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Phase I/II study of the WEE1 inhibitor adavosertib (AZD1775) in combination with carboplatin in children with advanced malignancies: Arm C of the AcSé-ESMART trial

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Abstract

Purpose: AcSé-ESMART Arm C aimed to define the recommended dose and activity of the WEE1 inhibitor adavosertib in combination with carboplatin in children and young adults with molecularly enriched recurrent/refractory malignancies.

Patients and methods: Adavosertib was administered orally, twice daily on Days 1 to 3 and carboplatin intravenously on Day 1 of a 21-day cycle, starting at 100 mg/m2/dose and AUC 5, respectively. Patients were enriched for molecular alterations in cell cycle and/or homologous recombination (HR).

Results: Twenty patients (median age: 14.0 years, range 3.4-23.5) were included, 18 received 69 treatment cycles. Dose-limiting toxicities were prolonged grade 4 neutropenia and grade 3/4 thrombocytopenia requiring transfusions, leading to two de-escalations to adavosertib 75 mg/m2/dose and carboplatin AUC 4; no recommended Phase 2 dose was defined. Main treatment-related toxicities were hematologic and gastrointestinal. Adavosertib exposure in children was equivalent to that in adults; both doses achieved the cell kill target. Overall response rate was 11% (95%CI, 0.0; 25.6) with partial responses in two patients with neuroblastoma. One patient with medulloblastoma experienced unconfirmed partial response and five patients had stable disease beyond 4 cycles. Seven of these eight patients with clinical benefit had alterations in HR, replication stress and/or RAS pathway genes with or without TP53 alterations, whereas TP53 pathway alterations alone (8/10) or no relevant alterations (2/10) were present in the 10 patients without benefit.

Conclusions: Adavosertib-carboplatin combination exhibited significant hematologic toxicity. Activity signals and identified potential biomarkers suggest further studies with less hematotoxic DNA damaging therapy in molecularly enriched pediatric cancers.