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# Will the real FDA please stand up

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**The FDA's shifting stance on the efficacy of PD-(L)1 drugs in first-line urothelial bladder cancer does little for those worried about the agency loosing its teeth.**

The US FDA summoned up some courage last week. After pandering to makers of anti-PD-(L)1 drugs and issuing approvals galore – some backed by distinctly flimsy evidence – it warned that Tecentriq and Keytruda might not, after all, be beneficial in first-line urothelial bladder cancer.

Anyone thinking that this spells a new, tough stance from the US regulator should think again, however. The mealy-mouthed safety alert stops well short of an approval revocation and, remarkably, comes over a year after it first became apparent that some anti-PD-(L)1s likely have no survival benefit in this cancer.

In the meantime, five such drugs are still available in the US for urothelial bladder cancer: Roche's Tecentriq, Merck & Co's Keytruda, Bristol-Myers Squibb's Opdivo, Astrazeneca's Imfinzi and Pfizer/Merck KGaA's Bavencio can all be prescribed second line, and the first two can also be given to first-line, chemotherapy-ineligible patients.

Most of the approvals were rushed through during a wild period in 2016/17 when PD-(L)1 blockade looked like it might cure every cancer going. The wake-up call came on May 10, 2017, when Roche's second-line Imvigor-211 trial showed Tecentriq to have no advantage over chemo in terms of survival or response rates.

Since Tecentriq's accelerated green light was conditional on a confirmatory trial, failure of Imvigor-211 should logically have resulted in revocation of the approval (*Tecentriq failure puts accelerated approval in a spin, May 10, 2017*). Perhaps because of patient pressure and the FDA not daring to risk bad PR this did not happen.

**Unapproved use**

Even more remarkable is the scope of Friday's safety alert. Not only does this say nothing about the controversial second-line setting of Imvigor-211, it does not even relate to some of these drugs' second approved urothelial cancer use in first-line, chemo-ineligible disease.

Rather, the alert concerns an unapproved setting: chemo-eligible first-line patients, specifically those whose cancers express low levels of PD-L1. This is based on interim analyses of the phase III Keynote-361 and Imvigor-130 trials, which suggest that these subjects will live longer on chemo than if given Keytruda or Tecentriq monotherapy.

The FDA's advice is merely that doctors continue prescribing Keytruda and Tecentriq according to these drugs' labels, and that patients with concerns talk to their physicians. Thus, treating chemo-ineligibles – in whom a

survival benefit has never been shown – and second-line subjects, and even the unapproved use in PD-L1-high first-lines, all appear to be fine with the regulator.

| Anti-PD-1/PD-L1 MAb approvals in urothelial bladder cancer | | | |
|---|---|---|---|
| **Approval date** | **Setting** | **Supporting trial** | **Results** |
| *Tecentriq (Roche)* | | | |
| 18 May 2016 | 2nd-line | Imvigor-210 | Single-arm: ORR 14.8%; ORR 26.0% in PD-L1 >5%, 9.5% in PD-L1 <5%. |
| 17 Apr 2017 | 1st-line (chemo ineligible) | Imvigor-210 | Single-arm: ORR 23.5%; ORR 28.1% in PD-L1 >5%, 21.8% in PD-L1 <5%. |
| *Opdivo (Bristol-Myers Squibb/Ono)* | | | |
| 2 Feb 2017 | 2nd-line | Checkmate-275 | Single-arm: ORR 19.6%, estimated median response duration 10.3mth. |
| *Imfinzi (Astrazeneca)* | | | |
| 1 May 2017 | 2nd-line | 1108 | Single-arm: ORR 17.0%; ORR 26.3% in PD-L1-high, 4.1% in PD-L1-low. |
| *Bavencio (Pfizer/Merck KGaA)* | | | |
| 9 May 2017 | 2nd-line | Javelin Solid Tumor | Single-arm: ORR 13.3% in patients followed for >13wk, 16.1% in patients followed for >6mth. |
| *Keytruda (Merck & Co)* | | | |
| 18 May 2017 | 2nd-line* | Keynote-045 | mOS 10.3mth, vs 7.4mth for chemo (HR 0.73, p=0.004); ORR 21% vs 11% for chemo (p=0.002). |
| 18 May 2017 | 1st-line (chemo ineligible) | Keynote-052 | Single-arm: ORR 28.6%. |
| *Note: *full approval; all others are on accelerated basis. ORR=overall remission rate. mOS=median overall survival.* | | | |

Why is the FDA being so lax? True, urothelial bladder cancer is a relatively tiny market, and second-line patients have few alternatives. Keytruda has, at least, managed to show a second-line survival benefit, but at best this suggests that not all anti-PD-(L)1s are equal.

Approval standards are there for a reason, and clamour for particular therapies obliges a regulator to exercise its regulatory function dispassionately to a greater, not lesser, extent.

Giving patients an ineffective drug risks unnecessarily exposing them to toxicities, though at least for PD-(L)1 agents these are not especially onerous. It also puts pressure on the US taxpayer if such ineffective treatments nevertheless have to be reimbursed.

None of this is to take away from the huge benefit that anti-PD-(L)1 drugs have shown in other indications; treatment of first-line lung cancer, for instance, looks to have been revolutionised by Keytruda, and this should be celebrated by pharma and patients alike.

But approvals not backed by real data do a disservice to drugs that really make a difference. The FDA should behave like a proper regulator.

| Selected phase III trials in urothelial bladder cancer | | | |
|---|---|---|---|
| **Study** | **Setting** | **Detail** | **Trial ID** |
| Imvigor-211 | Tecentriq vs chemo, 2nd-line | mOS 11.1mth vs 10.6mth for chemo (HR 0.87, p=0.41); ORR 23%, vs 22% for chemo | NCT02302807 |
| Imvigor-130 | Tecentriq +/- chemo, vs chemo, 1st-line | Early reviews suggest decreased survival vs chemo for PD-L1-low subjects given Tecentriq | NCT02807636 |
| Keynote-361 | Keytruda +/- chemo, vs chemo, 1st-line | Early reviews suggest decreased survival vs chemo for PD-L1-low subjects given Keytruda | NCT02853305 |

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