

# Regulatory and Labeling Challenges with Developing Immuno-Oncology Combination Therapies

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# Background

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- Oncology drug development moving into combinations with I-O products to improve outcomes for patients
- FDA requires evidence for contribution of effect of each agent in a regimen for which a labeled indication is sought
- What level of evidence will be acceptable to FDA to support labeling of different components for a new regimen?

# Definitions

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- Cross labeling: inclusion of information in product labeling of two (or more) oncology products approved in a combination regimen for a specific indication
- Regimen: two or more therapeutic products that are marketed separately but are approved for use in combination based upon one or more adequate and well controlled trials

# Issue

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- Cross labeling is already here in oncology
  - Over a dozen NDAs/BLAs in Office of Hematology and Oncology for cross-labeling
- Applications range from two novel agents to two supplemental indications and everything in between
- Supplemental BLAs and NDAs no longer require a user fee under PDUFA VI

# Unique world of oncology

- Overwhelming majority of oncology clinical trials measure ORR, either as key outcome measure or to direct clinical care.
- Malignancies generally do not spontaneously regress, thus responses attributed to the treatment intervention and not to natural history of the disease.
- ORR frequent basis of approval in the 1970s before moving to other outcome measures.
- Consistency of assessing response rates in oncology trials enables estimation of treatment effect contribution for each component in a regimen in oncology compared to other disease areas.
- If novel-novel regimen, development and cross labeling should follow guidelines set forth in co-development guidance (<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm236669.pdf>)

# Example #1: Dabrafenib+Trametinib

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- Approved as regimen for melanoma (adjuvant and metastatic), NSCLC and anaplastic thyroid cancer
- Initial indication in metastatic melanoma had randomized trials of D+T v D and D+T v vemurafenib
  - 1° endpoint OS in both, ORR assessed in both
  - Dabrafenib already approved in this setting as monotherapy based on randomized trial with PFS and ORR
- Subsequent indications had variety of data, from randomized trials to single-arm trials
  - Knowledge of dabrafenib monotherapy ORR in same/similar setting
  - Understanding of biology for this mutation and targeted therapy in most tumor settings
  - Evidence from prior approvals with D+T

## Example #2:

# **Pemetrexed+pembrolizumab/carboplatin**

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- Approved for first-line metastatic, non-squamous NSCLC with pembrolizumab and carboplatin as accelerated approval
  - Based on ORR, with PFS as secondary endpoint
  - PMR to provide OS results from a randomized trial in same setting
- Multiple approvals in NSCLC and many citations in literature regarding response rates both as monotherapy and in combination with platinum chemotherapy
- Monotherapy experience from pembrolizumab from other trials in this setting known
- Difficult/unethical to conduct multi-arm trial in which pemetrexed effect isolated in relation to the PPC combo given pemetrexed's position as SOC

# Example #3: Fulvestrant+palbociclib or abemiciclib

- Approved for combination with palbociclib or abemiciclib after progression on endocrine therapy in HER2-, HR+ advanced breast cancer
  - Based on ORR, with PFS as secondary endpoint
  - PMR to provide OS results from a randomized trial in same setting
- Multiple approvals in advanced breast cancer
  - Monotherapy in first-line HR+, HER2-
  - Monotherapy after endocrine therapy in HR+
  - Activity in setting of combination with CDK4/6 inhibitors well known
- Monotherapy experience with both palbociclib and abemiciclib from other trials in this setting known
- Difficult/unethical to conduct multi-arm trial in which fulvestrant effect isolated in relation to the combos given fulvestrant's position as SOC



# Labeling initiatives

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- Overall FDA goal to keep labels updated, even after generics have entered the market
  - Identified over 40 oncology products with generics on market that are commonly in use
  - Over half not even in PLR formatting required by FDA starting in 2006
- Two key interventions
  - Encourage supplements, including cross labeling
    - No user fee for supplements
  - Generic labeling update project

# Conclusions for cross labeling

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- Regulatory position of all products in the combination regimen must be considered (approved or NME, approved in specific disease, setting)
- All available data about a product to be included in the evaluation of a cross-labeling application (SOC, new in disease context, setting, biologic rationale)
- OCE is encouraging companies to submit cross-labeling applications

Thank you!

