Initial Data from Pivotal FIREFLY-1 Trial of Tovorafenib (DAY101) in Relapsed Pediatric Low-Grade Glioma

Investor Call and Webcast

June 13, 2022

Disclaimer

This presentation and the accompanying oral commentary contain forward-looking statements that are based on our management's beliefs and assumptions and on information currently available to our management. Forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified. In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "could," "expect," "plan," anticipate," "believe," "estimate," "predict," "intend," "potential," "would," "continue," "ongoing" or the negative of these terms or other comparable terminology. Forward-looking statements include all statements other than statements of historical fact contained in this presentation, including information concerning our future financial performance, including the sufficiency of our cash and cash equivalents to fund our operations, business plans and objectives, timing and success of our planned nonclinical and clinical development activities, timing and results of nonclinical studies and clinical trials, efficacy and safety profile of our product candidates, the execution of the Phase 2 clinical trial for DAY101 as designed, any expectations about safety, efficacy, timing and ability to complete clinical trials and to obtain regulatory approvals for DAY101 and other candidates in development, the ability of DAY101 to treat pLGG or related indications, the potential therapeutic benefits and economic value of our product candidates, potential growth opportunities, competitive position, industry environment and potential market opportunities, our ability to protect intellectual property, and the impact of the COVID-19 pandemic on our business and operations.

Forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. These factors, together with those that are described under the heading "Risk Factors" contained in our most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission ("SEC") and other documents we file from time to time with the SEC, may cause our actual results, performance or achievements to differ materially and adversely from those anticipated or implied by our forward-looking statements.

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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Agenda

Topic	Speaker
Opening Remarks	Jeremy Bender, PhD, MBA Chief Executive Officer
FIREFLY-1 Interim Analysis	Samuel Blackman, MD, PhD Chief Medical Officer & Founder
Future Program Updates	Samuel Blackman, MD, PhD Chief Medical Officer & Founder
Q&A	Jeremy Bender, PhD, MBA Chief Executive Officer Samuel Blackman, MD, PhD Chief Medical Officer & Founder Charles York, MBA Chief Operating & Financial Officer

Day One: Developing Targeted Therapies That Address The Urgent Needs of Children With Cancer

Mission That Creates Value

- Day One's mission is to help children with cancer, from day one and every day after
- Develop medicines for genomically-defined cancers
- Establish first-in-class position through rapid pediatric registration
- Expand to adolescent and adult populations in parallel and pursue those opportunities with the same commitment we do for children

Tovorafenib (DAY101) Lead Program

- Investigational, oral, CNS-penetrant pan-RAF inhibitor
- Being studied as tablets and pediatric-friendly liquid suspension
- Breakthrough Therapy Designation
- Rare Pediatric Disease Designation
- Orphan Drug Designation (US/EU)

Growing Portfolio and Runway Beyond Clinical Milestones

- Two clinical-stage MEKi assets, in-licensed for combination trials
- Projected cash runway into 2024
- Multiple key milestones:
  - Top-line data from FIREFLY-1 trial in Q1 2023, NDA submission in 1H 2023, if data are supportive
  - First patient dosed in frontline pLGG, Phase 3 (FIREFLY-2 /LOGGIC) trial expected Q3 2022

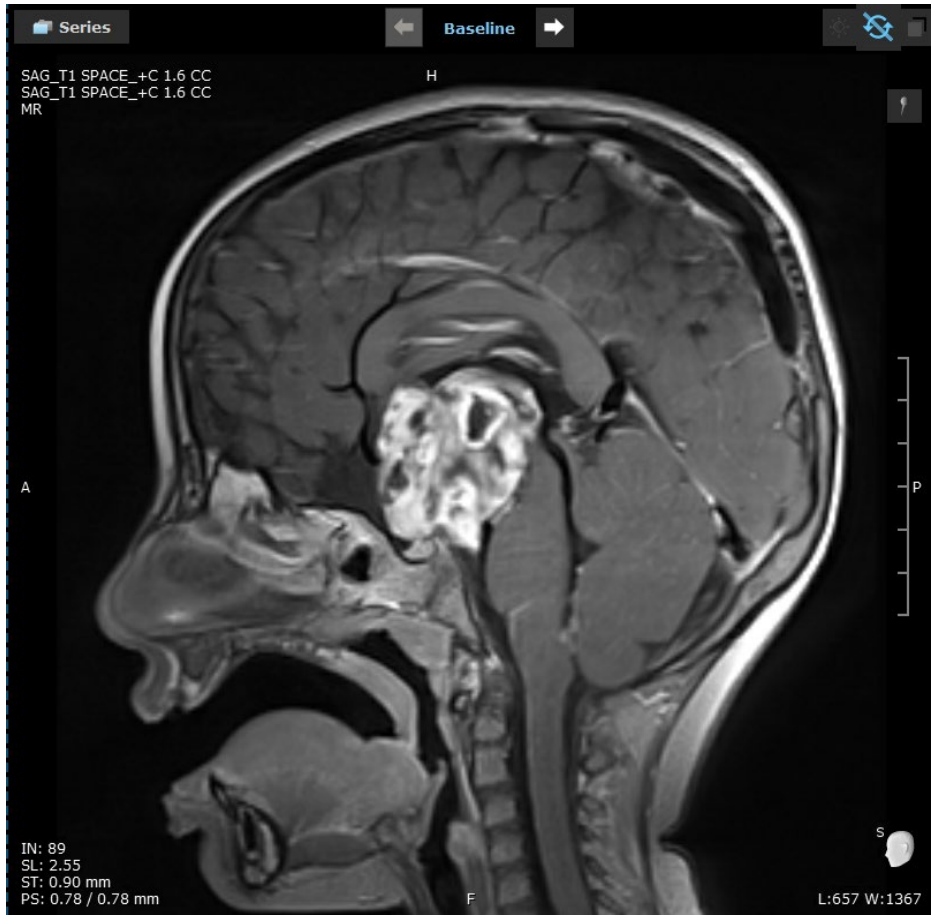
Our Pipeline

Product Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Recent & Anticipated Milestones
Tovorafenib (DAY101) Type II Pan-RAF Inhibitor ✓ FDA Breakthrough Therapy Designation for relapsed pLGG ✓ FDA Rare Pediatric Disease Designation (PRV Eligible) for pLGG ✓ FDA Orphan Drug Designation for gliomas ✓ EC Orphan Designation for gliomas	Relapsed pLGG	FIREFLY-1[1] (pivotal)				**Pivotal cohort enrollment complete:** May 2022 **Initial data presented:** June 2022 **Topline data expected:** Q1 2023
	Frontline pLGG	FIREFLY-2 (pivotal)				**First patient dosed expected:** Q3 2022
	RAF-altered solid tumors[2] (monotherapy)	FIRELIGHT-1*				**First patient dosed:** November 2021
Pimasertib MEK 1/2 Inhibitor	MAPK-altered solid tumors[3] (Combo w/Tovorafenib)	FIRELIGHT-1*				**First patient dosed:** May 2022

*Includes patients ≥12 years of age. [1] FIREFLY-1 Arm 1 expected to support registration. [2] DAY101 adult monotherapy Phase 1 dose escalation and expansion trial previously completed. [3] Pimasertib Phase 1 dose escalation and expansion trial previously completed. pLGG, pediatric low-grade glioma. Tovorafenib and Pimasertib are investigational products. Safety and efficacy have not been established by any health authority.

FIREFLY-1 Interim Analysis

Pediatric Low-Grade Gliomas (pLGG)

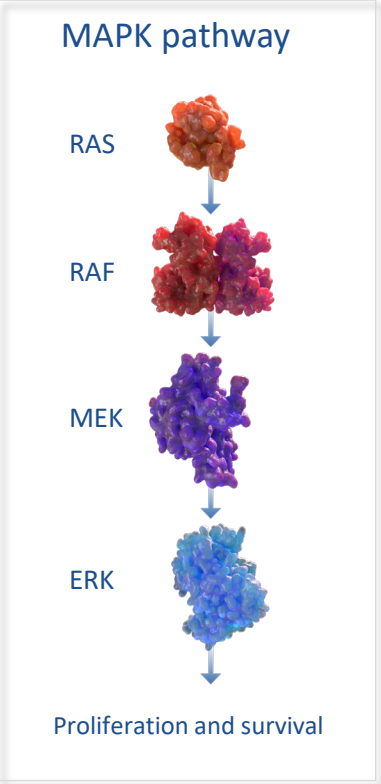


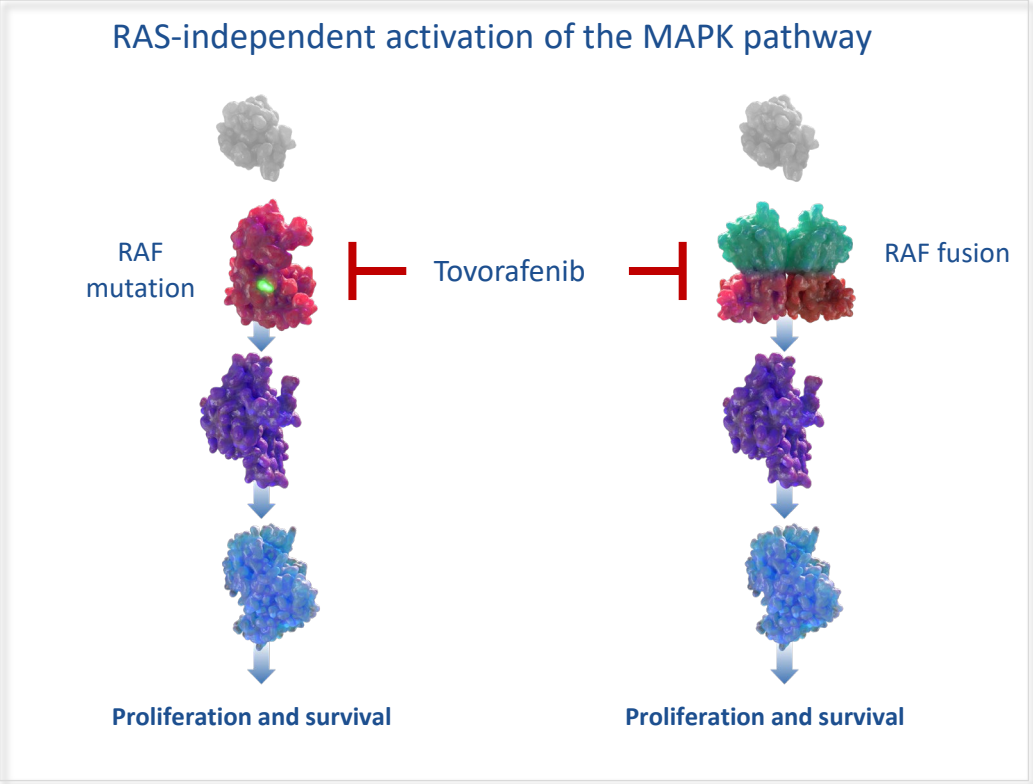
6 y/o with large relapsed BRAF fusion-positive optic pathway glioma

- **Despite being the most common brain tumor in children, there are no approved agents and no standard-of-care for patients with relapsed/progressive disease[1,2]**
  - 70% of patients will require systemic therapy
  - Patients have a high rate of recurrence and are frequently treated with multiple lines of systemic therapy over the course of their disease
- **The majority of pLGGs are driven by BRAF alterations[3]**
  - 85% of BRAF-altered tumors harbor a *KIAA1549-BRAF* gene fusion
  - 15% are driven by BRAF V600E mutation
- **Despite low-grade histology and high long-term survival, pLGGs are chronic and relentless[1-4]**
  - Goal of therapy is to stabilize or shrink tumors while minimizing treatment-associated toxicities from surgery, chemotherapy, and radiation
  - Many patients today suffer profound tumor and treatment-associated morbidity and significant late effects that persist throughout life

1. Ostrum QT et al., Neuro Oncol. 2015; 16(Suppl 10):x1-x36; 2. De Blank P. et al., Curr Opin Pediatr. 2019 Feb; 31(1):21-27. 3. Jones DTW et al., Cancer Res. 2008; 68:8673–77. 4. Traunwieser T et al., Neurooncol Adv. 2020; 2:vdaa094;

Tovorafenib (DAY101) Inhibits Both BRAF Fusions and BRAF V600 Mutations





- **Tovorafenib (DAY101) is an investigational, oral, selective, CNS-penetrant, type II pan-RAF inhibitor that was designed to inhibit both monomeric and dimeric RAF kinase**
  - Activity in tumors driven by both RAF wild-type fusions and BRAF V600E mutations
  - Tablet and pediatric-friendly liquid suspension; once weekly dosing
- **Currently approved type I RAFi are indicated for use only in adult patients with tumors harboring a BRAF V600 mutation**
  - Type I RAF inhibitors cause paradoxical MAPK activation in the setting of wild-type RAF, increasing the risk of tumor growth in *BRAF* fusion-driven and other non-V600 mutant cancers

1. Sun Y et al., Neuro Oncol. 2017; 19: 774–85; 2. Sievart AJ et al., PNAS. 2013; 110:5957-62; 3. Karajannis MA et al., Neuro Oncol 2014;16(10):1408-16;

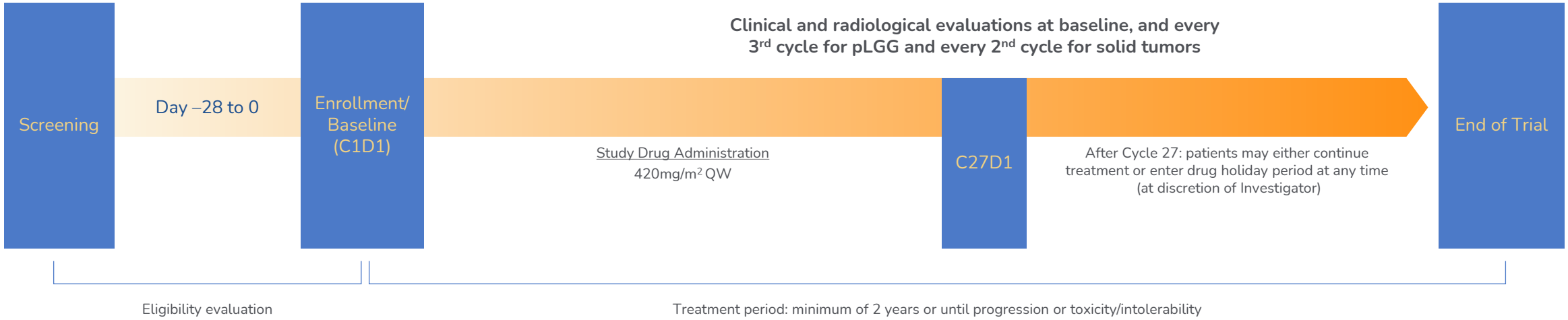
Pivotal Phase 2 Trial Of Monotherapy Tovorafenib (DAY101) In Relapsed Or Progressive pLGG (FIREFLY-1)

Trial Design

- Three arm, open-label, global registrational phase 2 trial
- Pivotal arm 1 (recurrent/progressive LGG): n = ~ 60 RANO-evaluable patients aged 6 months to 25 years harboring a *KIAA1549-BRAF* fusion or BRAF V600 mutation
- Arm 2 (expanded access recurrent/progressive LGG): patients aged 6 months to 25 years harboring an activating RAF alteration
- Arm 3 (extracranial solid tumors): patients aged 6 months to 25 years harboring an activating RAF fusion

Endpoints (Pivotal Arm 1)

- **Primary endpoint: ORR based on RANO criteria, assessed by blinded independent central review**
- Secondary endpoints: ORR by RAPNO criteria; PFS; safety

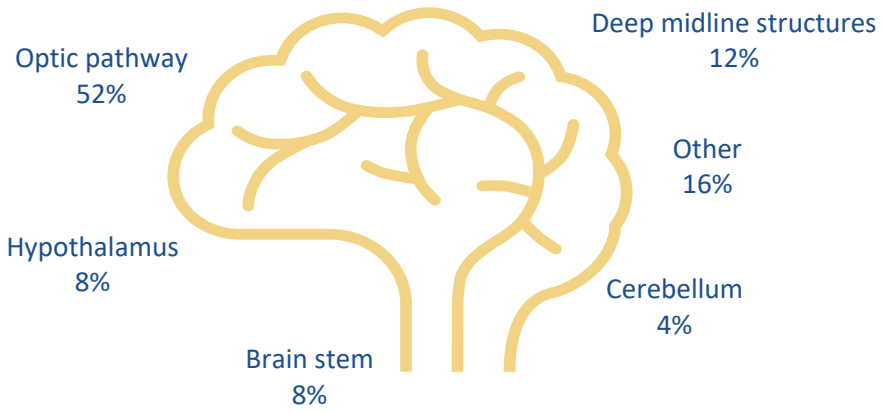


Abbreviations: C, cycle; D, day; LGG, low-grade glioma; ORR, objective response rate; PFS, progression-free survival.
NCT04775485

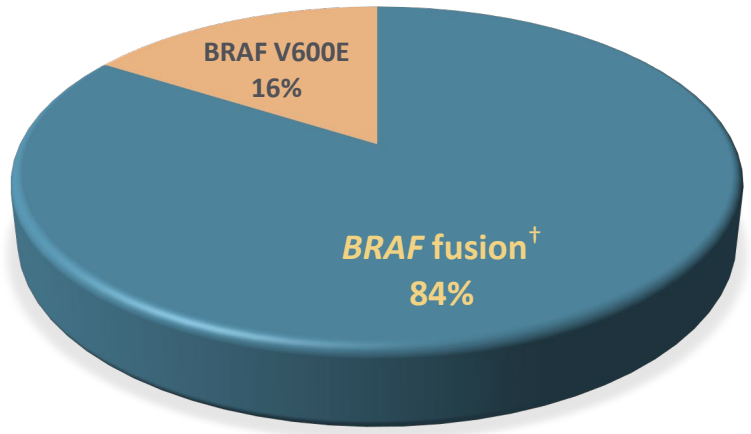
Baseline Characteristics

Characteristic	Arm 1 (N=25)
Median age, years (range)	8 (3-18)
Sex, n (%)	
Male	13 (52)
Female	12 (48)
Race, n (%)	
Black or African American	1 (4)
Asian	2 (8)
White	15 (60)
Other*	7 (28)
Karnofsky/Lansky performance status, n (%)	
50-70	1 (4)
80-100	24 (96)
Number of lines of prior therapy	
Median (range)	3 (1-9)
1, n (%)	5 (20)
2, n (%)	6 (24)
≥3, n (%)	14 (56)
Prior MAPK pathway targeted therapy, n (%)	
Yes	18 (72)
No	7 (28)

Location (n=25)

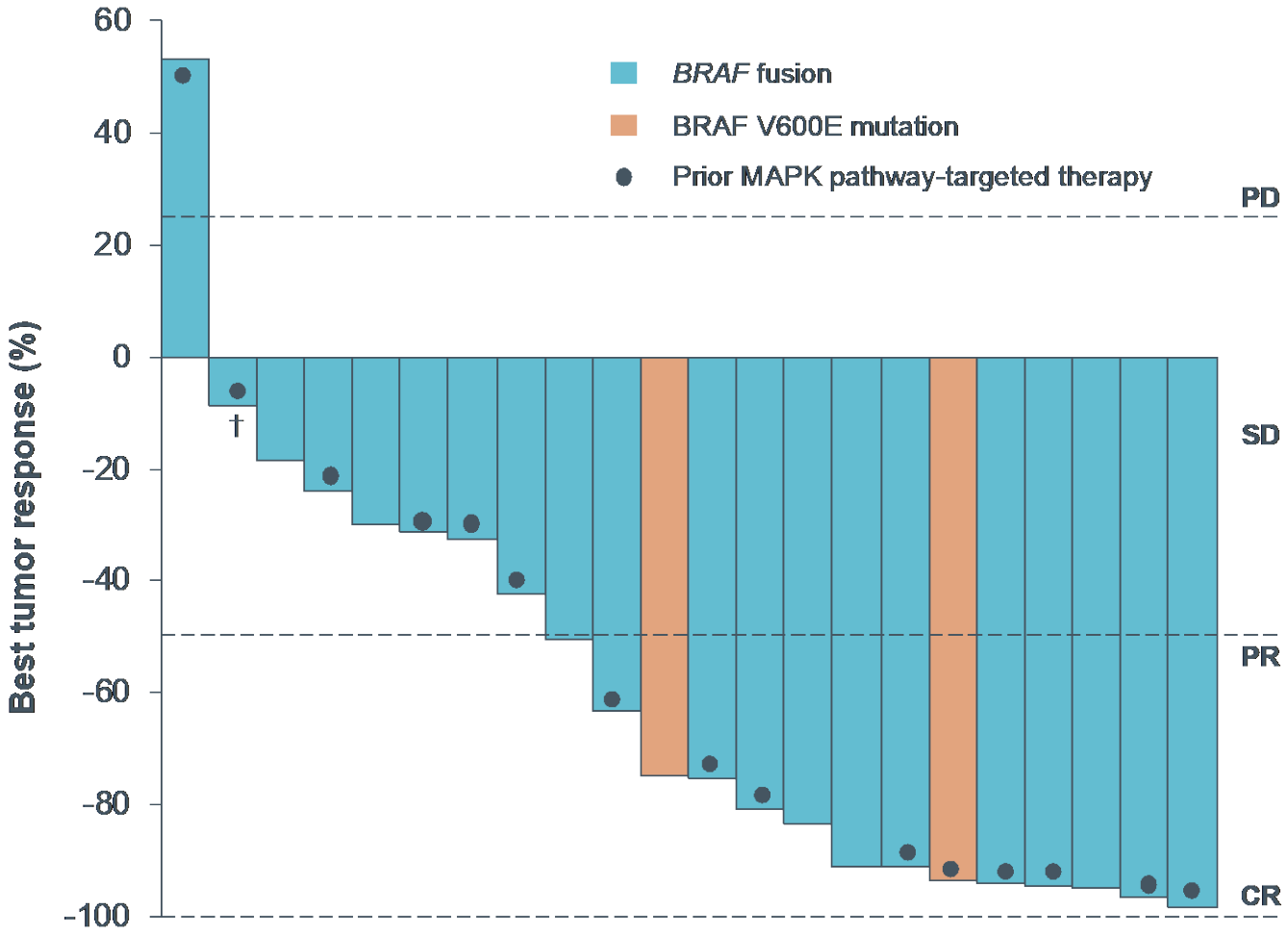


BRAF alteration (n=25)



Apr 14, 2022 data cutoff; *Includes 4 patients with race not specified. †Includes 2 patients with BRAF duplication and 1 with BRAF rearrangement per fluorescence in situ hybridization. MAPK, mitogen-activated protein kinase; prior MAPK pathway targeted therapy indicates either prior MEKi and/or prior type I RAFi therapy.

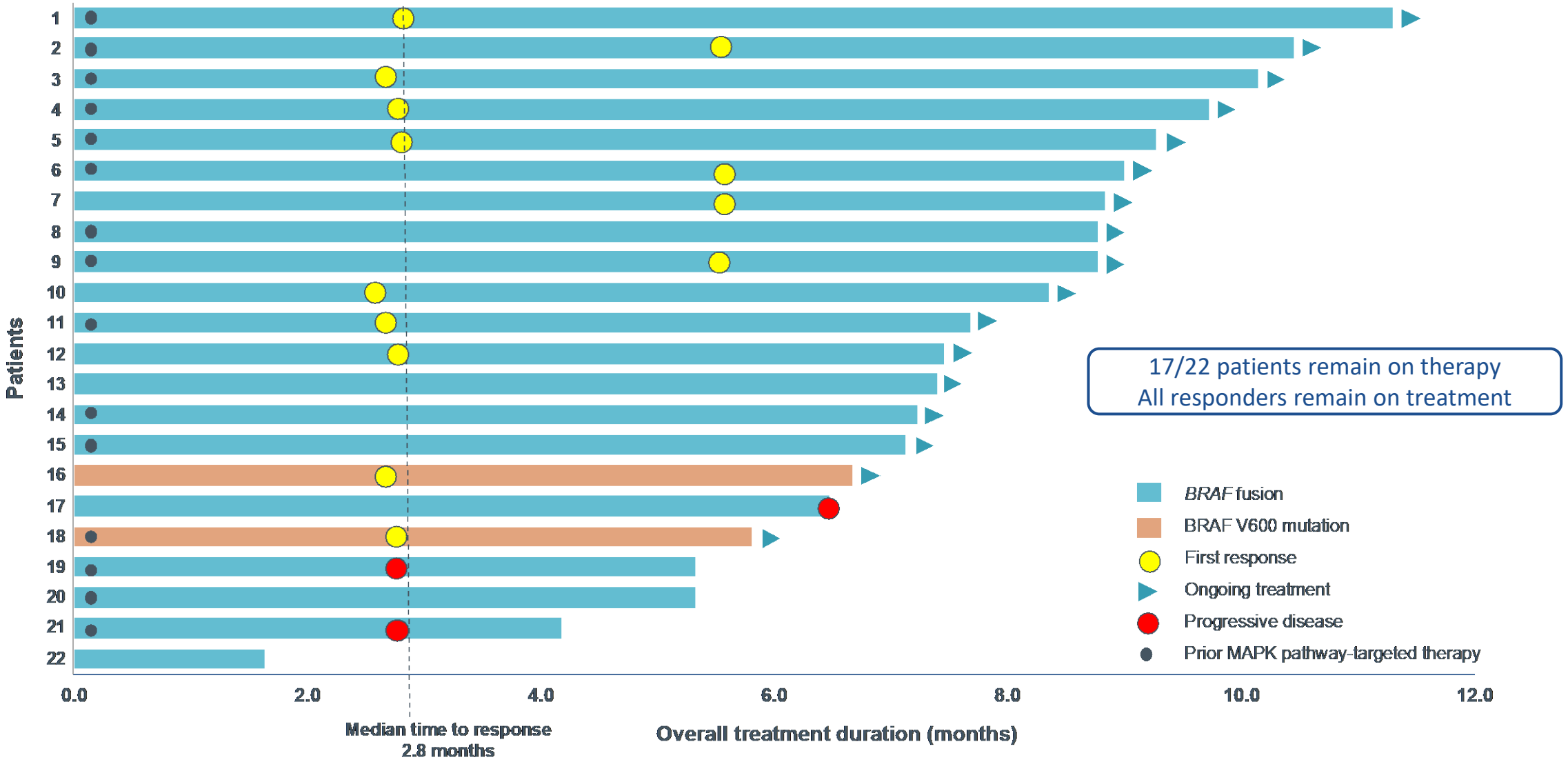
Tumor Response To Tovorafenib (DAY101) For All Patients With RANO-Evaluable Lesions (n=22)*



Response (IRC)	RANO Evaluable N=22*
ORR (95% CI)	64% (41-83)
BRAF fusion (n=20)	60%
BRAF V600E (n=2)	100%
CBR#	91%
Best overall response	
PR (13/22)	59%
uPR (1/22)	5%
SD (6/22)	27%

Apr 14, 2022 data cutoff. Total % of response maybe may be different than the sum of the individual overall response due to rounding. *3/25 patients lacked evaluable lesions per RANO criteria based on IRC evaluation. †Progressive disease due to presence of new lesions. #patients with best overall response of CR, PR/uPR and SD. CBR, clinical benefit rate; IRC, independent radiological review committee; ORR, overall response rate; MAPK, mitogen-activated protein kinase; PR, partial response; SD, stable disease; uPR, unconfirmed partial response

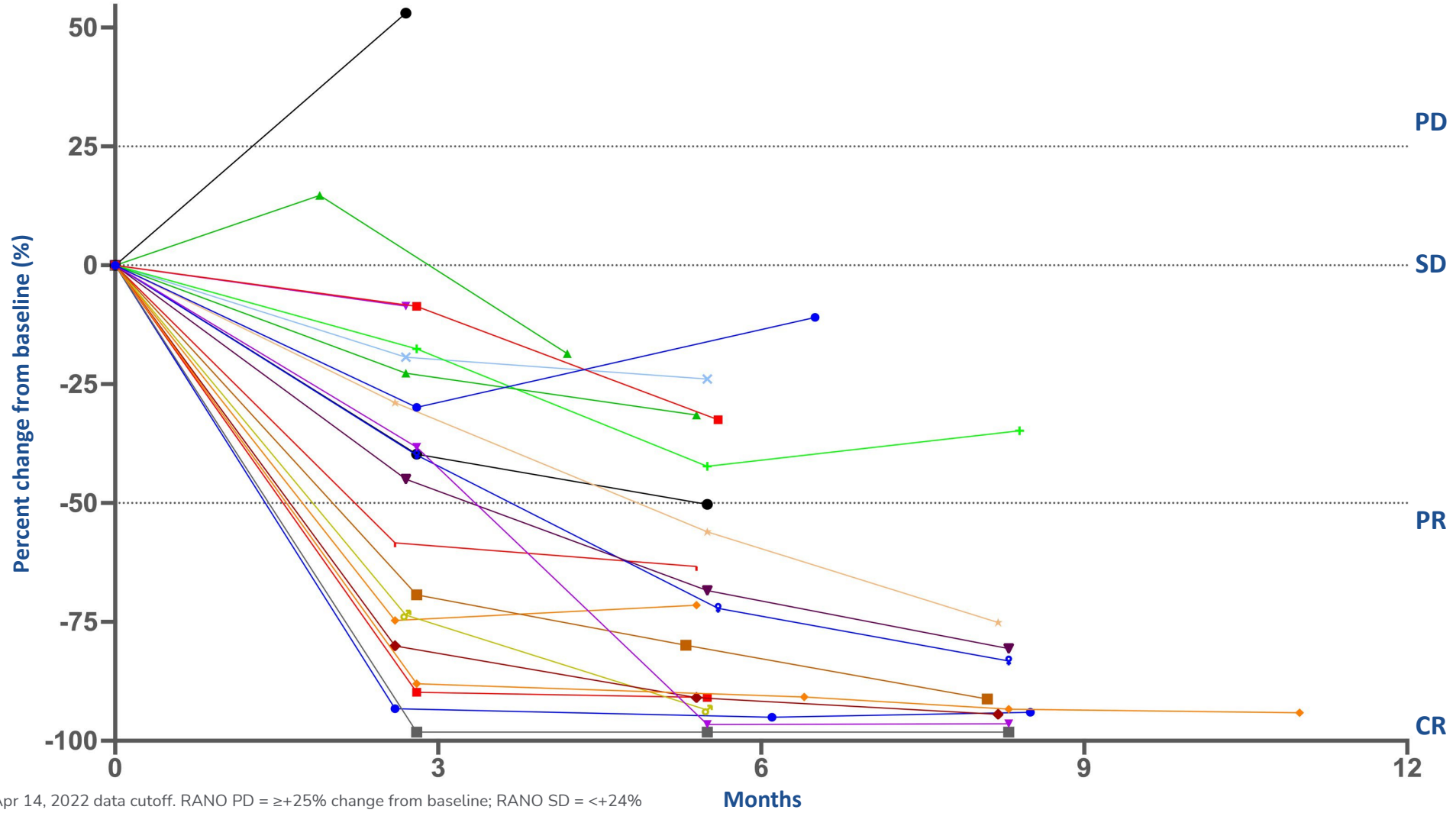
Duration of Tovorafenib (DAY101) Therapy For All Patients with RANO-Evaluable Lesions (n=22)



Apr 14, 2022 data cutoff.

Individual Patient Tumor Change From Baseline

(n=22 RANO-Evaluable By Blinded Independent Central Review)



Apr 14, 2022 data cutoff. RANO PD = ≥+25% change from baseline; RANO SD = <+24% to > -50% change from baseline; RANO PR = ≤ -50% change from baseline; RANO CR = -100% change from baseline.

Tovorafenib (DAY101) Safety Data For the First 25 Enrolled Patients (TEAEs ≥25% Any Grade)

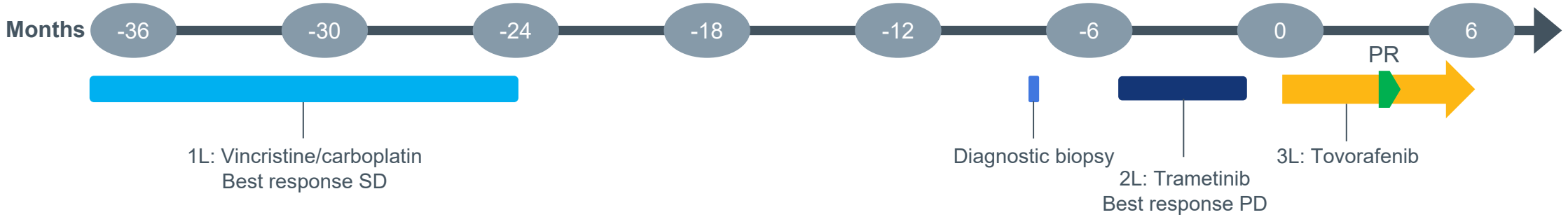
	Treatment-emergent AEs		Treatment-related AEs	
Preferred term, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood creatine phosphokinase increased	20 (80)	2 (8)	18 (72)	2 (8)
Hair color changes	17 (68)	-	17 (68)	-
Anemia	14 (56)	3 (12)	10 (40)	2 (8)
Aspartate aminotransferase increased	14 (56)	-	12 (48)	-
Vomiting	14 (56)	2 (8)	6 (24)	1 (4)
Rash*	13 (52)	3 (12)	13 (52)	3 (12)
Blood lactate dehydrogenase increased	12 (48)	-	9 (36)	-
Headache	10 40)	-	3 (12)	-
Dry skin	9 (36)	-	7 (28)	-
Epistaxis	9 (36)	-	4 (16)	-
Constipation	8 (32)	-	5 (20)	-
Hypocalcemia	8 (32)	-	6 (24)	-
Nausea	8 (32)	-	3 (12)	-
Alanine aminotransferase increased	7 (28)	1 (4)	4 (16)	1 (4)
Fatigue	7 (28)	-	7 (28)	-

- Most treatment-emergent AEs were grade 1 or 2 (96%)
- Other important treatment-emergent AEs included:
  - Decreased weight (24%)
  - Decreased appetite (16%)
  - Hyponatremia (16%)
- 7 patients (28%) required dose modifications due to treatment-related AEs
- No patient discontinued treatment due to AEs

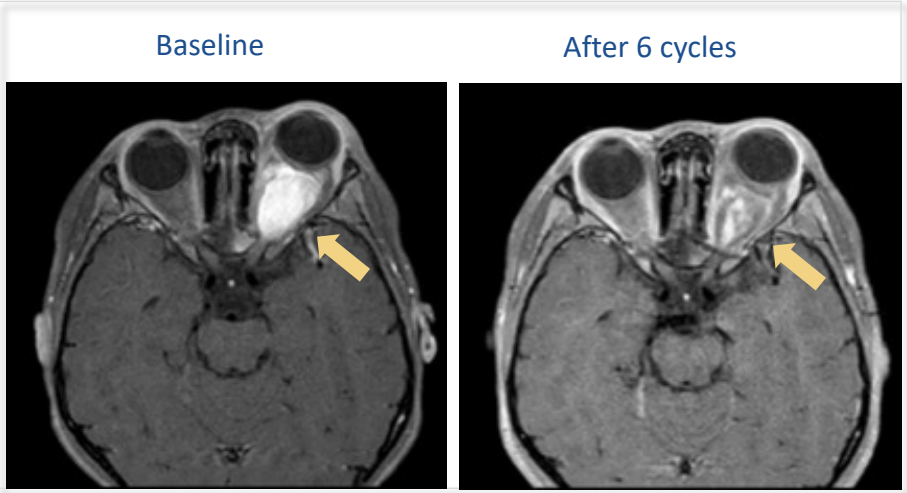
Apr 14, 2022 data cutoff. AE, adverse event. TEAE, treatment-emergent adverse event.
*Includes maculopapular and erythematous rash

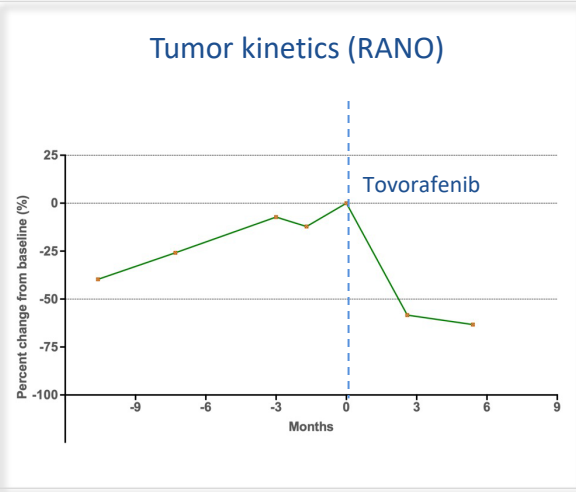
Case Study: Activity Of Tovorafenib (DAY101) In KIAA1549-BRAF Fusion Optic Pathway Glioma

A 7-years-old female child with an optic pathway glioma, with very poor vision, entropion, folliculitis, eczema, mouth ulceration and xerosis



- PR (-58%) and improvement in vision reported at cycle 3
- AEs included grade 3 erythematous rash requiring dose interruption and dose reduction (400 mg QW to 300 mg QW in cycle 1), and grade 2 eczema and maculopapular rash
- Patient continues to receive weekly tovorafenib

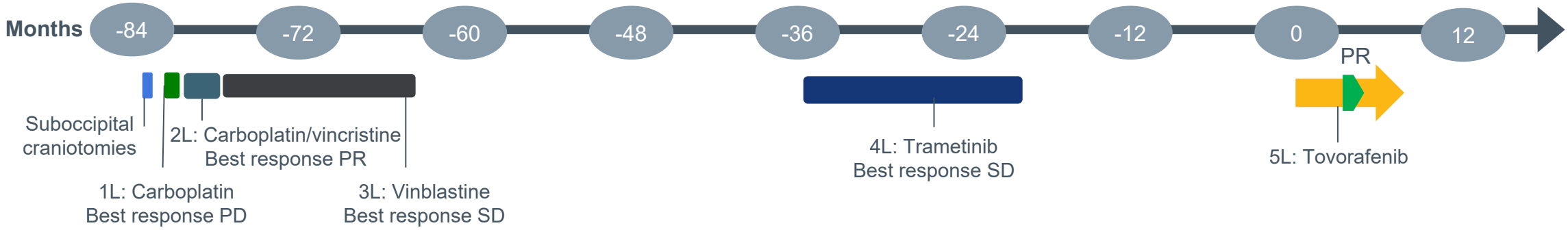




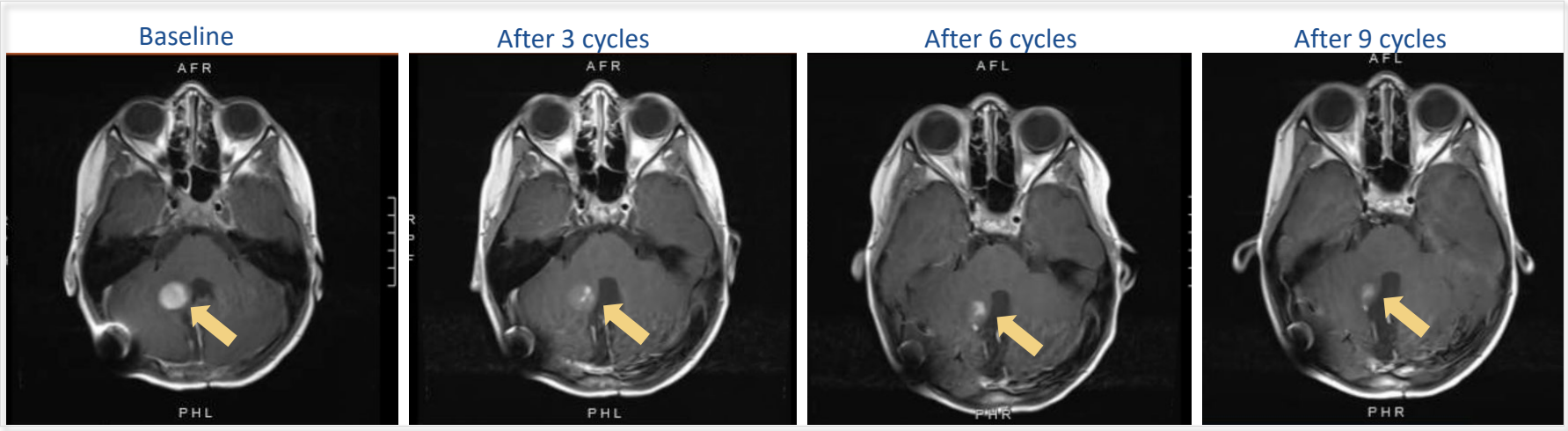
Apr 14, 2022 data cutoff. Tovorafenib is an investigational agent. Safety and efficacy have not been established by any health authority.

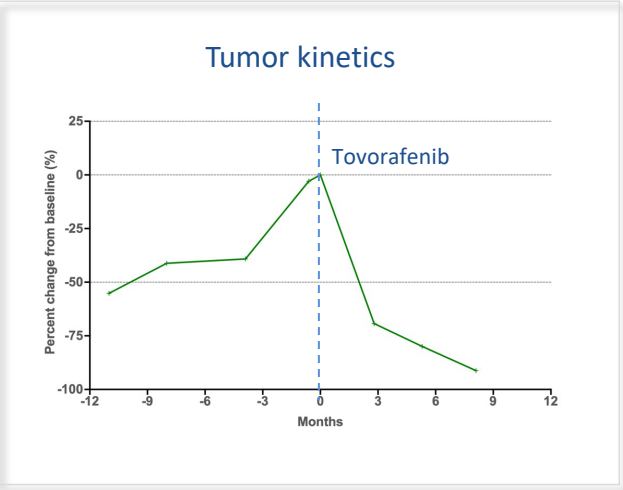
Case Study: Activity Of Tovorafenib (DAY101) In KIAA1549-BRAF Fusion Posterior Fossa Pilocytic Astrocytoma

An 8-years-old female child with a posterior fossa pilocytic astrocytoma, eczema, nausea and constipation



- PR (-69%) at cycle 3 with 500 mg QW tovorafenib, with a deepening of response (80% and 91% in cycles 6 and 9, respectively) over time
- AEs included grade 2 decrease in neutrophil count, pustular rash, and upper respiratory infection
- Patient continues to receive weekly tovorafenib





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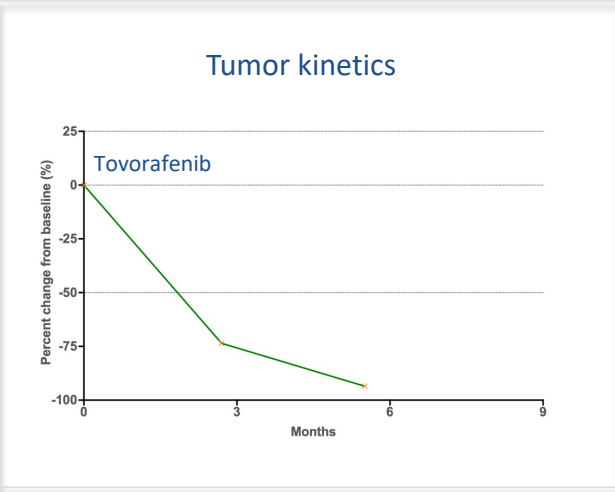
Case Study: Activity Of Tovorafenib (DAY101) In BRAF V600E Mutation Deep Midline Astrocytoma

A 9-year-old female child with deep midline BRAF V600E-mutant astrocytoma with precocious puberty

- PR (-74%) at cycle 3, with a deepening of response (-94%) at cycle 6
- AEs included grade 3 maculopapular rash and increased CPK, requiring drug interruption and dose reduction (500 mg QW to 400 mg QW in cycle 1)
- Tovorafenib dose was re-escalated back to 500 mg QW in cycle 4; patient continues on treatment



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Key Takeaways

- **Encouraging initial efficacy data from FIREFLY-1 for pediatric patients with relapsed LGG harboring *BRAF* fusion or BRAF V600 mutation, for whom there are no currently approved therapies**
  - 64% ORR and 91% clinical benefit rate (partial response/unconfirmed partial response + stable disease) in the 22 RANO-evaluable patients:
    - 14 partial responses (13 confirmed responses and 1 unconfirmed response)
    - 6 patients with stable disease
  - All patients with stable disease (n=6) were noted to have tumor shrinkage, ranging between 19% and 43%
  - Responses were observed in patients with both BRAF fusions and BRAF V600E mutations who received prior MAPK-targeted therapy
  - The median-time-to-response was 2.8 months
  - A heavily-pretreated population, with a median of 3 prior lines of therapy (range: 1-9)
  - All patients who responded remain on therapy (n=14) and no patients have discontinued treatment due to treatment-related adverse events
- **Initial safety data, based on the first 25 patients, indicated monotherapy tovorafenib (DAY101) to be generally well-tolerated**
  - Majority of AEs were grade 1 or 2; most common treatment-related AEs were CPK elevation, rash, and hair color changes
  - Treatment-related AEs of grade 3 or greater occurred in nine patients (36%)
- **Plan to present additional initial study results from FIREFLY-1 at an upcoming medical conference in 2H 2022**
- **Topline results from the full registrational cohort (n=~60) of FIREFLY-1 expected to be available 1Q 2023, with NDA submission planned for 1H 2023**
- **Early results from FIREFLY-1 support plan to evaluate tovorafenib (DAY101) in parallel Phase 3 frontline pLGG study (FIREFLY-2)**
  - Primary endpoint of ORR based on RANO criteria, assessed by blinded independent central review

Future Program Updates

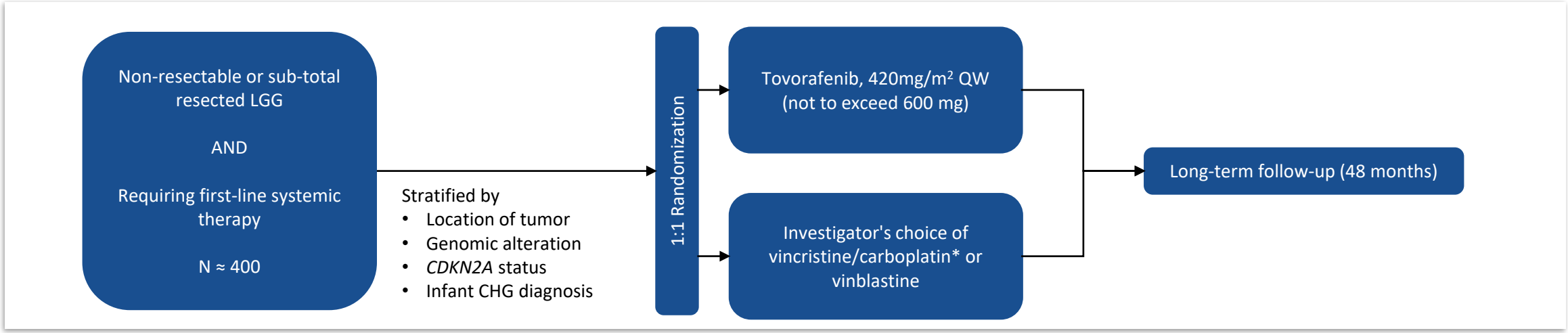
FIREFLY-2/LOGGIC Pivotal Phase 3 Trial Of Tovorafenib (DAY101) In Newly Diagnosed pLGG

Trial Design

- Randomized, global, registrational Phase 3 trial of monotherapy tovorafenib (DAY101) vs SoC chemotherapy
- Eligibility: Patients aged 6 months to <25 years with LGG harboring a RAF alteration and requiring first-line systemic therapy
- Tovorafenib (DAY101) available as tablets and pediatric-friendly liquid suspension
- Patients who progress after stopping tovorafenib (DAY101) may be re-challenged
- Patients who progress in the SoC arm during or post-treatment may cross-over to receive tovorafenib

Endpoints

- **Primary endpoint: ORR based on RANO criteria, assessed by blinded independent central review**
- Key secondary endpoints: PFS and DoR by RANO criteria, ORR by RAPNO criteria
- Other secondary endpoints: changes in neurological and visual function, safety, and tolerability
- Key exploratory objectives: QoL and health utilization measures



* COG or SIOPe-LGG regimen

Abbreviations: CHG, chiasmatic, hypothalamic glioma; DoR, duration of response; LGG, low-grade glioma; ORR, objective response rate; QoL, quality of life; QW, once weekly; SoC, standard of care

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FIREFLY-2/LOGGIC: Pivotal Phase 3 Study Of Tovorafenib (DAY101) In Newly Diagnosed pLGG

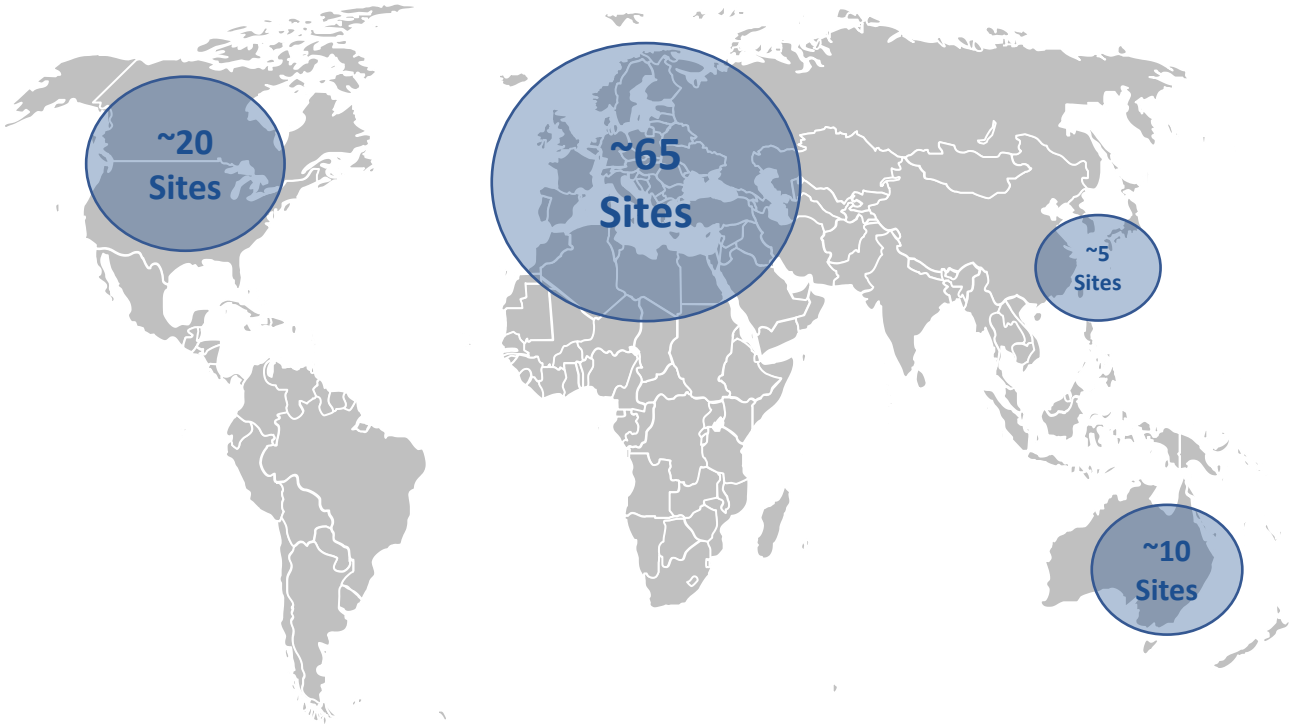
- **Collaboration between Day One and the LOGGIC consortium, internationally recognized experts in pLGG research**
  - Coupled with the LOGGIC-CORE molecular diagnostic program
  - Worked jointly on the study design and discussions with the U.S. and EU regulatory authorities
- **Approximately 100 potential sites (~65 from the LOGGIC consortium)**

LOGGIC EUROPE

LOGGIC: LOw Grade Glioma In Children

KiTZ Hopp Children's Cancer Center Heidelberg

German Cancer Research Center (DKFZ)
Heidelberg University Hospital
Heidelberg University



Thank you to the patients, their families, and the site investigators and staff who have partnered with us on this study. Together, we remain committed to redefining what is possible for children living with cancer, from Day One and every day after.