Immunotherapy and Radiotherapy Combinations Part 2: Regulatory Considerations

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Disclosures

• These slides represent my own perspective and do not necessarily reflect the official policy of the U.S. FDA or Office of Oncologic Diseases.

• I have no financial relationships to disclose.
Outline

• Overview of Oncology Center of Excellence (OCE)
• Rationale for combining immunotherapy and radiation
• Summary of FDA drug/biologics/device regulation
• Trial design considerations
The U.S. Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

**FDA does not** take into account cost or payment issues

**FDA does not** regulate “practice of medicine”
Oncology Center of Excellence

The Oncology Center of Excellence fosters unified interaction between 3 FDA centers

CBER
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

OCE
ONCOLOGY CENTER OF EXCELLENCE

CDER
CENTER FOR DRUG EVALUATION AND RESEARCH

CDRH
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

www.fda.gov
Era of Immune Checkpoint Inhibitors

- Ipilimumab, an anti-CTLA-4 antibody, was the first immune checkpoint inhibitor (ICI) FDA-approved on March 28, 2011, for unresectable or metastatic melanoma.

- More than 85 approvals of anti-PD-(L)1 antibodies across numerous tumor types, including tissue-agnostic approvals:
  - Meaningful survival advantages
  - Initially developed for treatment of advanced/metastatic disease
  - Gaining approvals for earlier stage disease

- Ongoing development of other ICIs with different targets

Rationale for Combining Radiation and Immunotherapy

• RT may improve antigen presentation by antigen presenting cells
• RT activates cGAS-STING pathway to trigger immune responses
• RT modifies tumor stromal microenvironment
  – Conventional fractionated RT may be immunosuppressive while SBRT may be immunostimulatory
• RT may increase density of tumor-infiltrating lymphocytes
• RT may upregulate PD-L1 expression
• Local RT may exert a systemic abscopal effect on non-irradiated tumors

Wang Y et al, *Front Pharmacol*, 2018
Zhang Z et al, *Sig Transduct Target Ther*, 2022
Unrealized Potential of Radiation and Immunotherapy Combinations

• Limited FDA approvals of drug-radiotherapy combinations
  – Cetuximab with concurrent RT for locally advanced head and neck cancer (2006)
  – Durvalumab following chemoRT for stage III unresectable non-small cell lung cancer (2018)
  – Nivolumab for resected esophageal/GEJ cancer with residual pathologic disease after neoadjuvant chemoRT (2021)

• Misconceptions regarding required nonclinical data

• No specific regulatory guidance; however, FDA Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination may provide a helpful framework

• Intelligent trial design may increase efficiency of clinical trials

Ahmad SS et al, Clin Cancer Res, 2018
PACIFIC Trial: Durvalumab after Chemoradiation for Unresectable Non-small Cell Lung Cancer (NSCLC)

- Landmark approval for stage III, unresectable NSCLC
- 5-year OS update: 47.5 mo (95% CI 38.1, 52.9) vs 29.1 mo (95% CI 22.1, 35.1)

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<thead>
<tr>
<th></th>
<th>Durvalumab N=476</th>
<th>Placebo N=237</th>
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<tr>
<td><strong>Overall Survival (OS)</strong></td>
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<tr>
<td>Median, mo (95% CI)</td>
<td>NR (34.7, NR)</td>
<td>28.7 (22.9, NR)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.68 (0.53, 0.87); p=0.0025</td>
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<tr>
<td><strong>Progression-Free Survival (PFS)</strong></td>
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<tr>
<td>Median, mo (95% CI)</td>
<td>16.8 (13.0, 18.1)</td>
<td>5.6 (4.6, 7.8)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.52 (0.42, 0.65); p&lt;0.0001</td>
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Durvalumab USPI
Spigel DR et al, *J Clin Oncol*, 2022
Oncology Drug Development

Early-Stage Development

Is the drug safe?
Is the drug active?

Investigational New Drug (IND)

Late-Stage Development

Does the drug provide meaningful benefit?

FDA review

Approval and Post-marketing

New Drug Application (NDA)
Biologics License Application (BLA)
Investigational New Drug (IND)

Investigational
• Any experiment in which a drug is administered or dispensed to or used involving one or more human subjects
• An experiment is any use of a drug except for the use of a marketed drug for an already approved indication

Drug
• Intended for the diagnosis, cure, mitigation, treatment, or prevention of disease
• Intended to affect the structure or any function of the body

Code of Federal Regulations; 21 CFR 312
IND Review Process

• 30-day safety review

• Determines if IND is “safe to proceed” or placed “on hold”

• Reviewed on the following criteria:
  – Does not pose an unreasonable or significant risk of illness or injury
  – Is adequately designed to meet its stated objectives

Code of Federal Regulations; 21 CFR 312
IND Content

- Cover Letter
- Forms (discuss with Regulatory Affairs at your institution)
- CV (check for qualifications)
- Investigator’s Brochure (summary of drug substance)
- Preclinical toxicology (*in vitro* and animal studies)
- Clinical Pharmacology (dose, drug interactions, etc.)
- Clinical Protocol(s)
- Informed Consent Document(s)
IND Review – Nonclinical Considerations

• Pharmacology /proof of concept studies conducted before a first-in-human (FIH) trial to characterize:
  – Toxicities to target organs and reversibility of toxicities
  – Dose and exposure dependence

• Safety evaluation in animal species of the drug *alone* needed prior to FIH radiation combination trial

• Animal studies with drug/RT combination may be helpful if drug being developed as a radiosensitizer
  – May help to select radiation dose based on extent of radiosensitization
IND Review – Dosing Considerations

• Rationale for dosing regimen
  – Is the dose safe?
  – Is there prior human experience?
  – May be based on toxicology data (nonclinical)

• Dose-limiting toxicities

• Dose modifications

• Overlapping toxicities with radiation
IND Review – Safety Monitoring

- Provide a calendar of events (testing schedule)
- Consider immune-related and radiation-related toxicities
- Potential for increased toxicity and overlapping toxicities (e.g., ILD/pneumonitis)
- Follow patients for long-term safety outcomes
  - Resolution of toxicities?
  - Capture late onset toxicities from cumulative radiation exposure
  - Assess quality of life
Pre-IND ("Type B") Meeting

• May request to meet to discuss an IND prior to submission
  - Scheduled within 60 days
  - Meeting includes the team that will review your application
  - FDA may respond with written responses or teleconference

• Include:
  - Specific questions
  - Provide detailed procedures for topics you want addressed
Radiation: Drug or Device?

- **Therapeutic radiation** (e.g., external beam radiation, brachytherapy) is a **device** rather than a drug, but often investigated in combination with drugs/biologics.

- **Radiopharmaceuticals** (e.g., lutetium Lu-177 vipivotide tetraxetan) are considered **drugs**.
Investigational Device Exemption (IDE)

- An IDE allows an investigational device to be used in a trial

- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the trial is initiated

- Clinical evaluation of devices not cleared for marketing requires:
  - Investigational plan approved by an institutional review board (IRB)
  - Informed consent from all patients
  - Labeling stating device is for investigational use only
  - Monitoring of study
  - Required records and reports

Code of Federal Regulations; 21 CFR 812
Significant vs Nonsignificant Risk Devices

• **Significant risk devices**
  – Potential for serious risk to health, safety, welfare of a subject
  – Examples: cardiac pacemakers, hydrocephalus shunts
  – Clinical evaluations must have approved IDE before trial is initiated

• **Nonsignificant risk devices**
  – Do not pose a significant risk to human subjects
  – Example: daily-wear contact lenses
  – Requires only IRB approval, not an IDE, prior to initiating trial
  – Most protocols with radiation, unless utilizing new devices, don’t require IDEs
## Trial Design Considerations: Stage of Disease

### Early-Stage

- **Goals of therapy:**
  - Improved survival
  - Improved organ function or organ preservation
- Curative-intent treatment → patients may have to endure long-term treatment related toxicities

### Late-Stage/Metastatic

- Patients may be less fit
- Palliative RT/immunotherapy to augment abscopal effect
- Oligometastatic disease
  - SBRT/immunotherapy for long-term disease control
Trial Design Considerations: Sequential vs Concurrent Therapy

• Sequential therapy
  – Neoadjuvant immunotherapy prior to RT/chemoRT
  – Adjuvant immunotherapy after RT/chemoRT
  – Neoadjuvant and adjuvant immunotherapy → need to demonstrate contribution of effect of both neoadjuvant and adjuvant therapy

• Concurrent therapy
  – Immunotherapy given concurrently with radiation
Neoadjuvant and Adjuvant Therapy
Example: KEYNOTE-689 for Head and Neck Cancer

- Treatment 1: Neoadjuvant treatment
  - Patient population
    • ≥18 years
    • Histologically confirmed new diagnosis of resectable, nonmetastatic, LA HNSCC
    • ECOG PS 0 or 1
  - Treatment Arm A
    - Pembrolizumab IV 200 mg Q3W (2 cycles)
    - No neoadjuvant treatment before surgery
  - Treatment Arm B
    - R 1:1

- Treatment 2: Adjuvant treatment
  - Surgery
  - High-risk: Pembrolizumab IV 200 mg Q3W (15 cycles) + RT + cisplatin
  - Low-risk: Pembrolizumab IV 200 mg Q3W (15 cycles) + RT
  - Follow-up for disease evaluation, safety, and survival
Concurrent Radiation and Immunotherapy
Example: EA3191 Trial for Head and Neck Cancer

- Ongoing trial from NCI
- Primary objectives:
  - Compare OS between pembrolizumab + RT and chemotherapy + RT arms
  - Compare OS between pembrolizumab monotherapy and chemotherapy + RT arms

ECOG-ACRIN: EA3191 Educational Material
https://ecog-acrin.org/clinical-trials/ea3191-educational-materials/
Efficacy Evaluations of RT and Immunotherapy Combinations

• Assess clinical outcomes important to patients
  – Improvement in survival, functioning, or tumor-related symptoms

• Overall survival is often preferred endpoint in pivotal oncology trials
  – Prolonging survival is meaningful to patients
  – Limits bias in terms of assessment
  – Endpoints such as progression-free survival and event-free survival based on objective assessment criteria may also be used

• Regulatory approval based on earlier endpoints could be considered; discuss use of early endpoints with FDA prior to initiating a trial
Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

• No specific guidance for RT and immunotherapy but principles in this guidance may be applicable

• Important to demonstrate the contribution of effect of each individual component of the combination therapy
Summary and Conclusions

- Immunotherapy and RT combinations hold promise for the treatment of patients with cancer
- There have been limited FDA approvals of therapies combining immunotherapy and radiation, potentially due to perceived challenges of trials
- Protocols combining immunotherapy and RT should be submitted as INDs and often don’t require IDEs
- Nonclinical data combining radiation and immunotherapy may not be required
- Safety monitoring should consider overlapping toxicities
- Sponsors may request meetings with FDA to discuss drug development and trial designs
Thank you!

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