EP670 ASCIMINIB RESPONSES IN PONATINIB-PRETREATED PATIENTS WITH CHRONIC MYELOID LEUKEMIA. A. Luna 1,*, J. M. Alonso-Dominguez 2 , N. Estrada 3 , C. Boque 4 , B. Xicoy 3 , *P. Giraldo 5* , A. Angona 6 , A. Alvarez-Larran 7 , *F. Sanchez-Guijo 8* , M. J. Ramirez 9 , E. Mora 10, P. Velez 11, A. Rosell 12, M. Colorado 13, B. Cuevas 14, M. Sagüés 15, M. Cortes 16, *M. Perez Encinas 17*, *L. F. Casado Montero 18*, M. Moreno Vega 19, L. Serrano 20, V. Gomez 21, C. Garcia-Hernandez 22, S. Lakhwani 23, A. Paz Coll 24, R. de Paz 25, S. Suarez-Varela 9 , A. Fernandez-Ruiz 26, R. Perez Lopez 27, A. Jimenez-Velasco 28, *J. C. Hernandez Boluda 29, J. L. Steegmann-Olmedillas 21, V. Garcia-Gutierrez 1* 1Hematology, Ramón y Cajal Hospital, 2Hematology, Hospital Universitario Fundación Jiménez Diaz, Madrid, 3Hematology, Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Josep Carreras Leukemia Research Institute, Badalona, 4Hematology, Institut Catala d'Oncologia, L'Hospitalet de Llobregat, 5Hematology, Hospital Quirón Zaragoza, Zaragoza, 6Institut Catala d'Oncologia, Girona, 7Hematology, Hospital Clinic, Barcelona, 8Hematology, IBSAL-Hospital Universitario de Salamanca, CIC and CIBERONC, Salamanca, 9Hospital de Jerez de la Frontera, Jerez de la Frontera, 10Hematology, Hospital Universitario y Politécnico La Fe, Valencia, 11Hospital Mutua Terrasa, Terrasa, 12Hospital Virgen de la Victoria, Malaga, 13Hospital Universitario Marques de Valdecilla, Santander, 14Hospital Universitario de Burgos, Burgos, 15Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Josep Carreras Leukemia Research Institute, Badalona, 16Hospital General de Granollers, Barcelona, 17Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, 18Hospital Virgen de la Salud, Toledo, 19Hospital Doctor José Molina Orosa de Lanzarote, Arrecife, 20Hospital General de Castellon, Castellon, 21Hospital Universitario La Princesa, Madrid, 22Hospital General de Alicante, Alicante, 23Hospital Universitario de Canarias, La Laguna, 24Hospital Universitario Puerto Real, Puerto Real, 25Hospital Universitario La Paz, Madrid, 26Institut Catala d'Oncologia, Barcelona, 27Hospital Universitario Clínico Virgen de la Arrixaca, Murcia, 28Hospital Regional Universitario de Málaga, Malaga, 29Hospital Universitario y Politécnico La Fe, Valencia, Spain

Background: Resistance or intolerance to second-generation tyrosine-kinase inhibitors (2GTKIs) is a rough issue in chronic myeloid leukemia (CML) patients. Asciminib, not yet commercially available, inhibits ABL kinase activity by a mechanism distinct to that of currently used TKIs and maintains activity against many resistant forms of BCR-ABL1.

Recent data from phase I-III trials showed high response rates with a good safety profile in patients failing to 2GTKIs. However, no studies have specifically addressed response rates with asciminib in ponatinib-pretreated (PPT) patients. Aims: To present data on responses to asciminib in PPT and non-PPT patients in the setting of clinical practice.

Methods: We gathered retrospective clinical data from 31 patients treated with asciminib after failure of several lines of TKI treatment. Eleven patients received ponatinib at some point for a median time of 18 months. A total of 29 patients were included in the efficacy analysis (2 patients were excluded due to short follow-up). We defined failure as either resistance (BCR-ABL1IS increase despite optimal TKI dosing) or intolerance (unacceptable toxicity leading to TKI termination). Asciminib use was provided by Novartis under a managed-access program (MAP). Data was collected from October 2018 to June 2020 in 25 institutions from the Spanish CML Group (GELMC). Results: The median time on asciminib for the entire cohort was 9 months (7 in the PPT group and 13 in the non-PPT group). Median time on previous TKI for the

entire cohort was 77 months (56 vs 105 for PPT and non-PPT patients, respectively). Median previous TKI lines before asciminib were 4, with no differences for PPT and non-PPT groups. Switch to asciminib was due to resistance in 5/11 (45%) vs 3/20 (15%) for the PPT and non-PPT, respectively, and due to intolerance in 6/11 (55%) and 17/20 (85%) for PPT and non-PPT groups. The median dose of ponatinib was 45mg in resistant patients and 15mg in intolerant patients. Responses rates according to asciminib indication and previous exposure to ponatinib are shown in table 1. The probabilities of maintaining or improving responses were 100%, 56% and 22% for complete cytogenetic response (CCyR), major molecular response (MMR) and MR4.5 respectively in non-PPT group versus 27%, 18% and 0% in PPT group, respectively. Probability of improving baseline responses were 78%, 47% and 22% for CCyR, MMR and MR4.5 respectively in non-PPT group versus 33%, 10% and 0% respectively observed in PPT patients. Concerning baseline mutational status, 12 (39%) of the 31 patients displayed BCR-ABL1 mutations (only 1 with T315I), with a heterogeneous pattern and no clear association with outcome: 7 patients in the nonPPT group (35%) and 5 patients in the PPT group (45%). In terms of tolerability, 10/17 (59%) in the non-PPT-intolerant subgroup displayed side effects; whereas in the PPT-intolerant subgroup 3/6 patients (50%) displayed side effects: grade 1 rash, grade 3 pancreatitis, and grade 4 thrombocytopenia, accordingly. At the end of follow-up, 27 (87%) continued receiving asciminib, 2 suffered from progression to blast phase and 2 patients showed loss of efficacy; notably, these 4 patients were in the PPT group, whereas all non-PPT continued on asciminib.

Best response to asciminib in non-PPT vs PPT patients

	Resistant (n=8)		Intolerant (n=21*)		Total (n=29*)	
	Non-PPT (n=3)	PPT(n=5)	Non-PPT (n=15*)	PPT (n=6)	Non-PPT (n=18*)	PPT (n=11)
CHR°	3/3 (100%)	5/5 (100%)	15/15 (100%)	6/6 (100%)	18/18 (100%)	11/11 (100%)
CCyR°	2/3 (66%)	1/5 (20%)	14/15 (93%)	2/6 (33%)	16/18 (100%)	3/11 (27%)
MMR°	0/3 (0%)	1/5 (20%)	10/15 (67%)	1/6 (17%)	10/18 (56%)	2/11 (18%)
MR4.5°	0/3 (0%)	0/5 (0%)	4/15 (27%)	0/6 (0%)	4/18 (22%)	0/11 (0%)
Patients without respective response at baseline						
CCyR°	2/3 (66%)	1/5 (20%)	5/6 (85%)	2/4 (50%)	7/9 (78%)	3/9(33%)
MMR°	0/3 (0%)	0/5 (0%)	7/12 (58%)	1/5 (20%)	7/15 (47%)	1/10(10%)
MR4.5°	0/3 (0%)	0/5 (0%)	4/15 (27%)	0/6 (0%)	4/18 (22%)	0/11 (0%)

Table 1. Responses to asciminib in non-ponatinib pretreated patients and ponatinib pretreated patients subgroups. PPT: ponatinib pretreated patients. CHR: complete hematological response, CCyR: complete cytogenetic response, MMR: major molecular response, MR4.5: detectable disease with BCR-ABL1° = 0.0032%. **Two patients were excluded from response analysis due to short follow-up. °Patients with CHR, CCyR, MMR, or MR4.5 at baseline were evaluable for hematologic, cytogenetic, or molecular response and were considered responders if they maintained their response. *Evaluable patients without a CCyR, MMR, or MR4.5 at baseline.

Summary/Conclusion: Asciminib constitutes a valid treatment option for patients failing 2GTKIs. However, our data suggest that response rates after ponatinib failure are poor, with these patients remaining a high risk group in which alternative treatments are needed.