Cancer Immunotherapy: an Emerging Paradigm

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Nevada Cancer Control Summit
Reno, November 6, 2017
T-Cell Response: Second Signals to Accelerate or Brake

Activating Signals
- CD28
- OX40
- GITR
- CD137
- CD27

Inhibitory Signals (brakes)
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

* Releasing these brakes activates T-cells against cancers

T-Cell Stimulation

T-Cell Inhibition

Mechanism of Action:
Ipilimumab releases the CTLA-4 brake on T-cells

Jim Allison
M.D. Anderson
Mechanism of Action:
PD-1 and PD-L1 antibodies release brakes on T-cells and enable antitumor cytotoxicity
FDA approval status of Immune CTLA-4 and PD-1 Checkpoint Inhibitors

• Ipilimumab (CTLA-4):
  – Melanoma (2011)

• Pembrolizumab (PD-1):
  – Melanoma (2014)
  – Non-small Cell Lung (2015)
  – Head and Neck cancers (2016)
  – Microsatellite-Instability High (MSI) solid tumors (2017)
  – Bladder cancers (2017)
  – Hodgkin lymphoma (2017)

• Nivolumab (PD-1):
  – Melanoma (2014)
  – Non-small Cell Lung (2015)
  – Renal (2015)
  – Hodgkin Lymphoma (2016)
  – Head and Neck Squamous (2016)
  – Bladder cancers (2017)
FDA approval status of PD-L1 Checkpoint Inhibitors

• Atezolizumab:
  – *Urothelial cancers* (2016)
  – *Non-small Cell Lung Cancers (NSCLC)*, (2016)

• Avelumab:
  – *NSCLC* (2016)

• Durvalumab:
  – *Urothelial cancers* (2017)
Melanoma
Nivolumab anti-PD-1 therapy in Metastatic Melanoma:

“Spider plot” of tumor size over time in individuals

Topalian et al., NEJM 366: 2443-54, 2012
Updated Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (Checkmate 067)

Jedd D. Wolchok,1 Vanna Chiarion-Sileni,2 Rene Gonzalez,3 Piotr Rutkowski,4 Jean-Jacques Grob,5 C. Lance Cowey,6 Christopher D. Lao,7 Dirk Schadendorf,8 Pier Francesco Ferrucci,9 Michael Smylie,10 Reinhard Dummer,11 Andrew Hill,12 John Haanen,13 Michele Maio,14 Grant McArthur,15 Dana Walker,16 Joel Jiang,16 Christine Horak,16 James Larkin,17* F. Stephen Hodi18*

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*Contributed equally to the study
Unresectable or Metastatic Melanoma

- Previously untreated
- 945 patients

**CA209-067: Study Design**

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone

- Treat until progression** or unacceptable toxicity
- NIVO 3 mg/kg Q2W + IPI-matched placebo
- NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W
- IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Stratify by:
- Tumor PD-L1 expression*
- BRAF mutation status
- AJCC M stage

Randomize 1:1:1

N=314

N=316

N=315

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.
Study Endpoints: NIVO+IPI or NIVO vs IPI

Co-primary endpoints:
• Progression-free survival (PFS) and overall survival (OS)

Secondary and exploratory endpoints:
• Objective response rate (ORR) by RECIST v1.1
• Efficacy by tumor PD-L1 expression level
• Safety profile (in patients who received ≥1 dose of study drug)

Current analysis:
• Efficacy and safety update with follow-up of at least 18 months
  – OS remains immature
### Progression-Free Survival

#### Median PFS, months (95% CI)
- **NIVO + IPI (N=314)**: 11.5 (8.9–16.7)
- **NIVO (N=316)**: 6.9 (4.3–9.5)
- **IPI (N=315)**: 2.9 (2.8–3.4)

#### HR (99.5% CI) vs. IPI
- **NIVO + IPI (N=314)**: 0.42 (0.31–0.57)*
- **NIVO (N=316)**: 0.55 (0.43–0.76)*
- **IPI (N=315)**: --

#### HR (95% CI) vs. NIVO
- **NIVO + IPI (N=314)**: 0.76 (0.60–0.92)**
- **NIVO (N=316)**: --
- **IPI (N=315)**: --

*Stratified log-rank P<0.00001 vs. IPI

**Exploratory endpoint

Number of patients at risk:
- **Nivolumab + Ipilimumab**: 314 | 219 | 174 | 156 | 133 | 126 | 103 | 48 | 8 | 0
- **Nivolumab**: 316 | 177 | 148 | 127 | 114 | 104 | 94 | 46 | 8 | 0
- **Ipilimumab**: 315 | 137 | 78 | 58 | 46 | 40 | 25 | 15 | 3 | 0

Database lock Nov 2015
## Response To Treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>57.6</td>
<td>43.7</td>
<td>19.0</td>
</tr>
<tr>
<td>Two-sided P value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>12.1</td>
<td>9.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>45.5</td>
<td>33.9</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.4</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>38.0</td>
<td>48.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>NR</td>
<td>22.3</td>
<td>14.4</td>
</tr>
<tr>
<td>Ongoing response among responders, %</td>
<td>72.5</td>
<td>72.4</td>
<td>51.7</td>
</tr>
</tbody>
</table>

*By RECIST v1.1. NR = not reached.*

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For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months).
# Response to Treatment by Tumor PD-L1 Expression*

<table>
<thead>
<tr>
<th>PD-L1 (≥5%)</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>72</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR</td>
<td>20.7</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-L1 (&lt;5%)</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>55</td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR</td>
<td>22</td>
<td>18</td>
</tr>
</tbody>
</table>

*Pre-treatment tumor specimens were centrally assessed by PD-L1 immunohistochemistry (using a validated BMS/Dako assay).

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## Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting event, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Grade</td>
<td>96</td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>57</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Grade</td>
<td>39</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>31</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

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Most Common Treatment-related Select AEs

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Skin AEs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>60.4</td>
<td>5.8</td>
<td>43.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35.1</td>
<td>1.9</td>
<td>20.4</td>
</tr>
<tr>
<td>Gastrointestinal AEs, %</td>
<td>47.6</td>
<td>15.3</td>
<td>21.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>11.5</td>
<td>8.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Endocrine AEs, %</td>
<td>32.3</td>
<td>5.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16.0</td>
<td>0.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10.2</td>
<td>1.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Hepatic AEs, %</td>
<td>31.6</td>
<td>19.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>17.9</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>15.7</td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Pulmonary AEs, %</td>
<td>7.3</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6.7</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Renal AEs, %</td>
<td>6.4</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>4.2</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

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Conclusions

- NIVO+IPI and NIVO alone significantly improved PFS and ORR versus IPI alone, in patients with untreated advanced melanoma

- The combination resulted in greater PFS and ORR than NIVO alone, including patients with poor prognostic factors

- Majority of treatment-related AEs resolved with immune-modulating medications
Squamous Cell Carcinomas of the Head and Neck
Nivolumab in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck After Platinum Therapy: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5, 9.1)</td>
<td>0.70 (0.51, 0.96)</td>
<td>0.0101</td>
</tr>
<tr>
<td>Investigator’s Choice (121)</td>
<td>5.1 (4.0, 6.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-year OS rate (95% CI)
Nivolumab: 36.0% (28.5, 43.4)
Investigator’s Choice: 16.6% (8.6, 26.8)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>240</th>
<th>167</th>
<th>109</th>
<th>52</th>
<th>24</th>
<th>7</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator’s Choice</td>
<td>121</td>
<td>87</td>
<td>42</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Survival by Tumor PD-L1 Expression

**PD-L1 ≥ 1%**

- **HR (95% CI)**: 0.55 (0.36, 0.83)
- Nivolumab (n = 88)
- Investigator’s Choice (n = 61)

**PD-L1 < 1%**

- **HR (95% CI)**: 0.89 (0.54, 1.45)
- Nivolumab (n = 73)
- Investigator’s Choice (n = 38)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Nivolumab</th>
<th>Investigator’s Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>67 44 18 6 0</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>42 20 6 2 0</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>52 33 17 8 3</td>
<td>0</td>
</tr>
<tr>
<td>38</td>
<td>29 14 6 2 0</td>
<td>0</td>
</tr>
</tbody>
</table>
# Treatment-Related Adverse Events

**Nivolumab in R/M SCCHN After Platinum Therapy**

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (n = 236)</th>
<th>Investigator’s Choice (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade n (%)</td>
<td>Grade 3–4 n (%)</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>139 (58.9)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (14.0)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.1)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (4.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (15.7)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>18 (7.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
</tbody>
</table>
Nivolumab is the first agent to demonstrate a significant improvement in survival in patients with SCCHN who progress after platinum-based therapy

- Nivolumab doubled the 1-year survival rate: 36% with nivolumab compared to 17% for investigator’s choice therapy

- Nivolumab demonstrated survival benefit regardless of PD-L1 expression or p16 status

- There were fewer treatment-related adverse events with nivolumab vs investigator’s choice therapy

- Nivolumab is a new standard-of-care option for patients with R/M SCCHN after platinum-based therapy
Non-Small Cell Lung Cancers
Nivolumab is superior to docetaxel in previously treated patients with NSCLC
Failure of first-line immunotherapy with nivolumab versus chemotherapy in NSCLC (“CheckMate-026”)  

• Primary endpoint: Progression free survival  
  – 4.2 m for nivo and 5.9 m for chemotherapy  

• 423 patients  

• PD-L1 expression ≥ 5%  

Carbone et al., NEJM 2017; 376: 2415-26
Pembrolizumab versus platinum-based chemotherapy first line in 305 NSCLC patients with high PD-L1 expression ("Keynote-024")

- Subset (25-30%) of patients with very high (> 50%) PD-L1 expression
  - PFS 10.3 m for pembrolizumab vs. 6.0 m for chemotherapy
  - HR for survival 0.60 in favor of pembro vs chemo

NEJM 2016; 375: 1823-33
KEYNOTE-024 Study Design (NCT02142738)

Key Eligibility Criteria
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

Key End Points
Primary: PFS (RECIST v1.1 per blinded, independent central review)
Secondary: OS, ORR, safety
Exploratory: DOR

Pembrolizumab
200 mg IV Q3W (2 years)

Platinum-Doublet Chemotherapy (4-6 cycles)

R (1:1) N = 305

• Reck ESMO 2016
Pembrolizumab versus platinum-based chemotherapy first line in NSCLC patients with high PD-L1 expression ("Keynote-024")
Keynote 024  Take Home

- First major change in treatment of first line since mEGFR inhibitors
- Establishes mono-immunotherapy as initial treatment
- Applies to about 30% of first line NSCLC patients (very high PDL-1)
- Caveat: 50% of control pts did not cross over, so Overall Survival (OS) might not reflect real world
- Leaves many unanswered questions: Dose? Duration of therapy?
CheckMate 012: Safety and Efficacy of First-line Nivolumab and Ipilimumab in Advanced NSCLC

Matthew D. Hellmann,1 Scott N. Gettinger,2 Jonathan Goldman,3 Julie Brahmer,4 Hossein Borghaei,5 Laura Q. Chow,6 Neal E. Ready,7 David E. Gerber,8 Rosalyn Juergens,9 Frances A. Shepherd,10 Scott A. Laurie,11 Tina Young,12 William J. Geese,12 Shruti Agrawal,12 Xuemei Li,12 Scott J. Antonia13

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Presented By Matthew Hellmann at 2016 ASCO Annual Meeting
Pilot Study Results

Nivolumab Plus Ipilimumab in First-line NSCLC: Kinetics of Response

Nivo 3 Q2W + Ipi 1 Q6W

- 12/15 responders (80%) in the Q6W arm and 14/18 responders (78%) in the Q12W arm had a response by time of first scan (week 11)
- 12/15 responders (80%) in the Q6W arm and 12/18 responders (67%) in the Q12W arm had an ongoing response at time of database lock

PD = progressive disease; SD = stable disease
Includes all patients with baseline target lesion and ≥1 post-baseline assessment of target lesion (n = 33)

Presented By Matthew Hellmann at 2016 ASCO Annual Meeting
Nivolumab Plus Ipilimumab in First-line NSCLC: Conclusions

- Nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg (Q6W or Q12W) is well tolerated
  - Frequency of treatment-related AEs leading to discontinuation was similar to nivolumab monotherapy (11%-13%)
  - There were no treatment-related deaths

- Nivolumab plus ipilimumab has promising efficacy
  - 39%-47% ORR; median duration of response not reached

- Efficacy with nivolumab plus ipilimumab is enhanced with increasing PD-L1 expression
  - ≥1% tumor PD-L1 expression: 57% ORR; 83%-90% 1-year OS rates
  - ≥50% tumor PD-L1 expression: 92% (12/13) ORR

- Nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W schedule is being evaluated in further studies, including the phase 3 CheckMate 227 trial (NCT02477826)
Nivolumab Antitumor Activity

*Waterfall plots of tumor regression*

**Melanoma**
- (n = 272)\(^1\)


**Advanced NSCLC**
- (N = 117)\(^2\)

**Advanced RCC**
- (N = 34)\(^3\)

**Hodgkin’s Lymphoma**
- (N = 23)\(^4\)
Pembrolizumab Antitumor Activity

Waterfall plots of tumor regression

Summary of Activity of PD-1/PDL-1 inhibitors

• \(\uparrow\) Survival: Melanoma, Lung, Renal, SCCHN

• \(\uparrow\) RR or PFS: Hodgkin’s, Merkel, MSI-H Colorectal

• > 10% RR: Anal, Bladder, Biliary, Breast, DBLCL, Esophageal, Gastric, HCC Mesothelioma, Myeloma, NPC, Ovarian, SCLC

• Not active: Colorectal (MSI-L), Pancreas, Prostate
Select immune-related adverse reactions

Hypophysitis
Thyroiditis
Adrenal insufficiency
Enterocolitis
Dermatitis

Pneumonitis
Hepatitis
Pancreatitis
Motor & sensory neuropathies
Arthritis

Lipson, ASCO 2014
Immunotherapy Adverse Events

• Onset:
  – Average is 6-12 weeks after initiation of therapy
  – Can occur within days of the first dose, after several months of treatment, and after discontinuation of therapy

• Patient complaints are autoimmune and drug-related until proven otherwise
  – Rule out infections, metabolic causes, tumor effects, etc.

• Early recognition, evaluation, and treatment are critical
General Principles of Immune-related Toxicity Management

- Generally based on severity of symptoms
- **Grade 1:**
  - Supportive care; +/- withhold drug
- **Grade 2:**
  - Withhold drug, consider redosing if toxicity resolves to ≤ grade 1; low-dose corticosteroids (prednisone 0.5 mg/kg/day or equivalent) if symptoms do not resolve within a week
- **Grade 3-4:**
  - Discontinue drug; high-dose corticosteroids (prednisone 1-2 mg/kg/day or equivalent) tapered over ≥1 month once toxicity resolves to ≤ grade 1

Slide courtesy of Joel Neal MD/PHD
Future Directions

• More than 800 trials of PD-1 inhibitors in many types of cancer

• Combinations with other immunotherapies, such as vaccines and other antibodies

• Utility in minimal disease settings, such as adjuvant therapies and consolidation for patients in clinical complete remission

• Predictive markers for response (PD-1, PDL-1, MSI)
Where we are now

Where we want to be

Survival vs. Time

- Control
- Targeted therapies
- Immune checkpoint blockade
- Combinations/sequencing/biomarker selection
Thanks to Dr. Daniel Hoth for insights and slides
The Future of Oncology is Bright!
Thank you!
Questions?