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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BACKGROUND

- MEK inhibitors (MEKi) have emerged as a promising therapy for pediatric low-grade glioma (pLGG), but blood-brain barrier penetrance and availability of oral formulations remain as obstacles to optimal efficacy.
- Mirdametinib (PD-0325901) is an investigational, oral, allosteric, small-molecule MEKi with high blood-brain-barrier penetration.
- Mirdametinib comes in dispersible tablet formulation which allows administration to patients who have difficulty swallowing capsules.
- We hypothesized mirdametinib would benefit patients with pediatric low-grade gliomas (pLGG) and launched SJ901clinical trial (NCT04923126) to determine the recommended Phase 2 dose (RP2D), safety, and efficacy.

OBJECTIVES

- Determine the safety and tolerability of mirdametinib
- Determine the recommended phase 2 dose (RP2D) of mirdametinib
- Assess preliminary efficacy of mirdametinib in patients with pLGG when administered continuously.

METHODS

- SJ901 is a multi-arm phase I/II trial of mirdametinib in patients ≥2 and <25 years with pLGG.
- Phase 1 required patients to have **no** prior exposure to MEKi, have recurrent/progressive pLGG with biopsy-proven MAPK pathway activation (except BRAF V600).
  - MAPK pathway activation is defined as *BRAF* fused or rearranged, *FGFR1/2/3* aberration, *NF1*, *NF2*, *PTPN11*, *SOS1*, *RAF1* mutations, *MYB* or *MYBL1* fused or rearranged, by IHC, FISH and/or DNA/RNA sequencing.
- Three escalating dose levels administered continuously in 28-day cycles were evaluated using a rolling 6 design
  - DL1: 2 mg/m^2/dose BID
  - DL2: 2.5mg/m^2/dose BID
  - DL3: 3mg/m^2/dose BID
- An expansion cohort was planned to evaluate the highest tolerated dose level in a total of 12 patients.
- RP2D was defined as the dose causing ≤3 dose-limiting toxicities (DLTs) in 12 patients.
- A DLT was defined as any dose-limiting toxicity occurring within the first cycle of therapy.
- Serial physical exams, labs, neurologic, MRI, ophthalmologic, and cardiac assessments were used to monitor all patients.
- Measurable disease changes were categorized as progressive (≥ 25%), stable (24.9% to -24.9%), minor (-25% to -49.9%), partial (-50% to -74.9%), major (-75% to -99.9%), complete (-100%).

RESULTS

- Between June 2021 and June 2024, 23 patients were enrolled on SJ901 Phase 1/Phase 1 expanded and followed .

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)	5.4 (3.6 - 13.9)	10.8 (7.9 - 21.9)	7.9 (2.5 - 13.9)	8.4 (2.5 - 21.9)
Gender				
Female	3 (60%)	3 (50%)	6 (50%)	12 (52%)
Male	2 (40%)	3 (50%)	6 (50%)	11 (48%)
Race				
Asian	1 (20%)			1 (4%)
Black		1 (17%)	1 (8%)	2 (9%)
White	2 (40%)	5 (83%)	11 (92%)	18 (78%)
Other	2 (40%)			2 (9%)
Primary Diagnosis				
Pilocytic astrocytoma	4 (80%)	4 (66%)	9 (75%)	17 (73%)
Diffuse glioma	1 (20%)	1 (17%)		2 (9%)
Glioneuronal tumor		1 (17%)	1 (8%)	2 (9%)
Low-grade glioma, not otherwise specified			2 (17%)	2 (9%)
MAPK Gene Abnormality				
BRAF	4 (80%)	3 (50%)	5 (42%)	12 (52%)
FGFR 1	1 (20%)		4 (33%)	5 (22%)
MYB		1 (17%)		1 (4%)
NF1		1 (17%)	2 (17%)	3 (13%)
RAF1		1 (17%)	1 (8%)	2 (9%)

Dose Limiting toxicity:

- Only 1 patient out of 12 at DL3 had a DLT (grade 3 thrombocytopenia) resulting in DL3 being declared the RP2D.

Treatment Related Adverse Events (TRAE), dose reductions, discontinuations:

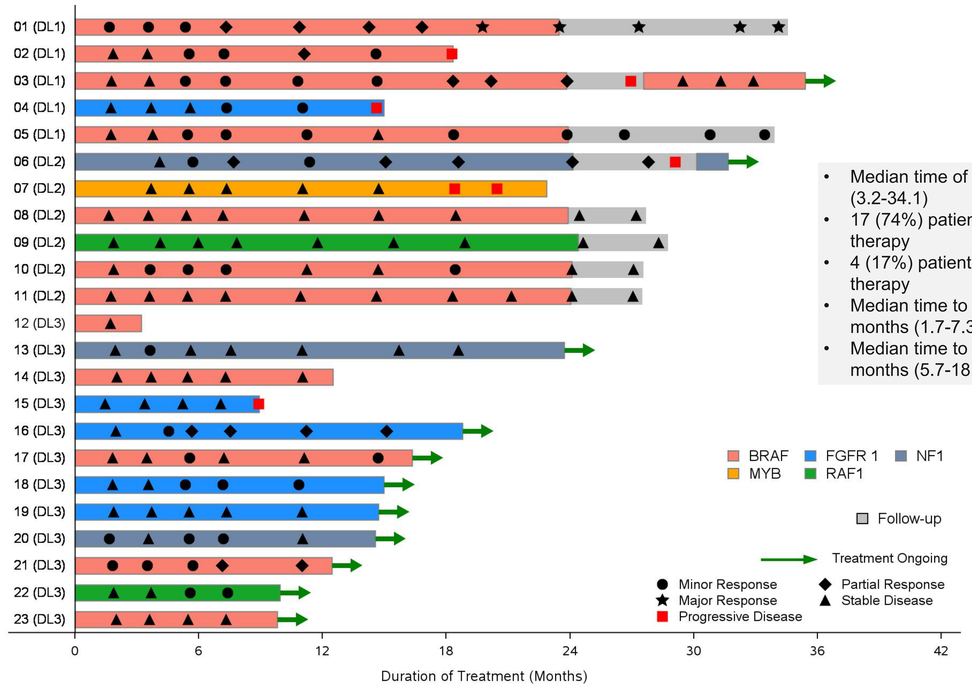
- 11 (48%) patients out of 23 developed 13 Grade 3/4 toxicities (see table):
- 7 (30%) patients underwent dose reductions
- 2 (9%) patients on DL3 discontinued for toxicities
  - 1 grade 2 rash (intolerable)
  - 1 grade 4 creatine phosphokinase (CPK) elevation

TRAE	Grade 3 N (%)	Grade 4 N (%)	Dose Reduction N (%)
Alanine aminotransferase increased	1 (4%)	0	1 (4%)
CPK increased	4 (17%)	1 (4%)	1 (4%)
Weight gain	5 (22%)	0	4 (17%)
Neutrophil count decreased	1(4%)	0	0
Platelet count decreased	1(4%)	0	1(4%)

- Most common TRAEs (all grades) were: elevated CPK (n=23), elevated AST (n=20), acneiform rash (n=13), dry skin (n=12), hypoalbuminemia (n=11), paronychia (n=11), anemia (n=10), weight gain (n=9), decreased neutrophil count (n=8), nausea (n=7), elevated alkaline phosphatase (n=6), elevated ALT (n=5), fatigue (n=5), hypernatremia (n=5), and maculo-papular rash (n=5).
- 2 patients developed Grade 2 decrease in left ventricular ejection fraction (defined as LVEF<50%): one at the end of therapy evaluation (LVEF return to normal on follow up studies) and 1 prior Cycle 3 (LVEF returned to normal with brief hold of study drug; no further decrease in LVEF was observed upon re-start without dose modification).
- No retinal toxicities of any grade were observed.

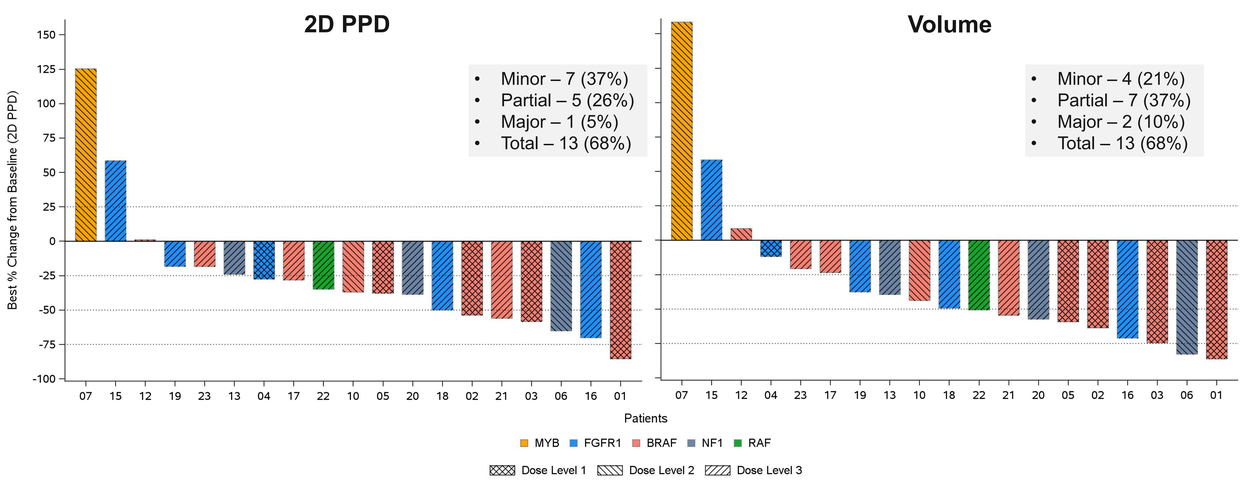
RESULTS

Swimlane plot showing duration of treatment and response by genetic alteration and dose level, calculated from treatment start date to data cutoff date (June 11, 2024).



- Median time of follow-up was 14.9 months (3.2-34.1)
- 17 (74%) patients completed or remain on therapy
- 4 (17%) patients progressed while on therapy
- Median time to ≥ minor response was 5.4 months (1.7-7.3).
- Median time to ≥ partial response was 7.6 months (5.7-18.4).

Waterfall plots showing best %change in tumor size from baseline measurements by 2-dimensional perpendicular diameter measure (2D PPD) and by Volumetric measure from treatment start date to data cutoff date (June 11, 2024).



- 19 of the 23 patients had measurable tumors. The following results were observed:
  - Objective responses were observed in all dose levels
  - 13 (68%) achieved ≥ minor response by 2D PPD and Volumetric measure .
  - 6 (32%) achieved ≥ partial response by 2D PPD
  - 9 (47%) achieved ≥ partial response by volumetric measure

CONCLUSIONS AND NEXT STEPS

- Mirdametinib can be safely and tolerably administered continuously in 28-day cycles
- The RP2D is 3 mg/m^2/dose BID administered continuously in 28-day cycles
- No significant cardiac or retinal toxicities were observed in this study population
- Mirdametinib is well-tolerated with expected MEKi toxicities that can be managed with supportive care and dose reductions.
- Mirdametinib has promising clinical activity in patients with recurrent/progressive pLGG across a variety of MAPK pathway aberrations including – *BRAF*, *NF1*, *FGFR1*, and *RAF1*
- Response results from volumetric tumor measurements, as compared to 2D PPD, suggest that assessment by 2D PPD may underestimate the degree of response.

Phase 2 is ongoing and recruiting pediatric and young adult patients to:

- complete the evaluation of efficacy in patients with recurrent/progressive pLGG (Cohort 2)
- establish safety and efficacy in patients with newly diagnosed pLGG (Cohort 1)
- establish safety and efficacy in patients with to previous exposure to MEKi (Cohort 3).
- capture functional visual, motor, and neurocognitive outcomes in this population. (All SJ901 patients can consent to receive serial ophthalmologic, neurologic, and neurocognitive evaluations on and after treatment)

ACKNOWLEDGMENTS

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Scan to read more about SJ901 clinical trial design, objectives and eligibility criteria