SESSION 3: CONSIDERATIONS IN OTHER THERAPEUTIC AREAS
Where Do We Go From Here?

Harpreet Singh, MD
Oncology Center of Excellence, FDA
Harpreet Singh, MD

I have no financial relationships to disclose.
FDA officials raise concerns with immunotherapy overuse for early-stage cancer patients: #AACR24

Situated in the audience, FDA’s cancer head Richard Pazdur took to the Q&A microphone toward the end of the session to add, “Once we approve a regimen — such as a perioperative regimen that has a survival advantage — that will become the framework for other drugs to be added onto.

“Unless we address this question, we’re going to be prolonging drug development without the consideration for generations of patients to come — and exposing generations and thousands and thousands of patients to unnecessary therapy,” Pazdur added. “So although we could say, ‘Well, this is a home run, and we should just put it away,’ we do have an obligation to patients — and we’ve heard this from many patients that they want less therapy — to optimize the therapy.”
Emerging Data Challenges the Status Quo

**Table: Cross-trial comparison limits interpretability – questions remain**

<table>
<thead>
<tr>
<th>Study</th>
<th>Nivo + Chemo (n=179)</th>
<th>Chemo (n=179)</th>
<th>Pembrol + Chem/Pembrol (n=397)</th>
<th>Placebo + Chemo/Placebo (n=400)</th>
<th>Nivo + Chem/Pembrol (n=305)</th>
<th>Placebo + Chemo/Placebo (n=374)</th>
<th>Nivo + Chem/Pembrol (n=229)</th>
<th>Placebo + Chemo/Placebo (n=232)</th>
<th>Pembrol (n=506)</th>
<th>Placebo (n=504)</th>
<th>Aleco (n=248)</th>
<th>Placebo (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage (PD-L1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFS/DFS</td>
<td>Median, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB-IIIA</td>
<td>31.6 (30.2, NE)</td>
<td>20.8 (14.0, 26.7)</td>
<td>NR (34.1, NE)</td>
<td>17.9 (14.3, 22.0)</td>
<td>NR (31.9, NE)</td>
<td>25.9 (18.9, NE)</td>
<td>NR (28.9, NE)</td>
<td>18.4 (13.6, 28.1)</td>
<td>58.7 (39.2, NE)</td>
<td>34.9 (28.6, NE)</td>
<td>NR (36.1, NE)</td>
<td>35.3 (29.0, NE)</td>
</tr>
<tr>
<td>IIIIB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIIB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB-III A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-III A PD-L1 ≥ 1% TC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.68 (0.49, 0.93)</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>
<td>0.76 (0.63, 0.91)</td>
<td>0.66 (0.50, 0.88)</td>
<td>0.66 (0.50, 0.88)</td>
<td>0.66 (0.50, 0.88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>Median, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.36, 1.05)</td>
<td>0.72 (0.59, 0.93)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p-value (alpha)</td>
<td>0.0079 (0.0033)</td>
<td>0.0103 (0.0109)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Additional Concern: Duration of Treatment

Eligibility
- Patients with a gynecologic malignancy
- No prior therapy

Randomized 1:1

SOC + Placebo → Placebo Up to 3 years
SOC + Drug A → + Drug A Up to 3 years

Remaining uncertainties: contribution of phase to regimen, duration of maintenance therapy
Drawing Parallels Across Disciplines

Hematologic Malignancies

- Neoadjuvant
- Induction
- Surgical Resection
- Consolidation
- Maintenance
- Adjuvant

Resectable Solid Tumors

Multiple-arm trials Re-randomization

FDA-AACR Workshop on HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES
When adding another drug to the ICI perioperative regimen, the sample size would depend on the expected additional benefit of Drug X to the ICI regimen.
Formal statistical comparisons between arms may or may not be required.
Need for Improved Patient Selection

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.
Future Directions

- Patient centric trial design → how to optimize their regimen
- Considerations for thoughtful trials demonstrating contribution to phase → mitigate overtreatment concerns, patient safety
- Sample size calculations for multiple arm trials vary → are formal statistical comparisons required between experimental arms?
- Emerging biomarkers should be prospectively evaluated
- Is there a role for a perioperative pragmatic trial?
SESSION 3: CONSIDERATIONS IN OTHER THERAPEUTIC AREAS

MODERATOR
Mirat Shah, MD
U.S. Food and Drug Administration

SPEAKER
Harpreet Singh, MD
U.S. Food and Drug Administration

ADDITIONAL PANELISTS
Stephanie Wethington, MD
U.S. Food and Drug Administration

Naomi Horiba, MD, MPH
U.S. Food and Drug Administration

Christine Gause, PhD
Merck

Manju George, PhD, MVSc
Colontown

Cristina Migali, MD, PhD
European Medicines Agency

Thomas Powles, MD
Barts-Cancer Institute, London
• Strategies to address potential overtreatment with perioperative regimens
• Lessons learned from trials in malignant hematology
• Treatment approaches beyond perioperative regimens which may lead to overtreatment
• A patient-centric path forward for multiphase regimens
CONCLUDING REMARKS

Harpreet Singh, MD
U.S. Food and Drug Administration

Workshop Survey