Ovarian Cancer and Modern Immunotherapy: Regulatory Strategies for Drug Development

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Overview

- Immune agents from a regulatory perspective:
  - Efficacy
    - Patterns of response, determining “clinical benefit,” and endpoints
- Regulatory considerations for trial design
- Biomarkers in immunotherapy trials
The Challenge

Challenge assumptions:
The primacy of the drug development paradigm derived from early experience with cytotoxic chemotherapy:
  - MTD, PFS, RECIST, toxicity attribution

Preclinical development: direct toxicity and efficacy studies impossible in cells and non-human species

No longer direct molecular action of drug on tumor cell
Interleukin-2

- Described in 1976
- Approved in 1992 (RCC) and 1998 (melanoma)

<table>
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<tr>
<th>Disease</th>
<th>Year</th>
<th>ORR</th>
<th>CR</th>
<th>DOR (PR)</th>
<th>DOR (CR)</th>
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<tr>
<td>RCC</td>
<td>1992</td>
<td>15%</td>
<td>7%</td>
<td>20m</td>
<td>NR</td>
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<td>Melanoma</td>
<td>1998</td>
<td>16%</td>
<td>6%</td>
<td>6m</td>
<td>NR</td>
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- Melanoma based on 8 trials all analyzed as single-arm

- No mechanism elucidated
- No predictive or prognostic biomarkers
Regulatory Considerations: Efficacy

• Traditional approval relies on overall survival as the gold standard

• Frequently, PFS has been used as a surrogate

• But, in the context of immunotherapy: We would not have recognized the benefit of these agents if relying on RR, PFS
Road to Approval: Ipilimumab

Limitations of PFS

- Approved 2011
- Toxicity spectrum new and challenging
- Toxicity management required new awareness

Road to Approval: Ipilimumab
PFS and ORR Inadequate

Figure 1: Overall Survival

SUBJECTS AT RISK

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MOUTHS

0  4  8  12  16  20  24  28  32  36  40  44  48  52  56
Nivolumab in Squamous NSCLC

• Nivolumab in squamous NSCLC
  – First demonstration of immunotherapy in non-RCC non-melanoma

• 272 patients treated at 3mg/kg q2w vs docetaxel 75mg/m² q3w

• PFS: 3.5m v. 2.8m

• **0.7m** PFS advantage for treatment arm
Nivolumab experience

- OS: 9.2m v. 6.0m
- 1 year survival: 42% v. 24%

Clinical Regulatory Pathway: Then

- Safe dose
- Preliminary effectiveness
- Pivotal RCT
- Post-marketing safety
Clinical Regulatory Pathway: Now Options for Rapid Translation

**Phase 0:**
PD evaluation; Biomarkers of target engagement

**Phase 1a:**
Safe dose

**Phase 1b:**
“Dose expansion”: Looking for activity in specific population; may be biomarker-selected

**Phase 2:**
Randomized: Accelerated approval

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**Early-Phase trials in other countries**

**FDA**

**Pivotal RCT**

**Post-marketing safety**
Road to Approval:
Pembrolizumab in Melanoma

- Pembrolizumab
  - Accelerated approval: based on a surrogate that requires confirmatory studies

  - Expansion cohort within Trial P001
    - 173 patients, post ipilimumab and BRAF inhibitor if V600 mutation, treated with pembro at 2 or 10 mg/kg
    - Several other disease-specific cohorts reported

  - ORR based on RECIST (24% in 2mg arm) with 1 CR and 20 PR, with 18 ongoing responses at data lock

Road to Approval: Pembrolizumab in Melanoma

Road to Approval: Nivolumab in Melanoma

• Accelerated approval based on ORR
• Phase 3, ipilimumab-refractory, randomized (2:1), open-label; 631 patients screened
  – Nivolumab
  – Dacarbazine
  – Carboplatin + paclitaxel

• Planned per-protocol interim analysis as a **single arm** after 120 patients were treated with nivolumab for a minimum of 24 weeks.

Nivolumab in Melanoma

Regulatory Considerations: Efficacy

• Regulatory pathways for accelerated approval

• PFS may not be an adequate measure of clinical benefit for these agents
  – irRC changes ORR, but inconsistently (Chiou 2015)
  – irRC is of limited value

• Prolonged DOR has been a hallmark of effective immunotherapy

• Better efficacy endpoints needed:
  – eg, tumor kinetics

Regulatory considerations: AEs

• Standardized approach to tox management
  – Greater community experience ➔ easier trials
  – Early recognition and prompt management
    • Immunosuppression doesn’t seem to blunt response
  – Familiarity ➔ fewer investigations

• Case definitions for adverse events
  – *Immune-mediated* adverse events vs other
  – Consistency: attribution vs immunosuppression
  – Fewer investigations ➔ greater variability in AE reporting
Biomarkers

• Checkpoint proteins
  • Current IHC strategies are predictive/selective biomarkers in specific diseases, while non-predictive in others

• CDRH rules for companion diagnostics
Anti-PD-L1 in UBC


PD-L1 staining in tumor cells of ≥50% correlated with OS with pembrolizumab treatment

Multiple checkpoint inhibition

• Tune intensity of breaking of self-tolerance to patient and tumor immune characteristics...?
PD-L1 Biomarker Predicts Response

Avelumab experience in OvCa

• 75 women with refractory/resistant OvCa
  – 51 patients with at least 3 prior regimens
  – 0 CR, 11 PR (15%) by RECIST
  – 2/2 clear cell responses

• Breaking the immunoRx barrier?

Change from baseline in sum of longitudinal diameter (%)

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Trial Design Considerations

• Does intensity of prior therapy independently impact immune influence?
  
  – More resistant/more heavily pretreated disease → higher mutational load → more antigen targets

  Vs:
  
  – More resistance mechanisms; more senescent immune system and other host factors

• Lines of prior therapy is likely to play a continued role in selecting patients
Trial Design Considerations

• Novel endpoints to consider
  – eg: Tumor kinetics
  – Endpoints for same drug may vary by disease setting
  – Novel analyses of conventional endpoints
    • eg: DOR > ORR

• Prolonged DOR demonstration is key for regulatory evaluation when median PFS benefit may be small
Take-home messages

• Be aware of strategies for accelerated approval
  – eg, planned interim analysis of single arm if adequate follow-up duration
• Consider need for alternative efficacy endpoints
  – DOR vs PFS to support ORR for accelerated approval
  – OS for traditional approval
• Explore single-agent efficacy first
Take-home messages

• Plan for treatment beyond initial RECIST progression

• Early and aggressive toxicity management

• Evaluate checkpoint target expression as predictor of response
  – Correlation with target expression is disease-specific, and perhaps treatment-specific/test-specific
  – Goal: Marker negative population should identify patients who do not respond to treatment