ABSTRACT

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First-in-child phase I/II study of the dual mTORC1/2 inhibitor vistusertib (AZD2014) as monotherapy and in combination with topotecan-temozolomide in children with advanced malignancies: arms E and F of the AcSé-ESMART trial.

Morscher RJ(1), Brard C(2), Berlanga P(3), Marshall LV(4), André N(5), Rubino J(6), Aerts I(7), De Carli E(8), Corradini N(9), Nebchi S(2), Paoletti X(2), Mortimer P(10), Lacroix L(11), Pierron G(12), Schleiermacher G(13), Vassal G(6), Geoerger B(14).

Author information:
(1)Gustave Roussy Cancer Campus, Department of Paediatric and Adolescent Oncology, Villejuif, France; INSERM U1015, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France.
(2)Gustave Roussy Cancer Campus, Biostatistics and Epidemiology Unit, INSERM U1018, CESP, Université Paris-Saclay, Université Paris-Sud, UVSQ, Villejuif, France.
(3)Gustave Roussy Cancer Campus, Department of Paediatric and Adolescent Oncology, Villejuif, France.
(4)Paediatric and Adolescent Oncology Drug Development Unit, The Royal Marsden Hospital & The Institute of Cancer Research, London, United Kingdom.
(5)Department of Paediatric Hematology & Oncology, Hôpital de la Timone, AP-HM, Marseille, France; UMR Inserm 1068, CNRS UMR 7258, Aix Marseille Université U105, Marseille Cancer Research Center (CRCM), Marseille, France.
(6)Gustave Roussy Cancer Campus, Clinical Research Direction, Villejuif, France.
(7)SIREDO Oncology Center, Institut Curie, PSL Research University, Paris, France.
(8)Centre Hospitalier Universitaire, Department of Paediatric Oncology, Angers, France.
(9)Pediatric Oncology Department, Institute of Pediatric Hematology and Oncology, Centre Leon Berard, Lyon, France.
(10)Astra Zeneca, Cambridge, United Kingdom.
(11)Department of Medical Biology and Pathology of Translational Research and Biobank, AMMICA, Laboratory INSERM US23/CNRS UMS3655, Gustave Roussy Cancer Campus, Université Paris-Saclay, 94805 Villejuif, France.
(12)Unité de Génétique Somatique, Service d'oncogénétique, Institut Curie, Centre Hospitalier, Paris, France.
(13)SIREDO Oncology Center, Institut Curie, PSL Research University, Paris, France; Laboratory of Translational Research in Paediatric Oncology - INSERM U830, Paris, France.
(14)Gustave Roussy Cancer Campus, Department of Paediatric and Adolescent Oncology, Villejuif, France; INSERM U1015, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France. Electronic address: birgit.geoerger@gustaveroussy.fr.

AIM: Arms E and F of the AcSé-ESMART phase I/II platform trial aimed to define the recommended dose and preliminary activity of the dual mTORC1/2 inhibitor vistusertib as monotherapy and with topotecan-temozolomide in a molecularly enriched population of paediatric patients with relapsed/refractory malignancies. In addition, we evaluated genetic phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian (or mechanistic) target of rapamycin (mTOR) pathway alterations across the Molecular Profiling for Paediatric and Young Adult Cancer Treatment Stratification (MAPPYACTS) trial (NCT02613962).

EXPERIMENTAL DESIGN AND RESULTS: Four patients were treated in arm E and 10 in arm F with a median age of 14.3 years. Main diagnoses were glioma and sarcoma. Dose escalation was performed as per the continuous reassessment method, expansion in an Ensign design. The vistusertib single agent administered at

75 mg/m2 twice a day (BID) on 2 days/week and vistusertib 30 mg/m2 BID on 3 days/week combined with temozolomide 100 mg/m2/day and topotecan 0.50 mg/m2/day on the first 5 days of each 4-week cycle were safe. Treatment was well tolerated with the main toxicity being haematological. Pharmacokinetics indicates equivalent exposure in children compared with adults. Neither tumour response nor prolonged stabilisation was observed, including in the 12 patients whose tumours exhibited PI3K/AKT/mTOR pathway alterations. Advanced profiling across relapsed/refractory paediatric cancers of the MAPPYACTS cohort shows genetic alterations associated with this pathway in 28.0% of patients, with 10.5% carrying mutations in the core pathway genes.

CONCLUSIONS: Vistusertib was well tolerated in paediatric patients. Study arms were terminated because of the absence of tumour responses and insufficient target engagement of vistusertib observed in adult trials. Targeting the PI3K/AKT/mTOR pathway remains a therapeutic avenue to be explored in paediatric patients.
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