Advances in Cancer Immunotherapy™ – Recent AACR and Related Updates

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Professor, Surgical Oncology
UC Davis
Disclosures

• None
AACR Highlights

- Combination Therapies (using checkpoint blockade)
- CAR T cells
- Novel Targets
- Biomarkers
- Microbiome
T-Cell Based Breakthroughs

- Checkpoint Blockade
  - CTLA-4
  - PD-1/ PD-L1
- CAR T-Cells

**CTLA-4 Critical in T cell Priming**

**PD-1 Critical in T cell Exhaustion**

- Homing
- Neo-antigen recognition
- Cytotoxic T cell
- PD-1 Upregulation and Exhaustion
- PD-L1 upregulation
Immune Checkpoint Therapy: What is Next?

Anti–PD-1/PD-L1

Your favorite treatment

The future of cancer therapy
The Complexity of Host-Tumor Immunoregulation
Tumor Microenvironment and Immune Surveillance

The ultimate goal of cancer immune therapy is to recruit and activate CD8+ T cells in tumors


Dual-Checkpoint Blockade

• Effective in melanoma and lung cancer, but with significant toxicity
DART (Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors)

- DART first NCI-sponsored basket study for rare tumors
- Ipilimumab/nivolumab combination being tested in patients with 37 types of rare cancer
- Dr. Sandip Patel (UCSD) presented data on a cohort of 33 patients with neuroendocrine tumors

DART for NET

- Rare tumors comprise 25% of US cancer diagnoses
- DART open at 800 sites
- Accrual in NET completed in 3 months
- Clinical trials in rare tumors are feasible

DART for NET

• Prior studies of checkpoint inhibitor monotherapy showed response rates of ~5%
• Ipilimumab at 1 mg/kg given intravenously every 6 weeks plus nivolumab at 240 mg IV every 2 weeks
• No responses in low grade tumors (44% response rate in high grade vs. 0% low/intermediate grade)

<table>
<thead>
<tr>
<th>Age</th>
<th>Median 60.5</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>41% Female</td>
</tr>
<tr>
<td></td>
<td>59% Male</td>
</tr>
<tr>
<td>Objective</td>
<td>25%</td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>6-month PFS</td>
<td>31%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>11 months</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Liver 9% (LFTs)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Colitis 6%</td>
</tr>
</tbody>
</table>
Dual Checkpoint Blockade for NET

- High grade extra-pulmonary NET behave like small cell lung cancer
- Checkpoint blockade has been approved for SCLC
- Dual agent checkpoint blockade shows evidence of activity in high grade NET
- Additional studies are underway

3rd Line Pembro in SCLC
Pembrolizumab as Third-Line Option for Extensive-Stage Small Cell Lung Cancer

- Pooled analysis of KEYNOTE-028 (phase Ib) and KEYNOTE-158 (phase II) of pembrolizumab in patients with advanced SCLC
- Immunotherapy naïve patients
- ≥ 2 prior lines of systemic therapy
- 10 mg/kg Q2W (KN028) or 200 mg Q3W (KN158) for 2 years, disease progression, or intolerable toxicity
- Response assessed by RECIST

3rd Line Pembro SCLC

- 64% had 2 prior lines of chemotherapy
- 36% had 3 or more prior lines of chemotherapy
- 57% had PD-L1 positive tumors

- Overall response rate was 19% (2% CR and 17% PR)
- 9/16 patients responded for > 18 months
- Median PFS was 2.0 months, and median OS was 7.7 months

Immunotherapy in Breast Cancer
Analysis of immune cell infiltrates as predictors of response to pembrolizumab in the neoadjuvant I-SPY 2 TRIAL

• I-SPY 2 trial (NCT01042379) is an adaptive phase II randomized, controlled, multicenter trial for women with stage II/III breast cancer

• Assessing new treatments and identifying novel therapies in specific patient subgroups based on molecular characteristics

• The primary endpoint is pathologic complete response at the time of surgery

https://www.ispytrials.org/
Immune Infiltration in Breast Cancer

• Until recently, results of checkpoint immunotherapy in breast cancer have been disappointing

• Perception that breast cancers are immunologically “cold”

Checkpoint Blockade Monotherapy

(Adapted from Dr. Elizabeth Mittendorf)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n=254)</th>
<th>Atezolizumab (n=112)</th>
</tr>
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<tbody>
<tr>
<td>Population</td>
<td>mTNBC</td>
<td>mTNBC</td>
</tr>
<tr>
<td>Overall ORR</td>
<td>4.7% (Cohort A; n=170)</td>
<td>10%</td>
</tr>
<tr>
<td>ORR in 1st line</td>
<td>23% (Cohort B; n=84)</td>
<td>26% (n=19)</td>
</tr>
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</table>

Survival in Responders

Phase III study IMPassion130

Previously untreated metastatic or inoperable locally advanced TNBC
N = 902 patients randomized

Stratification factors:
1. Prior taxane use
2. Liver metastases
3. PD-L1 on IC

Double blind; no crossover
R 1:1

Atezo + nab-P arm
ITT population: n = 451
PD-L1 IC+ patients: n = 185 (41%)

Plac + nab-P arm
ITT population: n = 451
PD-L1 IC+ patients: n = 184 (41%)

Key study endpoints
- Co-primary: PFS (ITT and PD-L1 IC+)
  OS (ITT and PD-L1 IC+)
- Secondary: ORR and DOR
- Safety and tolerability

Schmid P. et al., NEJM 2018; 379(22):2108-2121.
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (N = 451)</th>
<th>Placebo + nab-P (N = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>55 (20 – 82)</td>
<td>56 (26 – 82)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>68.3% Caucasian</td>
<td>66.7% Caucasian</td>
</tr>
<tr>
<td><strong>ECOG 0/1</strong></td>
<td>99.8%</td>
<td>99.8%</td>
</tr>
<tr>
<td><strong>Metastatic Disease</strong></td>
<td>89.8%</td>
<td>90.7%</td>
</tr>
<tr>
<td><strong>Previous Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>51.2%</td>
<td>51.0%</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>53.9%</td>
<td>53.7%</td>
</tr>
<tr>
<td><strong>PD-L1 Positive</strong></td>
<td>41.0%</td>
<td>40.8%</td>
</tr>
</tbody>
</table>

PFS – Intention to Treat

PFS – PD-L1+ Subgroup

OS – Intention to Treat

Stratified HR = 0.84 (95% CI: 0.69, 1.02)  
\( P = 0.0840^b \)

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (N = 451)</th>
<th>Plac + nab-P (N = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n</td>
<td>181</td>
<td>208</td>
</tr>
<tr>
<td>1-year OS</td>
<td>42% (34, 50)</td>
<td>40% (33, 46)</td>
</tr>
</tbody>
</table>

OS-PD-L1+ Subgroup

- Because of hierarchical statistical analysis procedure, testing of OS in PD-L1+ subgroup was not conducted

Immunotherapy for Breast Cancer

- BRCA status likely significant
- Impact of other systemic agents (cyclophosphamide, steroids, antibiotics)
- Biomarkers of response/resistance

- PD-1/ PD-L1 inhibitor monotherapy not effective
- IMpassion 130 a positive study
- FDA approval for combination therapy with PD-L1+ in March 2019 contingent on a follow up Phase 3 study
- Other combination studies are ongoing
**KEYNOTE - 355**

- Sample size: 828
- Recently or newly obtained tumor biopsy
- Central determination of TNBC and PD-L1
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of surgery or adjuvant treatment, whichever occurred last, ≥6 months prior to first disease recurrence
- ECOG PS 0-1
- No systemic steroids
- Physiologic dose
- No active autoimmune disease that required systemic treatment in past 2 years
- No active central nervous system metastases

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**Stratification factors**

1. Chemotherapy treatment on study (taxane vs gemcitabine/cisplatin)
2. PD-L1 tumor status (positive vs negative)
3. Prior treatment with same class chemotherapy in the (neo)adjuvant setting (yes vs no)

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Sponsor</th>
<th>Setting</th>
<th>Study</th>
<th>Trial ID</th>
<th>Primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keytruda + chemo</td>
<td>Merck</td>
<td>1st-line</td>
<td>Keynote-355</td>
<td>NCT02819518</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>
Cancer-Immunity Cycle

Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial

Immune cell infiltrates post pembrolizumab in the neoadjuvant I-SPY 2 TRIAL

- Pre-treatment biopsies analyzed for immune subsets by multispectral imaging (N = 54)
- Favorable immune infiltrates – expected
  - CD3+ T cells, CD8+ T cells, PD-1+ T cells
- Favorable immune infiltrates – unexpected
  - FoxP3+ Tregs
- Unfavorable immune infiltrates
- Tumor associated macrophages (TAMs)
Poll Question

Which of the following immune cell infiltrates are not associated with favorable outcomes in pembrolizumab treatment of TNBC?

- a. CD3+
- b. FoxP3+
- c. Tumor-associated macrophages (TAMs)
- d. CD8+
- e. PD-1+ T cells
Novel Targets
Macrophages and the Adaptive Immune Response

- Ilya Metchnikoff – “look for the macrophages”
TAMs Linked to Tumor Progression

NL Pancreas

Pancreatic Ductal CA

30-60% CD68+ cells in tumor

CD68

HR = 1.78 (1.41 - 2.26)
logrank P = 1.3e-06

Reducing TAMs in the TME

<table>
<thead>
<tr>
<th>Target</th>
<th>Compounds</th>
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<tbody>
<tr>
<td>CSF1R inhibitors</td>
<td>Pexidartinib</td>
</tr>
<tr>
<td></td>
<td>PLX7486</td>
</tr>
<tr>
<td></td>
<td>Emactuzumab</td>
</tr>
<tr>
<td>PI3Kγ inhibitors</td>
<td>IPI-549</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>TMP195</td>
</tr>
<tr>
<td>CD40 (pleiotropic)</td>
<td>APX005M</td>
</tr>
</tbody>
</table>
CD40 Agonism

Innate Immunity
- Macrophage
- NK cell
- Neutrophil

Adaptive Immunity
- Dendritic Cell
- B cell
- CD8+ T cell

Activation pathways:
- APX005M
- PD-1
- OX40
- GITR
- 4-1BB

Anti-cancer Abs
A Phase Ib study of APX005M with gemcitabine and nab-paclitaxel with or without nivolumab in untreated metastatic PDAC patients – CT004

- Monoclonal antibody targeting CD40
- CD40 a key member of the TNF receptor superfamily
- Expressed on APCs (monocytes, macrophages, and dendritic cells) as well as other immune and non-immune cells
- Critical in CD8 priming and CD4 help
- Reprograms Macs\textsuperscript{1}

Beatty GL et al., Science 2011, 331.
Phase Ib study of APX005M plus Chemo +/- Nivo in PDAC

- Previously untreated PDAC, N = 30
- 4 cohorts
- 24 patients were evaluable
- Median follow up 32 weeks

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Treatment Details</th>
</tr>
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<tbody>
<tr>
<td>Cohort 1</td>
<td>Gemcitabine, Nab-Paclitaxel, APX005M 0.1 mg/kg</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>Gemcitabine, Nab-Paclitaxel, APX005M 0.3 mg/kg</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Gemcitabine, Nab-Paclitaxel, APX005M 0.1 mg/kg Nivolumab</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>Gemcitabine, Nab-Paclitaxel, APX005M 0.3 mg/kg Nivolumab</td>
</tr>
</tbody>
</table>
Key Inclusion and Exclusion Criteria

Inclusion
- Metastatic pancreatic adenocarcinoma
- Measurable disease per RECIST 1.1
- Age ≥ 18
- ECOG status 0 or 1
- Baseline tissue mandatory
- Adequate hematologic, hepatic and renal function

Exclusion
- Previous systemic therapy in the metastatic setting
- Symptomatic CNS metastases
- Concurrent active invasive malignancy
- History of autoimmune disorders
- Concomitant use of immunosuppressive agent within 14 days of first dose
Results

**Toxicity**

<table>
<thead>
<tr>
<th>54% AEs leading to discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>42% treatment-related serious AEs</td>
</tr>
<tr>
<td>8% (N=2) grade 4/5 toxicity – sepsis/ neutropenia</td>
</tr>
</tbody>
</table>

**Efficacy**

<table>
<thead>
<tr>
<th>58% ORR (all partial)</th>
</tr>
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<tbody>
<tr>
<td>92% clinical benefit rate (CR + PR + SD)</td>
</tr>
</tbody>
</table>

Immune Correlative Studies

- Low CD8 and high macrophages in baseline TME
- Decrease in circulating mutant KRAS DNA
- Remodeling of myeloid compartment in TME
Promising Anti-tumor Activity

- Complete Response (CR): 0
- Partial Response (PR): 13 (54%)
- Confirmed PR: 11
- Unconfirmed PR: 2
- Stable Disease (SD): 9 (38%)
- Progressive Disease (PD): 1 (4%)
- Not Evaluable / No Scan: 1 (4%)
- Early Death: 1

- DLT- evaluable population (N=24): ORR = 54.2%
- Safety- evaluable population (N=30): ORR = 46.7%
## Grade 3 or 4 Treatment-Related AEs

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=7)</th>
<th>Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=7)</th>
<th>Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)</th>
<th>Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)</th>
<th>Total (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count decreased</td>
<td>5 (71.4%)</td>
<td>6 (85.7%)</td>
<td>5 (62.5%)</td>
<td>4 (50.0%)</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (42.9%)</td>
<td>5 (71.4%)</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (28.6%)</td>
<td>3 (42.9%)</td>
<td>4 (50.0%)</td>
<td>1 (12.5%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (42.9%)</td>
<td>2 (28.6%)</td>
<td>3 (37.5%)</td>
<td>0</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>0</td>
<td>4 (57.1%)</td>
<td>0</td>
<td>3 (37.5%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>4 (57.1%)</td>
<td>1 (12.5%)</td>
<td>1 (12.5%)</td>
<td>6 (20.0%)</td>
</tr>
</tbody>
</table>

- No grade 3/4 cytokine release syndrome was noted
Immune Profiling

O'Hara M,... Vonderheide R – CT004
Circulating Tumor DNA
Summary Points

• Phase I trial, so results should be taken in context
• Combination of chemotherapy and immunotherapy
  • Better in treatment-naive setting
  • Allows more time for induction of immune responses
• Risk of toxicity with multiple agents
• Rationale for induction chemotherapy with immunotherapy
  • Immunogenic cell death may sensitize to immunotherapy
  • Chemotherapy can be reintroduced on disease progression
Other TAM Targeting Agents

IPI-549 – PI3Ky inhibitor
Late-Breaking Presentation at SITC 33rd Annual Meeting - 2018

Phase 1/1b Trial of IPI-549 Monotherapy and in Combination with Nivolumab in ~200 Patients with Advanced Solid Tumors

- Accrual ongoing, but only 2/27 (7%) PR to date
HDAC Inhibitor Plus Pembrolizumab In Melanoma After Progression on Checkpoint Blockade
ENCORE-601 Study

- Entinostat is oral class I selective HDAC inhibitor
- Entinostat inhibits MDSCs
- Synergy with PD-1 inhibition in pre-clinical models

RJ Sullivan et al., – CT072
ENCORE-601 Study

Inclusion Criteria:
- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

Primary Endpoint
- ORR (irRECIST)

Secondary Endpoints
- CBR, PFS, OS, safety & tolerability

53 patients enrolled, last patient enrolled April 2018

RJ Sullivan et al., – CT072
Clinical Outcomes Entinostat + Pembro in Melanoma

- 10 confirmed responses (1 CR, 9 PRs)
- ORR 19% (95% CI: 9 – 32%)
- Median duration of response 13 months
- 9 patients with SD x > 6 months
- 36% CBR

RJ Sullivan et al., – CT072
Circulating Immune Biomarkers

Peripheral CD8+ T cells

Peripheral M-MDSCs (CD14+HLA-DR-/lo)

M-MDSCs in responders

Responders  Non-responders
Immune Signatures Following Treatment

Nanostring analysis on tumor tissue post treatment (N = 7)
Summary

• Entinostat + Pembro showed encouraging activity in patients with progressive melanoma after single/dual checkpoint blockade

• Toxicity primarily related to HDAC inhibition (nausea, fatigue, diarrhea)

• Preliminary predictors of response:
  • Reduction in circulating MDSCs
  • Baseline and tumor-specific increases in inflammatory pathways
CAR-T Cells
HER2-Targeted CAR T Cells in Sarcomas

• HER2 expressed in ~ 40% of osteosarcomas
• Limited success with HER2-directed therapies in sarcomas


• Phase I trial 10 heavily-preated sarcoma patients
• 3 infusions of HER2-directed CARs after lymphodepletion with fludarabine +/- cyclophosphamide
HER2-Targeted CAR T Cells in Sarcomas

- 1 x 10^8 cells/ m²
- All patients developed lymphopenia and neutropenia
- 8/11 developed grade 1-II CRS
- T cells expanded in 9/11 patients
- TCR sequencing showed clonal expansion in 1 CR patient

<table>
<thead>
<tr>
<th>Age</th>
<th>4 – 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>5 Osteosarcoma</td>
<td></td>
</tr>
<tr>
<td>3 Rhabdomyosarcoma</td>
<td></td>
</tr>
<tr>
<td>1 Ewing’s</td>
<td></td>
</tr>
<tr>
<td>1 Synovial Sarcoma</td>
<td></td>
</tr>
<tr>
<td>Best Response</td>
<td></td>
</tr>
<tr>
<td>2 CR</td>
<td></td>
</tr>
<tr>
<td>3 SD</td>
<td></td>
</tr>
<tr>
<td>5 PD</td>
<td></td>
</tr>
<tr>
<td>CAR T detection</td>
<td></td>
</tr>
<tr>
<td>qPCR 10/10</td>
<td></td>
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</table>

CAR-T Cells for Multiple Myeloma
Anti-BCMA CAR T-Cell Therapy in Relapsed or Refractory Multiple Myeloma

• Despite advances in systemic therapies, MM remains incurable

• B-cell maturation antigen (BCMA) is member of TNF superfamily and is primarily expressed on malignant and normal plasma cells as well as some mature B cells

• Bb2121 are autologous T cells with 2nd generation CAR incorporating anti-BCMA single-chain variable fragment with CD137 (4-1BB) and CD3-zeta domains

Survival and Differentiation of B Cells into Antibody-Producing Plasma Cells
Anti-BCMA CAR T-Cell Therapy in Relapsed or Refractory Multiple Myeloma

- 6 of 15 complete responders did relapse
- Median PFS was 11.8 months
- CAR-T expansion associated with response
- CAR T cells persisted up to 1 year

<table>
<thead>
<tr>
<th>Age</th>
<th>60 (37 – 75)</th>
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<tbody>
<tr>
<td>Best Response</td>
<td>15 CR (45%)</td>
</tr>
<tr>
<td></td>
<td>13 PR (40%)</td>
</tr>
<tr>
<td>Duration of</td>
<td>Median 10.9</td>
</tr>
<tr>
<td>Response</td>
<td>months</td>
</tr>
<tr>
<td>Grade 3 Toxicity</td>
<td>97%</td>
</tr>
<tr>
<td>– Any</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>85%</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>25 (76%)</td>
</tr>
<tr>
<td>Grade 3 = 2 (6%)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Grade 4 = 1 (3%)</td>
</tr>
</tbody>
</table>

Predictors of Response Anti-BCMA CARs

- Small sample size
- No statistical predictors of objective response
- Trend for superior responses in:
  - Low risk cytogenetics
  - Positive CRS syndrome
  - > 150 x 10^6 cells infused
  - In vivo CAR T expansion

Summary of Anti-BCMA CARs

- Heavily pre-treated population with evidence for anti-tumor activity
- Unlike anti-CD19 CARs, most responses don’t persist
- Toxicity remains prevalent
- Data emphasize need for ongoing translational research to improve both efficacy and safety of novel CAR T cell therapies
CAR-T Cells for Mesothelioma
Phase I Clinical Trial

- Mesothelin-directed CAR T cells
- Direct injections into the pleural cavity in 21 patients with malignant pleural disease
- 14 patients also received anti-PD1 checkpoint blockade
- 2 CR (based on PET), 5 PR, and 4 SD
Poll Question

Which of the following is **not** a common side effect of CAR-T therapy?

a. Lymphopenia  
b. Cytokine Release Syndrome (CRS)  
c. Neutropenia  
d. Neurologic Toxicity  
e. Dermatologic Toxicity
**Summary AACR Highlights**

- **Glass half-full**
  - Durable responses are possible

- **Glass half-empty**
  - Majority of patients do not respond

- T cell-based treatments remain the focal point of immuno-oncology

- Novel combinations and overcoming resistance remain focal point of PD-1/ PD-L1 based therapies

- Novel targets, homing, and avoiding off-tumor effects are critical areas in CAR T-cell approaches