Improving the Access to Immuno-Oncology in Europe: Barriers and Potential Solutions

Date: 31st Jan., 2017
Executive summary
Oncologists from 17 EU countries responded to the survey. 89% believed I-O therapies are very important, but <50% of oncologists were highly familiar with I-O and hence only <45% prescribed them. ~78% of oncologists were positive about the role of combination I-O therapies.

Solutions suggested to improve access to I-O therapies:
- Flexible reimbursement guidelines or cost-effectiveness decision parameters (83%)
- Less stringent regulatory review process (56%)
- Defining target population (44.4%)
- Clinical practice guidelines (38.9%)
- Training HCPs (27.8%)

>77% encountered challenges in prescribing I-O therapies. 83% faced challenges in selecting the right patient population. 100% support early access programs for I-O. ~39% strongly believed that uniformity and stratification of HTA will improve access.
Background
Cancer is a major healthcare concern in Europe demanding advanced treatment strategies.

- **New cancer cases per year**: 2.45 million
- **Deaths per year**: 1.23 million
- **Euros in total cost**: 126 billion
- **Euros in indirect cost**: 75 billion

\(^1\) Data from [source]
Growing trend of the global I-O market

- I-O therapies are gaining a strong foothold in the cancer treatment paradigm over conventional cancer treatment due to the following advantages:\(^3\,^4\):
  - Active immunity
  - Sustained response
  - Applicability in multiple indications
  - Favorable adverse effect profile
- 78% of the new oncology medicines launched between 2010 and 2014 were available within the greater EU by 2015\(^5\)

**Expected rise in the global I-O market (USD billion)**

- 2014: 1.4
- 2019: 14
- 2024: 34
The I-O arena is expecting several drug approvals, even for second and third indications.

2015:
- Pembrolizumab for melanoma
- Nivolumab for melanoma
- Atezolizumab (Approved by FDA in March 2016, Under review by EMA)

2016:
- Nivolumab for RCC (Extended approval)
- Avelumab
- Durvalumab

Ipilimumab for melanoma
Nivolumab for melanoma and NSCLC
Atezolizumab
Pidilizumab
Tremelimumab
Durvalumab
Survey objectives

- Limited and disproportionate access to I-O therapies across Europe despite demonstrated efficacy and safety in clinical trials\(^5,10\)
- A survey was conducted to explore the status of I-O therapies in European countries to understand the key hurdles that limit access and to develop solutions to overcome the same

**The survey objectives**

- To assess the oncologists’ awareness on the status of I-O therapies in the European countries
  - Assess the clinical practice patterns of oncologists in prescribing or recommending I-O therapies
  - Understand the barriers faced by oncologists in using I-O therapies
  - Encourage oncologists to propose solutions and recommendations to improve access to I-O therapies in Europe
  - Assess the causes of disparities in accessing cancer therapy across Europe
Methodology
Methodology

Questionnaire

- Extensive literature search in databases such as MedLINE, Google Scholar and various regulatory, government, and healthcare websites to identify key topics
- Questionnaire consisted of three sections and 13 questions overall

Participants

- Oncologists across the EU: Oncology practitioners involved in policy shaping activities or associated with leading oncology societies
- Dendron\textsuperscript{11} – A scientific platform by focus scientific research center (FSRC) where stakeholders from different fields interact, portray their activities, share knowledge and best practices
- Survey sent to 206 oncologists

Communication and survey platform

- Emails and LinkedIn
- Questionnaire was made available on a website (www.esurveyspro.com)
- Duration: three weeks between May – June 2016

Data collection

- Both quantitative and qualitative data were collected
- Individual responses and cumulative analysis reports were generated in Microsoft Excel
Results
Survey results

Findings from the survey

- Response rate: 9%
- 18 participants from Albania (AL), Austria (AT), Bosnia and Herzegovina (BA), Croatia (HR), Czech Republic (CZ), Denmark (DK), Italy (IT), Lithuania (LT), Poland (PL), Kosovo (RS), Portugal (PT), Romania (RO), Slovak Republic (SK), Slovenia (SI), Switzerland (CH), Ukraine (UA), and United Kingdom (UK)
- Most responses (66.7%) were from the emerging European countries (EEC)\(^{12}\)
- Most oncologists have a clinical experience of \(>5\) years and are associated with various universities across Europe

Evidence from secondary research

- Inequities in cancer care has led to more demands from the EEC\(^{10,13}\)
- Only \(1/3\rd\) of the former Eastern Bloc countries have access to at least one of the new targeted I-O\(^5\)
- The Czech Republic launched a mass cancer screening program focused on the increased demand of drugs due to the increased burden of cancer\(^{14}\)
PART 1: Experience with I-O therapies

The questions in this part were mainly on the basic scientific knowledge on the mechanism of action of I-O therapies, recent developments in this space, clinical experience with I-O therapies and challenges with I-O access.
Q1. How familiar are you with the concept of I-O therapies?

Findings from the survey

- Overall, 44% of the oncologists were highly familiar
- All oncologists in the DEC were moderate to extremely familiar
- In the EEC, 33% oncologists were only slightly familiar

Evidence from secondary research

- There was a lag between the advancing I-O field and knowledge among oncologists in the EU-5 and Greece in a survey\textsuperscript{15,16}
  - Only 35% oncologists from Europe interviewed in a survey were well-informed on I-O
  - There was a disparity in knowledge on I-O, irrespective of economic and scientific development, policy making, education and general population health
- As per another survey, 76% of oncologists wanted to be trained or educated on cancer immunotherapy\textsuperscript{4}

Figure 3: Knowledge about I-O

- Extremely familiar: 50.0%
- Moderately familiar: 66.6%
- Slightly familiar: 33.3%

Developed European Countries
Emerging European Countries
Q2. Compared to other oncology therapy measures (chemotherapy, radiation therapy, and surgery), what is the importance of I-O therapies in improving the outcomes of patients with cancer?

**Findings from the survey**

89% believe I-O is very important

**Evidence from secondary research**

- The overall attitude towards I-O therapies was largely positive amongst various HCPs\(^9\):
  - Oncologists: 48% positive
  - Surgeons: 65% positive
  - Nurses: 77% positive
- The overall optimism in I-O therapies is also shown by the number of new therapies getting approved\(^3,6,7,8\):

**Immuno-modulatory mAbs**

- Inhibitors of programmed cell death 1 (PD-1) receptors or their ligands
- Act against factors released in the tumor environment that diminish the immune system ability, (e.g. transforming growth factor \(\beta 1\))
- Inhibitors of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) receptors or their ligands
- Activation or stimulation of receptors expressed on the surface of immune effector cells like tumor necrosis factor

**Evidence from secondary research**

- The overall attitude towards I-O therapies was largely positive amongst various HCPs\(^7\):
  - Oncologists: 48% positive
  - Surgeons: 65% positive
  - Nurses: 77% positive
- The overall optimism in I-O therapies is also shown by the number of new therapies getting approved\(^3,6,7,8\):
Q3. Please indicate your clinical experience in recommending and/or prescribing following classes of I-O therapies

Findings from the survey
Positive trend towards recommendation of I-O therapies, however, not many prescribe them in clinical practice

Evidence from secondary research

- Common barriers in recommending/prescribing cancer immuno-therapies: cost and reimbursement issues (58%), past failures in clinical trials (45%), access/formulary restrictions (44%) and lack of long-term safety/efficacy data (40%)4,10,16-23.

- The Institute for Clinical Immuno-Oncology (ICLIO) educates clinicians and patients about the clinical implications and benefits of I-O in day to day practice24.

- The ESMO has developed clinical practice guidelines to facilitate the adaptation of I-O in clinical practice25.

Evidence from secondary research

Clinical experience with I-O therapies

- Recommended and Prescribed: 44.4%, 38.9%, 22.2%
- Recommended but did not prescribe: 44.4%, 50.0%
- Neither recommended nor prescribed: 16.7%, 16.7%, 27.8%

Legend:
- PD-1/PD-L1 inhibitors (nivolumab and pembrolizumab)
- CTLA-4 inhibitors (Ipilimumab)
- Combination of PD-1 inhibitor and CTLA-4 inhibitor
Q3. Please indicate your clinical experience in recommending and/or prescribing following classes of I-O therapies

Findings from the survey

- Out of the 14 oncologists extremely or moderately familiar with I-O therapies:
  - 8 prescribed PD1/PD-L1 inhibitors (4 in DEC and 4 in EEC)
  - 7 prescribed CTLA-4 inhibitors (4 in DEC and 3 in EEC)
  - Only 4 prescribed combination therapies (2 in DEC and 2 in EEC)

Evidence from secondary research

- Increased familiarity with I-O therapies does not necessarily increase prescribing
  - Nearly 68% of oncologists in a survey showed interest in immunotherapy; however, only 24% had direct experience with them⁴
- Practice gaps might be due to the availability of I-O therapies in the country and understanding the attributes of I-O therapies (e.g. mechanism of action, clinical efficacy and treatment response)²⁶
Q4. Have you experienced any barriers in recommending/prescribing I-O therapies to your patients?
Q5. Please assign ranking based on the challenges that you face while recommending/prescribing I-O therapies to your patients?

Findings from the survey

- All oncologists from DEC and about 66% from the EEC faced challenges
- The top three challenges were: Selecting the right patient population (83.3%), Cost/reimbursement of the drug (50%), AE profile of the drug (44.4%)

Evidence from secondary research

- Varied clinical response in trials depending on the status of the biomarker (E.g. No clear survival benefit for pembrolizumab in the subset of patients with EGFR mutation even in the presence of higher proportion score for PD-L1)
- Although efficacious, these drugs are not affordable to all patients
  - >50 HTA agencies exist in Europe, leading to unequal evaluation criteria and disparity in reimbursement decisions
- Oncologists need to be more aware on AEs for checkpoint inhibitors which have distinct side effects compared to conventional chemotherapy and may occur at different time intervals
- Conventional methods to determine MTD in clinical trials have failed to determine appropriate dosages or I-O drugs mandating the development of novel methods to determine the effective doses
- Delayed response or pseudoprogression are specific attributes of I-O therapies that limit compliance

Challenges with I-O therapies

- Target patient population: 83.3%
- Cost/Reimbursement: 50.0%
- Side-effect profile: 44.4%
- Dosing or duration of treatment: 22.2%
- Delayed response: 22.2%

Faced any challenges?

- Yes: 22.2%
- No: 77.8%
Q6. What do you think will be the role of combination therapy (i.e. combining two or more I-O products with different mechanisms of action?)

Findings from the survey

~78% oncologists were positive that combination therapy could perhaps improve outcome and prolong patients’ lives

Evidence from secondary research

- Combination therapy of nivolumab + ipilimumab showed tumor reduction of 80%, and more among 53% patients with advanced melanoma
- AEs related to combination therapy were similar in experience with monotherapy and were reversible
- Various I-O combinations are being investigated
  - mAbs + small molecules
  - mAbs + vaccines
  - I-O + radiotherapy/other chemotherapy
- Complications of combination therapy: Cumulative toxicities, extensive collaboration between pharma companies for development and research and difficult regulatory review

Role of combination therapy

- Some what improve outcome and prolong patients' lives: 22.2%
- Will improve outcomes and prolong patients' lives significantly: 77.8%
PART 2: Status of I-O therapies in respondent’s country

This part included questions on the status of reimbursement of I-O therapies in the respective countries and the role of the various government and public organizations and the pharmaceutical industry in controlling the access to I-O.
Q7. What is the reimbursement status of I-O therapies in your country?

Findings from the survey

- Reimbursement status of I-O therapies:
  - Not reimbursed in 6 countries in EEC: Romania, Slovak Republic, Albania, Ukraine, Kosovo and Bosnia and Herzegovina
  - Not reimbursed in 1 country in DEC: Portugal
  - Not available in Lithuania
  - Reimbursed completely or partially in DEC

Evidence from secondary research

- Disparities in pricing and reimbursement decisions for oncology drugs across the EU member states is widely known\(^\text{10}\)
  - Till 2015, while >25 innovative cancer drugs were covered under reimbursement in Netherlands, Italy and Switzerland; the EEC such as Czech Republic and Poland reimbursed <5 of these drugs\(^\text{39}\)
  - One example is Jakavi (ruxolitinib), which is reimbursed in the northern and central European countries but not in the eastern European countries\(^\text{40}\)

### Reimbursement status of I-O therapies

<table>
<thead>
<tr>
<th>Completely reimbursed</th>
<th>Partially reimbursed</th>
<th>Not reimbursed</th>
<th>I-O therapies not available in the country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed European Countries</td>
<td></td>
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<tr>
<td>50.0%</td>
<td>33.3%</td>
<td>16.6%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Emerging European Countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.6%</td>
<td>25.0%</td>
<td>50.0%</td>
<td></td>
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</tbody>
</table>

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Q8. Who plays a major role in improving access of oncology drugs in your country?

<table>
<thead>
<tr>
<th>Organizations and bodies influencing access</th>
<th>Examples of initiatives by various authorities/organizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advocacy groups (11.1%)</td>
<td>Partnership between WHO and European Society for Medical Oncology (ESMO) since 2002 driving efforts from all sectors to improve cancer care 47</td>
</tr>
<tr>
<td>Payers (33.3%)</td>
<td>BMS launched compassionate use program for Nivolumab in Ireland. It benefits 200 patients with advanced lung cancer and is free for these patients for 30 days 45,46</td>
</tr>
<tr>
<td>Pharmaceutical companies (38.8%)</td>
<td>NICE reviews all new cancer drugs and changes in indications for existing drugs in the UK NICE negotiated with BMS to reduce the pricing for Ipilimumab 43,44</td>
</tr>
<tr>
<td>Government (77.7%)</td>
<td>The ESMO Patient Advocates Working Group (PAWG) and Lung Cancer Europe educates HCPs and improves access 41,42</td>
</tr>
</tbody>
</table>
Part 3: Future recommendations to improve access to I-O therapies

This part included questions on suggestions from experts to improve access to I-O
Q9. In your country, what could be done to improve access to I-O therapies?

Findings from the survey

Most important suggestions were the improvisation in reimbursement guidelines or cost-effectiveness decision parameters (83%) followed by less stringent regulatory review process (56%) and defining target population (44.4%)

Evidence from secondary research

- Flexible reimbursement, funds and risk sharing agreements decrease cost burden\(^ {19,48-50}\):
  - Special innovation funds in Italy, CDF in UK for research and development
  - Ipilimumab was approved by NICE following price discounts by BMS
- Identification of target population can be easier with predictive biomarkers and companion diagnostics
  - Pembrolizumab was approved with companion diagnostics to determine responders based on PD-1 expression\(^ {20,21,28}\)
- Revisions in clinical trial methods will generate credible evidence and ease the adaptation of these drugs in clinical practice
  - Determine biologically efficacious doses instead of MTD\(^ {51}\)
  - Assess response through irRC\(^ {52}\)
- Many organizations are continuously working to educate HCPs
  - CIC and CIMT are working towards educating and improving clarity on I-O\(^ {15}\)
  - The ECPC has also developed a framework on awareness to improve access\(^ {53}\)
Q10. Do you believe that uniformity in Health Technology Assessment (HTA) model across European region and stratification of HTA (e.g. based on those who respond compared to those who do not) will help improve the access to I-O therapies across European region?

Findings from the survey

Seven out of the 18 (~39%) strongly believed that uniformity in the HTA process across Europe and its further stratification will improve access.

Evidence from secondary research

- More than 50 HTA agencies exist in Europe leading to inconsistencies in the evaluation criteria and disparity in access to oncology drugs.
  - Differences in reimbursement decisions (from 2002-2004) on cancer drugs in Europe: England rejected reimbursement in 21.52% cases, Sweden and France rejected only 3-4%. Germany had 1% non-favorable opinions and Spain and Netherlands had none.
  - Trastuzumab (Herceptin) is available widely in many countries, but it requires preapproval or is available to patients at out-of-pocket costs in some European countries.
  - NICE rejected reimbursement of Imbruvica (ibrutinib) contradictory to the decision by other EU countries such as Greece.
- Personalizing reimbursement schemes and developing precision medicines catering to a group of responders could be advantageous. E.g. Herceptin treatment coverage in UK applied only to patients showing higher degree of HER2 staining and responding better.
Q11. Should early access be provided to new I-O therapies?

Findings from the survey
All the oncologists supported early access programs for I-O therapies

Evidence from secondary research
• Early access or compassionate use programs have improved access in Europe\(^{55}\)
• Nivolumab was approved on compassionate grounds in Ireland. This program benefits 200 patients who get it free for 30 days\(^{44,56}\)
• Compassionate access programs for oncology drugs existing in Austria, Estonia, Greece, Hungary, Italy, Lithuania, Portugal, and Spain etc. have shown positive outcomes\(^{45}\)
Q12. In your view, what efforts could be taken by the following stakeholders to improve the access to I-O therapies in your country?

**Findings from survey**

- **Reimbursement**
  - Improved reimbursement guidelines, negotiated prices of these drugs and improved research funding are a priority for many researchers\(^{19,48-50}\)

- **Clinical trails transparency**
  - Literature suggests the lack of education and awareness on I-O. More training and education programs should be conducted as per HCPs\(^{4,15,16}\)

- **Healthcare reform**
  - Developing guidelines and recommendations for target populations, dose regimen, clinical evaluation and managing side-effects in addition to appropriate dissemination of clinical trial data will help better clinical adaptation\(^{20,21,30,51,52}\)

- **Resources**
  - Early access programs and fast tracking the review process will bring these drugs sooner to the market\(^{44,45,55,56}\)

- **Knowledge**
  - Strategic planning like the framework developed by the ECPC will help in healthcare reforms and suitable actions\(^{53}\)

**Evidence from secondary research**

- **Lowering cost**
  - Negotiating with pharma companies

- **Cost-effectiveness**
  - Sustainable steps

- **Guidelines**
  - Media attention

- **Rapid review**
  - Affordable

- **Target population**
  - Improved diffusion

- **More funds**
  - Easy access

- **Fast-track approval**
  - Correct information to patients

- **Treatment recommendations**
  - Strategic planning

- **Awareness**
  - Negotiating with pharma companies
Q13. Share your experience with I-O therapies

- High cost and lagging reimbursement standards are the most common barriers hindering the patient access to these drugs.
- Some of the oncologists in the EEC only experienced the drugs in clinical trial settings.
- Oncologists believe that these drugs will help reduce the burden of cancer.
- More funding and development of biomarkers will facilitate access.
Conclusion
Strengths and Limitations of the survey

**Strengths**

- Responses from oncologists from 17 of the 28 EU countries with varied economical and development status
- Five or more years of clinical experience of the participating oncologist, indicating their expertise
- Collection of qualitative responses - suggestions and recommendations

**Limitations**

- Response rate of ~10%
- Only one response from each country (except Poland)
- Results not analysed to assess the statistical significance
Conclusion
Conclusion

Despite the survey respondents believing that I-O may transform the standard of care in oncology, not many of them had used these therapies in clinical practice

Reasons cited by oncologists:
- High price
- Lack of awareness and education about the target population, dose, duration, efficacy, and safety profiles of these drug
- Disparities across Europe delaying the uniform use in clinical practice

Solutions suggested by the oncologists:
- Education, awareness and appropriate dissemination of clinical trial data
- Clear treatment policies
- Improvisation in reimbursement guidelines

The gaps should be addressed by reducing the economic and disease burden across the various member states in Europe


References (continued)

References (continued)

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THANK YOU

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