FDA-AACR Workshop on
HOW MUCH IS ENOUGH?
TRIAL DESIGNS FOR
TREATMENT REGIMENS
WITH MULTIPLE PHASES

May 9, 2024, 9 a.m.–4 p.m.
The Bethesda Marriott | Bethesda, MD
WELCOME AND INTRODUCTION
Elizabeth M. Jaffee, MD, FAACR
Sidney Kimmel Comprehensive Cancer Center

WORKSHOP OVERVIEW
Harpreet Singh, MD
U.S. Food and Drug Administration
FDA-AACR Workshop on

HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES

May 9, 2024, 9 a.m.–4 p.m.
The Bethesda Marriott | Bethesda, MD
SESSION 1: CURRENT LANDSCAPE FOR PERIOPERATIVE TRIAL DESIGNS

Current Therapeutic Landscape for Early-Stage Solid Tumors
Oladimeji Akinboro, MD, U.S. Food and Drug Administration

Biomarker-Guided Perioperative Clinical Trials
Valsamo Anagnostou, MD, PhD, Sidney Kimmel Comprehensive Cancer Center

Implementing Sequential, Multiple, Randomized (S.M.A.R.T.) Trial Designs
Kelley Kidwell, PhD, University of Michigan School of Public Health

SESSION 2A: OPTIMIZING PERIOPERATIVE TREATMENT REGIMENS

Optimizing the Regimen: Cooperative Group Perspective
Jhanelle Gray, MD, Moffitt Cancer Center

Cumulative and Long-Term Toxicity with Immunotherapy
Mark Yarchoan, MD, Sidney Kimmel Comprehensive Cancer Center

SESSION 2B: THE FUTURE OF REGISTRATIONAL TRIALS WITH MULTIPLE ARMS

Industry Perspective on Future Perioperative Trials: Efficacious vs Optimal Treatment
Minghua (Michael) Shan, PhD, Bayer Pharmaceuticals

Statistical Considerations for Future Perioperative Trials
Chi Song, PhD, U.S. Food and Drug Administration

SESSION 3: CONSIDERATIONS IN OTHER THERAPEUTIC AREAS

Where Do We Go from Here? Considerations for NSCLC and Other Therapeutic Areas
Harpreet Singh, MD, U.S. Food and Drug Administration
Fireside Chat with FDA Division Directors

- Harpreet Singh, MD  
  Oncology II
- Angelo de Claro, MD  
  Hematologic Malignancies I
- Nicole Gormley, MD  
  Hematologic Malignancies II
- Laleh Amiri-Kordestani, MD  
  Oncology I
- Steven Lemery, MD  
  Oncology III

Join the conversation:  
#AACRSciencePolicy
WELCOME AND INTRODUCTION

Elizabeth M. Jaffee, MD, FAACR
Sidney Kimmel Comprehensive Cancer Center

WORKSHOP OVERVIEW

Harpreet Singh, MD
U.S. Food and Drug Administration
SESSION 1: CURRENT LANDSCAPE FOR PERIOPERATIVE TRIAL DESIGNS
How Much is Enough?:
Trial Designs for Treatment Regimens with Multiple Phases in Solid Tumors

Oladimeji (Ladi) Akinboro, MD, MPH
Office of Oncologic Diseases
FDA
May 9, 2024

www.fda.gov
Clinical benefit of adjuvant therapy first established in oncology in node-positive breast cancer based on multiple RCTs

• Premise of Adjuvant Chemotherapy:
  – Treatment and potential cure of micro-metastases
  – Favorable benefit-risk anticipated for appropriately selected patients i.e., those with high-risk/locally-advanced disease
Clinical efficacy of neoadjuvant therapy shown to be comparable to adjuvant therapy in breast cancer based on RCT evidence\textsuperscript{1-3}

- **Premise of Neoadjuvant Chemotherapy:**
  - Treatment and potential cure of micro-metastases
  - Potential downstaging, increased tissue conservation, and/or reduced surgical complications
  - Opportunity for pathologic assessment of treatment effect and development of correlative biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Received lumpectomy</th>
<th>5-year DFS</th>
<th>5-year Distant DFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant</td>
<td>67%</td>
<td>66.7%</td>
<td>73.3%</td>
<td>79.6%</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>60%</td>
<td>67.3%</td>
<td>73.2%</td>
<td>80.0%</td>
</tr>
<tr>
<td>( p )-value</td>
<td>-</td>
<td>0.99</td>
<td>0.70</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Abbreviations: AC=adriamycin (doxorubicin) plus cyclophosphamide; DFS=disease-free survival; \( n \)=number; OS=overall survival.

Combined perioperative systemic regimens first established in oncology in lower esophageal/GEJ/gastric adenocarcinoma

<table>
<thead>
<tr>
<th>RCT</th>
<th>Investigational therapy</th>
<th>Control arm</th>
<th>Investigational treatment phase(s)</th>
<th>Primary Endpoint(s)</th>
<th>Status/Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multi-agent chemo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contribution of phases not isolated in RCTs **though**:

- Relatively limited duration of treatment: 2-4 cycles preop and 3-4 cycles postop
- OS primary endpoint

Abbreviations: AJCC=American Joint Committee on Cancer staging edition; CF=cisplatin plus continuous intravenous infusional 5-fluorouracil; chemo=chemotherapy; CX=cisplatin plus capecitabine; DFS=disease-free survival; ECX=epirubicin plus cisplatin plus capecitabine; ECF=epirubicin plus cisplatin plus continuous intravenous infusional 5-fluorouracil; ECX+bevacizumab+cisplatin plus capecitabine; EFS=event-free survival; FFCD=Fédération Francophone de Cancérologie Digestive; FLOT=Intravenous infusional 5-fluorouracil plus leucovorin plus oxaliplatin plus docetaxel; FNCLCC=Fédération Nationale des Centres de Lutte contre le Cancer; GEJ=gastroesophageal junction; ICI=immune checkpoint inhibitor; OS=overall survival; pCR=pathologic complete response; Q2W=every 2 weeks; Q3W=every 3 weeks; RCT(s)=randomized controlled trial(s); UICC=International Union against Cancer.

In ICI/targeted therapy era: Combined perioperative ‘regimen’ first approved in early-stage TNBC

KEYNOTE-522: Not designed to isolate contribution of phases

Women with high-risk, early stage TNBC

Pembrolizumab Chemotherapy

N=1174 R: 2:1

Placebo Chemotherapy

Pembrolizumab Q3W x 9 cycles

Surgery

pCR

EFS OS

Placebo Q3W x 9 cycles

Primary endpoints: pCR and EFS

Key secondary endpoint: OS

Abbreviations: EFS=event-free survival; ICI=immune checkpoint inhibitor; N=number; OS=overall survival; pCR=pathologic complete response; R=randomization; Q3W=every 3 weeks; R=randomization; TNBC=triple-negative breast cancer.


www.fda.gov
KEYNOTE-522: Improved EFS but additional toxicity (irAEs) with the investigational combined perioperative ‘regimen’ \(^1, 2\)

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + Chemotherapy (n=784)</td>
<td>16% (0.48, 0.82)</td>
<td>0.00031</td>
</tr>
<tr>
<td>Placebo + Chemotherapy (n=390)</td>
<td>24%</td>
<td>-</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + Chemotherapy (n=784)</td>
<td>0.63</td>
<td>0.72 (0.51, 1.02)</td>
</tr>
<tr>
<td>Placebo + Chemotherapy (n=390)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + Chemotherapy (n=784)</td>
<td>0.00031</td>
<td>-</td>
</tr>
<tr>
<td>Placebo + Chemotherapy (n=390)</td>
<td>-</td>
<td>(45%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI=confidence interval; EFS=event-free survival; HR=hazard ratio; IF=information fraction; imAEs=immune-mediated adverse events; OS=overall survival.

<table>
<thead>
<tr>
<th>RCT</th>
<th>Investigational ICI</th>
<th>Treatment phase(s)</th>
<th>Primary Endpoint(s)</th>
<th>Status/Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMpower030 (NCT03456063)</td>
<td>Atezo + chemo → Atezo</td>
<td>Neoadjuvant + Adjuvant</td>
<td>EFS</td>
<td>Ongoing</td>
</tr>
<tr>
<td>IMpower010 (NCT02486718)</td>
<td>Atezo</td>
<td>Adjuvant</td>
<td>DFS (a)</td>
<td>FDA-approved (b)</td>
</tr>
<tr>
<td>SKYSCRAPER-15 (NCT06267001)</td>
<td>Atezo + Tiragolumab</td>
<td>Adjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>AEGEAN (NCT03800942)</td>
<td>Durva + chemo</td>
<td>Neoadjuvant + Adjuvant</td>
<td>EFS, pCR (ongoing)</td>
<td></td>
</tr>
<tr>
<td>MERMAID-I (NCT04485601)</td>
<td>Durva</td>
<td>Adjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>BR.31 (NCT02273371)</td>
<td>Durva</td>
<td>Adjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>CheckMate-816 (NCT0259632)</td>
<td>Nivo + chemo</td>
<td>Neoadjuvant</td>
<td>EFS, pCR (ongoing)</td>
<td></td>
</tr>
<tr>
<td>CheckMate-77T (NCT0348693)</td>
<td>Nivo</td>
<td>Neoadjuvant</td>
<td>EFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>ANVIL (NCT02595941)</td>
<td>Nivo</td>
<td>Adjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-671 (NCT02878547)</td>
<td>Pembrolizumab</td>
<td>Neoadjuvant</td>
<td>EFS, MPR (ongoing)</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-091 (NCT03101841)</td>
<td>Pembrolizumab</td>
<td>Adjuvant</td>
<td>DFS (FDA-approved)</td>
<td></td>
</tr>
<tr>
<td>BTCRC-LUN18-153 (NCT04317534)</td>
<td>Pembrolizumab</td>
<td>Neoadjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>NCT04316364 (ex-U.S)</td>
<td>Pembrolizumab</td>
<td>Adjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>NCT05116462 (ex-U.S)</td>
<td>Pembrolizumab</td>
<td>Adjuvant</td>
<td>DFS (ongoing)</td>
<td></td>
</tr>
<tr>
<td>RATIONALE 315 (NCT04379635; ex-U.S/China-only)</td>
<td>Tislelizumab</td>
<td>Neoadjuvant + Adjuvant</td>
<td>EFS, MPR (ongoing)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NEOTORCH (NCT04158440; ex-U.S/China-only)</td>
<td>Toripalimab</td>
<td>Neoadjuvant + Adjuvant</td>
<td>EFS, MPR (a)</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

Abbreviations: Atezo=atezolizumab; chemo=platinum-based chemotherapy; DFS=disease-free survival; Durva=durvalumab; EFS=event-free survival; IC=immune checkpoint inhibitor; MPR=major pathologic response; Nivo=nivolumab; NSCLC=non-small cell lung cancer; pCR=pathologic complete response; PD-L1=programmed death (ligand)-1; Pembrol=pembrolizumab; RCTs=randomized controlled trials.

(a) Overall survival included in the protocol prespecified statistical testing strategy to control overall Type I error.  (b) Approved for those who are PD-L1-positive.  (c) Approved for patients who received prior chemotherapy.
Uncertainties due to study design

What is the relative contribution of the neoadjuvant and adjuvant ICI on efficacy endpoints? Are patients being overtreated?

ICI in both phases:
- As add-on therapy to chemotherapy in the neoadjuvant phase
- As a single agent in the adjuvant phase

Neoadjuvant phase
- Platinum-based chemotherapy + ICI for 3-4 cycles

Adjuvant phase
- ICI for up to 1 year of therapy
- Placebo for up to 1 year of therapy

Resectable NSCLC

Platinum-based chemotherapy ± Placebo for 3-4 cycles

SURGERY

Abbreviations: ICI=immune checkpoint inhibitor; NSCLC=non-small cell lung cancer.
Anti-PD-(L)1-based regimens in resectable NSCLC \textsuperscript{a}:

**Apparent comparable EFS/DFS treatment effect sizes across neoadjuvant-only RCT vs. perioperative RCTs**

<table>
<thead>
<tr>
<th></th>
<th>CheckMate-816 (Neoadjuvant only)</th>
<th>KEYNOTE-671 (Neoadjuvant + Adjuvant)</th>
<th>AEGERAN \textsuperscript{1,b} (Neoadjuvant + Adjuvant)</th>
<th>CheckMate-77T \textsuperscript{2,c} (Neoadjuvant + Adjuvant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (PD-L1)</td>
<td>IB-IIIA \textsuperscript{d}</td>
<td>II-IIIB \textsuperscript{e}</td>
<td>II-IIIB \textsuperscript{e}</td>
<td>II-IIIB \textsuperscript{e}</td>
</tr>
<tr>
<td></td>
<td>Median, months (95% CI)</td>
<td>Median, months (95% CI)</td>
<td>Median, months (95% CI)</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td></td>
<td>31.6 (30.2, NE)</td>
<td>20.8 (14.0, 26.7)</td>
<td>17.0 (14.3, 22.0)</td>
<td>25.9 (18.9, NE)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18.4 (13.6, 28.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63 (0.45, 0.87)</td>
<td>0.58 (0.46, 0.72)</td>
<td>0.68 (0.53, 0.88)</td>
<td>0.58 (0.42, 0.81)</td>
</tr>
<tr>
<td>p-value (alpha)</td>
<td>0.0052 (0.0262)</td>
<td>&lt; 0.0001 (0.0092)</td>
<td>0.004 (0.009)</td>
<td>0.00025</td>
</tr>
<tr>
<td>OS</td>
<td>Median, months (95% CI)</td>
<td>Median, months (95% CI)</td>
<td>Median, months (95% CI)</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.57 (0.38, 0.87)</td>
<td>0. (0.56, 0.93)</td>
<td>0. (0.56, 0.93)</td>
<td>0. (0.56, 0.93)</td>
</tr>
<tr>
<td>p-value (alpha)</td>
<td>0.0079 (0.0033)</td>
<td>0.0103 (0.0109)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** Atezo=atezolizumab; chemo=platinum-based chemotherapy; CI=confidence interval; Durva=durvalumab; EFS=event-free survival; HR=hazard ratio; IQR=inter-quartile range; n=number; NA=not applicable; NE=not estimable; Nivo=nivolumab; NR=not reached; NSCLC=non-small cell lung cancer; OS=overall survival; pCR=pathologic complete response; PD-(L)1=programmed death (ligand) 1; Pembro=pembrolizumab; TC=tumor cells.

\textsuperscript{1} Heymach J, et al. N Eng J Med, 2023;398(18):1672-84. \textsuperscript{2} Cascone T. ESMO 2023; LBA1.
\textsuperscript{a} Based on data provided in the product labels for the respective anti-PD-(L)1-based agents except where specific references are cited.
\textsuperscript{b} Results at the first interim analysis of AEGEAN.
\textsuperscript{c} Results at the interim analysis of CheckMate-77T.
\textsuperscript{d} Based on the American Joint Committee on Cancer TNM 7\textsuperscript{th} staging edition.
\textsuperscript{e} Based on the American Joint Committee on Cancer TNM 8\textsuperscript{th} staging edition.
### Perioperative anti-PD-(L)-1-based regimens in NSCLC

**EFS/DFS treatment effect sizes comparable across trials**

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pembro + Chem/Pembro (n=397)</th>
<th>Placebo + Chemo/Placebo (n=400)</th>
<th>Durva + Chemo/Durma (n=366)</th>
<th>Placebo + Chemo/Placebo (n=374)</th>
<th>Nivo + Chemo/Nivo (n=229)</th>
<th>Placebo + Chemo/Placebo (n=232)</th>
<th>CheckMate-816 (n=179)</th>
<th>Chemo (n=179)</th>
<th>Chem/Pembro (n=397)</th>
<th>Placebo (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage (PD-L1)</strong></td>
<td>I-IIIA f</td>
<td>I-IIIA g</td>
<td>I-IIIA h</td>
<td>I-IIIA i</td>
<td>I-IIIA f</td>
<td>I-IIIA g</td>
<td>I-IIIA j</td>
<td>I-IIIA k</td>
<td>I-IIIA f</td>
<td>I-IIIA g</td>
</tr>
<tr>
<td><strong>EFS/DFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>31.6 (30.2, NE)</td>
<td>17.0 (14.3, 22.0)</td>
<td>25.9 (21.9, NE)</td>
<td>18.4 (13.6, 22.0)</td>
<td>NR (31.9, NE)</td>
<td>58.7 (29.2, NE)</td>
<td>NR (19.0, NE)</td>
<td>20.8 (14.0, 26.7)</td>
<td>20.8 (14.0, 26.7)</td>
<td>20.8 (14.0, 26.7)</td>
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<td>0.58 (0.42, 0.81)</td>
<td>0.73 (0.60, 0.89)</td>
<td>0.66 (0.50, 0.88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td><strong>p-value (alpha)</strong></td>
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<td>0.004 (0.009)</td>
<td>0.00025</td>
<td>-</td>
<td>0.004 (0.009)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| **OS** |                               |                                |                            |                                 |                          |                                |                       |                |                   |                 |
| Median, months | -                             | -                              | -                           | -                               | -                        | -                              |                       |                 |                   |                 |
| **HR (95% CI)** | -                             | -                              | -                           | -                               | -                        | -                              |                       |                 |                   |                 |
| **p-value (alpha)** | 0.0079 (0.0033)               | -                              | -                           | -                               | -                        | -                              |                       |                 |                   |                 |

**Abbreviations:**

- Atezo = apezolizumab
- chemo = platinum-based chemotherapy
- CI = confidence interval
- DFS = disease-free survival
- Duval = durvalumab
- EFS = event-free survival
- HR = hazard ratio
- IQR = inter-quartile range
- n = number
- NA = not applicable
- NE = not estimable
- Nivo = nivolumab
- NR = not reached
- NSCLC = non-small cell lung cancer
- OS = overall survival
- pCR = pathologic complete response
- PD-(L)1 = programmed death (ligand) 1
- TC = tumor cells

**Notes:**

- a Based on data provided in the product labels for the respective anti-PD-(L)-1-based agents except where specific references are cited.
- b Results at the first interim analysis of AEGEAN.
- c Results at the interim analysis of CheckMate-77T. d At IA2 for patients in KEYNOTE-091 who received prior adjuvant chemotherapy (86% of the overall intention-to-treat population in both arms). e All patients in IMpower010 received prior adjuvant chemotherapy (80% of the overall intention-to-treat population in both arms). f Based on the American Joint Committee on Cancer TNM 7th staging edition. g Based on the American Joint Committee on Cancer TNM 8th staging edition. h Based on the American Joint Committee on Cancer TNM 8th staging edition.

**References:**

2. Cascone T. ESMO 2023; LBA1.
Add-on Designs in Resectable NSCLC

- Despite remaining questions on optimal regimen and concern for overtreatment, add-on designs are being proposed
- Raises potential for increased toxicity with unknown benefit

Abbreviations: EFS=event-free survival; ICI=immune checkpoint inhibitor; NSCLC=non-small cell lung cancer; OS=overall survival; pCR=pathologic complete response.
Three-arm design of perioperative trials evaluating new product ‘Drug A’ as add-on to SoC

Neoadjuvant phase

- SoC regimen + Drug A
- SoC regimen + Drug A
- SoC regimen ± Placebo

Adjuvant phase

- SoC regimen (if applicable) + Drug A
- SoC regimen (if applicable) ± Placebo
- SoC regimen (if applicable) ± Placebo

Abbreviations: SoC = standard of care.
Alternative trial designs to isolate the treatment effects of neoadjuvant and adjuvant phases

- Upfront randomization to receive investigational regimen vs SoC in neoadjuvant phase
- Re-randomization to investigational product vs. placebo/SoC in adjuvant phase

Re-randomization (± patient-selection based on path CR, ctDNA etc.,)

Abbreviations: ctDNA=circulating tumor deoxyribonucleic acid; path CR=pathologic complete response; SOC=standard of care.
Well-designed patient-centric perioperative trials *that isolate contributions of neoadjuvant and adjuvant treatment phases* present several opportunities including…

- Clinical benefit of each treatment phase in ‘add-on’ and ‘replacement’ therapeutic strategies

- Clear assessment of the added toxicity of the additional/prolonged therapy that may be unnecessary for some patients

- Development of early endpoints of clinical benefit, e.g., path CR, for regulatory purposes

- Development of biomarkers, e.g., ctDNA, to aid treatment optimization strategies in perioperative treatment settings

Abbreviations: ctDNA=circulating tumor deoxyribonucleic acid; path CR=pathologic complete response.
ACKNOWLEDGEMENTS

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• Harpreet Singh
• Erin Larkins
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• Naomi Horiba
• Richard Pazdur
• Tatiana Prowell
• Steven Lemery
• Toneisia Gross
• Angela James

AACR
• Rukiya Umoja
• Jon Retzlaff
• Nicholas Warren
• Tristen Tellman
Biomarker-Guided Perioperative Clinical Trials: The emerging role of liquid biopsies

Valsamo Anagnostou, MD, PhD
Associate Professor
Leader, Precision Oncology Analytics
Co-leader, Molecular Tumor Board & Lung Cancer Precision Medicine Center of Excellence
Director, Thoracic Oncology Biorepository, Sidney Kimmel Cancer Center
Johns Hopkins School of Medicine, Baltimore, MD

@ValsamoA  @MolecularOncLab @HopkinsThoracic @Hopkins_MTB
Valsamo Anagnostou

I have the following relevant financial relationships to disclose:

- Consultant for: Astra Zeneca and Neogenomics
- Grant/Research support (to Johns Hopkins University) from: Astra Zeneca, Personal Genome Diagnostics, Delfi Diagnostics, Bristol Myers Squibb
- Honoraria from: Foundation Medicine, Personal Genome Diagnostics

- and -

My additional financial relationship disclosures are:

I am an inventor on patent applications (63/276,525, 17/779,936, 16/312,152, 16/341,862, 17/047,006 and 17/598,690) submitted by Johns Hopkins University related to cancer genomic analyses, ctDNA therapeutic response monitoring and immunogenomic features of response to immunotherapy that have been licensed to one or more entities. Under the terms of these license agreements, the University and inventors are entitled to fees and royalty distributions.
Liquid biopsy approaches for sensitive and specific detection of cancer

Bruhm et al., Nat Genet, 2023, Mattox et al., Cancer Discov, 2023, Wang et al., PNAS, 2023, Sivapalan et al., Clin Can Res, 2023, Foda et al., Cancer Discov, 2023
ctDNA MRD is prognostic

Moding et al., Cancer Discov, 2021
Clinical sensitivity of ctDNA MRD

Zhong et al., BMC Medicine, 2023

A

Liu N 2022
Xia L 2021
Wang S 2022
Akbob C 2017
Zhang J 2022
Peng M 2020
Wulczak S 2022
Qu B 2013
Chen K 2019
Zhang J 2022
Meng J 2020
Chaudhuri AA 2017
Zhao A 2020

Pooled Sensitivity = 0.71 (0.65 to 0.78)
Chisquare = 95.30; df = 14 (p = 0.0000)
Inconsistency (I2 square) = 76.9%

B

Zhu A 2020
Meng J 2020
Yao D 2022
Peng M 2020
Wulczak S 2022
Akbob C 2017
Qu B 2013
Zhen S 2020
Liu N 2022
Chen K 2019
Wang S 2022
Zhang J 2022
Xia L 2021
Chaudhuri AA 2017
Zhu A 2020

Pooled Specificity = 0.71 (0.67 to 0.78)
Chisquare = 40.72; df = 14 (p = 0.0000)
Inconsistency (I2 square) = 66.1%

C

D

E

F

Zhong et al., BMC Medicine, 2023

FDA-AACR Workshop on HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES
Landmark ctDNA MRD for NSCLC

- Tumor-informed anchored multiplex PCR enrichment
- Assay sensitivity using a 50-variant panel at 0.01% VAF was > 90% at DNA input > 20 ng
- LOD 95 VAF 0.008% (80 PPM)
- Landmark ctDNA MRD assessed within 120 days of surgery: 25% ctDNA MRD+
- Clinical sensitivity 49% (fraction of ctDNA MRD+ among those who recurred)
- Landmark ctDNA MRD+ patients had a hazard ratio of 5.3 for OS and a hazard ratio of 6.8 for freedom from relapse relative to MRD- (P<0.001)
- Landmark-positive patients had the longest lead times (228 days)
- Patients relapsing in the first year of surgery are more likely to be MRD positive

Abbosh et al., Nature, 2023
What does ctDNA MRD “-” mean?

- In the ctDNA-guided group of the DYNAMIC trial, recurrence or death occurred in 15 of 246 ctDNA-negative patients (6%).
- A fraction of ctDNA MRD-negative patients experience disease recurrence.

Tie et al., NEJM, 2022
IMvigor010: ctDNA MRD is predictive for adjuvant immunotherapy

Powles et al., *Nature*, 2021

Probability of disease-free survival

<table>
<thead>
<tr>
<th>ctDNA⁻</th>
<th>ctDNA⁺</th>
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<tbody>
<tr>
<td>Atezolizumab</td>
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<tr>
<td>Observation</td>
<td>183</td>
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Probability of overall survival

<table>
<thead>
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<td>Observation</td>
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Powles et al., *Nature*, 2021

FDA-AACR Workshop on HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES
IMpower-010: Adjuvant IO may delay ctDNA MRD emergence

Felip et al., presented at ESMO Immuno-Oncology, 2022
Pre-op ctDNA clearance predicts pCR and EFS with neoadjuvant chemo-IO

Forde et al., NEJM, 2022
Pre-op ctDNA clearance predicts pCR

- Patients without ctDNA clearance were unlikely to achieve pCR (NPV > 84.0% at C2D1 in both arms)
- Patients who achieved ctDNA clearance in the D arm vs the PBO arm were more likely to achieve pCR (PPV = 50.0% vs 14.3% at C2D1)

*In the BEP, pCR (25.6% vs 6.3%) and MPR (44.4% vs 18.8%) rates were higher in the D arm vs the PBO arm. *The plots include all evaluable patients at each timepoint. NPV, negative predictive value; PPV, positive predictive value.

Reck et al., presented at ESMO 2023
Post-neoadjuvant IO ctDNA clearance is associated with overall survival

Provencio et al., JCO, 2022

FDA-AACR Workshop on HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES
ctDNA assessment may help refine the heterogeneity of non pCR

Kelly, Landon et al., Nat Med, 2024
The Tic Tac Toe trial

**Primary endpoint:** ctDNA MRD correlation with 2-year DFS/EFS rate

**Secondary endpoint:** ctDNA MRD correlation with 2-year OS rate

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cycle 2 Neoadj tx</th>
<th>Pre-op</th>
<th>Landmark MRD</th>
<th>Baseline Adj tx</th>
<th>@ 3 months</th>
<th>@ 6 months</th>
<th>@ 12 months</th>
<th>@ 18 months</th>
<th>Recurrence</th>
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<td>Oncogene-driven NSCLC</td>
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</table>

- Adjuvant IO therapy
- Neoadjuvant IO therapy
- Adjuvant TKI+/chemotx
- ctDNA MRD replicate
- ctDNA MRD monitoring
- Resected tissue
- 40mL, 4 x streck tubes
- 4-6w post-op
ctDNA MRD holds promise in navigating the evolving therapeutic landscape of early stage cancers

- ctDNA MRD may inform stratification and enrichment strategies in clinical trials for patients with early stage cancers.

- ctDNA MRD assays continue to evolve and are reaching an analytical sensitivity suitable for clinical implementation.

- Critical need to validate the clinical sensitivity of ctDNA MRD.
Acknowledgements

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Karen Padilla

@ValsamoA  @MolecularOncLab @HopkinsThoracic @Hopkins_MTB
SMART Cancer Clinical Trials

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University of Michigan School of Public Health, Ann Arbor, MI
Kelley Kidwell

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- Grant/Contract support from PCORI, FDA, NIH.
- Co-owner of smart-workshops.com
How Do Providers Treat Individuals?

- Ongoing care and follow up
- Therapies are not set in stone
- Therapies can be changed, intensified, discontinued
- Treatment decisions can be based on health progress, treatment adherence, side effects, and patient choice
- Follow-up therapy based on experience, guidelines, clinical trials
Dynamic Treatment Regimen

- DTR, a.k.a. adaptive intervention, adaptive treatment strategy, stepped care, treatment policies
- Sequence of **individually tailored decision rules** that specify whether, how and/or when to alter the intensity, type, dose or delivery of intervention at critical decision points in the course of care, prevention, implementation, or education
- **Guide/Formula for treatment**
- **Evidence-based**
- Goal: operationalize sequential decision making with the aim of improving clinical practice
DTR Example: Chronic Lymphocytic Leukemia

- First start with combination treatment I+O+V.
- If there is not minimal residual negative disease with complete remission at one year, continue I maintenance therapy.
- If there is minimal residual negative disease with complete remission at one year, then discontinue I therapy.
Questions to Consider to Develop DTR

1. What is the best **first-line** intervention?
2. What is the best **measure of response** to see if the intervention is successful?
3. When is the best **time to measure response** to the initial intervention?
4. What is the best **subsequent** treatment among non-responders?
5. What is the best **subsequent** treatment among responders?
Sequential, multiple assignment, randomized trial

A type of multi-stage randomized design

Trial participants are randomized to a set of treatment options at critical decision points over the course of treatment
  - Critical decisions occur in short time frame

All individuals participate in all stages of the trial

Subsequent randomization is based on information leading up to that point

DTRs embedded in design

Goal: Develop/Construct effective DTRs
SMART Design: Example 1

The diagram illustrates a SMART (Stratified Treatment Allocation Randomization) design for a clinical trial. The trial begins with treatment group A, which is then divided into responders and non-responders. Responders proceed to treatment group C, while non-responders proceed to treatment group E. The non-responders from group A then move to treatment group B, where responders proceed to treatment group C, and non-responders proceed to treatment group E. Further, the responders from group B proceed to treatment group D, and non-responders proceed to treatment group F.
Embedded DTRs: Example 1

- **A**
  - Responders: R
  - Non-responders: B

- **R**
  - Responders: C
  - Non-responders: D

- **D**
  - Responders: E
  - Non-responders: F

- **B**
  - Responders: C
  - Non-responders: D

- **C**
  - Responders: F

- **E**
  - Responders: F
Embedded DTRs: Example 2
Number of Embedded DTRs: 8
SMART Design: Example 2, DTRs=4

A, C, E
A, C, F
B, C, E
B, C, F
SMART Benefits

• **Delayed Effects** – treatment synergies or antagonisms

• **Prescriptive Effects** – initial treatment may elicit symptoms to better match individual to subsequent treatment

• **Sample Selection Effects** – individuals who enroll in, remain in or are adherent in a SMART may be different from those in other designs
SMART Example: Precursor to A041702

- Related to NCT03737981
- Design considered for Alliance trial A041702
- Outcome: Progression Free Survival (PFS)
- Objectives:
  - Does ibrutinib (I) + venetoclax (V) + Obinutuzumab (O) with ibrutinib maintenance (IM) have superior PFS compared to I+O+IM
  - Does treatment strategy of I+V+O+IM for patients without minimal residual disease complete response or I+V+O+IM discontinuation for patients with minimal residual disease complete response have superior PFS compared to I+O+IM
- N = 488

SMART: 2 randomizations in sequence

Why a SMART design?

- Simultaneously address the effectiveness of treatments at each stage and the effectiveness of embedded adaptive interventions.
- Which sequential treatments work better than standalone treatment?
- Investigate the interplay between treatment strategies and disease development.
- Allows those who are doing well on initial therapy to stay on it.
- Approximate clinical care.
1. Receive I+O, followed by IM [regardless of minimal residual disease complete response at one year].

2. Receive I+V+O, followed by IM [regardless of minimal residual disease complete response at one year].

3. Receive I+V+O, followed by IM if no minimal residual disease complete response at one year and discontinue IM if minimal residual disease complete response.

Comparing 3 vs 1 can determine if more aggressive initial therapy and discontinued therapy for patients with best responses is superior to less aggressive initial therapy with continued therapy for all patients.
Common SMART Study Aims

1. Minimal residual disease complete response rates between I+O vs. I+V+O at 1 year.
   Comparison of initial treatments

2. Among those who start with I+V+O and reach minimal residual disease complete response, is PFS better for those who receive IM or discontinue IM?
   Comparison of 2nd stage strategies

3. Estimate embedded (dynamic) treatment regimen effects and identify the most promising. Explore moderators of first and second stage treatment.
   Building/comparing DTRs
Sample Size & Analysis Depends on Aim

- Aims that do not consider DTRs, use standard methods
  - Two arm comparison as usual
  - May need to up weight sample size by proportion of (non-)responders / subset data for analysis

- Aims that include DTRs: SMART specific methods
  - Account for restricted randomization, simultaneous estimation of DTR effects
  - Various applets and R packages exist (see https://d3c.isr.umich.edu/available-software/)
Logistics

- Consent (to potential multiple randomizations) once at start of SMART
- Randomize upfront or sequentially
- Consider viable DTRs: tolerability, missed response assessment

- In analysis: do not compare treatment pathways; compare DTRs
  - SMART designs do not inherently increase bias to trial
Dynamic treatment regimens are evidence-based guidelines for clinical practice.

A SMART is a clinical trial design that can provide evidence for effective DTRs.

The sample size of a SMART is highly dependent on the primary aim; analytic methods depend on the objective.

R packages and applets are available to help in design and analysis for a SMART: [https://d3c.isr.umich.edu/software/](https://d3c.isr.umich.edu/software/) & other R packages e.g. DTR.
Resources: Articles & Texts

- Website
  - https://d3c.isr.umich.edu/experimental-designs/sequential-multiple-assignment-randomized-trials-smarts/

- Articles:

- Texts:
Thank you!

Interested in learning more?

https://smart-workshops.com

- SMART Workshop, June 13-14, 10-330 ET – recorded if cannot attend synchronously
  - https://smart-workshops.com/smart-design-info

- Small sample SMART Workshop, Aug 13-14, 10-330 ET – recorded if cannot attend synchronously
  - https://smart-workshops.com/snsmart-design-info

kidwell@umich.edu
SESSION 1: CURRENT LANDSCAPE FOR PERIOPERATIVE TRIAL DESIGNS

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HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES
Session 1 Panel Discussion

- Feasibility of S.M.A.R.T trial designs
- Regulatory perspective on perioperative trials
- Patient-centric perioperative trials
- Industry perspective on perioperative trials
- Impact on clinicians’ treatment decisions