MEDICAL ONCOLOGY UPDATE 2019

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I HAVE NO CONFLICTS OF INTEREST WITH THIS PRESENTATION AND WILL NOT DISCUSS OFF LABEL DRUG USAGE
GOALS OF PRESENTATION

• Provide an understanding of the present state of medical oncology care in the US.

• Briefly familiarize you with the science of new treatment modalities:
  • So that you might be effective within the team of decision makers for your patients

• Bullet point standard of care for four major malignancies

• Minimally discuss surgery, radiation and cancer screening
Cancer burden: Tennessee
All Types of Cancer, 2016

In Tennessee in 2016, there were **36,598 new cases of cancer**. For every 100,000 people, **456 cancer cases were reported**.

The same year, there were **14,460 people who died of cancer**. For every 100,000 people in Tennessee, **181 died of cancer**.

### Top 10 Cancers by Rates of Cancer Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Rate per 100,000 People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and Bronchus</td>
<td>53.3</td>
</tr>
<tr>
<td>Female Breast</td>
<td>21.9</td>
</tr>
<tr>
<td>Prostate</td>
<td>20.9</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>15.2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>10.9</td>
</tr>
<tr>
<td>Leukemias</td>
<td>7.4</td>
</tr>
<tr>
<td>Ovary</td>
<td>7.4</td>
</tr>
<tr>
<td>Liver and Intrahepatic Bile Duct</td>
<td>6.7</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>6.2</td>
</tr>
<tr>
<td>Brain and Other Nervous System</td>
<td>4.7</td>
</tr>
</tbody>
</table>
Rate of New Cancers by Age Group, All Races, Both Sexes

All Types of Cancer
Rate per 100,000 people

CDC 2016
Rate of New Cancers by Sex and Race/Ethnicity

All Types of Cancer
Rate per 100,000 people

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>466.1</td>
<td>418.5</td>
</tr>
<tr>
<td>Black</td>
<td>499.8</td>
<td>388.5</td>
</tr>
<tr>
<td>AI/AN</td>
<td>281.9</td>
<td>272.6</td>
</tr>
<tr>
<td>API</td>
<td>278.0</td>
<td>279.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>353.8</td>
<td>327.5</td>
</tr>
</tbody>
</table>

CDC 2016
Rate of New Tobacco-associated Cancers by State

All Tobacco-associated Cancers, Male and Female, United States, 2016
Rate per 100,000 people

Rate per 100,000 people

- 122.8 - 172.8
- 175.3 - 186.1
- 186.7 - 196.4
- 199.4 - 235.8
PREVENTION

1. Stop smoking
2. Stay thin
3. Choose your relatives
4. Consider sun screen
5. Treat underlying infections
   a. H pylori
   b. HIV
   c. Hep B and C
6. Tamoxifen or aromatase inhibitor
7. Vaccinate HPV

Prevention is the best Treatment
PREVENTION

Fig. 2. Worldwide estimated percentage of HPV-associated cancer, HPV-associated warts, and papillomatosis to be prevented by Gardasil®. Estimates are based on the prevalence and the sum of percent contributions of vaccine HPV types to different HPV-associated (cervical, vaginal, anal, vulvar, penile, head and neck) cancers, genital warts including recurrent respiratory papillomatosis. For example, 95% protection against cervical cancer is based on the fact that HPV16 is associated with (55.9%), HPV18 (15.3%), HPV16 (9.9%), HPV31 (3.8%), HPV33 (1.1%), HPV52 (0.8%), and HPV58 (1.0%) of cervical cancer cases worldwide.
# LUNG CANCER SCREENING

## Table Harms Vs Benefits

The table below shows the trade-offs of low-radiation-dose CT screening for lung cancer:

<table>
<thead>
<tr>
<th>Potential Benefits</th>
<th>Potential Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality benefits</strong></td>
<td><strong>Harms related to test characteristics</strong></td>
</tr>
<tr>
<td>• 20% relative decrease in lung cancer death (from 1.66% to 1.33%, or 3 fewer deaths per 1,000 screened)</td>
<td>• Radiation exposure from screening CT</td>
</tr>
<tr>
<td>• 7% relative reduction in all-cause mortality</td>
<td>• False reassurance (aggressive cancers may develop in intervals between screening examinations)</td>
</tr>
<tr>
<td></td>
<td>• Overdiagnosis of clinically insignificant cancers (15% to 20% of tumors detected)</td>
</tr>
<tr>
<td><strong>Psychosocial benefits and behavioral changes</strong></td>
<td><strong>Harms related to findings of test</strong></td>
</tr>
<tr>
<td>• Reassurance if normal CT</td>
<td>• False positives and other incidental findings</td>
</tr>
<tr>
<td>• Teachable moment for smoking cessation</td>
<td>• Potential harms from downstream evaluation of findings</td>
</tr>
</tbody>
</table>

MODALITIES OF TREATMENT

1. Surgery
2. Radiation
3. Cytotoxic chemotherapy
   1. Immuno-chemotherapies
4. Targeted therapies
5. Immunotherapies
   1. Checkpoint inhibitors
   2. CAR-T
   3. Allogeneic bone marrow transplant
• Immune Therapy
Fig 1. Immune system activation and regulation in the antitumor response. APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/2, programmed death ligand 1/2; TCR, T-cell receptor.
IMMUNE RESPONSIVE TUMORS

- Melanoma
- Non Small Cell Lung Cancer
- Renal Cell
- Hodgkin’s Lymphoma
- Urothelial Cancer
- Head and Neck cancer
- Hepatocellular Cancer
MELANOMA 2000-MELANOMA NOW

J Clin Oncol 37:867-875. © 2019 by American Society of Clinical Oncology

![Graph showing survival data by stage—ECOG](image1)

**Stage IV Disease:**
**Survival Data by Stage—ECOG**

- **Skin/SQ/Node**
- **Lung**
- **Other + LDH**

**Survival Probability** vs **Survival Time (months)**

SQ = subcutaneous; LDH = lactate dehydrogenase


![Graph showing Kaplan-Meier plots](image2)

**A**
- **PFS (%)**
- **Time (months)**

**B**
- **OS (%)**
- **Time (months)**

**Fig. 2.** Kaplan-Meier plot of (A) progression-free survival (PFS) and (B) overall survival (OS) in patients who received NIVO+IP1 (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg) or NIVO+IP3 (nivolumab 1 mg/kg plus ipilimumab 2 mg/kg). Symbols indicate censored observations. Median PFS was 9.92 months in the NIVO+IP1 group and 8.94 months in the NIVO+IP3 group (hazard ratio, 1.06; 95% CI, 0.79 to 1.40). Median OS was not reached in either group (hazard ratio, 1.09; 95% CI, 0.73 to 1.62).
Kaplan–Meier Curves for Overall Survival.

- Median Overall Survival:
  - Nivolumab (N=135): 9.2 (7.3–13.3) mo
  - Docetaxel (N=137): 6.0 (5.1–7.3) mo

- 1-Yr Overall Survival:
  - Nivolumab: 42 (34–50) % of patients
  - Docetaxel: 24 (17–31) % of patients

- No. of Deaths:
  - Nivolumab: 86
  - Docetaxel: 113

Hazard ratio for death: 0.59 (0.44–0.79) P<0.001

No. at Risk:

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
<td>103</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>69</td>
<td>45</td>
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<tr>
<td>12</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>21</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status.

A Progression-free Survival in Cohorts with Colorectal Cancer

B Overall Survival in Cohorts with Colorectal Cancer

C Progression-free Survival in Cohort with Mismatch Repair–Deficient Noncolorectal Cancer

D Overall Survival in Cohort with Mismatch Repair–Deficient Noncolorectal Cancer

Figure 2. Structure of CARs and T-Cell Receptors.

Panel A shows the structure of a T-cell receptor, which consists of heterodimeric and antigen-specific α and β chains that closely associate with the invariant ε, δ, γ, and ζ chains of the CD3 complex. The T-cell receptor binds to the HLA allele that has a bound peptide derived from a tumor antigen on the target cell. Panel B shows the CAR, which includes the single-chain variable fragment (scFv) that binds to tumor antigens, fused to a spacer and transmembrane domain. The intracellular domain contains costimulatory domains, such as CD28 and 4-1BB and the CD3ζ chain, which drive signal activation and amplification of CAR T cells. S–S denotes disulfide bond.
• Targeted Therapy
RAS PATHWAY

The organisation and function of the Ras-Raf-MEK-ERK pathway

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press
Overall Survival.
High Response Rates for the Seven NCCN Targets in Lung Adenocarcinoma

**EGFR**: >70% RR to 1°-2° Gen TKIs; ~60% RR to 3° Gen TKIs in resistant cancers

**KRAS**: 35% RR to MEK inhibitors + Chemotherapy

**MET exon 14**: >50% RR to Crizotinib

**ALK**: 65% RR to Crizotinib; ~70% RR to 2° Gen TKI Ceritinib in resistant cancers

**HER2 (ERBB2) mutation**: >50% RR to Afatinib; ~20% RR to Dacomitinib

**ROS1**: 70% RR to Crizotinib

**BRAF (V600E)**: >60% RR to BRAF + MEK inhibitor combo

**RET**: 40% RR to Cabozantinib

**MET**: >50% RR to Crizotinib

**RIT1**: (2.2%)
Kaplan–Meier Estimates of Radiographic Progression-free Survival and Overall Survival.
Fig 1. Mechanism of actions of active drugs for advanced and metastatic renal cell carcinoma.

Published in: Rana R. McKay; Dominick Bossé; Toni K. Choueiri; Journal of Clinical Oncology 2018 363615-3623.
DOI: 10.1200/JCO.2018.79.0253
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PEMBROLIZUMAB PLUS AXITINIB FOR RENAL-CELL CARCINOMA

A Overall Survival

Hazard ratio for death, 0.53 (95% CI, 0.38–0.74)
P<0.0001

No. at Risk
Pembrolizumab–axitinib: 432, 417, 378, 256, 136, 18, 0
Sunitinib: 429, 401, 341, 211, 110, 20, 0

NEW ENGLAND J MED 2019;380:1116-27.
DOI: 10.1056/NEJMOA1816714
Silver Bullets
TARGETED CHEMOTHERAPY
THE SILVER BULLET

- Immuno-Chemotherapy
  - Breast Cancer
  - Diffuse Large cell Lymphoma
  - Hodgkin’s lymphoma
  - T cell lymphoma

- Immuno-radiotherapy lymphoma
The mechanism of action of pertuzumab and trastuzumab.


CCR Drug Updates
TDM-I BREAST CANCER
## TOXICITIES

### IMMUNOTHERAPIES
1. Colitis
2. Pneumonitis
3. Nephritis
4. Endocrine
5. Cutaneous

### TARGETED THERAPIES
1. Cutaneous
2. GI
3. Hand-Foot
4. Fatigue
5. Hypertension
6. Renal
### Management of Immune Checkpoint Inhibitor-Related Toxicities

<table>
<thead>
<tr>
<th>Gastrointestinal Adverse Event(s)</th>
<th>Assessment/Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (G1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Stool evaluation to rule out infectious etiology&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Consider holding immunotherapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture</td>
<td>Loperamide or diphenoxylate/atropine</td>
</tr>
<tr>
<td>道 diarrhea or colitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C. difficile</td>
<td>Hydration</td>
</tr>
<tr>
<td>Moderate (G2)&lt;sup&gt;b&lt;/sup&gt; or Severe (G3–4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ova &amp; parasites; molecular testing for Giardia and Crypto. pot. spp. and E. histolytica; consider microsporidia, Cyclospora/Cryptosporidium spp</td>
<td>Close monitoring&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Viral pathogens testing when available</td>
<td>Hold immunotherapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Based on institutional availability, consider lactoferrin/capreolactone</td>
<td>Prednisone/methylprednisolone&lt;sup&gt;i&lt;/sup&gt; 1 mg/kg/day&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Consider abdominal/pelvic CT with contrast</td>
<td>No response in 2–3 days:</td>
</tr>
<tr>
<td></td>
<td>Consider GI consultation</td>
<td>Increase dose to 2 mg/kg/day&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy or flexible sigmoidoscopy + esophagogastroduodenoscopy (EGD) with biopsy</td>
<td>Consider adding infliximab&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity&lt;sup&gt;i&lt;/sup&gt;</td>
<td>G4: Permanently discontinue immunotherapy agent responsible for toxicity&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Consider inpatient care for provision of supportive care</td>
<td>Consider inpatient care for provision of supportive care</td>
</tr>
<tr>
<td></td>
<td>Intravenous (IV) methylprednisolone&lt;sup&gt;i&lt;/sup&gt; (2 mg/kg/day)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No response in 2 days:</td>
</tr>
<tr>
<td></td>
<td>No response in 2 days:</td>
<td>Continue steroids, consider adding infliximab&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>G4: Permanently discontinue immunotherapy agent responsible for toxicity&lt;sup&gt;i&lt;/sup&gt;</td>
<td>If infliximab-refractory, consider vedolizumab</td>
</tr>
</tbody>
</table>

<sup>a</sup>Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever. Blood in the stools and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignancy bleeding.

<sup>b</sup>Fewer than 4 bowel movements above baseline per day and no colitis symptoms.

<sup>c</sup>4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.

<sup>d</sup>More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic megacolon).

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials. NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
PROBING THE BLOOD FOR TUMOR MATERIAL

CTCs
ctDNA
miRNA
Exosomes
Methylation
Proteins

Source: Diaz, JCO; 2014
GLIOBLASTOMA
24 MONTH OS 43% VS 29%,
AVOID SURGERY?

Organ Preservation in Responders With Rectal Cancer

- A retrospective review of patients at Memorial Sloan Kettering Cancer Center showed that patients with stage I to III rectal cancer who achieved a clinical complete response to neoadjuvant therapy can often forego resection.
- Cohorts with clinical complete responses and those with pathologic complete responses who underwent surgery had similar disease-free survival and overall survival.
- Of the nonoperatively managed patients, 77% had rectal preservation.
- The local recurrence rate was 26%; all but one patient was successfully salvaged.
Kaplan–Meier Estimates of Survival According to Study Group.

NON SMALL CELL LUNG CANCER

1. Resection alone if node negative and < 4 cm
2. Resection with adjuvant chemotherapy if > 4 cm or node positive
3. Chemotherapy and radiation followed by checkpoint inhibition if mediastinal nodes involved
4. Resection with stereotactic radiation for cure if solitary brain met
5. Checkpoint inhibition and chemotherapy if advanced disease
6. Checkpoint inhibition only if PD L1 > 50%
7. Stereotactic radiation ablation of oligo-metastasis
**BREAST CANCER**

1. Resection with no adjuvant chemotherapy for most tumors < 1 cm
2. Lumpectomy plus radiation equivalent to mastectomy when possible
3. Axillary lymph node dissection not necessary if no clinically positive nodes and positive sentinel nodes < 3.
4. Adjuvant hormonal therapy for all hormone receptor positive
5. Adjuvant chemotherapy for most patients with lymph node positive, guided by Oncotype DX
6. Adjuvant chemotherapy for all hormone receptor negative cancers > 1 cm
7. Trastuzumab adjuvant therapy for all Her 2 positive patients > .5 cm
8. Hormonal therapy for all metastatic hormone sensitive patients with or without CDK4/6 inhibitors as first line
9. Her 2 therapies for Her 2 positive metastatic disease
10. Chemotherapy eventually for most metastatic cancer
PROSTATE CANCER

1. Screening with PSA reasonable after discussions
2. Resection or radiation if localized and likely to affect mortality
3. Active surveillance if not likely to affect mortality
4. Observation or hormonal therapy if biochemical relapse without metastases
5. Hormone reduction therapy if hormone sensitive metastatic disease with addition of either short course chemotherapy, androgen blockade or testosterone production inhibitor (abiraterone)
6. Consideration of second generation androgen blocker for castrate resistant biochemical-only relapse
7. Chemotherapy, abiraterone, second generation androgen blocker for metastatic castrate resistant disease
8. Bisphosphonates or Rank ligand inhibitor for bone disease
9. Radiation if needed for painful metastases
10. Checkpoint inhibitors or PARP inhibitors for certain molecular types
1. Resection only of most tumors with negative nodes for colon lesions; for rectal cancer, same if tumor does not invade through bowel wall and nodes negative

2. Adjuvant chemotherapy if node positive or high risk node negative: 3-6 months depending on number of nodes

3. Adjuvant chemotherapy and radiation for rectal cancers through bowel wall or node positive: preop, postop or total neoadjuvant

4. Resection for cure with solitary or oligo metastases to liver, lung or brain

5. Chemotherapy with anti EGFR therapy for metastatic disease from left sided colon lesions if mutations negative

6. Chemotherapy +/- bevacizumab if right sided or mutation positive

7. Targeted therapies for specific mutations

Cancer By the numbers

72% of Americans believe cancer drug costs are unreasonable

Hidden Costs of Cancer
- Medical accessories
- New clothes
- Child care
- Eating out
- Lodging
- Gas
- Parking
- Losing a job
- Missing work
- Travel costs
- Nutritional supplements

$172.8 Billion
Estimated cost of cancer care in the United States by 2020

Direct Cancer Costs
- Medication (24%)
- Hospital/Outpatient facilities (54%)
- Physician fees (22%)

Cancer patients are 2.5 X more likely to file for bankruptcy than those without cancer
137.4 BILLION DOLLARS 2010
Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval

Bishal Gyawali, MD, PhD; Spencer Phillips Hey, PhD; Aaron S. Kesselheim, MD, JD, MPH

### Table 2. Recent Cancer Drug Indications That Received Accelerated Approval From US Food and Drug Administration Without Overall Survival Changes in the Postapproval Trial

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Basis for Accelerated Approval</th>
<th>Primary End Point for Confirmatory RCTs</th>
<th>Results of Confirmatory RCTs</th>
<th>Current FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Glioblastoma</td>
<td>RR in phase 2</td>
<td>OS</td>
<td>OS HR, 0.95 (95% CI, 0.74-1.21); (P = .65); PFS improved(^{25})</td>
<td>Converted to regular approval</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Melanoma after Ipilimumab/</td>
<td>RR in phase 3</td>
<td>OS</td>
<td>OS HR, 0.95 (95.54% CI, 0.73-1.24)</td>
<td>Submitted/undecided (April 2019 status: delayed)</td>
</tr>
<tr>
<td></td>
<td>BRAF-inhibitor</td>
<td></td>
<td></td>
<td>PFS not improved(^{36})</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Urothelial</td>
<td>RR in phase 2</td>
<td>OS</td>
<td>OS HR, 0.87 (95% CI, 0.63-1.21); (P = .41)</td>
<td>Submitted/undecided (April 2019 status: submitted)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Head and neck cancer</td>
<td>RR in phase 2</td>
<td>OS</td>
<td>OS HR, 0.82 (95% CI, 0.67-1.01) in 2018</td>
<td>Submitted/undecided(^{a}) (April 2019 status: delayed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS HR, 0.80 (95% CI, 0.65-0.98) PFS not improved(^{34})</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial; RR, response rate.

\(^{a}\) This trial was considered as “confirmation of benefit” for our analysis.
UNDERSTAND LEGITIMATE GOALS OF CARE VS SURROGATE GOALS OF CARE

<table>
<thead>
<tr>
<th>LEGITIMATE</th>
<th>SURROGATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cure</td>
<td>- Response rate</td>
</tr>
<tr>
<td>- Prolong survival</td>
<td>- Time to progression</td>
</tr>
<tr>
<td>- Improve quality of life</td>
<td>- Progression free survival</td>
</tr>
<tr>
<td>- Prevent impending disaster</td>
<td>- Metastasis free survival</td>
</tr>
<tr>
<td></td>
<td>- Phase II trials</td>
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