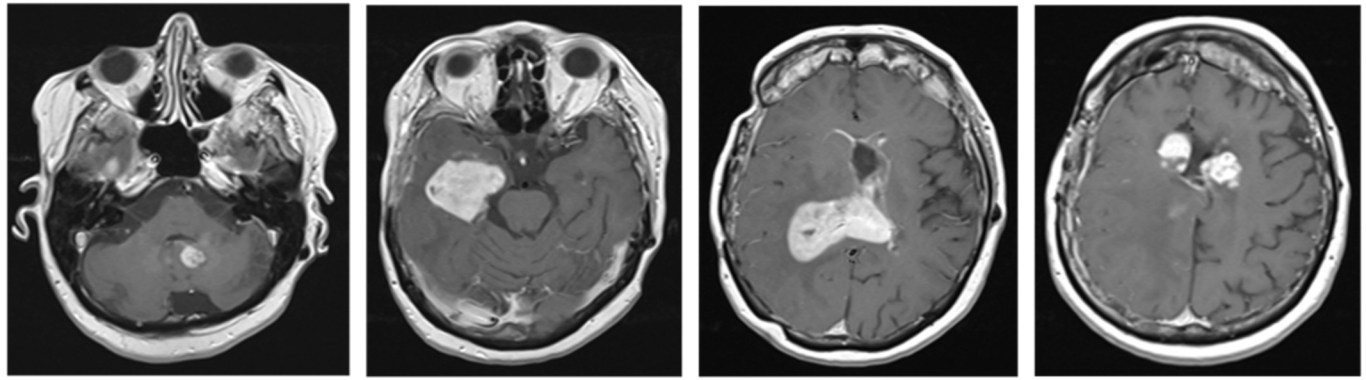
September 2021

Regorafenib 2 cycles

Dec 2022 - Jan 2023

Progression Disease

February 2023



MET FUSION AND VARIANT TRANSCRIPT ANALYSIS				
Gene	Method	Analyte	Result	Fusion/Isoform
MET	Seq	RNA-Tumor	Likely Pathogenic Fusion	PTPRZ1:MET

Patient enrolled in the SPARTA protocol

1st March 2023

CLINICAL TRIAL PROTOCOL

SPARTA

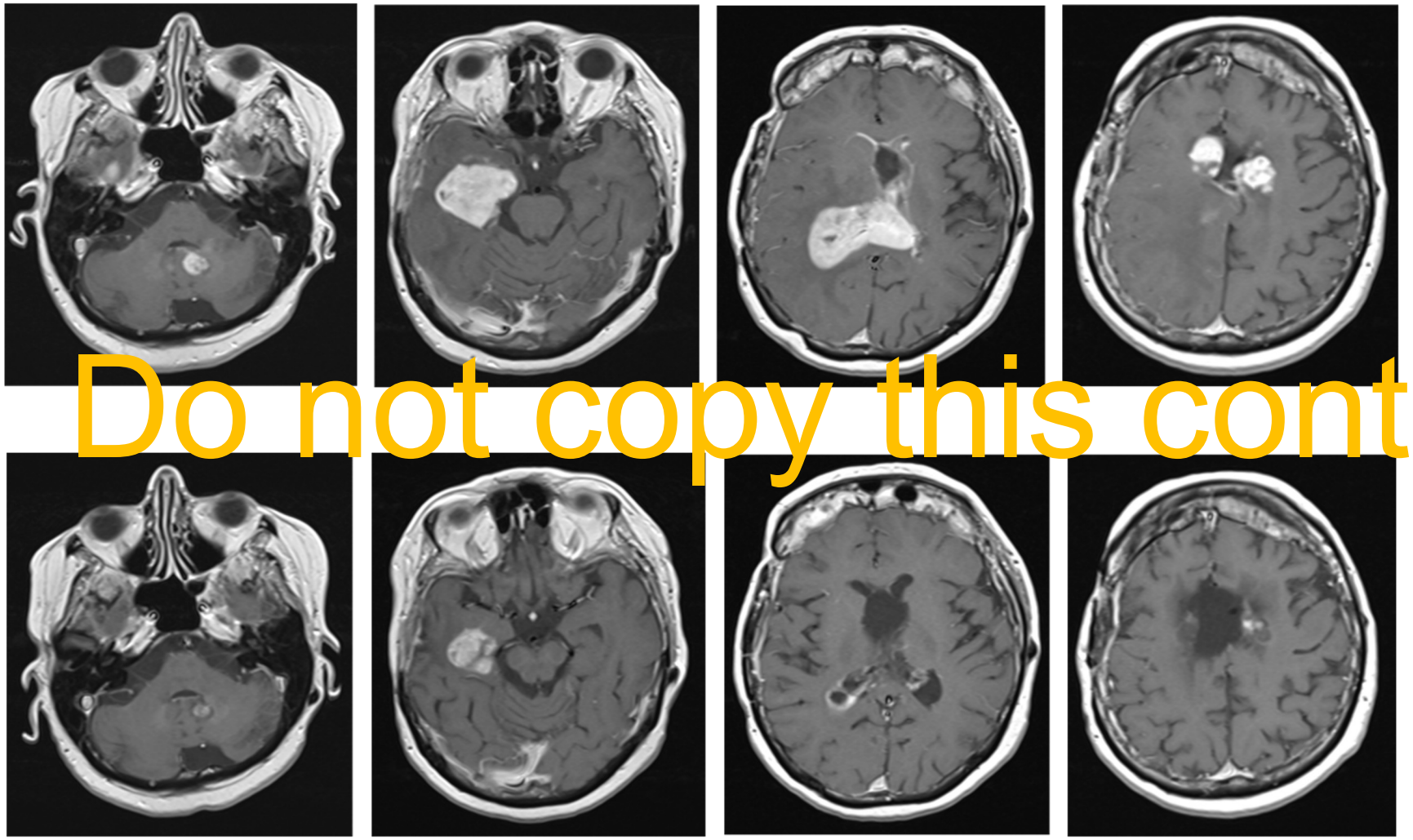
Researching Ways to Battle Cancer

Study Title:	Phase 1 / 2 Multicenter Study of the Safety, Pharmacokinetics, and Preliminary Efficacy of APL-101 in Subjects with Non-Small Cell Lung Cancer with c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors
Study Number:	APL-101-01 (SPARTA)
Study Phase:	1 / 2
Product Name:	APL-101 (Vebreltinib, formerly Bozitinib)
IND Number:	131,638
EudraCT Number:	2019-001757-54
Indication:	Select advanced solid tumors and NSCLC

Impressive response after 2 cycles

February 2023

April 2023



Patient in good general clinical condition, no APL-101 related adverse events

MET

- MET is a tyrosine kinase receptor that stimulates cell scattering, invasion, protection from apoptosis and angiogenesis
- It is aberrantly activated because of mutations, fusions, amplification or aberrant ligand production
- The incidence of MET exon 14 mutations has been proposed as driver mutation in lung adenocarcinoma (3%)

Case 1 →

Case 2 →

Kind of MET alteration	Incidence in gliomas
MET amplification	1-5%
MET fusions (PTPRZ1-MET fusion)	1-2%
MET exon 14 mutations	0.4%

Oliveres, H., Pineda, E., & Maurel, J. (2020). MET inhibitors in cancer: pitfalls and challenges. Expert opinion on investigational drugs, 29(1), 73–85

MET inhibition in gliomas

- Cabozantinib
- Crizotinib
- Capmatinib
- Tepotinib
- Savolitinib

cancers

MDPI

Article

Safety and Efficacy of Crizotinib in Combination with Temozolomide and Radiotherapy in Patients with Newly Diagnosed Glioblastoma: Phase Ib GEINO 1402 Trial

María Martínez-García [1,2,3,*], Guillermo Velasco [4,5], Estela Pineda [6], Miguel Gil-Gil [7], Francesc Alameda [8], Jaume Capellades [9], Mari Cruz Martín-Soberón [10], Israel López-Valero [4], Elena Tovar Ambel [4], Palmira Foro [11], Álvaro Taus [1,3], Montserrat Arumi [7], Aurelio Hernández-Laín [12] and Juan Manuel Sepúlveda-Sánchez [10,*]

- Phase Ib trial
- 38 newly diagnosed GBM pts received crizotinib with standard radiotherapy/temozolomide followed by maintenance with crizotinib
- 32% presented grade ≥3 adverse events
- With median follow up of 18.7 months, median PFS was 10.7 m with a 6 m PFS and 12 m PFS of 71.5% and 38.8%, respectively
- Molecular biomarkers showed no correlation with efficacy.

MET inhibition in gliomas

- Cabozantinib
- Crizotinib
- Capmatinib
- Tepotinib
- Savolitinib

Journal of Neuro-Oncology (2020) 146:79–89
https://doi.org/10.1007/s11060-019-03337-2

CLINICAL STUDY

Check for updates

A Phase Ib/II, open-label, multicenter study of INC280 (capmatinib) alone and in combination with buparlisib (BKM120) in adult patients with recurrent glioblastoma

Martin van den Bent[1] · Analia Azaro[2] · Filip De Vos[3] · Juan Sepulveda[4] · W. K. Alfred Yung[5] · Patrick Y. Wen[6] · Andrew B. Lassman[7] · Markus Joerger[8] · Ghazaleh Tabatabai[9] · Jordi Rodon[5] · Ralph Tiedt[10] · Sylvia Zhao[11] · Tiina Kirsilae[10] · Yi Cheng[11] · Sergio Vicente[10] · O. Alejandro Balbin[12] · Hefei Zhang[11] · Wolfgang Wick[13]

- Phase II trial with capmatinib alone in recurrent GBM with MET amplification
- 10 pts received Capmatinib: no patient achieved partial (PR) or complete response (CR). Best response was stable disease (SD) in 3 of 10 patients

- Also the combination of capmatinib + buparlisib demonstrated very limited activity in phase Ib (33 patients)

MET inhibition in gliomas

- Cabozantinib
- Crizotinib
- Capmatinib
- Tepotinib
- Savolitinib
- Vebreltinib

CLINICAL TRIAL PROTOCOL

SPARTA
Researching Ways to Battle Cancer

Study Title:	Phase 1 / 2 Multicenter Study of the Safety, Pharmacokinetics, and Preliminary Efficacy of APL-101 in Subjects with Non-Small Cell Lung Cancer with c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors
Study Number:	APL-101-01 (SPARTA)
Study Phase:	1 / 2
Product Name:	APL-101 (Vebreltinib, formerly Bozitinib)
IND Number:	131,638
EudraCT Number:	2019-001757-54
Indication:	Select advanced solid tumors and NSCLC

AINO Giovani Meeting

30/05/2023

Impressive response to Entrectinib in a patient with ROS1 fusion: beautiful that way!

Giulia Cerretti

Associazione Italiana di Neuro-Oncologia

Male, 68
Headache, confusion,
weakness right leg

Radical resection

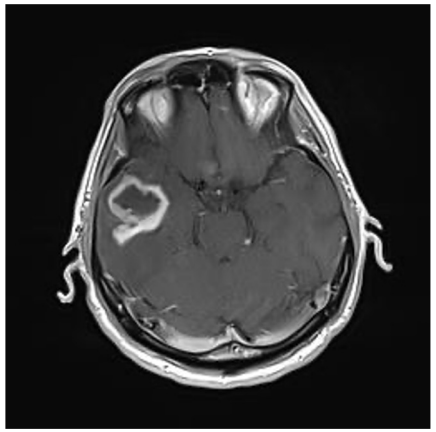
Glioblastoma
IDH1 wild type
unmethylated MGMT promoter

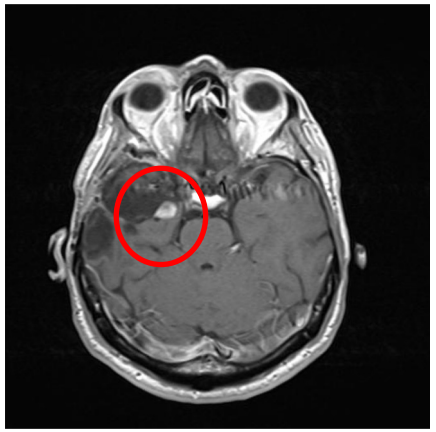
Concomitant chemo-radiotherapy
(60 Gy/30 fractions +
TMZ 120 mg/day)

Standard TMZ
12 cycles

First **PD**

July 2020 | Sep - Nov 2020 | Dec 2020 - Dec 2021 | Jan 2022





FOUNDATION MEDICINE®

FMI Test Order #	Subject ID	Report Date
ORD-1112140-01	IOV-1361-Prescreening	12 Jun 2021

Study GO40782 Clinical Trial Assay

Potential Enrollment Eligible Alterations

GENE	ALTERATION
ROS1	ROS1-GOPC fusion

GENOMIC FINDINGS

NOTE: This is a comprehensive list of cancer-related alterations detected in this patient's sample.

GENE	ALTERATION
PTEN	loss
MTAP	loss
CDKN2A	loss
CDKN2B	loss
ROS1	ROS1-GOPC fusion
EGFR	T263P
PIK3R1	K448del
TERT	promoter -146C>T

STARTRK2

PROTOCOL

TITLE: **AN OPEN-LABEL, MULTICENTER, GLOBAL PHASE II BASKET STUDY OF ENTRECTINIB FOR THE TREATMENT OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS THAT HARBOR *NTRK1/2/3*, *ROS1*, OR *ALK* GENE REARRANGEMENTS**

Inclusion criteria:
- Histologically confirmed diagnosis of locally advanced or metastatic solid tumor that harbors an **NTRK1/2/3, ROS1, or ALK gene rearrangement** that is predicted to translate into a fusion protein with a functional TrkA/B/C, ROS1, or ALK kinase domain,
respectively, without a concomitant second oncodriver (e.g., EGFR, KRAS), as determined by **Foundation Medicine**, Inc. laboratory
- Measurable disease
- Adequate organ function

Exclusion criteria:
- Prior treatment with approved or investigational
Trk, ROS1, or ALK inhibitors in patients who
have tumors that harbor those respective gene
Rearrangements
- Cardiovascular contraindications

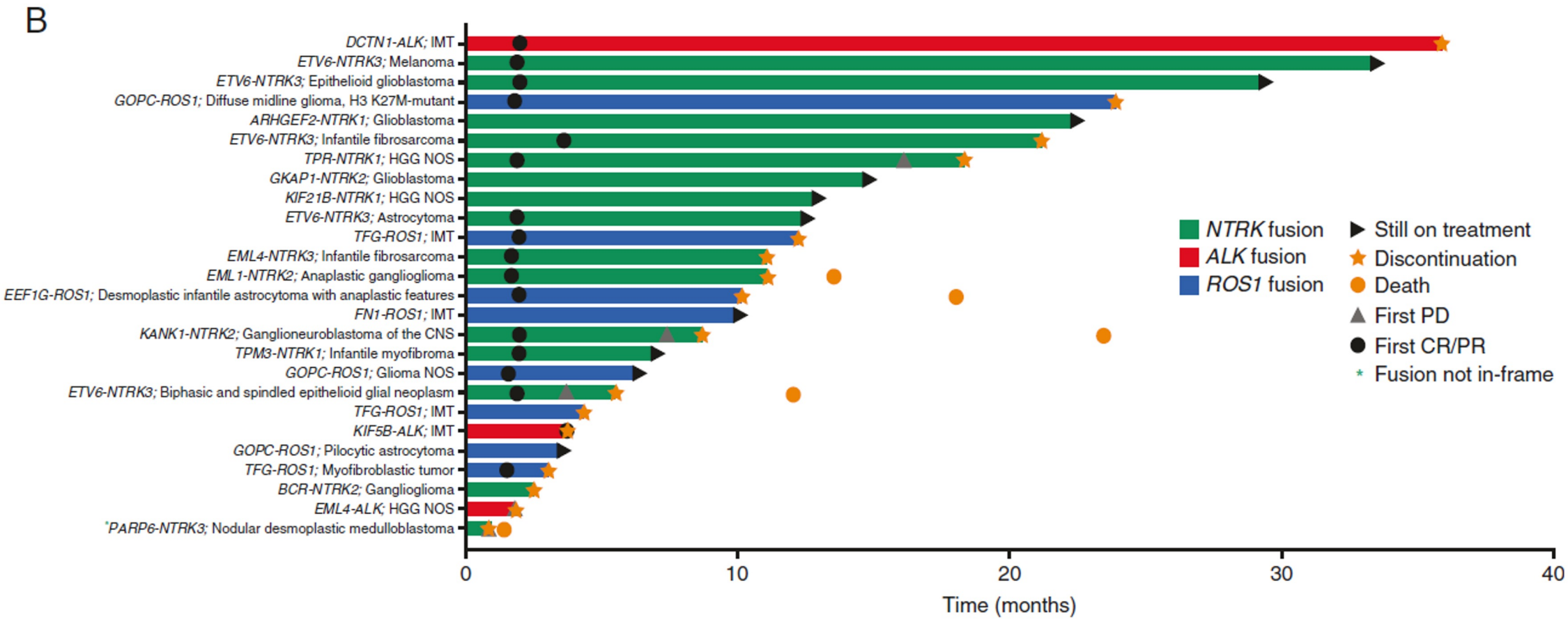
1776

Neuro-Oncology

24(10), 1776–1789, 2022 | https://doi.org/10.1093/neuonc/noac087 | Advance Access date 8 April 2022

Entrectinib in children and young adults with solid or primary CNS tumors harboring *NTRK*, *ROS1*, or *ALK* aberrations (STARTRK-NG)

ROS1 fusions (about 7%) were found in a small number of gliomas, mostly in infants.



Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG) , Desai AV, 2022

Primary CNS (brain) tumor	16 (37.2)
Glioblastoma	3 (7.0)
Astrocytoma	4 (9.3)
Ganglioglioma	2 (4.7)
Epithelioid glial neoplasm	1 (2.3)
Medulloblastoma	1 (3.7)
High-grade glioma NOS	3 (7.0)
Glioma NOS	1 (2.3)
Ganglioneuroblastoma	1 (2.3)

Table 3. Summary of BICR-Assessed Best Overall Confirmed Responses in Patients With Tumors Harboring Target Gene Fusions, According to Fusion Kinase and Tumor Type

Response, n (%)	Fusion Kinase			Tumor Type		Total (n = 26)
	NTRK1/2/3 (n = 15)	*ROS1* (n = 8)	*ALK* (n = 3)	Primary CNS (n = 16)	Extracranial Solid (n = 10)	
Objective response rate, % (95% CI)	60.0 (32.3, 83.7)	62.5 (24.5, 91.5)	33.3 (0.84, 90.6)	50.0 (24.7, 75.4)	70.0 (34.8, 93.3)	57.7 (36.9, 76.7)
Complete response	5 (33.3)	1 (12.5)	1 (33.3)	4 (25.0)	3 (30.0)	7 (26.9)
Partial response	4 (26.7)	4 (50.0)	0	4 (25.0)	4 (40.0)	8 (30.8)
Stable disease	4 (26.7)	2 (25.0)	1 (33.3)	5 (31.3)	2 (20.0)	7 (26.9)
Progressive disease	1 (6.7)	0	1 (33.3)	2 (12.5)	0	2 (7.7)
Missing/unevaluable	1 (6.7)	1 (12.5)	0	1 (6.3)	1 (10.0)	2 (7.7)

Abbreviations: *ALK*, anaplastic lymphoma kinase; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease; *ROS1*, ROS proto-oncogene 1.

Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG) , Desai AV, 2022

Entrectinib
600 mg/day

COMPLETE RESPONSE

Entrectinib
600 mg/day

Best response: CR

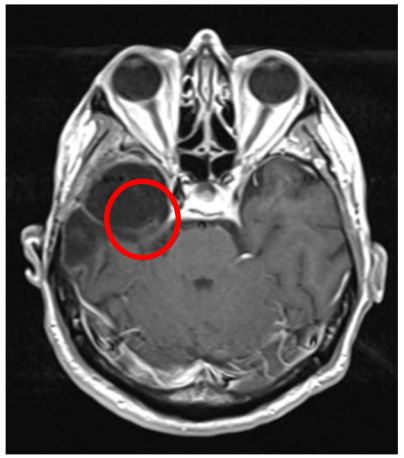
No AEs

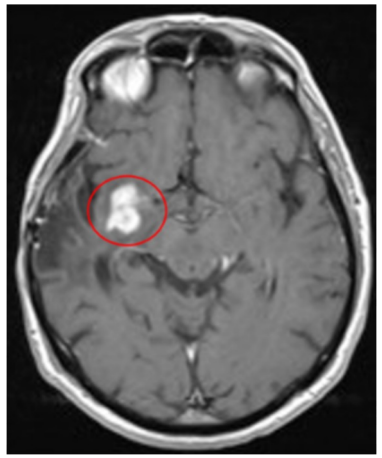
Second **PD**

Second surgery

Clinical deterioration
BSC

Feb 2022 - Aug 2022 | Aug 2022 - Jan 2023 | Jan 2023 | Apr 2023





Target therapy in gliomas/GBMs: take home messages

- Targeted therapy at glioblastoma recurrence may be considered
- Among our 3 cases, we reported a dramatic response to a MET inhibitor and a prolonged response to ROS1 fusion inhibitor
- In no case target therapy was interrupted for toxicity
- Deeper explorations are needed in targeting MET and ROS1 (need for prospective trials such as umbrella and basket trials)