The Role of Tissue/Circulating Based Biomarkers in Clinical Trials: Regulatory Perspective

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Disclosure Information

I have no financial relationships to disclose

And

I will not discuss off label use and/or investigational use in my presentation
Outline

• Biomarker Background
• Options for Clinical Trials
• Regulatory Pathways
• Conclusions
Biomarker

- Prognostic
- Predictive
- Diagnostic
- Response
Biomarker

Response

Safety
Pharmacodynamic
Efficacy-Response
Surrogate Endpoint
Molecular Genomic Biomarker

Tissue or Liquid (e.g. CTCs, circulating cell-free tumor DNA)
Ovarian Cancer Biomarker Clinical Trials

- Stratification

Platinum-resistant, recurrent ovarian $\rightarrow$ Gene Expression Test $\rightarrow$ Biomarker

Signature positive $\rightarrow$ Therapy

Signature negative $\rightarrow$ Standard of Care

Therapy $\rightarrow$ Standard of Care
Ovarian Cancer Biomarker Clinical Trials

- Enrichment

Platinum-resistant, recurrent ovarian $\rightarrow$ Gene Expression Test $\rightarrow$ Therapy

Signature positive $\rightarrow$ Standard of Care

Signature negative $\rightarrow$ Standard of Care
Ovarian Cancer Biomarker Clinical Trials

Platinum-resistant, recurrent ovarian

Genetic Analysis e.g. NGS

Biomarker Defined Sub-Group Pathways (hypothetical options)

- PI3K/RAS
- NOTCH
- CDK, Cyclin D1/Rb
- Homologous Recomb

Targeted therapy or combination

Control arm*

Targeted therapy or combination

Control arm*

Targeted therapy or combination

Control arm*

Targeted therapy or combination

Control arm*

*Standard chemotherapy-containing regimen
Ovarian Cancer Biomarker Clinical Trials

- Marker of response
  - Go/No Go decision

Time point X

- Targeted therapy or combination
- Control arm

ctDNA

- ctDNA positive
- ctDNA negative
Ovarian Cancer Biomarker
Clinical Trials

– Marker of response
  • Prognostic indicator
  • Predictive indicator of early decision to switch therapy
Ovarian Cancer Biomarker Clinical Trials

- Marker of response
  • Surrogate Endpoint

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Time point X

ctDNA Positive Negative
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PFS OS
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Ovarian Cancer Biomarker
Clinical Applications

• Patient Selection for specific treatment
  – e.g. gBRCA and olaparib
• Prognosis
• Need to switch therapy
• Need to treat
• Early diagnosis
Regulatory Options for Biomarker Development

- IND- Therapeutic product (Drug/Biologic)

- Biomarker Qualification Program
Biomarker Development

Context of Drug/Biologic: Clinical Trial(s)

- CDRH- Companion Diagnostic Development
  - Investigational Device Exemption (IDE)
    - Exempt- No IDE
    - Non-significant Risk- abbreviated IDE
    - Significant Risk- IDE application

- CDER
  - Biomarker development plan
  - Clinical Trial design
Biomarker Development
Context of Drug/Biologic: Submission/Approval

- **CDRH:** premarket submission/application
  - Companion Diagnostic: Essential for safe and effective use of therapeutic product
  - Premarket review

- **CDER:** (s)NDA/(s)BLA
  - Multidisciplinary Review
  - Incorporate biomarker/FDA-approved device into label
Biomarker Qualification Program

Initiation

- Letter of Intent
- Review team formed

Consultation Advice Stage

- Briefing Document

Review

- Full Submission
- Review

Acceptance

- Meetings
- Meetings Recommendation
Qualified Biomarkers

- Interpretation and application in drug development/clinical trials
- No reconfirmation of acceptance within context of use
- Prognostic- COPD/Polycystic Kidney Disease
- Diagnostic- Fungal Infection
- Safety/Response- Nonclinical
Conclusions

• Consider biomarkers throughout drug development

• Communicate early and often with FDA
  – Biomarker Trial design
  – Endpoints
  – Companion Diagnostic
  – Biomarker Qualification
References

• DDT Qualification Guidance

• IVD Companion Diagnostic Guidance

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