In the last year, two programmed death (PD-1) oncology immunotherapies have gained regulatory approval in several markets across the globe for treating multiple cancer types. These treatments, pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb), are monoclonal antibodies targeted to the T-cell PD-1 receptor.

In normal circumstances, when the PD-1 receptor binds to its ligand (PD-L1) expressed on other immune cells, it acts as a brake or checkpoint promoting tolerance and preventing tissue damage in chronic inflammation. Tumors that express PD-L1 have a worse prognosis, because they are thought to avoid immune surveillance by reducing T-cell antitumor functionality. Blockade of the PD-1 receptor provides sustained antitumor immune potentiating effects1.

Both pembrolizumab and nivolumab have shown promising results from early-stage trials and in a wide range of cancers, leading to relatively quick and intense competition between the two drugs. With the PD-1 space estimated as bringing in $21 billion in sales by 2022, the respective manufacturers have needed to make rapid strategic decisions to maximize the impact of their brands and ensure optimal market and patient access.

### OBJECTIVES
- The objective of this research was to understand the early lifecycle management strategies of the PD-1 immunotherapies, pembrolizumab and nivolumab; specifically, the aims were to:
  - Track the approvals in major global markets (Europe, Japan, United States)
  - Analyze competitive landscape within the oncology immunotherapy space
  - Identify key lifecycle management strategies and market trends

### METHODS
- Targeted secondary research was used to identify source literature which was then analyzed for trends to make evidence-driven conclusions and insights; specifically:
  - Online search strategy was designed to include combinations of key words ("PD-1", "Keytruda", "Opdivo", "FDA", "clinical trial", "pembrolizumab", "nivolumab", "approval", "immunotherapy AND oncology")
  - Global online data sources (including PubMed and ClinicalTrials.gov, as well as news articles, press releases and grey literature) were mined for literature
  - Literature was abstracted and information was analyzed qualitatively for relevance and prioritized by importance
  - Key themes were discussed in a consensus meeting and implications of findings were synthesized to form conclusions

### RESULTS
- In the 16 months since nivolumab was first approved in Japan for advanced melanoma, another 9 marketing authorizations have been granted to nivolumab and pembrolizumab by the FDA and EMA in advanced melanoma and non-small cell lung cancer (NSCLC) indications2-4.

### DISCUSSION
- The entry of PD-1 therapies into the market has seen high levels of competition between the two major players, highlighting that even substantial improvements in clinical efficacy in one indication is no longer sufficient for success.
- With the potential for therapeutic advantage across multiple indications, manufacturers of innovative products need to consider various lifecycle management strategies for creating, maintaining and increasing product value and market share.

### CONCLUSIONS
- Several lifecycle management strategies were identified from secondary research, including: early access, indication expansion, use in seen areas of therapy, portfolio management, biomarkers, and combining with other drug treatments, often through collaborations and partnerships.

### Figure 1. PD-1 mechanism of action
- **T-cell**
- **PD-1**
- **PD-1 immunotherapy**

### Figure 2. Methodology overview
- 1. Design search strategy
- 2. Online search
- 3. Abstract and analysis
- 4. Synthesize conclusions

### Figure 3. Approval history of PD-1 therapies
- **Nivolumab**
  - 2nd-line (s & n-sq) in September 2014
  - 1st-line (s & n-sq) in March 2015
  - Priority review of 1st-line in August 2015
  - Approval in 8 indications on 6 markets: Keytruda (US) - September 2014, October 2015, September 2015

- **Pembrolizumab**
  - Approval for Melanoma in 2nd-line (s & n-sq) in December 2014
  - Approval for NSCLC in 2nd-line (s & n-sq) in July 2015

### Figure 4. Lifecycle management strategies
- **Key strategies in lifecycle management**
  - Early access
  - Indication expansion
  - Earlier treatment
  - Drug combinations
  - Patient segmentation
  - Forming collaborations

### Strategy 1: Early access
- Gaining early access through specific national programs has been a critical step in the approval process of both nivolumab and pembrolizumab, as they leverage the opportunity to earn first-mover advantage.
- In the US, breakthrough therapy designation was awarded to both therapies with preliminary clinical evidence indicating substantial improvement over existing therapies1.
- In Europe, the UK has expedited access for both drugs via the Early Access to Medicines Scheme, aimed to accelerate access to as yet unlicensed medicines where there is a high unmet need5.

### Strategy 2: Indication expansion
- Both approved PD-1 therapies have moved from approval in melanoma to approval in NSCLC and are in numerous clinical trials for other cancers in an aim to maximize target market size.
- Nivolumab has recently achieved FDA breakthrough therapy status in kidney cancer, placing the drug on a faster approval pathway and may be the first to gain a third cancer indication.
- Meanwhile, pembrolizumab is currently being investigated in 9 difficult-to-treat cancers in an ongoing basket trial – a trial design that allows for the study of multiple sub-populations within one study6.

### Strategy 3: Earlier treatment
- Recognizing the advantage of becoming the primary frontline option in the physician armamentarium, both PD-1s obtained first-line indication for melanoma in Europe with additional programs in untreated patients.
- In Japan and US, the PD-1s were first approved as second-line treatments, while pembrolizumab may become the frontline option in the US as it is currently under FDA Priority Review in first-line3.

### Strategy 4: Drug combinations
- Offering the potential to combine with another drug means giving physicians further options in treating patients and will be advantageous for the product that is able to be part of a combined regimen.
- Nivolumab has the competitive advantage in this case, having been approved in combination with ipilimumab, offering increased efficacy in patients with BRAF V600 wild-type advanced melanoma8.
- The pembrolizumab development program encompasses more than 30 tumor types in over 130 clinical trials, of which at least 70 trials combine pembrolizumab with other cancer drugs9.

### Strategy 5: Patient segmentation
- Targeting specific patient sub-groups, as an a priori commercial strategy or as a by-product of clinical trial data, has offered the PD-1 drugs the chance to carve a niche, if they can demonstrate superiority.
- Pembrolizumab may have the competitive advantage here, as in NSCLC, the therapy has been approved alongside a companion diagnostic for targeting of patients with high PD-L1 expression.

### Strategy 6: Forming collaborations
- In an effort to cement position as market leaders and ward off competition from other manufacturers, there has been a huge amount of deal-making activity between big pharma and smaller biotech firms.
- Bristol-Myers Squibb has formed a research collaboration with Kyowa Hakko Kirin involving their respective established products, nivolumab and mepactumab10.
- Meanwhile, Merck is investigating pembrolizumab in combination with MacroGenics’ margetuximab in patients with advanced gastric cancer and is co-developingavelumab with Pfizer11,12.

### REFERENCES

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