Bempegaldesleukin Plus Nivolumab in Untreated Advanced Melanoma: The Open-label, Phase 3 PIVOT IO 001 Trial Results

JCO.23.00172R1 Supplemental Material
PIVOT IO 001 Plain Language Summary

Why was the PIVOT IO 001 study performed?

- New treatments for advanced melanoma have improved patient outcomes[1]
- Immunotherapies, drugs that activate a person's immune system (the body's natural defense system), are a type of treatment that can help shrink tumors and lengthen patient survival[1,2]
- Nivolumab (NIVO) and interleukin-2 (IL-2) are immunotherapies that can be used to treat melanoma and other cancers[3,4]
    - Bempegaldesleukin (BEMPEG) is an alternative form of IL-2, which is being studied to learn if it can activate a person's immune system to fight cancer in a way like IL-2[5,6]
    - Because NIVO and BEMPEG activate the immune system in different ways, it was tested to learn if using them together could improve outcomes beyond either drug alone
- A phase 2 study, PIVOT-02, showed that using BEMPEG and NIVO together had promising outcomes in patients with advanced melanoma[7]
- This current, randomized phase 3 study (PIVOT IO 001)[8] was performed in a larger number of patients than the phase 2 study, to better understand the efficacy and safety of BEMPEG and NIVO compared with NIVO alone in patients with advanced melanoma

Who took part in the study?

- A total of 783 patients with advanced melanoma were enrolled in the PIVOT IO 001 study and, among all patients,
    - Most (~90%) had not received drug treatment for melanoma, before enrollment
    - 58% were men, and 42% were women
- At the time of data analysis, 387 patients received BEMPEG and NIVO, and 382 patients received NIVO alone
    - Overall, study treatment (BEMPEG and NIVO or NIVO alone) was discontinued by approximately 60% of patients, largely because their cancer was getting worse

What were the results?

- The combination of BEMPEG and NIVO, compared with NIVO alone, did not provide additional antitumor activity (*Supplemental figure*); results of the study included the following:
    - Objective response rate (percentage of patients whose tumor partially or completely shrank in size after receiving treatment)
    - Progression-free survival (time from the start of the study until the cancer became worse)
    - Overall survival time and the proportion of patients alive at the time the results were analyzed
- No unexpected side effects were reported
    - More people who received BEMPEG and NIVO had side effects related to the study treatment compared with those who received NIVO alone
    - Specifically, the risk of blood- or brain-related side effects (such as blood clots or bleeding events in the brain) was higher in people who received the combination of BEMPEG and NIVO

How can we better understand these results?

- Cancer cells might have different molecules (proteins) on their surface than non-cancer cells, which can disrupt the normal function of a person's immune system; this includes preventing the immune system from killing tumor cells
    - After recognizing a tumor cell, the immune system might respond by increasing the number of overall immune cells, including those that have the potential to kill tumor cells (for example, CD8 T cells and natural killer cells)
    - At the same time, cancer cells may block this response by
        1. Having proteins on their surface that prevent the immune system from recognizing tumor cells
        2. Increasing the number of regulatory T cells that help suppress (slow down or stop) an immune response
- PIVOT IO 001 researchers wanted to learn if there were any differences in tumor factors or immune system activity in patients who received BEMPEG and NIVO instead of NIVO alone[6]
    - To do this, blood and tumor biopsy samples were collected from patients before and during treatment
- Initially, the total number of immune cells in the blood of people treated with BEMPEG and NIVO increased more than it did in people treated with NIVO alone; the following additional details were learned with further investigation[9]:
    - Compared with levels before starting treatment, BEMPEG and NIVO increased CD8 T cells and natural killer cells, but also increased the number of regulatory T cells (cells that decrease and suppress the activity of CD8 T cells)
    - The initial increase in dividing (multiplying) and activated CD8 T cells by BEMPEG and NIVO decreased over time
    - Antitumor immune cells in the tumor and its surrounding environment did not significantly differ between treatment groups, suggesting that the addition of BEMPEG to NIVO did not increase the number of tumor-killing immune cells compared with the use of NIVO alone
- The following are potential reasons for the lack of improved outcomes with the use of BEMPEG and NIVO compared with NIVO alone[9]:
    - Observations in the peripheral blood suggest increases in some cells that suppress an immune response (ie, regulatory T cells with CD4 and CD25 on their surface) with the combination, especially in later treatment cycles. At the same time, other factors that activate an immune response (ie, CD8 T cells) were decreased
    - Over time, the body's ability to respond to BEMPEG and NIVO is reduced, resulting in less activation of antitumor T cells
    - Inability of T cells that are growing in number in the blood to relocate to the tumor itself

What were the main conclusions reported by the researchers?

- Compared with NIVO alone, the combination of BEMPEG and NIVO did not improve outcomes for patients with advanced melanoma
- These results may advise future development of IL-2–based treatments and other immunotherapies to treat melanoma or other solid tumors

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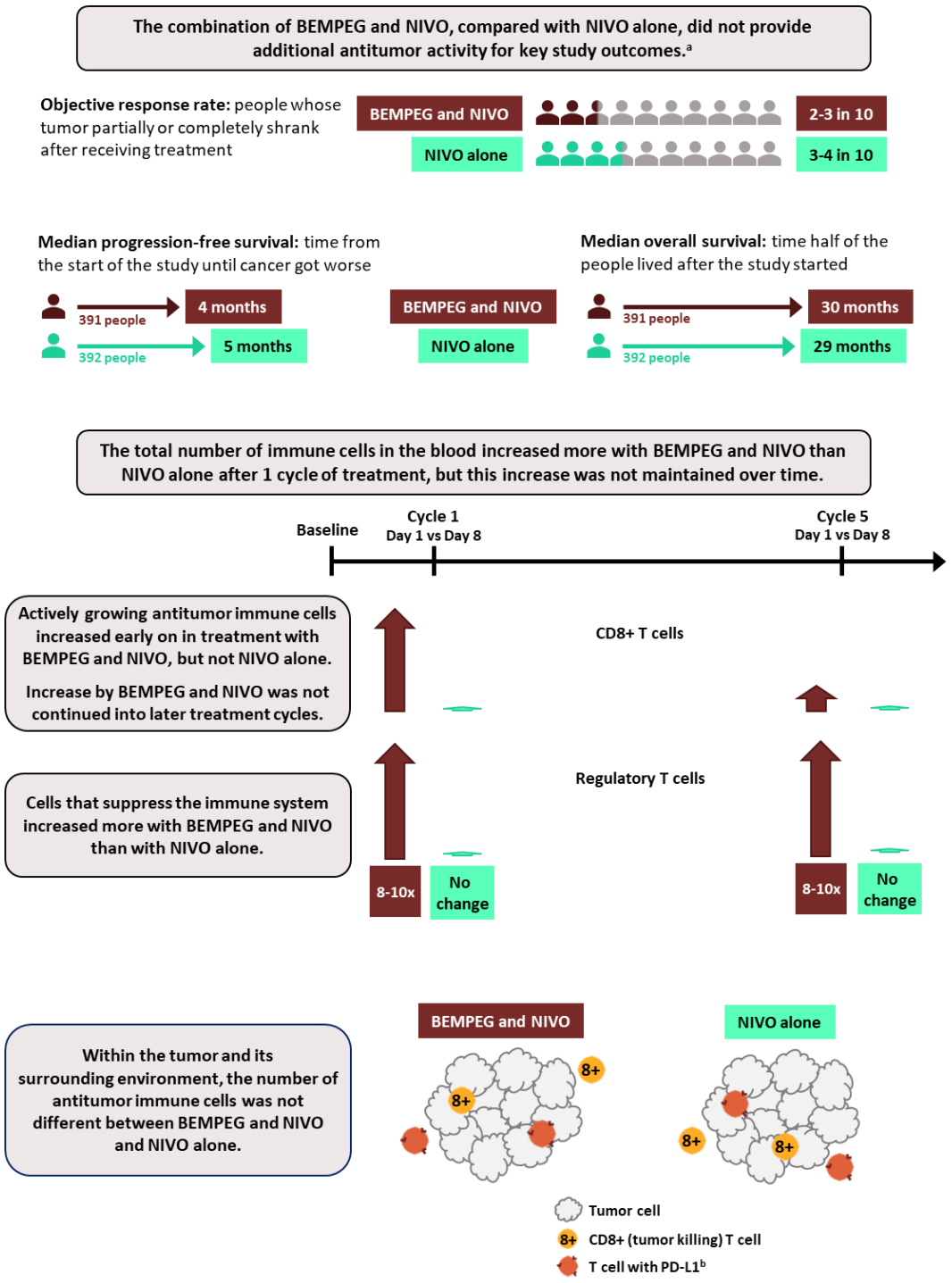
Supplemental Figure: Key outcomes from the PIVOT-IO 001 study.



[a]At the time data were collected (February 1, 2022), one-half of the people had received study treatment for 4 months. Overall survival and progression-free survival data were gathered from all of the patients enrolled in the study, along with response rate data from all patients enrolled who had at least 6 months of follow-up. [b]Cells that have PD-L1 on their surface interact with cells that have PD-1, which then slows down the immune response. NIVO covers PD-1 to stop it from interacting with PD-L1, which keeps the immune system active to fight tumor cells.