3655 Triple Combination of Ruxolutinib, Nilotinib and Prednisone Is Safe and Shows Promising Activity for the Treatment of Myelofibrosis Patients, Results of a Phase Ib Clinical Trial (RUNIC).

Program: Oral and Poster Abstracts

Session: 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Poster III

Hematology Disease Topics & Pathways:

Clinical Trials, Clinical Research

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Rosa Ayala, MD, PhD[1], Rafael Alonso Fernández, MD[2*], **Valentín Garcia Gutierrez, MD, PhD[3]**, Alberto Alvarez-Larran[4*], Santiago Osorio, MD[5*], Jose M. Sanchez, MD[6*], Gonzalo Carreño Gomez-Tarragona, MD[7*], **María Teresa Gómez-Casares, MD, PhD[8*]**, Antonia Duran[9*] and Joaquín Martínez-López[10*] [1]Hematology Department, Hospital Universitario 12 de Octubre, MADRID, Spain [2]Translational Hematology Group, Hospital 12 de Octubre-CNIO, Madrid, Spain [3]**Hematology Service, Hospital Universitario Ramón y Cajal, Madrid, Spain** [4]Hematology Department, Hematology Department, Hospital ClíNic, Barcelona, Spain [5]Hospital General U. Gregorio Marañón, Madrid, Spain [6]Department of Hematology, Hospital Universitario 12 de Octubre, Madrid, ESP [7]Hematology Department, Hospital Universitario 12 de Octubre,, Madrid, Spain [8]**Hospital Universitario de Gran Canaria Dr. Negrin, Las Palmas de Gran Canaria, Spain** [9]Hospital Universitario Son Espases, Palma de Mallorca, Spain [10]Haematological Malignancies Clinical Research Unit, Hospital 12 de Octubre Universidad Complutense, CNIO, CIBERONC, Madrid, Spain*

Background: Ruxolitinib is the standard of care for myelofibrosis (MF). However not all patients respond to ruxolitinib and other lose response while on treatment or require discontinuation due to adverse events. Therefore, several clinical trials with ruxolitinib in combination with other drugs are being conducted. We previously showed the synergistic effect of the combination ruxolitinib/nilotinib/prednisone in ex vivo models of peripheral blood mononuclear cells from MF patients and cell lines.

Aims: This phase Ib/II study, non-randomized, open-label, evaluates safety and tolerability of ruxolitinib in combination with nilotinib and prednisone in patients with naïve or ruxolitinib-resistant MF.

Methods: Between November 2017 and June 2020, 21 patients were included in RUNIC (EudraCT Number:2016-005214-21) at 6 Spanish sites. Six patients were considered screening failures. A total of 15 patients received at least one dose of ruxolitinib and were included in the intention-to-treat (ITT) or the per-protocol (PP) populations. The study design is summarized in figure 1.

Out of 15 evaluable patients whose median age was 66.5 years (53.4-70.8). Six patients (40%) had a diagnosis of primary MF, 4 patients (26.7%) post-polycythemia vera MF, and 4 patients (26.7%) post-essential thrombocythemia MF. Most patients had International

Prognostic Scoring System (IPSS) intermediate-1 or -2 disease (5 [33.3%] and 4 [26.7%], respectively), and 9 patients (60%) had JAK2 V617F mutation. Most of the patients (n=13; 86.7%) had received ruxolitinib as previous anti-neoplastic therapy for MF.

Results: Eight patients completed 7 cycles (53.3%), and six patients 12 cycles (40%) and nine patients withdrawn because of disease progression, lack of efficacy, or no clinical benefit (n=5), withdrawal of consent (n=2), adverse event (AE) (pulmonary thromboembolism, n=1), and investigator's medical judgment (n=1).

All patients experienced at least one AE during the study (the most common were hyperglycemia, asthenia and thrombocytopenia, and 14 patients registered at least one treatment-related AE (the most common were hyperglycemia (22.2%), thrombocytopenia (13.3%), and anemia (8.9%)). Five treatment-related serious adverse events (SAEs) were reported in 2 patients (13.3%), all of them related to nilotinib: one patient had pericardial effusion and bilateral pleural effusion, the other had congestive heart failure, pleural effusion, and pulmonary hypertension. No deaths were registered throughout the study.There were 2 patients with at least one adverse event meeting criteria for dose-limiting toxicity: grade 4 anemia and lumbar pain.

Only eight patients were evaluated for spleen lengths at screening and cycle 7 (Figure 2B). Of these, 6 experienced a palpable spleen reduction, 4 of them with a 100% reduction. In contrast, one patient remained with the same spleen length, and one patient experienced a 25% increase.Six patients had both symptom evaluation at screening and cycle 7 (Figure 2D). Four experienced a total symptom score reduction, one patient remained with the same total symptom score, and two patients reported an increase.Six patients had spleen length measures recorded both at screening and at cycle 12. From those, 4 showed a spleen length reduction, 3 of them with a 100% reduction.

Conclusions: Ruxolitinib in combination with nilotinib and prednisone showed relevant clinical activity in patients with naïve or ruxolitinib-resistant MF. The tolerability of this combination was acceptable, and the hyperglycemia was the treatment-related AE most frequent. The main cause of trial withdrawn was disease progression, lack of efficacy, or no clinical benefit. Based on these results, this triple combination should be explored in phase II/III clinical trials.

Figure 1. Study design

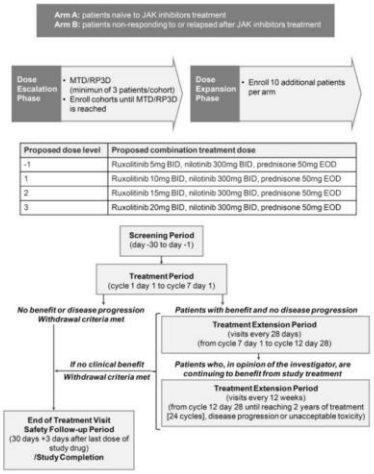
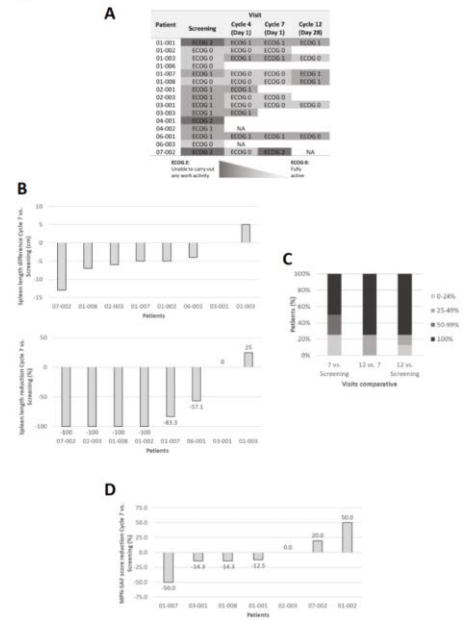


Figure 2



Disclosures: Ayala: *Incyte Corporation:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Astellas:* Honoraria; *Celgene:* Honoraria. **Garcia Gutierrez:** *BMS:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria, Research

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