Neoadjuvant platform: Endpoints and regulatory opportunities

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Surrogate endpoint

- 21 CFR 314- “A drug that provides meaningful benefit over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit OR a clinical endpoint that can be measured earlier than an effect on irreversible morbidity and mortality that is reasonably likely to predict an effect of IMM or other clinical endpoint” may be eligible for approval under **accelerated approval**.

Neoadjuvant platform

- Historically (Bristow meta-analysis 2006)- neoadjuvant chemo with interval debulking was associated with inferior OS, compared to primary surgery.
- More recent data (Vergote 2010) suggest that neoadjuvant chemotherapy followed by interval debulking is not inferior to primary debulking surgery.
- Most neoadjuvant trials have utilized OS as primary endpoint, and PFS as secondary.

Neoadjuvant platform

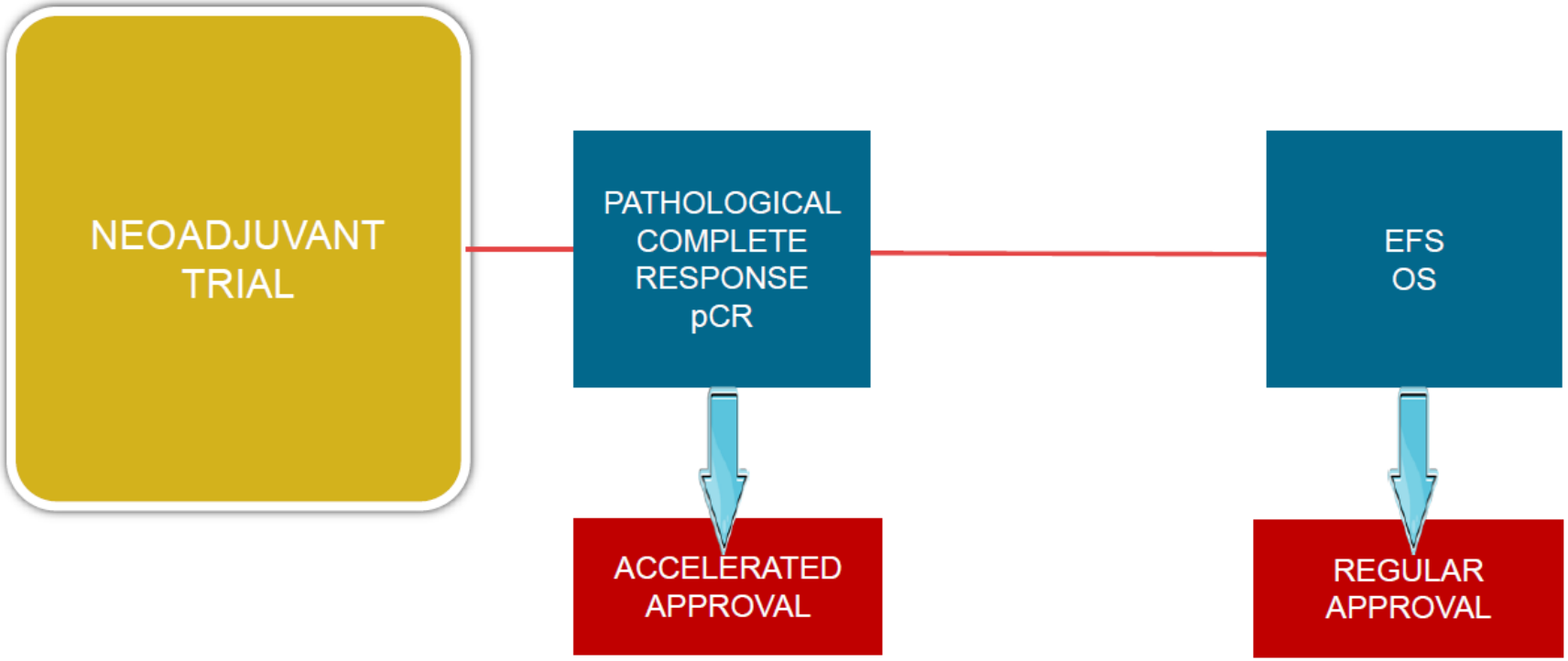
Breast cancer

- Relatively straightforward surgery
- Well-delineated pathologic sampling
- Chemotherapy:
  - Neoadj = Adjuvant in outcomes

Ovarian cancer

- Complex surgery, multiple sites/ lesions
- Pathologic evaluation very complex
- Chemotherapy
  - Adjuvant > Neoadj for OS.

Breast Neoadj Trial Design

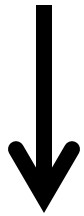


Info needed for regulatory path: Neoadj breast cancer setting

Is pCR associated with long-term clinical benefit (EFS or OS)?

Which pCR definition best associated with long-term clinical benefit?

What magnitude of pCR improvement predicts long-term clinical benefit?



Pooled analysis of randomized neoadjuvant trials

Facts learned from breast cancer pooled analysis

- There was correlation between pCR and long-term outcome at the **patient level** (responder analysis).
- There was no correlation between pCR and long-term outcome at the **trial level**.
- If true in ovarian cancer, this could be problematic in allowing for comparison of new agents in the neoadjuvant setting.

Cortazar, et al. Lancet 2014; 384: 164-72.

Three questions

1) In ovarian cancer are:
   Neoadj chemo→ surgery = surgery→ adj. chemo?

2) How is pCR measured in ovarian cancer?

3) Is there a link between pathologic complete response (pCR) and long-term outcome in ovarian cancer?

Issues

- If a new agent could improve the ability to achieve pCR compared to standard NACT, could this lead to drug approval?
- Are there potentially therapies that may be able to achieve an improvement in pCR after just the 3 cycles allotted for NACT?
- Correlation with EFS and/or OS would be necessary, but what magnitude?
- Problem of combining new agents with carboplatin/taxol backbone.

Final Advice

- Talk to the FDA early and often during the development process!

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