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RESEARCH

Six-year follow-up of phase II study exploring chemo-free treatment association with idelalisib and obinutuzumab in symptomatic relapsed/ refractory patients with Waldenström's macroglobulinemia

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Abstract

We present the 6-year update of a phase 2 study evaluating the combination of obinutuzumab and idelalisib in relapse/refractory Waldenstrom macroglobulinemia. The results of the REMODEL trial demonstrated interesting efficacy in a high-risk genotype profile population. The primary endpoint was achieved with a median PFS of 25.4 months (95% CI, 15.7 to 29.0). However, a major limitation of idelalisib is its toxicity. With a median follow-up of 70.9 months, median OS was still not reached, and 5-year OS was 72.9% (95% CI, 61.3 to 86.6). We confirm that *CXCR4* mutations had no impact on PFS or OS. However, *TP53* mutated patients had shorter OS. At the time of analysis, six patients are alive without relapse and 40 had progressive disease. Among the 38 patients who received a new treatment, the median time to second progression was not reached in ibrutinib treated patients (n = 17) *versus* 30.8 months in patients treated with other options (95% CI, 16.9 to NA), p = 0.005. With longer follow-up our prospective study is the first to show an impact of *TP53* mutations in patients treated with fixed duration chemo-free regimen leading to a significant shorter OS in this population. Moreover, ibrutinib remains an effective treatment after this combination. This study was registered on the clinicaltrial.gov web (NCT02962401, November 9, 2016).

Keywords Waldenstrom magroglobulinemia · Relapse/refractroy · Obinutuzumab · Idélalisib

Introduction

Over the past ten years, better understanding of the biology of Waldenström's macroglobulinemia (WM) has identified new therapeutic targets and agents [1]. Current treatment options for relapsed/refractory (R/R) patients consist of different types of drugs including immunochemotherapy (ICT), proteasome inhibitors and BTK-inhibitors (BTKi) [2]. Other emerging drugs (BCL2-inhibitors [3], anti-CXCR4 monoclonal antibodies associated with ibrutinib [4, 5]) could be an option in this population. The results of the REMODEL trial (NCT02962401) showed interesting efficacy of obinutuzumab—idelalisib combination in this high-risk genotype profile population (56.1% *CXCR4*^{MUT}, 24.4% *TP53*^{MUT}). However, a major limitation of idelalisib, a Pi3Kδ inhibitor, is its toxicity, particularly on liver and digestive tracts [6].

We report the 6-year update of idelalisib—obinutuzumab combination and evaluate the impact of mutational profiling on R/R WM patients.

Matériel and method

REMODEL was a single-arm multicenter phase II study designed to assess the efficacy and safety of idelalisib—obinutuzumab combination. The trial comprised two phases: an induction phase of six cycles during which idelalisib was administered continuously at 150 mg × 2 /d PO in combination with obinutuzumab IV 100 mg on D1, 900 mg on

These data were presented at the 11th International Workshop on Waldenström's Macroglobulinemia in Madrid, 29 October 2022 (oral presentation), and at the 43rd French Society of Hematology annual meeting, Paris, 29 March 2023 (oral poster presentation).

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D2 and 1000 mg on D8 and 15 of cycle 1, then on D1 of monthly cycles 2 to 6, followed by maintenance with idelalisib monotherapy at the same dose for 18 months. Study design details have been published [6].

The primary endpoint was progression-free survival (PFS), calculated from the date of inclusion to progression or death. Secondary endpoints included response rates (according to the IWWM-6 criteria [7]), time to next treatment (TTNT), overall survival (OS), and safety. We assessed the effect of *CXCR4* and *TP53* mutations on survival.

Gene mutation analysis is detailed in supplementary data and have been previously published. Qualitative variables are expressed in frequency and percentage; quantitative variables in mean ± standard deviation or median (range) depending on the distribution. Survival curves have been calculated with the Kaplan- Meier method and comparison made with the log-rank test.

Every participant provided their consent.

Results

Fifty patients were screened, 49 analyzed between February 2017 and July 2018. Patient distribution and treatment exposure are displayed in Supplementary Fig. 1 (previously published). Among them, one died (unknown cause) before any treatment and 48 received the combination induction. Among the 48 treated patients, 14 interrupted the induction phase (seven for progressive disease and seven for adverse events (AE)). Among the 27 patients who started maintenance, nine completed and 18 stopped (5 for progression, 13 for AE). The median number of prior lines of treatment (ICT in 90% of cases) was one (1–3), with three patients previously treated with ibrutinib. The mutation profile was 46 (93.9%) *MYD88*^{L265P} mutated, 27 (56.1%) *CXCR4* mutated, and 11 (24.4%) *TP53* mutated. Baseline characteristics of patients and mutations are listed in Supplementary Table 1 (previously published).

The primary endpoint was achieved with a median PFS of 25.4 months (95% CI, 15.7 to 29.0). With a median follow-up of 70.9 months (95% CI, 69.2 to 74.7), the median OS was still not reached, and the 5-year OS was 72.9% (95% CI, 61.3 to 86.6). Sixteen patients died: six from progression (two after the first relapse and four after the second), one from Richter syndrome, four from infection, one from stroke, one from gliobastoma, one from unspecified deterioration in general condition, and two from unknown causes (including 1 before any treatment). With longer follow-up, we confirm that *CXCR4* mutations had no impact on PFS or OS with a median PFS of 25.7 (95% CI, 12.4 to 42.7) *versus* 25.3 (95% CI, 14 to 50.8) months (p = 0.9); 5-year PFS rates of 24.0% *vs* 15.4% and with 5-year OS rates of 69.2% (95% CI, 53.6 to 89.5) *versus* 80.9% (95% CI, 65.8 to 99.6), p = 0.68, in *CXCR4*^{MUT} patients *versus* *CXCR4*^{WT} patients, respectively (Fig. 1a, b).

However, *TP53* mutated patients had shorter OS with median time of 53.5 months *versus* not reached and with a 5-year OS at 45.5% (95% CI, 23.8 to 86.8) *versus* 82.3% (95% CI, 70.3 to 96.2), p = 0.005 (Fig. 1c, d). Only *TP53* mutations were screened by NGS. Of the 11 patients with *TP53* mutations, 9 relapsed and 7 died, including 4 from progression. Of the 11 other patients who died and were not *TP53* mutated, only 2 had progressive disease.

At the time of analysis, six patients are still alive without relapse and 40 had progressive disease. Among the 38 patients who received a new line of therapy, the median PFS was not reached (Fig. 2a) and 3-year PFS was 69.4% (95% CI, 55.2 to 87.4). According to treatment, the median time PFS2 was not reached in ibrutinib-treated patients ($n = 17$) *versus* 30.8 months in patients treated with other options [$n = 21$ including 16 ICT (13 bendamustine + rituximab)] (95% CI, 16.9 to NA), p = 0.005 (Fig. 2b). Patients treated with ibrutinib had a 3-year PFS2 of 93.8% (95%CI, 82.6 to 100) *versus* 47.2% (95%CI, 28.3 to 78.6) for those receiving with other treatments. Twelve secondary relapses were observed including two patients treated with ibrutinib.

There were 13 secondary cancers in 12 patients: eight cutaneous, one glioblastoma, one bladder, two prostate and one myelodysplasia (MDS) evolving into acute myeloid leukemia.

Discussion

The updated results of this trial with a 6-year median follow-up confirmed that the fixed-duration idelalisib—obinutuzumab combination is an effective relapse treatment despite the initial toxicity. There was no evidence of delayed toxicity. Median PFS was shorter (25.4 months) than with continuous BTKi therapy: 54% at 5 years with ibrutinib [8], 82% at 24 months with acalabrutinib [9]) and 78% at 42 months with zanubrutinib [10]) in R/R setting. Moreover, ibrutinib remains an effective treatment after this combination with a 3-year PFS of more than 90%. The treatment strategy of administrating a BTKi after or before a Pi3K inhibitor is not new in the treatment of B-cell malignancies and has been proposed in patients with indolent non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). Ibrutinib and idelalisib were the first two approved B-cell receptor pathway inhibitors [11]. However, WM is a specific entity and the results of trials in similar pathologies cannot be extrapolated. Studies dedicated to this disease are essential. Indeed, in a retrospective single-center study, ibrutinib-withdrawal symptoms (most commonly fever, body aches, arthralgia and night sweats) were reported in 19% of WM-patients who underwent an ibrutinib pause. One-third of patients

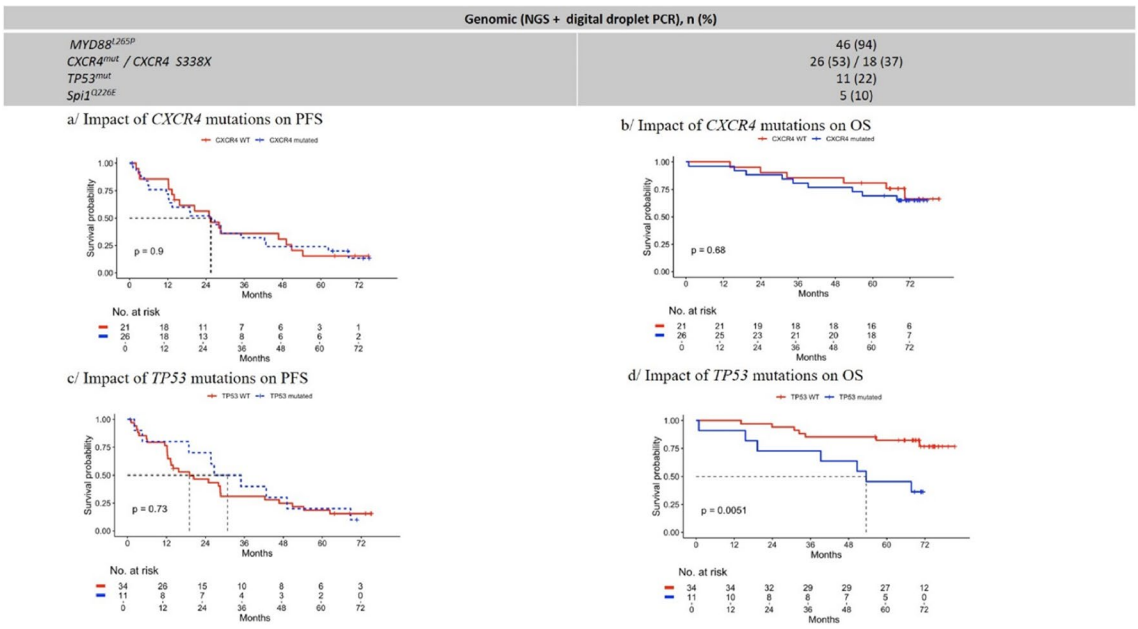

Fig. 1 Impact of *CXCR4* (**a**, **b**) and *TP53* (**c**, **d**) mutations on survival rates. Blue line: presence of mutation (MUT), red line: absence of mutation (WT). PFS: progression-free survival, OS: overall survival

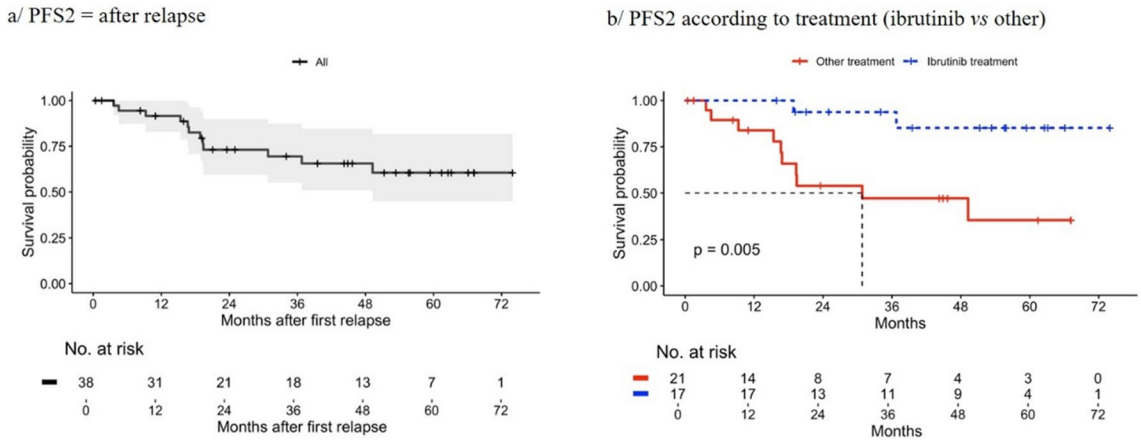

Fig. 2 Progression-free survival after relapse (PFS2). PFS: progression-free survival, *vs: versus*

presented symptoms in the context of progressive disease, while two-thirds presented symptoms with no evidence of disease progression [12]. Tolerability of ibrutinib/venetoclax (IV) is also different in WM and CLL patients: in the multicenter Phase II CAPTIVATE, first-line fixed-duration IV combination achieved deep and durable responses in patients with CLL or SLL (with 30-month PFS rates ≥ 95%) [13]. In WM patients, Castillo et al. reported a higher-than-expected rate of ventricular arrhythmia with this combination (occurring in 4 patients, including 2 deaths), which led to early termination of the trial, although results were encouraging with very good partial response achieved in 42% of patients, PFS and OS of 76% and 96%, respectively [14].

The other published fixed-duration, chemo-free approach using novel agents demonstrated a 24-month PFS of 80% in R/R patients treated with venetoclax monotherapy [3]. These results appear to be highly promising, although a notable decline in the PFS rate was observed upon cessation of treatment. This finding suggests that combining drugs may be a preferable option in fixed-duration strategy.

The benefits of a fixed-duration, chemo-free combination include a reduction in adverse effects during the treatment-free period, a reduction in a potential clonal selection pressure and limited costs. Our results do not demonstrate a lack of efficacy, but rather that the BTK inhibitors may produce longer PFS outcomes if taken continuously. To overcome these limitations in the future, the current clinical trials are assessing the efficacy of BTKis as part of combination regimens: BTKis are being tested in combination with a variety of others molecules, including targeted agents (ibrutinib + BCL2i APG-2575 [NCT04260217], zanubrutinib + BGB-11417 [NCT06547866], ibrutinib + CXCR4 inhibitor mavorixafor [NCT04274738]), monoclonal antibodies (ibrutinib + anti-CXCR4 monoclonal antibody ulocuplumab [NCT03225716]),proteasome inhibitors (ibrutinib + bortezomib + rituximab [NCT03620903], zanubrutinib + ixazomib [NCT04463953], ibrutinib + carfilzomib [NCT04263480]). The discrepancy in the availability of treatments across different geographical areas represents a significant obstacle to the utilization of the obinutuzumab—idelalisib combination. Indeed, apart from BTKi, few drugs have been approved by the FDA or the EMA in recent years. It is therefore important to continue developing options with different mechanisms of action in clinical trials. Idelalisib is a first-generation PI3K inhibitor that has demonstrated efficacy in patients with R/R WM, although this is accompanied by significant toxicities. The development of next-generation agents with more targeted activity and a reduced delayed onset of action may offer an alternative solution.

To the best of our knowledge, only one prospective study to date has investigated the impact of *TP53* mutations in WM patients treated with continuous targeted agents. The phase 3 ASPEN trial compared zanubrutinib and ibrutinib [15]. Samples were available for 98 and 92 patients treated with zanubrutinib and ibrutinib, respectively. A *TP53* mutation was detected in 24.8% of cases in population comprising both treatment-naive and relapsed patients. A significantly lower major response rate was observed in the *TP53*-mutated population for patients treated with ibrutinib (63.6% *vs* 85.7%; p = 0.04) but not for those treated with zanubrutinib (80.8% *vs* 81.9%; p = 0.978). Additionally, a longer PFS was noted for those treated with zanubrutinib although it did not reach statistical significance (not reached *vs* 44.2 months; HR, 0.66; p = 0.37, respectively). In the present trial, *TP53*-mutated patients exhibited a shorter median OS of 53.5 months *versus* not reached and a lower 5-year OS of 45.5% (95% CI, 23.8 to 86.8) *versus* 82.3% (95% CI, 70.3 to 96.2), p = 0.005. The present data set does not allow for the demonstration of an impact of *TP53* mutations on PFS, which considers the first relapse. *TP53* mutations remain a negative prognostic marker which has an impact on OS, which takes into account subsequent relapses. As with ICT [16], these data indicate that deficiencies in *TP53* lead to an unfavorable prognosis in WM patients treated with targeted therapies.

Conclusion

A longer follow-up period allows our prospective study to demonstrate, for the first time, the impact of *TP53* mutations in patients treated with a fixed-duration, chemo-free regimen, which leads to a significantly shorter OS in *TP53*-mutated patients. In contrast to what is observed with ibrutinib, *CXCR4* mutations did not affect PFS or OS. Nevertheless, given the potential efficacy of this class of agents, next-generation PI3K inhibitors in combination with obinutuzumab may limit the toxicity issues observed in this phase II trial and may prove an effective treatment option, particularly in WM patients who have previously undergone treatment with both BTKi and BCL2 inhibitors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-024-06076-1.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989), the 48th (Somerset West, 1996), the 52nd (Edinburg, 2000) World Medical Assemblies, the 64th

(Fortazela, 2013) notes for clarification added by the WMA General Assembly on paragraph 29 (Washington 2002) and on Paragraph 30 (Tokyo 2004) and amendment laid down by the 59th (Seoul, October 2008) World Medical Assemblies.

The trial was approved by the following competent authorities: health autority (ANSM) autorisation date: August 25, 2016 and ethics comittee (CPP OUEST III): August 31, 2016.

Competing interests The authors declare no competing interests.

References

1. Garcia-Sanz R, Varettoni M, Jiménez C, Ferrero S, Poulain S, San-Miguel JF, Guerrera ML, Drandi D, Bagratuni T, McMaster M, Roccaro AM, Roos-Weil D, Leiba M, Li Y, Qiu L, Hou J, De Larrea CF, Castillo JJ, Dimopoulos M, Owen RG, Treon SP, Hunter ZR (2023) Report of Consensus Panel 3 from the 11th International workshop on Waldenström's Macroglobulinemia: Recommendations for molecular diagnosis in Waldenström's Macroglobulinemia. Semin Hematol 60(2):90–96
2. Castillo JJ, Advani RH, Branagan AR, Buske C, Dimopoulos MA, D'Sa S et al (2020) Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. Lancet Haematol 7(11):e827–e837
3. Castillo JJ, Allan JN, Siddiqi T, Advani RH, Meid K, Leventoff C et al (2022) Venetoclax in Previously Treated Waldenström Macroglobulinemia. J Clin Oncol 40(1):63–71
4. Treon SP, Meid K, Hunter ZR, Flynn CA, Sarosiek SR, Leventoff CR et al (2021) Phase 1 study of ibrutinib and the CXCR4 antagonist ulocuplumab in CXCR4-mutated Waldenstrom macroglobulinemia. Blood 138(17):1535–1539
5. Treon SP, Buske C, Thomas SK, Castillo JJ, Branagan AR, Dimopoulos MA et al (2021) Preliminary clinical response data from a phase 1b study of mavorixafor in combination with ibrutinib in patients with Waldenstrom's acroglobulinemia with *MYD88* and *CXCR4* mutations. Blood 138(Supplement 1):1362
6. Tomowiak C, Poulain S, Herbaux C, Perrot A, Mahé B, Morel P et al (2021) Obinutuzumab and idelalisib in symptomatic patients with relapsed/refractory Waldenström macroglobulinemia. Blood Adv 5(9):2438–2446
7. Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G et al (2013) VIth International Workshop on Waldenström macroglobulinaemia. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. Br J Haematol. 160(2):171–6
8. Treon SP, Meid K, Gustine J, Yang G, Xu L, Liu X et al (2021) Long-Term Follow-Up Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenstrom Macroglobulinemia. J Clin Oncol. 39(6):565–575
9. Owen RG, McCarthy H, Rule S, D'Sa S, Thomas SK, Tournilhac O et al (2020) Acalabrutinib monotherapy in patients with Waldenstrom macroglobulinemia: a single-arm, multicentre, phase 2 study. Lancet Haematol 7(2):e112–e121
10. Dimopoulos MA, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G et al (2023) Zanubrutinib Versus Ibrutinib in Symptomatic Waldenstrom Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study. J Clin Oncol 41(33):5099–5510
11. Jerkeman M, Hallek M, Dreyling M, Thieblemont C, Kimby E, Staudt L (2017) Targeting of B-cell receptor signalling in B-cell malignancies. J Intern Med. 282(5):415–428
12. Castillo JJ, Gustine JN, Meid K, Dubeau T, Severns P, Treon SP (2018) Ibrutinib withdrawal symptoms in patients with Waldenström macroglobulinemia. Haematologica. 103:e307–e310
13. Tam CS, Allan JN, Siddiqi T, Kipps TJ, Jacobs R, Opat S et al (2022) Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood 139(22):3278–3289
14. Castillo JJ, Branagan AR, Sermer D, Flynn CA, Meid K, Little M et al (2024) Ibrutinib and venetoclax as primary therapy in symptomatic, treatment-naive Waldenstrom macroglobulinemia. Blood 143(7):582–591
15. Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G et al (2024) Biomarker analysis of the ASPEN study comparing zanubrutinib with ibrutinib for patients with Waldenstrom macroglobulinemia. Blood Adv 8(7):1639–1650
16. Poulain S, Roumier C, Bertrand E, Renneville A, Caillault-Venet A, Doye E et al (2017) TP53 mutation and its prognostic significance in Waldenstrom's macroglobulinemia. Clin Cancer Res. 23(20):6325–6335

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