mutations did not preclude pirtobrutinib efficacy. Approximately half of pts did not acquire *BTK* mutations and 29% did not acquire any mutations in this targeted panel, suggesting alternate resistance mechanisms. Whether similar patterns of resistance would manifest if pirtobrutinib was utilized in earlier lines of therapy or prior to cBTKi treatment remains uncertain. This abstract was accepted and previously presented at EHA2023.

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COMPARISON OF BLEEDING-RELATED EVENTS IN PATIENTS WHO RECEIVED PIRTOBRUTINIB WITH AND WITHOUT ANTITHROMBOTIC AGENTS

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Objectives: Bruton tyrosine kinase inhibitors (BTKi) are associated with an increased risk of bleeding events. Pirtobrutinib, a non-covalent (reversible) BTKi FDA approved for treatment of R/R MCL after 2 lines of therapy including a BTKi, demonstrated efficacy and tolerability across multiple B-cell malignancies. The incidence of bleeding events in pts treated with pirtobrutinib and concomitant antithrombotic therapy have not been specifically reported. We analyze bleeding events in pts from BRUIN who received pirtobrutinib with antithrombotic therapy. **Material and methods:** Pts with B-cell malignancies (317 CLL, 166 MCL, 290 other) who enrolled in the open-label, multicenter Phase 1/2 BRUIN study (NCT03740529) were analyzed. Concomitant antithrombotic therapy (direct factor XA inhibitors, heparin anticoagulants, platelet aggregation inhibitors) at time of enrolment was permitted (excluding warfarin). Pirtobrutinib was administered once daily in 28-day cycles) until disease progression or discontinuation due to toxicity. Common Terminology Criteria for Adverse Events V5.0 were used to determine grade and type of bleeding events. Descriptive analyses were performed. **Results:** As of 29 July 2022, 773 pts received at least 1 pirtobrutinib dose of pirtobrutinib monotherapy, including 216 with concomitant antithrombotic therapy (median age: 72 years [IQR 65-77]and the proportion who were ≥75 years: 34%). Median time on pirtobrutinib with and without antithrombotic therapy was 10.6 (IQR 4.0-19.9) and 9.3 months (IQR 3.1-17.3). Any-grade bleeding events were reported in 44.9% (97/216) pts with antithrombotic therapy vs 32.5% (181/557) without. Most bleeding events (>90%) in both groups were grade ≤2. The most common bleeding events (≥3%) in pts with antithrombotic therapy were contusion (22.7%), hematuria (5.6%), epistaxis (5.1%), petechiae (3.7%), and hematoma (3.2%). Of the 6 (2.8%) pts on antithrombotic therapy with a grade3 bleeding event, 2 (0.9%) were deemed related to pirtobrutinib by investigators: an upper GI bleeding with anemia and a hemarthrosis from a knee injury (1each). Grade≥3 bleeding events occurred in 11 (2%) pts not taking antithrombotics. Any-grade hemorrhage/hematoma occurred in 13/79 (16.5%) pts who received direct factor XA inhibitors, 10/39 (25.6%) who received heparins and 18/112 (16.1%) who received platelet aggregation inhibitors (some received >1 class). Among pts with antithrombotic therapy, median time to onset of any-grade bleeding event was 8.1 weeks (IQR 2.6-24) and median duration of a bleeding event was 2.1 weeks (IQR 0.6-4.3). Among pts who received antithrombotic therapy, bleeding events required dose interruption of pirtobrutinib in 5 pts (2.3%) and no bleeding events led to dose reduction or permanent discontinuation of pirtobrutinib. **Conclusion and discussion:** Concomitant antithrombotic therapy with pirtobrutinib was associated with an increased rate of bleeding events relative to pirtobrutinib alone, though most events were grade ≤2. High-grade bleeding events were infrequent (<2%). This supports the safety of pirtobrutinib administration in pts requiring antithrombotic therapies. Previously presented at EHA 2023.

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LEUCEMIA LINFOCÍTICA CRÔNICA ASSOCIADA A ANEMIA HEMOLÍTICA AUTOIMUNE COM RESPOSTA SOMENTE APÓS INTRODUÇÃO DE IBRUTINIBE

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Objetivo: Relatar caso de paciente com diagnóstico de leucemia linfocítica crônica (LLC) associada a anemia hemolítica autoimune (AHAI) por anticorpos quentes refratária a várias terapias, com resposta após início de ibrutinibe. **Metodologia:** Descrição de caso clínico realizado através da coleta de dados em sistema digital do HSPE. **Relato de caso:** Homem, 62 anos, com diagnóstico de LLC em 2013. Indicado tratamento com fludarabina, ciclofosfamida e rituximabe (FCR) devido anemia, com remissão da doença até o segundo semestre de 2022, quando iniciou acompanhamento no HSPE. Evoluiu com cansaço, linfonodomegalias, esplenomegalia, hemoglobina (Hb) 4,8 g/dL, leucócitos (Lt) 202 mil/mm^3 com 197 mil linfócitos, plaquetas 42 mil/mm^3, aumento de DHL e bilirrubina indireta, testes de Coombs direto e indireto positivos. Realizado tratamento com corticoide, seguido de imunoglobulina e rituximabe, porém sem melhora clínica e laboratorial. O mielograma evidenciou ausência de displasias e presença de 93% de linfócitos morfologicamente maduros,

achados confirmados em biópsia de medula óssea. A imunofenotipagem confirmou LLC e o estudo citogenético não mostrou alterações. Após resultado destes exames foi optado pelo tratamento com protocolo FCR, porém sem resposta depois de 2 ciclos, sendo substituído por ibrutinibe 420 mg ao dia. Em dez dias deste tratamento evoluiu com Hb acima de 7 g/dL, e após seis meses com Hb 12,7 g/dL, Lt 12.330/mm^3, linfócitos 7400/mm^3 e plaquetas 123 mil/mm^3. Segue em tratamento e assintomático. **Discussão:** A AHAI é um evento autoimune comum em pacientes com LLC, geralmente por produção de anticorpos do tipo IgG quentes direcionados contra as hemácias. Envolve células apresentadoras de antígenos, linfócitos B e T, citocinas pró-inflamatórias e produção dos autoanticorpos. O tratamento de condições autoimune associada a LLC é semelhante ao empregado caso ocorresse de forma espontânea. Diante da refratariedade aos tratamentos, deve ser considerado terapia direcionada para a LLC. Novos agentes terapêuticos vêm sendo estudados nesses casos, como os inibidores da tirosina quinase de Bruton (BTK). Esses atuam na inativação dos linfócitos B / plasmócitos, complemento, monócitos e macrófagos no baço e assim impedindo a destruição do eritrócito por citotoxicidade celular ou fagocitose no baço. Os dados mais extensos disponíveis até o momento são baseados em relatos de casos e em uma subanálise do estudo RESONATE de fase III (ibrutinibe vs. ofatumumabe em pacientes com LLC R/R) avaliando os efeitos desse agente em pacientes com AHAI e/ou PTI concomitantes. Nesses estudos, foi evidenciado melhora do quadro e manutenção da resposta durante um acompanhamento médio de 17,5 meses, corroborando com o caso clínico apresentado acima. **Conclusão:** A presença de AHAI é um evento autoimune comum em pacientes com LLC, com o uso de inibidor de BTK em relatos de estudos clínicos e neste caso apresentado demonstrando bons resultados e com a necessidade de seguimento para avaliação de permanência de resposta.

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MATCHING-ADJUSTED INDIRECT COMPARISON OF PIRTOBRUTINIB VS VENETOCLAX CONTINUOUS MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY CLL PREVIOUSLY TREATED WITH A COVALENT BTK INHIBITOR

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Objectives: Venetoclax-based therapy is a standard option for pts with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) previously treated with a covalent BTK inhibitor (cBTKi). Pirtobrutinib is a highly selective, noncovalent (reversible) BTKi designed to overcome the pharmacologic limitations of cBTKi and restore BTK inhibition. Pirtobrutinib has demonstrated marked efficacy and a favorable safety profile. This unanchored MAIC was designed to estimate the treatment effect of pirtobrutinib (BRUIN, NCT03740529) vs venetoclax continuous monotherapy (NCT02141282) in pts with R/R CLL previously treated with a cBTKi. **Materials and methods:** Data from pts with R/R CLL previously treated with at least 1 cBTKi and without prior venetoclax exposure who received pirtobrutinib were analyzed (n = 146). Only 1 prospective trial of venetoclax (administered as a continuous monotherapy) for pts previously treated with a cBTKi (n = 91) was identified. Progression-free survival (PFS), overall survival (OS), investigator-assessed overall response rate (ORR), and grade≥3 treatment-emergent adverse events (TEAEs) regardless of attribution were evaluated. Pt-level data from the pirtobrutinib cohort were re-weighted to match the venetoclax cohort using method of moments approach, adjusting for well-established prognostic factors reported in both studies (age, IGHV mutation status, *TP53* aberrancy, del(17p), del(11q); number of prior lines of therapy, and reason for prior cBTKi discontinuation). KaplanMeier PFS and OS curves from the venetoclax trial were digitized (using WebPlotDigitizer) for time-to-event analyses. Fishers exact test was used to compare proportional outcomes (ORR, TEAEs); time-to-event outcomes (PFS, OS) were compared using Cox regression model and log-rank test. **Results:** The median age in pirtobrutinib and venetoclax cohorts was 66.5 and 66.0 years; all other prognostic factors were well matched in both cohorts. Median follow-up was 21.3 months and 14 months for the pirtobrutinib and venetoclax cohorts, respectively. PFS and OS were comparable with no significant differences noted for pirtobrutinib versus venetoclax (both $p > 0.05$). ORR was 80% for pirtobrutinib (inclusive of PR-L) vs 65% for venetoclax ($p = 0.01$). Grade ≥3 TEAEs reported in both trials indicated that febrile neutropenia, neutropenia, anemia, and thrombocytopenia were significantly lower for pirtobrutinib vs venetoclax in adjusted analyses (all $p < 0.01$). No differences were observed for pneumonia ($p = 0.06$) or for discontinuation due to TEAEs (3% vs 7%, $p = 0.32$) in adjusted analyses. Unadjusted results were consistent with the adjusted analyses. **Conclusions and discussion:** The efficacy of pirtobrutinib was comparable to continuously administered venetoclax monotherapy in pts with R/R CLL previously treated with a cBTKi. Pirtobrutinib was associated with improved ORR and favorable overall safety profile for most TEAEs vs venetoclax. This study raises questions regarding optimal treatment sequencing of pirtobrutinib and venetoclax in cBTKi-treated CLL, but the lack of prospective direct comparisons and limited long-term follow-up preclude definitive conclusions. Randomized Phase 3 studies of pirtobrutinib in pts with CLL are ongoing. Previously presented at EHA 2023.

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