Results from the Phase 1 and Phase 1 expansion cohorts of SJ901: A Phase 1/2 trial of single-agent mirdametinib (PD-0325901) in children, adolescents, and young adults with low-grade glioma

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Disclosures

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Background, hypothesis, and study objectives

- Mirdametinib is an investigational, oral, selective MEK1/2 inhibitor (MEKi) that is CNS-penetrant and has favorable characteristics for young children
  - Preclinically
    - **Higher brain to plasma ratio** when compared to selumetinib following i.v. administration (0.6 vs 0.02 ng/ml)[1]
    - **Minimally restricted** by drug efflux transporters, P-gp and BCRP[1]
    - **Highest brain concentration** among MEKi (selumetinib and trametinib) following oral administration of a dose that resulted in a clinically feasible plasma concentration[1]
    - Has **in vivo inhibition of pathway activity** in PDOX glioma model[2]
  - Clinically
    - Available in dispersible tablets for **oral suspension (liquid)**
    - Dosing schedule does **not require fasting**

- We hypothesized that mirdametinib would benefit patients with pLGG and launched the Phase 1 and expansion components of SJ901 (NCT04923126) to determine:
  - The **safety and tolerability** when administered continuously
  - The recommended phase 2 dose (**RP2D**)
  - The **preliminary efficacy** in patients with pLGG

1. de Gooijer M. et al. Int. J. Cancer: 142, 381-391 (2018)
2. He C. et. al. Nat Commun 12: 4089 (2021)

Eligibility and Study Design for Phase 1/expansion

Eligibility criteria:	Design:	Design (cont):

• ≥2 and <25 years-old
• MEKi-naïve
• have recurrent/progressive pLGG
• biopsy-proven MAPK pathway activation (except *BRAF* V600)
  • ***BRAF*** fused or rearranged
  • ***FGFR1/2/3*** aberration
  • ***NF1***, ***NF2***, ***PTPN11***, ***SOS1***, ***RAF***, ***RAS*** mutations
  • ***MYB*** or ***MYBL1*** fused or rearranged
	• **Three dose levels** administered continuously in 28-day cycles and evaluated using rolling six design
	  • DL1: 2 mg/m^2/dose BID (max 8 mg daily)
	  • DL2: 2.5mg/m^2/dose BID (max 9 mg daily)
	  • DL3: 3mg/m^2/dose BID (max 10 mg daily)
	• **Expansion cohort** to assess the highest tolerated dose level in a total of 12 patients.
	• **RP2D** is the dose causing ≤3 dose-limiting toxicities (DLTs) in 12 patients within the first cycle of therapy.
		• **Measurable disease changes (RAPNO)**
		  • **Progressive disease** ≥ 25% increase
		  • **Stable disease** <25% increase to <25% reduction
		  • **Minor response** ≥ 25% to <50% reduction
		  • **Partial response** ≥ 50% to <75% reduction
		  • **Major response** ≥ 75% to <100% reduction
		  • **Complete response** 100% reduction
		• **Efficacy** is defined as a ≥ partial response sustained for over 8 weeks
		• **Duration of therapy** is 2 years on therapy without progression with 5-year follow up or if progresses after stopping then option to restart.

Results: Patient Characteristics

- Between June 2021 and August 2023, **23 patients** were enrolled on SJ901 Phase 1/Phase 1 expansion
- As of Oct 23, 2024 (data cutoff), 17 are on therapy or in follow up, 6 are off-study.

Patient Characteristics	Dose Level 1 (N=5)	Dose Level 2 (N=6)	Dose Level 3 (N=12)	Total (N=23)
Age at Diagnosis				
Median (Min – Max)	5.43 (3.6 - 13.9)	10.81 (7.9 - 21.9)	7.89 (2.5 - 13.9)	**8.35 (2.5 - 21.9)**
Gender				
Female	3 (60.0%)	3 (50.0%)	6 (50.0%)	**12 (52.2%)**
Male	2 (40.0%)	3 (50.0%)	6 (50.0%)	**11 (47.8%)**
Race				
White	2 (40.0%)	5 (83.3%)	11 (91.7%)	**18 (78.3%)**
Black		1 (16.7%)	1 (8.3%)	**2 (8.7%)**
Asian	1 (20.0%)			**1 (4.3%)**
Other	2 (40.0%)			**2 (8.7%)**
Primary Diagnosis				
Pilocytic astrocytoma	4 (80.0%)	4 (66.7%)	9 (75.0%)	**17 (73.9%)**
Diffuse glioma	1 (20.0%)	1 (16.7%)		**2 (8.7%)**
Glioneuronal tumor		1 (16.7%)	1 (8.3%)	**2 (8.7%)**
Low-grade glioma, not otherwise specified			2 (16.7%)	**2 (8.7%)**
MAPK Gene Abnormality				
BRAF	4 (80.0%)	3 (50.0%)	5 (41.7%)	**12 (52.2%)**
FGFR 1	1 (20.0%)		4 (33.3%)	**5 (21.7%)**
NF1		1 (16.7%)	2 (16.7%)	**3 (13.0%)**
RAF1		1 (16.7%)	1 (8.3%)	**2 (8.7%)**
MYB		1 (16.7%)		**1 (4.3%)**

Results: Safety, Tolerability, RP2D

TRAE for All Patients						
ADVERSE EVENTS	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
CPK increased	11	7	**4**	**1**		23
Aspartate aminotransferase increased	20	1	.	.		21
Rash acneiform	9	4	.	.		13
Dry skin	9	3	.	.		12
Hypoalbuminemia	11	.	.	.		11
Paronychia	9	2	.	.		11
Anemia	8	1	.	.		9
Weight gain	2	1	**6**	.		9
Neutrophil count decreased	3	4	**1**	.		8
Eczema	3	4	.	.		7
Nausea	7	.	.	.		7
Rash maculo-papular	6	1	.	.		7
Alanine aminotransferase increased	4	1	**1**	.		6
Alkaline phosphatase increased	6	.	.	.		6
Fatigue	5	.	.	.		5
Hypernatremia	5	.	.	.		5
Proteinuria	4	1	.	.		5
Skin and subcutaneous tissue disorders - Other, specify	3	2	.	.		5
Diarrhea	2	2	.	.		4
Hair color changes	4	.	.	.		4
Hyperphosphatemia	4	.	.	.		4
Hypomagnesemia	4	.	.	.		4
Lymphocyte count decreased	4	.	.	.		4
Platelet count decreased	3	.	**1**	.		4
Renal and urinary disorders - Other, specify	4	.	.	.		4
Ejection fraction decreased	.	3	.	.		3

Events that were considered consequential to patients are bolded

Dose Limiting toxicity:

- No DLT in DL1 or DL2
- 1 patient out of 12 at DL3 had a DLT (grade 3 thrombocytopenia)

TRAE resulting in dose reductions, discontinuations:

- 7 (30%) patients underwent dose reductions
- 2 (9%) patients on DL3 discontinued for toxicities
  - 1 grade 2 rash (intolerable per patient)
  - 1 grade 4 creatine phosphokinase (CPK) elevation

Adverse Events of Special Interest:

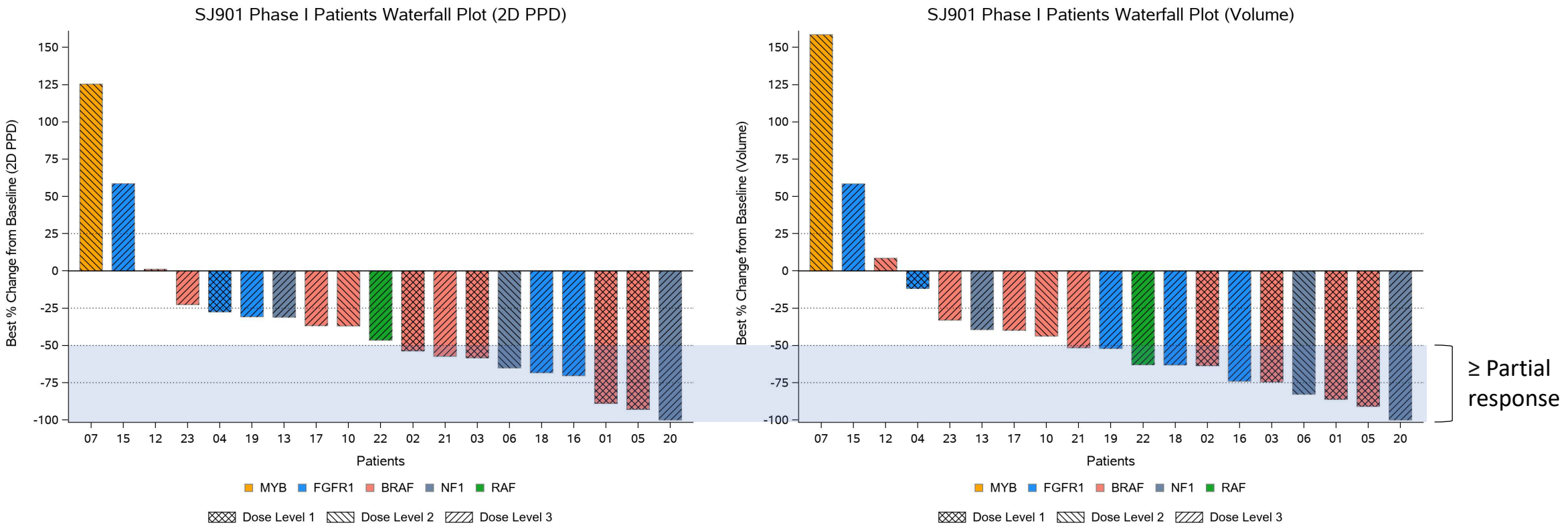
- No retinal toxicity of any grade was observed with serial eye exams
- 3 Grade 2 Ejection fraction decreases (defined as LVEF<50%) were observed each with spontaneous resolution

RP2D:

- DL3 - 3mg/m^2/dose BID oral continuously over 28 days

Data cutoff – Oct 23, 2024

Results: Objective response to therapy



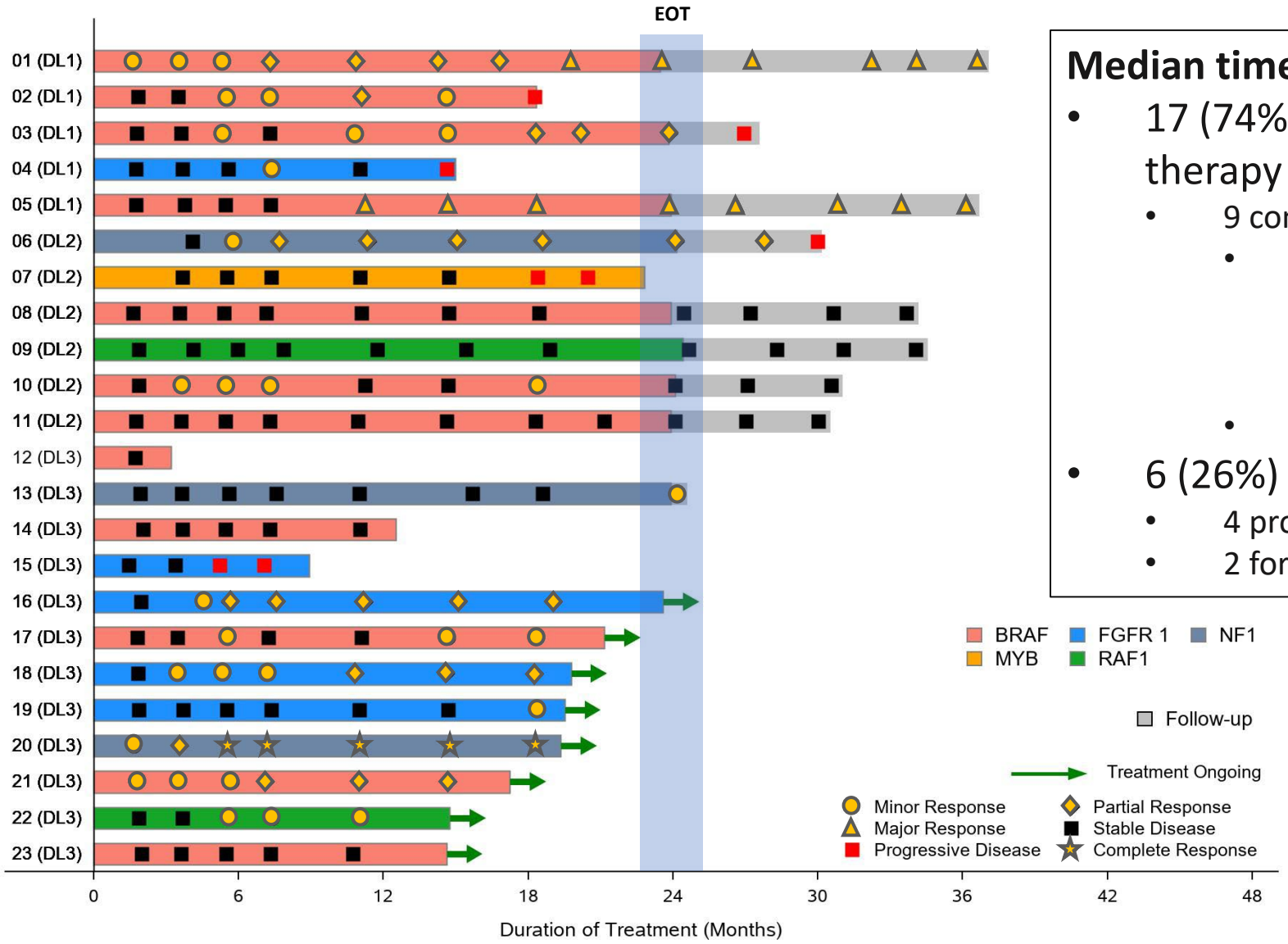
19 of the 23 patients had measurable tumors:

- **15 (79%)** achieved ≥ minor response by 2D PPD and Volumetric measure .
- **9 (47%)** achieved ≥ partial response by 2D PPD
- **11 (58%)** achieved ≥ partial response by volumetric measure

2D PPD: 2-Dimensional Perpendicular diameter

Data cutoff – Oct 23, 2024

Results: Treatment duration and Time to response



Median time of follow-up = 18.4 mo (3.2-36.6)

- 17 (74%) patients completed or remain on therapy
  - 9 completed 2 yrs
    - 7 have stayed off
      - 2 have maintained response for more than 1 yr off therapy
      - 5 are less than 1 yr
    - 2 are being retreated
- 6 (26%) patients discontinued therapy
  - 4 progressed on therapy (**2 FGFR**, **1 MYB**, **1 BRAF**)
  - 2 for toxicity (rash, CPK increase)

Median time to response (using 2PPD)

- ≥ minor response = **4.6 mo (1.7-24)**
- ≥ partial response = **11.2 mo (3.4-18.4)**

EOT: End of Therapy
Data cutoff – Oct 23, 2024

Results: Responses have been observed in tumors with different driver mutations

4 yo, F: progressive PA

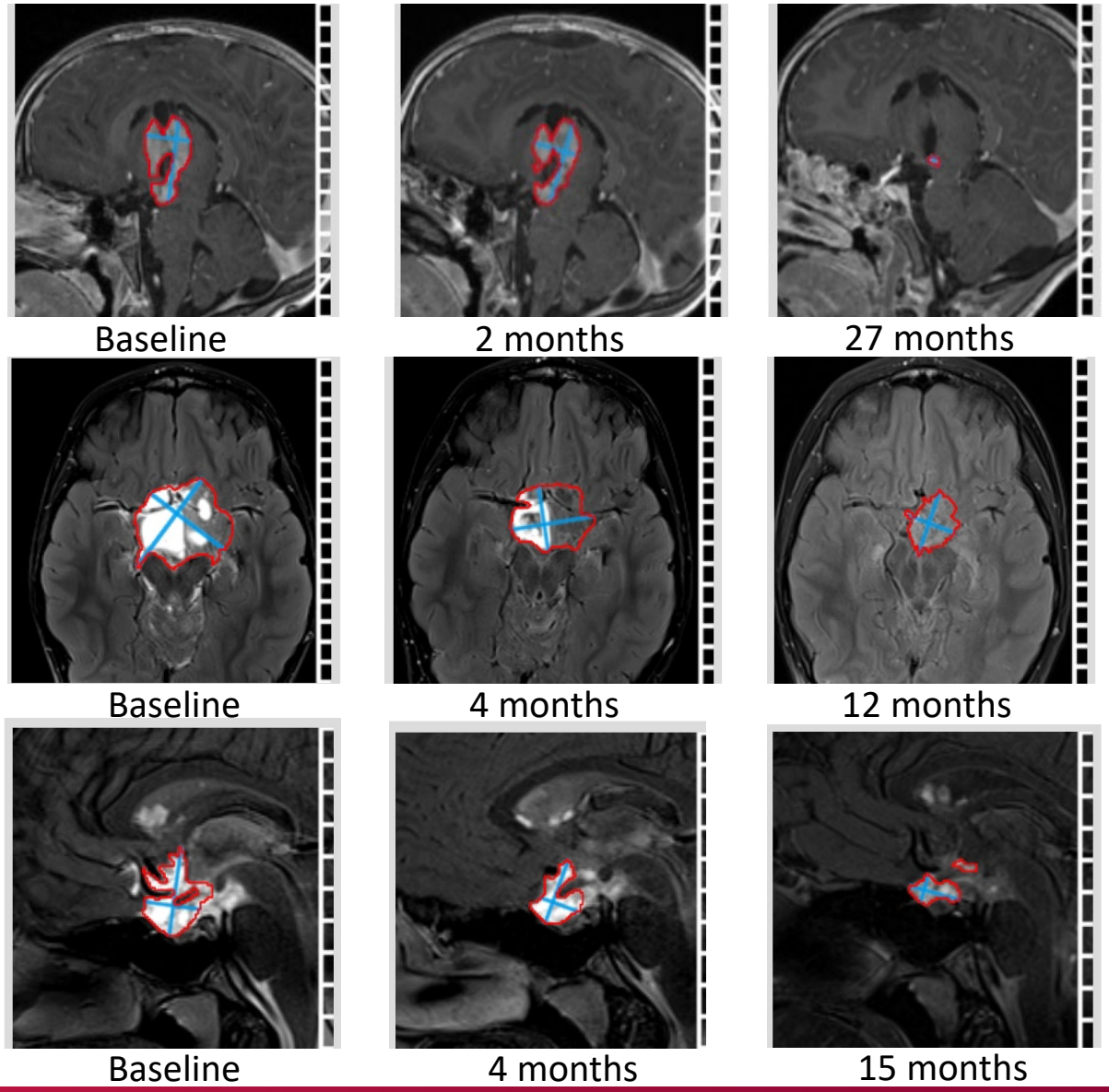
- **KIAA1549-BRAF fusion**
- Best % change: 89% decrease (major response)
- Now off therapy x 1yr without progression

6 yo, M: progressive, metastatic PA

- **PTPN11 E69K; FGFR1 K656E**;
- Best % change: 70% decrease (partial response)
- On therapy

11 yo, F: progressive, metastatic PA

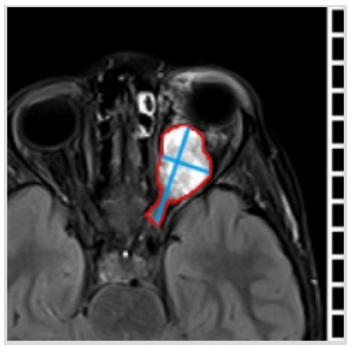
- **FGFR1 K656E; FGFR1 K38Q**
- Best % change: 49.9% decrease (minor response)
- On therapy



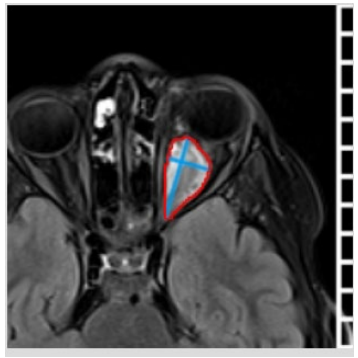
Results: Responses have included improvements in QOL

8 yo, M: progressive PA

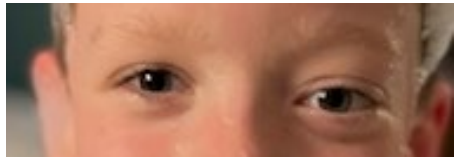
- BRAF duplication
- Best % change: 36.7% decrease (minor response)
- **Near complete resolution of proptosis**
- On therapy

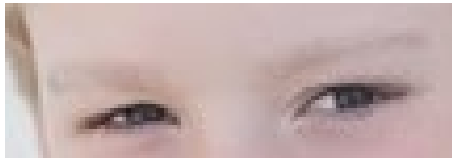


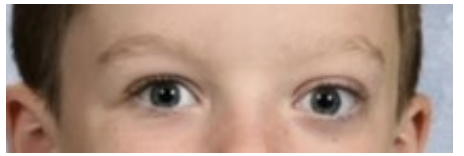
Baseline



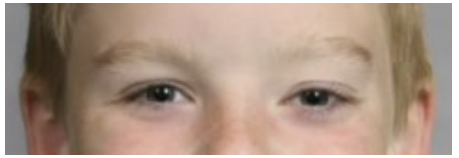
18 months







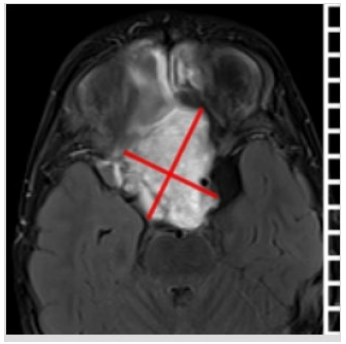
Baseline



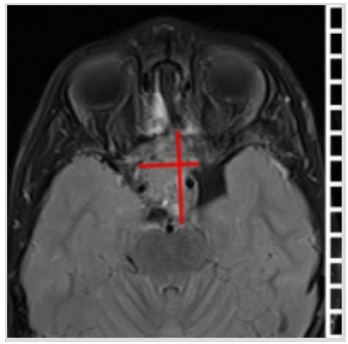
18 months

4 yo, F: progressive, PA

- KIAA1549-BRAF fusion
- Best % change: 57% decrease (partial response)
- **Resolution of diencephalic syndrome**
- On therapy



Baseline



15 months

Baseline
10.5 Kg (<3%)

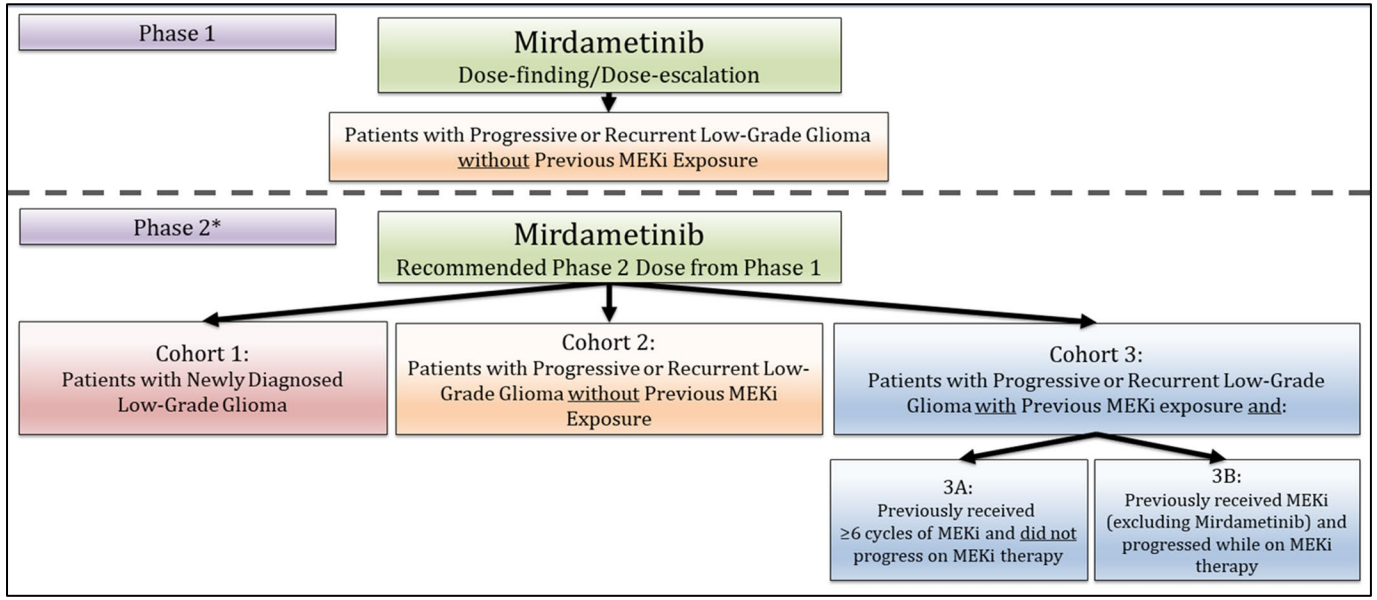
15 months
13.4 kg (33%)

Photographs shown with parental permission

Conclusions

- SJ901 Phase 1/expansion shows Mirdametinib in pLGG is **well tolerated** with expected MEKi toxicities
  - Weight gain, rashes, paronychia, CPK elevations, and hair color change are notable toxicities
  - No significant retinal or cardiac toxicities were observed
- We found the **RP2D to be 3 mg/m²/dose BID administered continuously in 28-day cycles**
- We observed **responses (≥ minor response in ~80%** and **≥ partial response in ~50%)** across a variety of MAPK pathway aberrations
  - ***BRAF*, *NF1*, *FGFR1*, *PTPN11*, and *RAF1***

SJ901 Schema



- Early observations suggest that **2D PPD may underestimate the degree of response as compared to volumetric tumor measurements** (more to come)
- In addition to measurable reductions, we observed **improved QOL** in patients on therapy
- SJ901 is now in phase 2 and enrolling **newly diagnosed patients** (cohort 1), **recurrent MEKi naïve patients** (cohort 2), and **recurrent patients previously treated with MEKi** (cohort 3). Objectives include assessing **efficacy, comparing radiographic measurement techniques, and evaluating changes in QOL**.