https://www.scientificarchives.com/journal/journal-of-clinical-haematology

Journal of Clinical Haematology Short Communication

Atezolizumab Monotherapy as First-line Treatment in Patients with Advanced *BRAF*^{V600} Wild-type Melanoma

Juliano C. Coelho[1,2*], Taiane F. Rebelatto[1,2], Rodrigo R. Pereira[1,2,3], Pedro E. R. Liedke[1,2,3], Andrea B. Zanon[1], Sergio J. Azevedo[1,2,3]

[1]Unidade de Pesquisa Clínica em Oncologia, Porto Alegre, Brazil

[2]Oncology Department, Oncoclinicas Group, Porto Alegre, Brazil

[3]Department of Oncology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

[*]Correspondence should be addressed to Juliano C. Coelho; juliano.oncologia@gmail.com

Received date: May 20, 2021, **Accepted date:** June 28, 2021

According to the GLOBOCAN [1], approximately 324,635 new cases and 57,043 deaths due to melanoma were estimated worldwide for 2020. In parallel to this, there has been a significant improvement over the last decade in treatment options for advanced melanoma, such as molecularly targeted therapies and immune-checkpoint inhibitors. These treatments have had a positive impact on mortality rates. The main role of molecularly targeted therapies is to treat those with *BRAF* ^{V600}-mutated melanoma, while immune-checkpoint inhibitors - Programmed cell death 1 protein (PD-1), Programmed cell death-ligand 1 (PD-L1), and antibody directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) - play an important role in both *BRAF* ^{V600}-mutated and *BRAF*^{V600} wild-type (WT) melanoma [2-6].

Immunotherapy is the standard treatment for patients with advanced *BRAF*^{V600}-WT melanoma, which represents approximately 40-60% of cases. Ipilimumab, an anti-CTLA-4 versus chemotherapy showed overall survival (OS) benefits [7]. However, PD-1 checkpoint inhibitors have become the preferred first-line treatment option due to its better safety profile and higher activity. The PD-1 checkpoint inhibitors agents can be used alone or in combination with anti CTLA-4 [2-4]. More recently, the anti-PD-L1 antibody atezolizumab has been considered as a first-line treatment alternative for advanced *BRAF*^{V600}-WT melanoma [8].

Atezolizumab, as an anti-PDL1 inhibitor, may offer similar efficacy with theoretically better safety profile compared to anti-PD1 agents. To evaluate the preliminary efficacy, safety, and pharmacokinetics of atezolizumab monotherapy in untreated patients with *BRAF*^{V600}-WT metastatic or unresectable locally advanced melanoma, a phase Ib trial was performed.

Here we discuss the cohort C results of an open label, multicohort, global, multicenter, phase 1b study (NCT03178851). Patients with previously untreated, unresectable or metastatic histologically confirmed stage III or IV melanoma, with known *BRAF*^{V600} wild type, were enrolled to receive atezolizumab monotherapy. Patients had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; Eastern Cooperative Oncology Group performance status 0 or 1; adequate hematologic and organ function. Patients who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease were excluded from the study.

The co-primary end points for the study were confirmed objective response rate (ORR - proportion of patients who had complete response [CR] or partial response [PR] on two consecutive occasions 4 weeks apart) and disease control rate (DCR - proportion of patients with CR, PR or stable disease [SD] at week 16), both assessed by the study investigator per RECIST version 1.1. Tumor assessments were also conducted by an independent review committee (IRC). Progression-free survival (PFS), OS, and safety were secondary end points. Patients were treated with atezolizumab 1,200 mg intravenously every 3 weeks until investigator-determined disease progression, unacceptable toxicity, or death, whichever occurred first.

From June/2017 through December/2018, a total of 52 patients were enrolled in cohort C, in 17 centers in

Europe, South America, and South Africa. At database lock on September 21, 2020, the overall study population had been followed up for a median of 13 months (1–26 months) and the most common reason for study discontinuation was progressive disease (27 patients [59%]). Baseline demographic and disease are summarized in Table 1. The median age was 60.5 years, most patients were male (67%), had lactate dehydrogenase (LDH) levels less than or equal to normal (75%), without liver metastases (81%), and had not received adjuvant treatment (77%).

Parameters	Cohort C (n: 52 patients)
Age, years, median (range)	60.5 (37–82)
Sex, *n* (%)	
Male	35 (67)
Female	17 (33)
ECOG performance status, *n* (%)	
0	23 (44)
1	29 (56)
Staging †, *n* (%)	
M0	2 (4)
M1a	16 (31)
M1b	18 (35)
M1c	16 (31)
Lactate dehydrogenase level, *n* (%)	
>ULN	12 (23)
≤ULN	39 (75)
Unknown/missing	1 (2)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; ULN: Upper Limit of Normal.

† Per *American Joint Committee on Cancer Staging Manual*, 7th edition.

The median time from initial diagnosis to study entry was 361 days (56-3440). The median number of atezolizumab doses received during the study was 13 (range, 1-37), with a median treatment duration of 8.8 months (range, 0-25 months). Twelve patients (23%) missed at least one dose. No dose reduction of atezolizumab was allowed and a dose intensity of 100% per protocol was achieved.

According to modified RECIST version 1.1 criteria assessed by the study investigator 4 patients (7.7%) had complete responses, 16 patients (30%) had partial responses, and 11 patients (21%) had stable disease. The objective response rate assessed by the investigators was 35% (range 25.3-52,9%) and the disease control rate according to the investigator and by the IRC was 46% (range 32.2 – 60.5%) and 38% (range 24.3 – 54.5%), respectively. At the time of the data base lock, 16 patients (30%) continued to present ORR. The median PFS was 3.7 months (95% CI, 2.1–7.4) according to the investigators, similar of the analysis of the IRC (3.7 months; 95% CI, 2.1–11.7). A total of 25 patients (48%) died, with an OS of 22 months (95% CI, 11.7 – NE).

Subgroup analyses showed consistent results with those of the primary analysis. Among the 26 patients with positive PD-L1 status (immune cells [ICs] 1/2/3), objective response was achieved in 9 patients (35%), of those, 1 patient (4%) had complete response. The disease control in this subgroup was 46% with a PFS assessed by the IRC was 3.7 months (95% CI, 2.1–NE). Among the patients with LDH levels less than or equal to the upper limit of normal, 16 patients (41%) had objective responses, with 3 (9%) complete responses and 13 (32%) partial responses. A DCR of 49% and a median PFS as assessed by the IRC of 3.9 months (95% CI, 2.3–NE) was achieved in this subgroup.

Atezolizumab was a well-tolerated therapy and most (56%) of the adverse events (AE) were mild or moderate (grade 1-2). Although all patients (100%) presented at least one side effect, the proportion of atezolizumab related adverse events were 83%. Grade ≥ 3 AEs occurred in 23 patients (44%); hypertension (15%), anemia (6%), and lipase increased (6%) were the most common. Three patients (6%) discontinued atezolizumab as consequence of an AE.

Similarly, to previous reported studies with anti-PD1 agents, atezolizumab monotherapy, as first-line treatment in patients with advanced *BRAF*^{V600} wild-type melanoma, showed high anti-tumoral activity and safe profile. In addition, atezolizumab has been assessed in combination with targeted therapies. In the phase 3 IMspire150 trial, atezolizumab was evaluated in combination with the MEK inhibitor cobimetinib and the BRAF inhibitor vemurafenib showing significant improvement in PFS (15.1 *vs* 10.6 months; hazard ratio [HR] 0.78; 95% CI 0.63–0.97; p=0.025) when compared with vemurafenib and cobimetinib in patients with BRAFV600 mutation. On the other hand, in the phase 3 IMspire 170 trial, in which atezolizumab plus the MEK inhibitor cobimetinib was compared with pembrolizumab in *BRAF*^{V600} wild-type patients did not meet the primary endpoint [9,10].

In conclusion, atezolizumab monotherapy showed high objective response and disease control rates in patients with *BRAF*^{V600} wild-type melanoma. Aside from its clinical efficacy, no safety concerns were identified. Considering the results of this study as well as prior studies with atezolizumab combinations, further evaluations in phase 3 trials are warranted to determine the best treatment option and sequence for patients with advanced melanoma.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021 May;71(3):209-49.

2. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. The Lancet Oncology. 2019 Sep 1;20(9):1239-51.

3. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. New England Journal of Medicine. 2015 Jan 22;372(4):320-30.

4. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. New England Journal of Medicine. 2019 Oct 17;381(16):1535-46.

5. Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, De Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Annals of Oncology. 2017 Jul 1;28(7):1631-9.

6. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. New England Journal of Medicine. 2014 Nov 13;371(20):1867-76.

7. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New England Journal of Medicine. 2011 Jun 30;364(26):2517-26.

8. de Azevedo SJ, de Melo AC, Roberts L, Caro I, Xue C, Wainstein A. First-line atezolizumab monotherapy in patients with advanced BRAFV600 wild-type melanoma. Pigment Cell & Melanoma Research. 2021 Jan 21; 00:1-5.

9. Gutzmer R, Stroyakovskiy D, Gogas H, Robert C, Lewis K, Protsenko S, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): Primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2020 Jun 13;395(10240):1835-44.

10. Gogas H, Dreno B, Larkin J, Demidov L, Stroyakovskiy D, Eroglu Z, et al. Cobimetinib plus atezolizumab in BRAFV600 wild-type melanoma: primary results from the randomized phase III IMspire170 study. Annals of Oncology. 2021 Mar 1;32(3):384-94.