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Letter to the Editor

FDA precedents in drug approvals: Contradiction in promoting more treatment options

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Dear Editor

On October 22th, 2021, Agenus® voluntarily withdrew its anti-PD1 monoclonal antibody balstilimab's submission for a Biologics License Application (BLA) to the US Food and Drug Administration (FDA) in relapsed cervical cancer [1]. This announcement came after the regular FDA approval of pembrolizumab in the front-line, in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS $\geq$ 1), and the simultaneous conversion of a prior accelerated approval to regular approval as a single agent for patients with advanced or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS $\geq$ 1) [2].

Balstilimab had been poised to receive accelerated approval in relapsed disease based on similar data to pembrolizumab's accelerated approval (20% response rate with balstilimab in PD-L1 positive patients vs. 14.3% with pembrolizumab). Yet, the conversion of pembrolizumab's approval closed the window of opportunity for balstilimab, in a surprise to industry analysts. One issue was timing: the planned BLA application for balstilimab would have occurred by December 2021, while the FDA due date for pembrolizumab's regular approval was slated to occur beyond this (January 2022). As such, the agency could have permitted both approvals, but sped up the former decision resulting in balstilimab being blocked from the market.

The regulatory history of balstilimab shows contradictions in the FDA's thinking. Three things are currently

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true at the FDA. First, multiple next-in-class drugs can receive accelerated approval with virtually identical data in a single line. Second, a drug can receive regular approval in a tumor type in the front-line setting, but the FDA still allows subsequent accelerated approvals of that class in a latter line. Third, if a drug has accelerated approval in a latter line then gains regular approval in the front line, thereby satisfying the post marketing commitment, no further accelerated approvals in the latter line are permitted (balstilimab). These three rules create an odd tension where the agency errs on the side of introducing competition in most cases, while capriciously closing the door to new approvals in other cases using data from a different drug in a different line.

Let's consider these three precedents. First, recall the history of PD1/PDL1 antibodies in second line urothelial cancer. The FDA granted accelerated approval to atezolizumab (May 2016), nivolumab (February 2017), durvalumab (May 2017), and avelumab (May 2017). Multiple next-in-class drugs being available did not close the opportunity to competitors. Ultimately, avelumab was the first drug to achieve approval after initial therapy in the maintenance setting (a prior line), in June 2020.

Second, consider extensive-stage small-cell lung cancer (ESCLC). Atezolizumab was granted regular approval on March 18, 2019, in combination with carboplatin and etoposide, for the first-line treatment of ESCLC. The approval was based on the IMpower 133 trial showing an improvement in overall survival (OS) with a median OS being 12.3 months in the atezolizumab arm as compared with 10.3 months in the control arm (hazard ratio for death = 0.70; 95% CI: 0.54, 0.91; p = 0.0069) [3]. On June 17, 2019, pembrolizumab was granted accelerated approval for patients with ESCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. This approval was based on a pooled analysis of two multi-cohort trials (KEYNOTE-158 Cohort G or KEYNOTE-028 Cohort C1) and mainly based on the overall response rate (ORR) of 19% in 83 patients. In ESCLC, pembrolizumab had a post-marketing commitment to show a survival advantage in the front line. Yet, the KEYNOTE-604 confirmatory phase III trial, in the front-line setting, did not improve OS, and pembrolizumab was withdrawn from this indication on March 1, 2021, by Merck [4]. In this case, a front-line approval of a checkpoint inhibitor did not close the opportunity to a rival.

Now, consider the case of balstilimab. On June 12, 2018, pembrolizumab was granted accelerated approval for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS $\geq$ 1) as determined by an FDA-approved test [5]. The accelerated approval was based on an ORR of 14.3% in 77 patients. As with pembrolizumab in ESCLC, regular approval for pembrolizumab in cervical cancer hinged on a frontline randomized trial with a goal date of January 2022. Balstilimab, competing in the second-line setting, successfully completed 3 FDA pre-approval inspections, scheduling the Prescription Drug User Fee Act (PDUFA) on December 16, 2021. Balstilimab had applied for accelerated approval in the same setting as pembrolizumab first accelerated approval, as is a common practice, and the application was supported based on 20% response rates in PD-L1 positive patients [6].

On October 13, 2021, four months earlier than the FDA goal date, pembrolizumab was granted regular approval in the frontline setting, based on an RCT in this line. The accelerated approval for relapsed disease was converted into regular approval, though no further data was brought regarding efficacy of the drug in the second line setting. This last approval closed the window for balstilimab application.

The front-line approval of pembrolizumab in cervical cancer is identical to the situation of atezolizumab in ESCLC, though the latter did not block competition. The second-line accelerated approval of pembrolizumab for cervical cancer is identical to the situation of atezolizumab in urothelial cancer, though that did not block nivolumab, durvalumab, and avelumab. Yet, somehow the combination of these 2 events was able to keep balstilimab from market.

A tension exists in the FDA's thinking. A randomized trial in the front-line can convert a subsequent line's accelerated approval to regular approval and block competition in the cervical cancer example, while a randomized trial in the front line does not block a subsequent line approval in the case of SCLC, and we can have infinite drugs receive accelerated approval with largely similar data (urothelial cancer).

One may argue that the distinguishing feature is that in the cervical cancer example, pembrolizumab had already demonstrated a response rate in a latter line and held accelerated approval, while this did not occur with atezolizumab, but this distinction is arbitrary. Balstilimab is able to generate a response rate in the latter line in cervical cancer just as pembrolizumab was able to generate a response rate in a latter line in SCLC. Arguably, patients in both cancers should now receive checkpoint inhibition in the front-line setting, based on RCTs data. For the few patients who escaped this treatment, we simply have fewer options in the case of cervical cancer.

There are several ways to resolve the tension. The FDA can limit the number of me-too drugs it grants accelerated approval, after all, the "unmet need" has closed. Alternatively, the FDA could demand confirmatory randomized trials be performed in the same line as initial accelerated approval. Had they done that, this would mean balstilimab was blocked for a logical reason—pembrolizumab had shown what it could not,

improved OS in the latter line. The status quo however appears untenable. The FDA decision making uses an arbitrary regulatory fact to punish a small biotechnology company. Implications for this on investment and innovation must be considered.

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Conflict of interest statement

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