



Immunotherapy in cervical cancer: historic breakthroughs beating checkpoints

Richard T. Penson^{1,2,3}

¹Harvard Medical School, Boston, MA, USA; ²Massachusetts General Hospital, Boston, MA, USA; ³Dana-Farber/Harvard Cancer Center, Boston, MA, USA

Correspondence to: Richard T. Penson, MD, MRCP. Associate Professor of Medicine, Harvard Medical School, Boston, MA, USA; Clinical Director of Medical Gynecologic Oncology at Massachusetts General Hospital, Boston, MA, USA; IRB Chair, Dana-Farber/Harvard Cancer Center, Yawkey 9-064, 32 Fruit St., Boston, MA 02114, USA. Email: Penson.Richard@mgh.harvard.edu.

Provenance: This is an invited Editorial commissioned by Guest Section Editor Kaiping Zhang (Academic Director, AME Publishing Company).

Comment on: Frenel JS, Le Tourneau C, O'Neil B, *et al.* Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1-Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial. *J Clin Oncol* 2017;35:4035-41.

Received: 20 November 2018; Accepted: 26 November 2018; Published: 30 November 2018.

doi: 10.21037/whi.2018.11.01

View this article at: <http://dx.doi.org/10.21037/whi.2018.11.01>

Who benefits from immunotherapy? What constitutes a breakthrough? Where do the blockbuster pharmaceutical come from? When are clinical and scientific dreams realized? Why does getting a drug to market require such a huge, long and costly investment? How do we pick the winners? We live in exciting times appropriately culminating in the awarding of this year's Nobel prize in Physiology or Medicine jointly to James Allison PhD and Tasuku Honjo MD PhD for their discovery of a new field in anticancer therapeutics by "inhibition of negative immune regulation" (1). This strategic advance came from the pursuit of scientific understanding of the blinkers and blocks of immune surveillance.

Tasuku Honjo was screening for apoptosis related genes in 1992 when he and his team at Kyoto University discovered and named programmed cell death protein-1 (PD-1) (2). Murine knockout models demonstrated PD-1 as important for preventing autoimmune disease and established PD-1 as a negative regulator of immune responses. Jim Allison identified cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) as an inhibitory molecule restricting T-cell responses, and in 1996, Allison was the first to demonstrate that CTLA-4 blockade could trigger immune activation and tumor responses (3).

It has taken more than 20 years to see this field evolve into the most exciting area in oncology. In 2006 Carven, Eenennaam and Dulos at Organon developed a humanized

antibody against PD-1, and the company was then bought by Schering-Plough in 2007, and again purchased by Merck in 2009. Pembrolizumab (KeytrudaTM) was originally approved by the FDA September 4, 2014 for the treatment of advanced malignant melanoma. In gynecologic tumors it was granted accelerated approved for any tumor with the predictive biomarker, microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) May 23, 2017 irrespective of tumor origin or type, and June 12, 2018 pembrolizumab was approved for previously treated patients with recurrent or metastatic cervical cancer whose tumors express PD-L1 based on Merck's KEYNOTE-158 trial (NCT02628067) (4).

In KEYNOTE-158, pembrolizumab was given at 10 mg/kg every 2 weeks for up to 24 months. Frenel *et al.* reported a response rate of only 17% (4). However, of those, 91% had a response duration of ≥ 6 months. It was a small study of 24 patients. Median age was 42 years (range, 26–62 years), 22 patients (92%) had received prior radiation therapy, and most (63%) had received ≥ 2 lines of therapy.

The most common side effects of pembrolizumab are fatigue, rash, fever, anemia, itch, diarrhea, and hypothyroidism. Serious adverse reactions occurred in 21%, with life-threatening autoimmune reactions reported in 3%. Clinicians have had to learn new sensibilities, retool their clinical acumen, and broaden their clinical connections to respond to a new spectrum of toxicities. At MGH we now

have a “SIC” service (Serious Immune Complications Team) to deal with the serious complications of immunotherapy.

For on-label use of pembrolizumab, patients' tumors have to express PD-L1 based on an approved companion diagnostic, presently 22C3 pharmDx (Dako North America Inc.) in the US. Controversy remains about whether tumor cells' or immune cells' expression is the most important, but there does appear to be a correlation between the level of expression and chance of response. In KEYNOTE-158, no responses were observed in patients whose tumors did not have PD-L1 expression [combined positive score (CPS) <1] (4), and in lung cancer it is established that the best responses happen with a CPS >50%.

Clinicians are rightly skeptical about adding stable disease to the measure of clinical benefit, but in KEYNOTE-158 while four patients (17%) achieved a confirmed partial response, a further three patients (13%) had stable disease, meaningfully adding to survival (median), especially for those individuals. Median duration of response for the four patients who achieved a partial response was 5.4 months (4.1 to 7.5 months). The paper does not report the durability of stable disease, but from the ‘swimmer plot’ it looks to be between 5 and 7 months. Another hint at significant benefit is that one patient did respond in a previously irradiated site. Looking at the “spider plot” there is a clear cluster of tumors that progress unchecked. Interestingly, those that responded had all achieved the response by the 2-month CT scan, faster than the typically described 90 days for T-cell activation.

Similar results have been reported in CheckMate-358, the phase I/II study of nivolumab in patients with virus-associated tumors with a response rate of 26% in metastatic or recurrent cervical cancers (5). However, this was a less heavily pre-treated population with 30% of patients were receiving nivolumab as first-line treatment for advanced disease, and 29% receiving ≥ 2 lines of therapy. Toxicity was essentially identical.

A number of other immune checkpoint inhibitors are also in development against cervical cancer: ipilimumab (YervoyTM) targets CTLA-4, nivolumab (OpdivoTM), durvalumab (ImfinziTM), and cemiplimab (LibtayoTM) are anti-PD-1s, and atezolizumab (TecentriqTM) an anti-PD-L1. Cemiplimab (LibtayoTM) is being evaluated in GOG 3016/ENGOT-cx 9, an ongoing, open-label, multinational, randomized phase III trial comparing cemiplimab with investigator's choice of chemotherapy. A number of combination immunotherapeutics show promise, such as ipilimumab and nivolumab (ipi/nivo) and adding a drug

targeting LAG-3 or HDAC inhibition to augment antigen expression. We have seen remarkably durable responses with the combination of ipi/nivo.

Wonderfully, two trials are evaluating immunotherapy in the upfront setting. Atezolizumab is being studied in the first-line for recurrent, persistent, or stage IVB cervical cancer in a 404 participant phase III called BEATcc in a classic design using GOG-240 (paclitaxel cisplatin bevacizumab) +/- atezolizumab 1,200 mg IV Q21. This combination was safe and effective in non-small cell lung cancer (NSCLC) in the Empower150 study, though with a bigger dose of paclitaxel. KEYNOTE-826 is a very similar phase III with the same control arm in 600 participants though using a different dose and schedule than KEYNOTE-158, pembrolizumab 200 mg IV Q21. KEYNOTE-826 uses a co-primary end-point of progression-free (PFS) and overall (OS) survival which is appropriate for the more complex anticipated benefit of immunotherapy.

A number of other immune related strategies are also in development. The most exciting is adoptive T-cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) selected for human papillomavirus (HPV) E6- and E7-oncogene reactivity (HPV-TIL). The phase II reported durable complete regression of metastatic cervical cancer (6). TIL technology developed by Lovance Biotherapeutics (formerly Lion Biotechnologies) is in phase II. Live attenuated *Listeria monocytogenes*-based immunotherapy ADXS11-001 (axalimogene filolisbac), which generates CD8+ T cells that target HPV-E7-transformed cells while suppressing immune tolerance to these lesions, has shown promise in early clinical trials and a second phase II study reported a 39% rate of survival at 12 months in a heavily pretreated population, and phase III trials were under development (7). However, European marketing application for axalimogene filolisbac was withdrawn in July 2018.

Predicting the future is notoriously difficult, but the immune system is built on the maxim that prevention is better than cure. In cervical cancer, one hope is that augmenting immune surveillance in high risk patients may eradicate malignant clones before disease develops. Using that preventive strategy, VGX-3100, a synthetic DNA vaccine targeting the HPV E1 and E7 proteins, has shown efficacy against high grade dysplasia/cervical intraepithelial neoplasia in early clinical trials (8).

The staggering cost of immunotherapy is all the more of a concern in this patient population, typically significantly socio-economically disadvantaged. The large majority of

cervical cancer deaths, estimated at 87% in 2012, occur in the developing world, where it is the second most common cancer in women (9). There is a telling lack of discussion about immunotherapy as an option for these patients.

Unequivocally, immunotherapy is the most significant recent advance and a milestone in the history of our weapons against cervical cancer. The last approved cytotoxic was topotecan in 2006 which improved median OS 50% from 6 to 9 months in combination compared to cisplatin alone and doubled the response rate (27% *vs.* 13%) (10). Bevacizumab was approved in combination with paclitaxel or topotecan plus cisplatin in 2014, and improved OS by 26% and pushed up the response rate from 34% to 45% (11). Although other targeted therapies have merit, and PIK3CA and EGFR remain promising, immunotherapy has eclipsed all other competitors and transformed both the field, the options, and our hopes for better patient outcomes.

Acknowledgements

None.

Footnote

Conflicts of Interest: Scientific Advisory Boards: Amgen Inc., Genentech, Inc., AstraZeneca, Eisai Inc., Baxalta Oncology, AbbVie, Clovis Oncology, Mersana Therapeutics, Inc., Sutro Biopharma, Tesaro, Vascular Biogenics Lt. Research funding: Array BioPharma Inc., AstraZeneca., Cerulean Pharma Inc, Eisai Inc., Genentech, Inc., Regeneron, Sanofi-Aventis US LLC, Tesaro Inc., Vascular Biogenics Ltd.

References

1. The Nobel Prize in Physiology or Medicine 2018. Available online: <https://www.nobelprize.org/prizes/medicine/2018/summary>
2. Ishida Y, Agata Y, Shibahara K, et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J* 1992;11:3887-95.
3. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J Exp Med* 1995;182:459-65.
4. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1-Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial. *J Clin Oncol* 2017;35:4035-41.
5. Hollebecque A, Meyer T, Moore KN, et al. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. *J Clin Oncol* 2017;35:abstr 5504.
6. Stevanović S, Draper LM, Langan MM, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J Clin Oncol* 2015;33:1543-50.
7. Basu P, Mehta A, Jain M, et al. A Randomized Phase 2 Study of ADXS11-001 Listeria monocytogenes-Listeriolysin O Immunotherapy With or Without Cisplatin in Treatment of Advanced Cervical Cancer. *Int J Gynecol Cancer* 2018;28:764-72.
8. Trimble CL, Morrow MP, Kraynyak KA, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015;386:2078-88.
9. World Health Organization. Cervix uteri. International Agency for Research on Cancer. Available online: <http://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-Uteri-fact-sheet.pdf>
10. Long HJ 3rd, Bundy BN, Grendys EC Jr, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* 2005;23:4626-33.
11. Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;370:734-43. Erratum in: Improved Survival with Bevacizumab in Advanced Cervical Cancer. [*N Engl J Med* 2017].

doi: 10.21037/whi.2018.11.01

Cite this article as: Penson RT. Immunotherapy in cervical cancer: historic breakthroughs beating checkpoints. *Womens Health Investig* 2018;1:3.