THE IMLYGIC® STORY: A WINDING PATH TO INNOVATION

EBE Workshop
EU CASSS
22 May 2017

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WHY DO WE INNOVATE?

Today, one of these children has Stage IV pancreatic cancer...
TOPICS FOR TODAY

- Metastatic Melanoma
- IMLYGIC® (talimogene laherparepvec) Overview
- Clinical Strategies and Challenges
- CMC Strategies and Challenges
- Champion 21st Century Innovation
- Take Home Messages, Conclusion and Questions
# MELANOMA

Melanoma is a type of cancer that develops from damage to the pigment-containing cells known as melanocytes, due most often to DNA damage caused by ultraviolet light (UV) exposure in persons with low levels of skin pigment.

Metastatic melanoma includes Stage III and IV cancer involving the spread of melanoma into the lymph nodes and other areas of the body such as the brain, lungs, liver and other organs.

Metastatic melanoma has a 10-year survival rate of less than 10% (NIH 2009), with a life expectancy of 2-7 months, depending on the number of organs the cancer has spread to (Treatment Trials 2010).

The rates of melanoma have consistently been rising for the last 30 years.
METASTATIC MELANOMA

5-Year Survival

16%
Distant Metastases
- Lung, Stage IVM1b
- Skin or Lymph node, Stage IVM1a
- Liver, Stage IVM1c

20-70%
Regional Metastases
- Lymph node, Stage IIIC
- In-transit, Stage IIIB/C

98%
Primary Tumor

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MELANOMA DISEASE CONTINUUM

Local 
Dermatologist

Regional 
Surgical Oncologist

Distant 
Medical Oncologist

Tumor Burden

Primary Tumor

Surgery +/- IFN-α

Systemic Therapy

Surgery

Surgery

Surgery

Recurrence

Unresectable

Rapid Progression

Death

Clinical Detection

Time

Surgery +/- IFN-α

Systemic Therapy

Local Therapy
- Intralesional injection
- Topical imiquimod
- Radiation

Regional therapy
- Isolated limb infusion/perfusion
- Systemic therapy

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SYSTEMIC MELANOMA TREATMENT PRIOR TO 2011

- Dacarbazine (1975)
- High Dose Interleukin-2 (1998)

*Unmet medical need during primary clinical strategy development for IMLYGIC®

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SIX DRUGS APPROVED FOR MELANOMA FROM 2011-2015

Immunotherapies

Ipilimumab (2011)

Pembrolizumab (2014)

Nivolumab (2014)

Targeted Therapies

Vemurafenib (2011)

Dabrafenib (2013)

Trametinib (2013)

Dabrafenib/Trametinib Combination (2014)

Last patient enrolled in the OPTiM study

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IMLYGIC® IS A VERY COMPLEX PRODUCT

Aspirin
MW: 180 g/mole
0.7 nm diameter

Denosumab
MW: 147,350 g/mole
16 nm diameter

Talimogene Laherparepvec
MW: > 300,000,000 g/mole
~ 220 nm diameter

Aspirin and denosumab are scaled by diameter
IMLYGIC® IS AN HSV-1 DERIVED ONCOLYTIC VIRUS IMMUNOTHERAPY

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IMLYGIC® TARGETS TUMOR SELECTIVE REPLICATION AND ONCOLYSIS

- Infects normal cell
  - Anti-viral response
  - Limited replication

- Infects cancer cell
  - No anti-viral response
  - Replication
  - Infection of adjacent tumor cell
    - Oncolysis

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SYSTEMIC EFFECT DEMONSTRATED IN MURINE MODEL

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Days 0

Implant A20 tumor cells, grow to ~0.5 cm

Day 0

Days 7, 9, and 11

Tumor Measurements

Contralateral Uninjected Tumor

Measurements

Injected Tumor

OncoVEX without mGM-CSF

OncoVEXmGM-CSF

Vehicle Control

Balb/c mice, n = 10/group.
DUAL MECHANISM OF ACTION
RESPONSES IN INJECTED LESIONS

Baseline

Cycle 14

PR by cycle 5 and CR by cycle 11 per EAC
CR ongoing at last EAC assessment at cycle 19

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RESPONSES IN INJECTED AND UNINJECTED SKIN METASTASES

Cycle 1

Cycle 13

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RESPONSES IN DEEP NON-INJECTED, NON-VISCERAL LESIONS

Cycle 1

Cycle 10
<table>
<thead>
<tr>
<th>Context</th>
<th>Impact on MAA</th>
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<tbody>
<tr>
<td>Prior to 2011, no therapy for melanoma had demonstrated an improvement in OS Only IL-2 and dacarbazine were approved • From 2011 to 2014, several new therapies were approved for melanoma</td>
<td>MAA was not submitted until OS primary analysis results were able to be included resulting in a 2-3 year delay</td>
</tr>
<tr>
<td>DRR selected as primary endpoint - no other therapy had demonstrated OS benefits in melanoma at that time • New therapies (eg, ipilimumab) demonstrated improvement in OS</td>
<td>Important to demonstrate clinical benefit of DRR, evolving treatment landscape raised the bar and increased the importance of OS</td>
</tr>
<tr>
<td>IMLYGIC® hypothesized to have a dual mechanism of action with both local and systemic effects</td>
<td>Other than the OS secondary endpoint, the Phase 3 trial was not prospectively designed to assess evidence of systemic effect</td>
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## SAFETY CHALLENGES: CONFIRMING AN ACCEPTABLE SAFETY PROFILE

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<td>Talimogene laherparepvec is an attenuated HSV-1 virus that has been modified to selectively replicate in tumors and not normal tissues</td>
<td>Risk of herpetic infection is a safety concern, particularly among immunocompromised patients; it is important to detect herpetic infection due to talimogene laherparepvec (via qPCR testing)</td>
</tr>
<tr>
<td>FDA released draft guidance on design and analysis of shedding studies for oncolytic viruses in 2014 (Final guidance released in August 2015)</td>
<td>Accidental exposure and secondary transmission are a safety concern</td>
</tr>
<tr>
<td></td>
<td>Results from dedicated shedding and biodistribution study were important during the review to inform the risk of secondary transmission</td>
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**Modality impacted content of Risk Management Plan (RMP)**
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# MULTIPLE CONTROL ELEMENTS FOR THE COMMERCIAL MANUFACTURING PROCESS

## Manufacturing Process and Facility Design Features
- Closed systems
- Single product facility
- Robust environmental control and monitoring of particulate and microbial contamination
- Restrictions on personnel and material movement
- Validated cleaning and decontamination procedures for reusable equipment
- Physical barriers for segregation

## Materials and Components
- Cell banks and virus seed stocks free of adventitious agents
- Adventitious virus testing of bulk harvest material
- Raw materials and components with predefined specifications for adventitious agents
- Disposable sterile single use components

## Operating and Procedural Controls
- Environmental cascades of processing steps
- Stringent bioburden and endotoxin limits using validated methods
- Validated pool hold times and temperature controls
- Validated processing durations
- Filter validation and excess filter retentive capability
- Filter integrity testing
- Routine periodic media fill simulations
- Sterility and endotoxin testing of drug product prior to release

Control strategy minimizes potential for ingress and proliferation of contaminants protecting the product and patient
IMLYGIC® CMC RISK SUMMARY

Impact of Risk

Low

Medium

High

Likelihood of Risk

Low

Medium

High

Low product yields

Validation package

Facility/staff readiness

Facility modifications

Company integration challenges

Priority review approval and product availability

CAPA backlog

Analytical methods

Low product yields

Cold chain distribution

Release testing

Labeling and storage challenges (-80°C)

Filing package

Facility modifications

Company integration challenges

PAI readiness

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SPECIAL CONSIDERATIONS IN MANUFACTURING FOR A LIVE VIRUS

- Harvest testing for in vitro and in vivo adventitious virus testing on parallel cell culture sample
- No viral removal filter as this is a virus
- Sterile filtration
- Sterile DS aseptically sampled for activity to inform on dilution target
- Labeling must occur directly after fill, prior to freezing
- Storage at -80°C
Sterile filtered drug substance stored in a production suite refrigerator

Sterile filtered drug substance aseptically sampled for potency determination to calculate necessary dilution to meet target drug product concentration

Multiple drug product lots (up to 3) are filled from a single sterile filtered drug substance pool
## CMC CHALLENGES:
**FACILITY MODIFICATIONS AND STERILITY ASSURANCE**

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| Amgen implemented modifications to the manufacturing facility to support commercialization and PAI during MAA review  
  - no changes to process  
  - improve flows through the facility  
  - added RABS unit around fill line                                       | Resulted in multiple Information Requests (IRs) requesting hundreds of documents that Amgen typically provides during inspection |
| Updated facility details and facility diagrams were provided 4 months into review after notifying reviewer of the changes | Resulted in 3 month delay in the U.S. (major amendment) in approval following submission of one of the large responses to these questions |
| The last sterile filtration step before filling into vials is performed during drug substance manufacturing              | Major CMC objection pertaining to sterility assurance of the drug product    |

Amgen was challenged to make facility modifications to support commercial manufacturing in order to deliver a needed therapy to patients in a timely manner.
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GOVERNED BY CGMP AND ICH GUIDELINES

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Contract Manufacturing Arrangements for Drugs: Quality Agreements
Guidance for Industry

Guidance for Industry
CGMP for Phase 1 Investigational Drugs

Part 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

Expectation of sponsors is to stay current with regulations and guidance
Regulations must stay current and align with technological innovation

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TAKE HOME MESSAGES

• Novel endpoints must be adequately supported and in line with current disease and treatment landscape
  – Rapidly changing treatment landscape will influence registration and benefit-risk evaluation

• Seek greater clarity on requirements to support benefits and risks of novel product
  – Sponsor could pursue greater clarity on review outcome in the absence of demonstrated systemic effects
  – Integrate biomarkers into the development program early to have translational evidence of effects

• Greater initial investment by sponsor in the Target Product Profile (TPP), facility readiness, commercial manufacturing and distribution
  – Investment could have been more robust once BioVex and talimogene laherparepvec were acquired
  – Greater focus on external engagement and advocacy is required for innovative and novel therapies
WHAT DO WE INNOVATE?

While my childhood friend fights for his life, he is hopeful we can innovate to save his life…