Immunotherapy and Radiotherapy Combinations Part 2: Regulatory Considerations

Paz J. Vellanki, MD, PhD
Medical Oncologist
United States Food and Drug Administration
Center for Drug Evaluation and Research, Office of Oncologic Diseases

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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

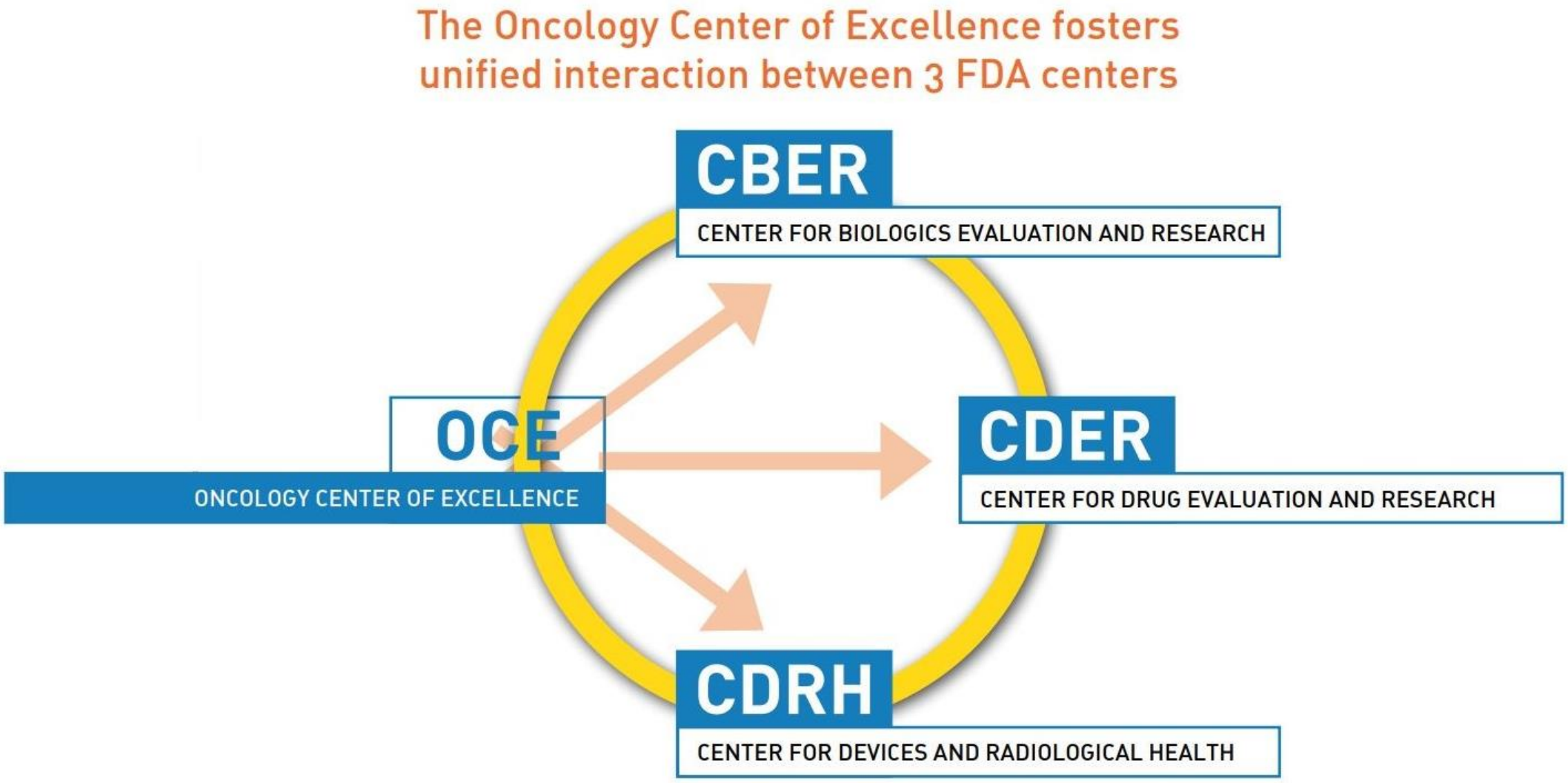
FDA Mission

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



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

* Beaver JA, Pazdur R, *N Engl J Med*, 2021

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

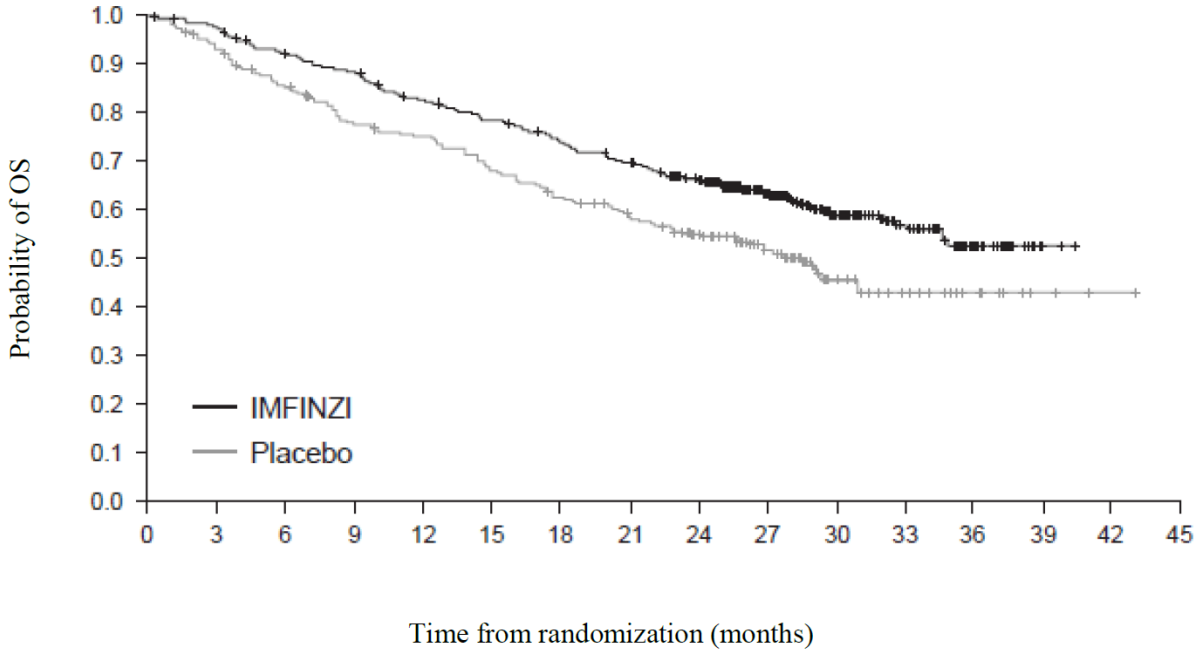
Wang Y et al, *Front Pharmacol*, 2018
Zhang Z et al, *Sig Transduct Target Ther*, 2022

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)

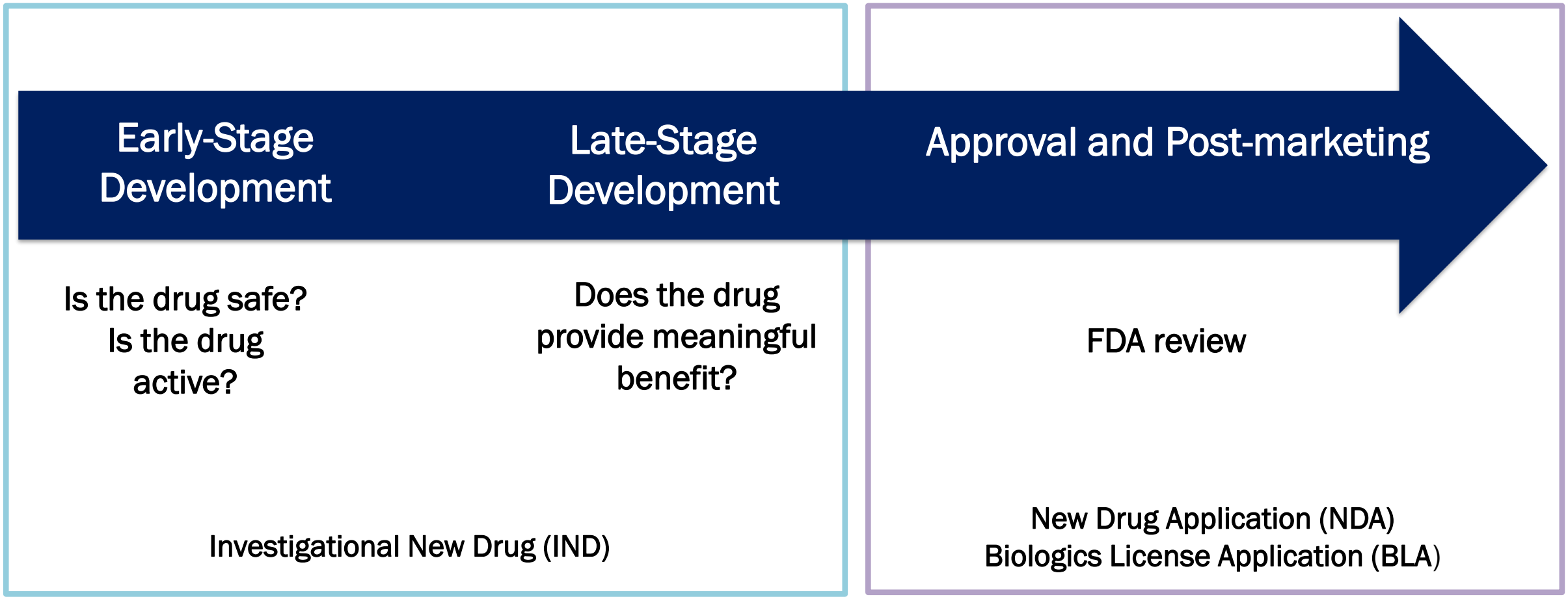


	Durvalumab N=476	Placebo N=237
Overall Survival (OS)		
Median, mo (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)
HR (95% CI)	0.68 (0.53, 0.87); p=0.0025	
Progression-Free Survival (PFS)		
Median, mo (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
HR (95% CI)	0.52 (0.42, 0.65); p<0.0001	

- 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)

Durvalumab USPI
Spigel DR et al, *J Clin Oncol*, 2022

Oncology Drug Development



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:
  - <u>Specific</u> questions
  - Provide <u>detailed</u> 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

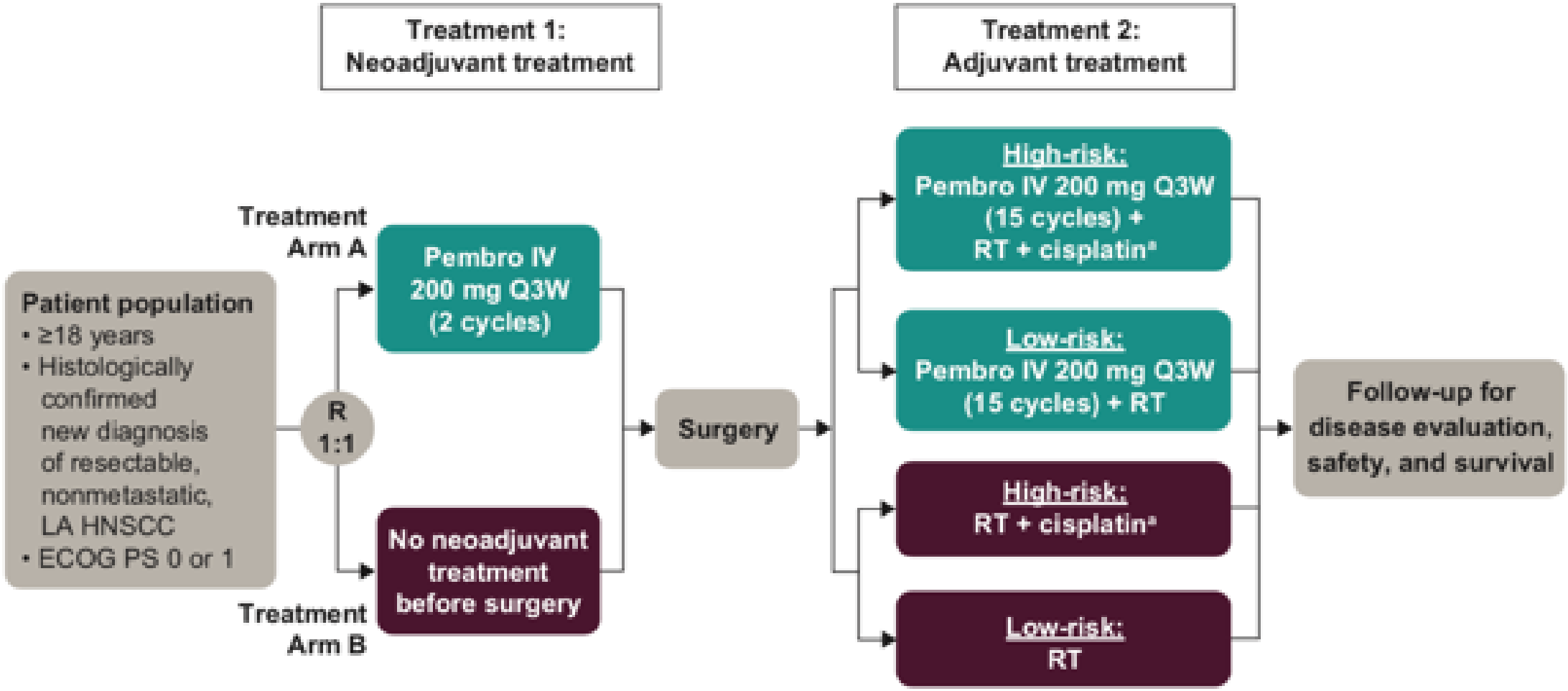
Late-Stage/Metastatic

- Patients may be less fit
- Palliative RT/immunotherapy to augment abscopal effect
- Oligometastatic disease
  - SBRT/immunotherapy for long-term disease control

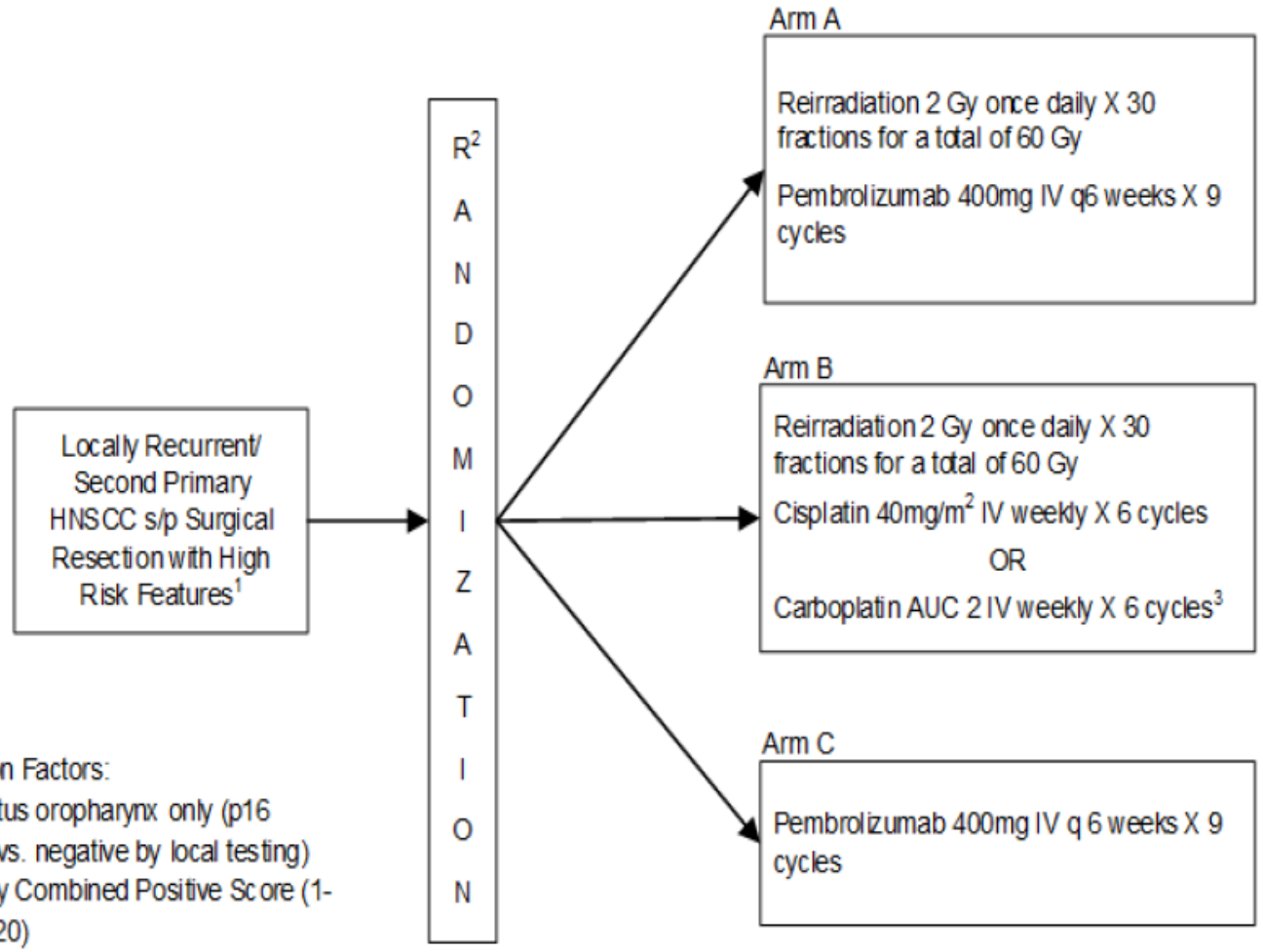
Trial Design Considerations: Sequential vs Concurrent Therapy

- 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



Concurrent Radiation and Immunotherapy Example: EA3191 Trial for Head and Neck Cancer



Stratification Factors:

- HPV status oropharynx only (p16 positive vs. negative by local testing)
- PD-L1 by Combined Positive Score (1-19 vs. ≥20)
- Received prior anti-PD-1/PD-L1 as part of curative intent therapy: Yes vs. No

- 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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical

- 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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