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FDA Perspective on Advancing Neo-adjuvant Immunotherapy Toward Clinical Practice

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Disclosures

- No disclosures

Outline

- Landscape of early stage cancer therapy
- Review of clinical practice guidelines
- Overview of neoadjuvant immunotherapy
- Regulatory considerations
- Biomarkers
- Future directions

Immunotherapy adjuvant approvals

- 2015: ipilimumab for patients with cutaneous melanoma with involvement of lymph nodes following complete resection
- 2017: nivolumab for adjuvant treatment of melanoma
- 2019: pembrolizumab for adjuvant treatment of patients with melanoma
- **No neoadjuvant approvals**, but studies ongoing in multiple tumor types

Neoadjuvant immunotherapy examples

- **Melanoma:** OpACIN trial and others demonstrate improved RFS in patients with pCR after neoadjuvant nivolumab + ipilimumab[1]
- **NSCLC:** Meta-analyses of neoadjuvant chemotherapy demonstrate a survival benefit in stage IA-III NSCLC[2]
- **Recurrent glioblastoma:** Improved OS in patients who received neoadjuvant pembrolizumab[3]
- **Colorectal cancer:** pathologic responses in MMR-proficient and deficient early stage cancers[4]
- **TNBC:** immunotherapy + chemotherapy has led to increased pCR rate

[1]Pelster M Curr Treat Options in Oncol 2020 [2]Song W, J Thorac Oncol, 2010
[3]Cloughesy TF, Nat Med 2019 [4]Chalabi M, Nat Med 2020 [5]Bergin, F1000Res 2019

Potential advantages of neoadjuvant therapy

- May be better tolerated
- Reduction of tumor burden
- Shorter trial timelines
- Determination of on-treatment response
- Pathologic response may predict long-term outcome
  - New endpoints: pCR, MPR

Blumenthal G, J Thorac Oncol 2018

Neoadjuvant immunotherapy

- Increased neoantigen load may result in increased therapy efficacy
- Expansion of neoantigen specific T-cell clones
- Increased durability of anti-tumor T-cell responses

Gajewski T, NEJM 2018
Liu J, Cancer Discov 2016

Regulatory considerations for neoadjuvant drug development

- Biomarkers as new endpoints should lie in the causal pathway of the disease process
- Accelerated approval: *reasonably likely* to predict benefit
- New endpoint for accelerated approval:
  - Should be prognostic at the individual level
  - Demonstrates that the magnitude of difference between arms predicts long-term benefit

Blumenthal G, J Thorac Oncol 2018

pCR vs. MPR:

Relationship with long-term outcome not established

- pCR observed in <10% of patients receiving cisplatin-based chemotherapy; not feasible as endpoint for some tumor types
- MPR (10% or less residual tumor cells) proposed as primary/secondary endpoint in some trials
- Pertuzumab, trastuzumab, and chemo approved as neoadjuvant tx for early stage HER2+ breast cancer based on pCR
- No trial-level relationship between improvement in pCR and improvement in long-term outcome has been established (CTneoBC trial)

FDA Guidance for Industry, July 2020

Liquid biopsy

- Emerging approach to monitor response during and after neoadjuvant therapy
- Broad range of ctDNA positivity across stage/tumor types
- Residual levels of ctDNA after curative-intent surgery or RT may be a marker for patients at risk of recurrence

Future directions

- Data in additional cancers to support use of neoadjuvant endpoints for accelerated approval
- Standardization of pathologic endpoints for use across all neoadjuvant trials
- Meta-analyses to assess relationship of neoadjuvant endpoints to survival
- Use of residual tumor to understand biology of persistent tumor cell survival and response to therapy

Blumenthal G, J Thorac Oncol 2018

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