INTRODUCTION

Proteus Syndrome

Proteus syndrome (PS) is an ultra-rare disease characterized by progressive, disproportionate, segmental overgrowth that can affect any organ or tissue in the body. It occurs sporadically in a mosaic form. The diagnosis is based on strict clinical criteria first defined in 1999 and confirmed by the presence of a somatic gain of function mutation in c.49G>A, p.Glu17Lys in the oncogene AKT1, encoding the AKT kinase.

Patients with PS develop numerous severe medical complications, including vascular anomalies (capillary, venous and lymphatic), deep venous thrombosis, pulmonary cystic malformations, severe scoliosis with megavertebral, epilepsy, cardiac abnormalities, renal and spinal overgrowth.

AKT is a critical component in the PI3K/AKT/ mTOR pathway and somatic mutations in the AKT1 gene can also act as oncogenic drivers. Patients with PS have also a higher risk of both benign and malignant tumors, and monomorphic mutations in the AKT1 gene can also act as oncogenic drivers. Patients with PS develop numerous severe medical complications, including vascular anomalies (capillary, venous and lymphatic), deep venous thrombosis, pulmonary cystic malformations, severe scoliosis with megavertebral, epilepsy, cardiac abnormalities, renal and spinal overgrowth.

Miransertib

Miransertib (ARRY-010) is an investigational orally available potent and selective allosteric pan-AKT inhibitor that inhibits both the active and inactive forms of AKT, AKT1, AKT2, and AKT3. Linhardt et al. demonstrated that miransertib reduced phosphorylation of AKT and downstream targets of AKT in a concentration-dependent manner in cells and tissues from patients with PS. Preclinical in vivo studies also show that miransertib exhibits strong anti-tumor activity on tumor models harboring mutant AKT1-E742K or with an activated AKT pathway. We report the efficacy of this AKT inhibitor treatment in a patient with PS and an AKT1 (c.49G>A, p.Glu17Lys) protein-coding mutation.

CASE HISTORY

PS Progression Complicated by Development of Ovarian Cancer

A 16-year-old female was diagnosed with PS at the age of 3 years old in Rome, Italy. During the first 6 years of life, the patient underwent several surgical procedures for PS, including amputation of the distal part of the right leg and the left arm. She also underwent a total skin grafting above the knee on the right leg and the extrahepatic segment of the portal vein. Major surgery was deemed necessary due to the multiple significant compression-related problems, including vertebral synostosis of the cervical spine, making flexible ventilation extremely difficult. Due to portal vein thrombosis, treatment with chemotherapy or hormonal therapy with an aromatase inhibitor was not recommended.

We submitted an application to the Institutional EC to treat this patient with miransertib made available by Arqule for single patient use. Upon approval on March 21st, 2017, she underwent stage 2B ovarian cancer with metastatic disease in the bone and received the first dose of oral miransertib 50 mg daily.

TREATMENT AND RESULTS

Partial Response and CA-125 Normalization

March 2017 baseline evaluation:

- Full-body CT scan: target lesion maximum diameter 6.29 cm; CA-125: 95kU/L

Full-body CT scan and CA-125 measurements were performed every 8 weeks for the first 24 weeks and every 12 weeks thereafter.

- May 2017:
  - Resolution of ascites: CA-125 decreased to 38 kU/L; stable measurable disease on CT

- July 2017:
  - CA-125 normalized (at 16 weeks of treatment)

- September 2017:
  - CT showed partial response (PR) according to RECIST 1.1 criteria; residual pelvic mass 4.39 cm (15%)

- June 2018:
  - 15-month CT scan confirmed ongoing PR; residual pelvic mass 3.23 cm (50% from baseline)

- CA-125 still within normal limits

- October 2018:
  - 19-month CT scan confirmed ongoing PR; residual pelvic mass 2.63 cm (63% from baseline)

CONCLUSIONS

- Personalized treatment with the AKT inhibitor miransertib in a patient with PS and a relapsed AKT1 (E742K) mutant LGSOC led to a clinically significant and sustained anti-tumor response and improvements of PS-associated symptoms.

REFERENCES & ACKNOWLEDGEMENTS


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