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The Efficacy and Safety of Pembrolizumab in advanced cervical cancer – a real world treatment study

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Background

Cervical cancer is one of the most common gynaecological tumours, the majority of early-stage patients achieving good outcomes with surgery and concurrent chemoradiation[1]. For patients with recurrent disease effective treatment is rare. Programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors are a potential choice to improve the clinical outcomes of these patients with limited options.

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor, blocking its interaction with PD-L1 and PD-L2. This releases PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. PD-L1 expression has been identified in virus induced cancers[2]. Given the presence of a virus leading to antigen production in the oncogenesis of cervical cancer, evaluating immune checkpoint inhibition as a treatment strategy in the setting of advanced or metastatic cervical cancer is of great interest.

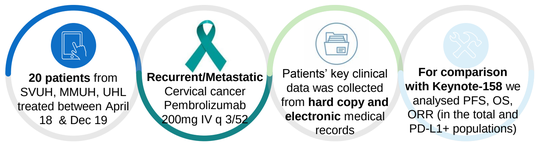
Pembrolizumab was granted accelerated approval by the FDA in June 2018 for treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1], based on the results from the KEYNOTE-158. KEYNOTE-158 is a phase 2 basket study investigating the antitumor activity and safety of pembrolizumab in multiple advanced solid tumour types. Overall Response Rate (ORR) was 12.2% (95% CI, 6.5% to 20.4%), with three complete and nine partial responses. All 12 responses were in PD-L1- positive tumours, for an ORR of 14.6% (95% CI, 7.8% to 24.2%). 65.3% of patients had treatment related adverse events[3].

In Ireland, The National Centre of Pharmacoeconomics (NCPE) is involved in the approval of drugs for reimbursement. Pembrolizumab has been approved for reimbursement by the NCPE for unresectable or advanced melanoma, first line treatment for metastatic NSCLC with PD-L1 ≥ 50%, and relapsed or refractory classical Hodgkin lymphoma.

Pembrolizumab is available for use in the treatment of cervical cancer outside the NCPE approval process as directed by the Government. All women with cervical cancer in Ireland are entitled access to Pembrolizumab where clinically recommended.

The aim of this study is to assess our experience with Pembrolizumab in patients with advanced cervical cancer in an Irish Healthcare Setting.

Methodology



Patients with advanced cervical cancer treated with Pembrolizumab at three oncology centres in Ireland were included in this study; Saint Vincent's University Hospital (SVUH), University Hospital Limerick (UHL) and Mater Misericordiae University Hospital (MMUH). Ethical approval was obtained from treating hospitals.

All patients had recurrent or metastatic cervical cancer.

Patients' key clinical data was collected from hard copy and electronic medical records.

Patients must have received at least one dose of Pembrolizumab. Pembrolizumab 200mg IV was administered once every three weeks.

To enable us to compare our results with the reported outcomes from Keynote-158 we analysed Progression Free Survival (PFS), Overall Survival (OS), and Overall Response Rate (ORR), using SPSS software. These outcomes were anaylsed in both in the total and PD-L1 positive populations.

We also collected data on the safety profile of the drug.

Table 1. Demographic and Disease Characteristics

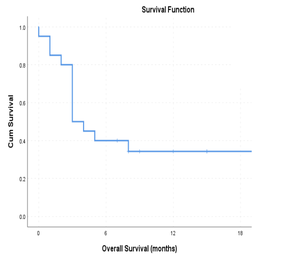
Characteristic	N = 20	Keynote 158 N=98
Median age (range) – yrs	41 (27 – 77)	46 (24-77)
FIGO Stage – no (%)		
IIIB	1 (5)	4 (4.1)
IVB	19 (95)	92 (93.9)
PD-L expression status – no (%)		
Positive	10 (50)	82 (83.7)
Negative	4 (20)	15 (15.3)
Unknown	6 (30)	1 (1)
Histology no – (%)		
SCC	14 (70)	92 (93.9)
Adenocarcinoma	4 (20)	5 (5.1)
Mixed large/small cell	1 (5)	
Unknown	1 (5)	
Number of Metastatic Disease sites no – (%)		
1	7 (35)	
2	4 (20)	
3	7 (35)	
4	1 (5)	
5	1 (5)	

Table 2. Treatment Characteristics

Characteristic	N=20	Keynote 158 N=98
Previous Radiotherapy n – (%)	18 (90)	85 (87)
Previous lines of systemic treatment in metastatic setting		
0	2 (10)	0(0)
1	15 (75)	30 (30.6)
2	2 (10)	34 (34.7)
3	1 (5)	16 (16.3)
4	0 (0)	10 (10.2)
≥5	0 (0)	4 (4.1)
Previous antineoplastic agents		
Cisplatin in metastatic setting	18 (90) 5 (25)	79 (80.6)
Carboplatin	15 (75)	66 (67.3)
Taxol	13 (65)	85 (86.7)
Gemcitabine	5 (25)	
Bevacizumab	7 (35)	41 (41.8)
Vinorelbine	1 (5)	
Etoposide	1 (5)	

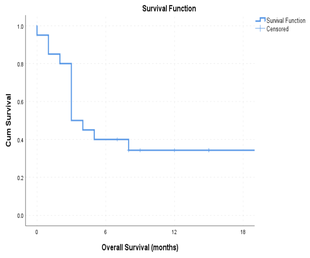
Results

Fig 1. Median OS



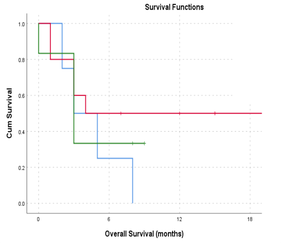
Median OS = 8.9months (95% CI, 5.2 – 12.5)

Fig 2. Median PFS



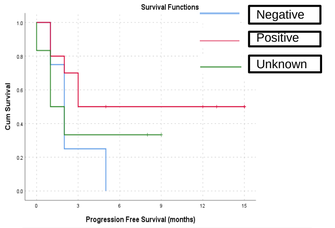
Median PFS: 6.4months (95% CI, 3.5 - 9.2)

Fig 3. Median OS by PD-L1 status



Median OS PDL1+: **11.2months** (95% CI, 5.7 – 16.7)
Median OS PDL1-: 4.5months (95% CI, 1.9 - 7.1)

Fig 4. Median PFS by PD-L1 status



Median PFS PDL1+: **8.3months** (95% CI, 4.1 - 12.5)
Median PFS PDL1-: 2.5months (95% CI, 0.8 - 4.2)

Table 3. Response to Treatment

Response	N=20	Keynote-158 N=98
Type of Response – n(%)		
Complete	1 (5)	3 (3.1)
Partial	4 (20)	9 (9.2)
Stable Disease	1 (5)	18 (18.4)
Progression	14 (70)	55 (56)
Response Rate (%) **-in PDL1+**	25 **30**	12.2 14.6
Disease Control Rate (%)	30	30.6
Duration of Response months – median (Range)	13 (8 – 15)	NR (3.7 - 16.6)
Duration on Tx months – median (range)	2.5 (1-20)	2.9 (1-22.1)
Amount of Tx – median (range)	4 (1-30)	5 (1-33)

Adverse Events

Adverse events of all grades were reported in 13(65%) of patients, with 2(10%) reporting Grade 3-4 which led to a discontinuation of pembrolizumab

Table 4. Adverse events

Adverse Event	Grade 1-2	Grade ≥3
Hypothyroidism	4(20%)	0
Hepatitis	2(10%)	1(5%)
Rash	2(10%)	0
Oral Ulcers	1(5%)	0
Nausea	1(5%)	0
Arthralgia	1(5%)	1(5%)

Discussion and Conclusion

- The observed clinical activity in our patient population is superior to the interim results from KEYNOTE-158. This may be in part due to the fact our population of patients had less lines of treatment than KEYNOTE-158.
- We report a consistent safety profile with no new safety signals
- This study shows a **favourable response rate** of 30% in PDL1+ patients with a promising median OS of 8.9 months for entire population (11.2 months for PDL1+).
- No responses were seen in PDL1- tumours; however because of the **small number of patients with PDL1- tumours** enrolled, this study lacks the power to reliably distinguish response rates between PDL1+ and PDL1- patients
- The key limitations in the study include:
  - Retrospective study
  - Small sample size
  - PD-L1 status unknown in 30%
  - Varied PD-L1 testing methods
  - No standardised management protocols between hospitals
  - Short follow-up time
- Although limitations exist, we believe, based on our findings, **Pembrolizumab should be considered as a standard option** for those with advanced PDL1+ cervical cancer.
- There are **limited therapeutic options** in these symptomatic and often terminally ill patients with advanced cervical cancer.
- Additionally, all of the alternate treatments create a significant toxicity profile **impacting hugely on the patients' quality of life**.
- In our real life experience, **Pembrolizumab provides an effective and much improved toxicity profile alternative** in this patient population.

References
1. Lalit Kumar, Integrating Chemotherapy in the Management of Cervical Cancer: A Critical Appraisal,Oncology 2016;91(suppl 1):8–17 **2.** Rubio-Perez, C. et al. In silico prescription of anticancer drugs to cohorts of 28 tumor types reveals novel targeting opportunities. *Cancer Res.* **75**, 2983 (2015) **3**.Chung et al, Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer, *Journal of Clinical Oncology* 37, no. 17 (June 10, 2019) 1470-1478.