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1520O

REGISTRI: Regorafenib in first-line of KIT/PDGFR wild type advanced GIST: Capatalize the A Spanish (GEIS), Italian (ISG) and French Sarcoma Group (FSG) phase II trial

J. Martin Broto[1], C. Valverde[2], N. Hindi[1], B. Vincenzi[3], J. Martinez-Trufero[4], G. Grignani[5], A. Italiano[6], J. Lavernia[7], R. Gonzalez-Campora[8], A. Vallejo[9], D. Hernandez-Jover[10], A. Gutierrez[11], C. Serrano[12], D. Moura[13], J.A. Lopez-Guerrero[14], J. Cruz[7], A. Fernández-Serra[14], J-Y. Blay[15], E.R. Fumagalli[16], V. Martinez Marin[17]

[1] Medical Oncology, Fundación Jimenez Diaz University Hospital, Madrid, Spain, [2] Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [3] Medical Oncology, University Campus Bio-Medico, Rome, Italy, [4] Medical Oncology, HU Miguel Servet, Zaragoza, Spain, [5] Division of Medical Oncology, Candiolo Cancer Institute, FPO-IRCCS, Turin, Italy, [6] Medical Oncology, Institute Bergonié, Bordeaux, France, [7] Medical Oncology, Fundación I.V.O., Valencia, Spain, [8] Pathology, Hospital Quironsalud Cordoba, Cordoba, Spain, [9] Pathology, HU Virgen Macarena, Seville, Spain, [10] Radiology, HU Sant Pau, Barcelona, Spain, [11] Hematology, HU Son Espases, Palma de Mallorca, Spain, [12] Sarcoma Translational Research, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [13] ATBsarc group, CITIUS III, Seville, Spain, [14] Molecular Biology, Fundación I.V.O., Valencia, Spain, [15] Medicine Department, Centre Léon Bérard, Lyon, France, [16] Medicine Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy[17] Medical Oncology, Hospital Universitario La Paz, Madrid, Spain

Background

Around 15% of adult GIST are wild type for *KIT/PDGFRA* mutations (KPWT), usually have SDH deficiencies, and are resistant to imatinib (IM). The underlying mechanisms include overexpression of HIF1α in SDH deficient-GIST, high IGFR signaling through MAPK, BRAF mutation or STAT3 activation. Regorafenib (RE), targeting these pathways, could be more active as upfront therapy in KPWT GIST.

Methods

Patients (pts) >18, with advanced non pretreated KPWT GIST were eligible after central confirmation by next-generation sequencing (NGS). Eligible pts received RE at 160mg/d for 21/28d cycles. Primary end-point was disease control rate (DCR) at 12 weeks (RECIST 1.1) by central radiological assessment (CRA). Secondary objectives were PFS, OS, ORR (RECIST,Choi), safety and QoL. An amendment allowed previous IM (adjuvant). Statistical assumptions [H0 73% and H1 90% (α 0.1 and β 0.2)], defined a sample size of 20 pts.

Results

From May 2016 to October 2020, 30pts with KPWT GIST (by Sanger) underwent central molecular screening. Among the 15 non-eligible pts, 8 harbored KIT exon 11 mutations, 3 exon 9 and 3 PDGFRA exon 18 by NGS. The remaining 16 (53.3%) molecularly eligible pts were enrolled and started RE except one pt due to COVID-19 pandemic. The trial was prematurely closed due to low recruitment, especially after COVID outbreak. Demographics and treatment details in the table. Based on CRA, 12w-DCR was 86.7%. With a median (m) FU of 26 (5-44) months (mo), 10/15 pts progressed, with a mPFS of 10.8 mo (95% CI 6.9-14.8). 6 mo, 9 mo and 12 mo PFS rates were 65%, 48% and 29% respectively. 2 pts were PD-free at 25 and 43 mo from start of RE. 6/15 pts died, with a mOS of 33.5 mo (95% CI NR).Table: 1520O

CHARACTERISTIC	n (%)
Age, median (range)	57 (17-72)
Gender Female Male	8 (53) 7 (47)
SDH complex activity Preserved Deficient Not evaluable	3 (20) 10 (66) 2 (13)
Stage at treatment initiation Locally advanced unresectable Metastasic	2 (13) 13 (87)
Previous imatinib Yes No	5 (33) 10 (66)
Median cycles of regorafenib (range)	7.8 (0.3-39)
Treatment reductions No Yes	7 (47) 8 (53)
Treatment interruptions No Yes	1 (7) 14 (93)
G3-4 toxicities GOT/GPT increase Palmo-plantar erythrodysesthesia Skin disorders Anemia Diarrhea Hypertension Pruritus	3 (20) 2 (13) 2 (13) 1 (7) 1 (7) 1 (7) 1 (7)
Best RECIST response CR PR SD PD NE	0 1 (7) 12 (84) 1 (7) 1 (7)

Conclusions

The study results approach the prespecified activity threshold. The low recruitment rate could have affected this attainment.

Other analysis of secondary endpoints are ongoing. The high percentage of overlooked mutant GIST by Sanger raises the need of NGS in presumed KPWT GIST.

Clinical trial identification

NCT02638766.

Legal entity responsible for the study

Spanish Group for Research on Sarcoma (GEIS).

Funding

Bayer.

Disclosure

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