Other checkpoint inhibitors, combined approach including radiation, chemotherapy and targeted agents

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Disclosures

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• Research funding: Astra-Zeneca
Outline

• Why combination?
• Which combination?
• What are the results?
• How to select?
Immune checkpoint inhibitors- broad anti-tumor activity

“Midas touch”?

HNSCC

Lymphoma

NSCLC treated with nivolumab

Merkel cell carcinoma treated with pembrolizumab

Responses are durable
Making immune checkpoint inhibitors work better

NEGATIVE Trials

CM-026

OS (%)

Mos

Median OS, mos 14.4 13.2
HR (95% CI) 1.02 (0.80-1.30)

Chemotherapy

Nivolumab

IMvigor211

Overall Survival

100
80
60
40
20
0

No. at Risk

Atezolizumab 116 100 85 78 71 65 60 56 51 47 42 38 34 30 26 22
Chemotherapy 118 100 86 80 75 70 65 60 55 50 45 40 34 29 24

12-mo OS Rate

Atezolizumab 46% (37, 56)
Chemotherapy 41% (32, 50)

HR = 0.87 (95% CI: 0.63, 1.21) P = 0.41

POSITIVE Trials

KN-024

PFS (%)

Mos

Median PFS, mos 10.3 6.0
HR (95% CI) 0.50 (0.37-0.68); P < .001

CM-057

OS (%)

Time (mos)

18-mo OS rate = 33%
18-mo OS rate = 23%
18-mo OS rate = 33%
18-mo OS rate = 51%
Making immune checkpoint inhibitors work better

Progression:
Absence of anti-tumor immunity (cold tumor)?
Responders: 20% only
How to induce CR?
Stable disease
Further improvement in response
Insufficient T cell immunity (warm tumor)?

Room for improvement through combination therapy: converting a “cold tumor” to a “hot tumor”

Change in sum of longest diameters (SLD) from baseline (%)
Time on study (days)
Potential combination strategies:

Immune checkpoint inhibitor is an ideal backbone

1. Broad anti-tumor activity
2. Favorable toxicity profile

Chemotherapy
Targeted & biologic therapy
Immunotherapy: MoAb, cytokines, vaccines, ACT
Radiotherapy
Selecting the ideal partner to combine

1. Agents must be safe in combination
2. The additional therapy should not interfere with the immunotherapeutic mechanism of action that is driving the anti-tumor response
3. Synergistic activity
• Combining checkpoint inhibitors:
  – Combining inhibitors that act at different points in the cancer immunity cycle can potentially have a synergistic effect.
CM-067: Nivo/mpi v nivo v mpi

- Treatment-related Grade 3/4 AEs: nivolumab+ipilimumab 55.0%, nivolumab 16.3%, ipilimumab 27.3%
- Immune-related Grade 3/4 AEs:
  - Diarrhoea (9.3% nivolumab+ipilimumab, 2.2% nivolumab, 6.1% ipilimumab)
  - Colitis (7.7%, 0.6% and 8.7%)
  - Increased alanine aminotransferase level (in 8.3%, 1.3% and 1.6%)

PFS
- Nivo/mpi 11.5m
- Nivo 6.9m
- mpi 2.9m

HR vs mpi
- 0.42, P<0.001
- 0.57, P<0.001

Larkin NEJM 2015
Checkmate 214: 1L Nivo+ipi in RCC

**PFS per IRRC**

- **Nivo + Ipi**
  - mPFS, mos: 11.6 months
  - HR (99.1% CI): 0.82 (0.64-1.05); P = .0331

- **Sunitinib**
  - mPFS, mos: 8.4 months

**OS**

- **Nivo + Ipi**
  - mOS, mos (n = 425): NR
  - HR (99.8% CI): 0.63 (0.44-0.89); P < .0001

- **Sunitinib**
  - mOS, mos (n = 422): 26.0 months

Escudier ESMO 2017
CheckMate 012: Nivolumab + ipilimumab in first-line NSCLC

Nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 12 weeks

Nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks

1L line nivolumab/ ipilimumab: high response rate and durable response

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab q2w + ipilimumab q12w (n=38)</th>
<th>Nivolumab q2w + ipilimumab q6w (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>Median DoR, mo (95% CI)</td>
<td>NR (11.3–NR)</td>
<td>NR (8.4–NR)</td>
</tr>
</tbody>
</table>

CheckMate 012: ORR increases with higher tumour PD-L1 expression levels

The magnitude of clinical benefit achieved with the combination treatment was enhanced with higher PD-L1 expression, rising to more than 90% in patients with 50% or more tumour PD-L1 expression.

## CheckMate 012: TRAEs

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Nivolumab q2w + ipilimumab q12w (n=38)</th>
<th>Nivolumab q2w + ipilimumab q6w (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment exposure (mths)</td>
<td>9.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>31 (82)</td>
<td>28 (72)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>14 (37)</td>
<td>13 (33)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>4 (11)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Led to death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- The most common TRAEs in the nivolumab q2w + ipilimumab q12w group were pruritis (24%), diarrhoea (21%), and nausea, fatigue, increased amylase and rash (all 16%)
- The most common TRAEs in the nivolumab q2w + ipilimumab q6w group were fatigue (23%), diarrhoea (21%) and nausea (15%)

Phase I of durvalumab/Tremelimumab: responses unrelated to PD-L1 status

Unknown if PD-L1 status is a predictive biomarker

Antonio Lancet Oncol 2016
MYSTIC: IO v combination IO v chemo

AstraZeneca reports initial results from the ongoing MYSTIC trial in Stage IV lung cancer

Imfinzi plus tremelimumab combination did not meet a primary endpoint of progression-free survival compared to chemotherapy

The MYSTIC trial continues as planned to assess the additional primary endpoints of overall survival for Imfinzi monotherapy and for the Imfinzi plus tremelimumab combination

Stratification:
PD-L1 status (+/-)
Histology (Sq/ nonSq)
# Tolerability of combination therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>G3-4 TRAE</th>
<th>Treatment related discontinuation</th>
<th>G5 TRAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonia</td>
<td>NSCLC</td>
<td>Durvalumab</td>
<td>Tremelimumab</td>
<td>36%</td>
<td>28%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hellman</td>
<td>NSCLC</td>
<td>Nivolumab</td>
<td>Ipilimumab</td>
<td>33-37%</td>
<td>11-13%</td>
<td>0%</td>
</tr>
<tr>
<td>Antonia#</td>
<td>SCLC</td>
<td>Nivolumab</td>
<td>Ipilimumab</td>
<td>13-30%</td>
<td>7-11%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Postow</td>
<td>Melanoma</td>
<td>Nivolumab</td>
<td>Ipilimumab</td>
<td>54%</td>
<td>47%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Larkin</td>
<td>Melanoma</td>
<td>Nivolumab</td>
<td>Ipilimumab</td>
<td>55%</td>
<td>36.4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

IDO (indoleamine di-oxygenase)

IDO1
Catabolises tryptophan to kynurenine
Suppresses T-cell function
Induces Treg activation and antigen-specific immune tolerance

KN-037: Epacadostat+ pembrolizumab (HNSCC)

N=38
Prior Tx
1-2  3+
ORR:  39%  14%  34%
DCR:  65%  43%  61%
DoR  18w+
**T cell bispecific Ab**

Simultaneous binding to the CD3e subunit of the TCR and a tumor surface antigen.

TCR engagement, T cell activation, tumor cell killing with cytokine release and T cell proliferation.

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**Atezolizumab + CEA-TCB in 3L+ MSS mCRC**

<table>
<thead>
<tr>
<th>Confirmed ORR</th>
<th>5-160mg (n=25)</th>
<th>80-160mg (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>12%</td>
<td><strong>18%</strong></td>
</tr>
<tr>
<td>SD</td>
<td>40%</td>
<td><strong>64%</strong></td>
</tr>
<tr>
<td>DCR</td>
<td>52%</td>
<td><strong>82%</strong></td>
</tr>
</tbody>
</table>

Bacic Clin Cancer Res 2016, Tabernero ASCO 2017
IO+ novel IO combinations

Killing of cancer cells
- PD-L2
- LAG3
- TIM3
- VISTA
- Tryptophan pathway
- TGF-beta signaling
- Adenosine pathway

Priming and activation
- OX40
- CD137
- GITR
- CD40
- CD27
- ICOS
- IL-2
- Vaccines

Cancer antigen presentation
- IFN-g
- KIR
- MUC1
- TLR
Immunotherapy with targeted or chemotherapies

combining targeted therapy with immunotherapy may lead to more durable responses and prolonged survival
Combination IO+ targeted/chemotherapy

Knowledge of the immunomodulatory effects of targeted or chemotherapy can influence the design of novel, effective treatments.
## Immune modulating effects of targeted therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Depletes Treg</td>
</tr>
<tr>
<td>EGFR-targeting mAb</td>
<td>Promotes ICD</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Upregulates NKG2D ligands</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Promotes expansion of circulating NK cells, tumor infiltration by CTLs</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Promotes tumor infiltration by CTLs</td>
</tr>
<tr>
<td>MAPK inhibitors</td>
<td>Upregulates expression of MHC class I molecules</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Depletes Treg</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Increases CTL/Treg ratio</td>
</tr>
</tbody>
</table>
MEK inhibition:
intratumoral T-cell accumulation
MHC I upregulation

Phase I: Atezolizumab + Cobimetinib + vemurafenib in metastatic melanoma

### Outcomes

<table>
<thead>
<tr>
<th>Atezo+ V+C</th>
<th>Atezo+ V+C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>18.4%</td>
</tr>
<tr>
<td>ORR</td>
<td>81.6%</td>
</tr>
<tr>
<td>DoR</td>
<td>NR</td>
</tr>
<tr>
<td>PFS</td>
<td>12.9m</td>
</tr>
</tbody>
</table>

**IMspire150 (1L BRAF-mutant)**

Cobimetinib + vemurafenib +/- atezolizumab

Sullivan ASCO 2017
Phase I: Atezolizumab + Cobimetinib in CRC

COTEZO IMblaze370: 3L mCRC

1. Atezolizumab
2. Cobimetinib + Atezolizumab
3. Regorafenib

N=23 (KRAS MT, n=22)
Partial responses: 4/21 :

MSI status of CRC patients: 3 of 4 responders were mismatch-repair proficient; 1 responder had unknown MSI status and was not evaluable

On treatment biopsies: PD-L1 upregulation, CD8 T-cell infiltration, and major histocompatibility complex I expression

Bendell. ASCO 2016
Atezolizumab + Cobimetinib in CRC
Heavily pre-treated met CRC, KRAS MT MSS

Combination IO+ targeted agents
Multiple studies ongoing
PARP inhibitors, epigenetic agents, anti-angiogenic agents
Toxicities of PD1/ PD-L1 inhibitor + targeted therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Treatment</th>
<th>Treatment</th>
<th>G3-4 TRAE</th>
<th>Treatment related discontinuation</th>
<th>G5 TRAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahn</td>
<td>NSCLC</td>
<td>Durvalumab</td>
<td>Osimertinib</td>
<td>59%</td>
<td>59%</td>
<td>0%</td>
</tr>
<tr>
<td>Gibbons</td>
<td>NSCLC</td>
<td>Durvalumab</td>
<td>Gefitinib</td>
<td>55%</td>
<td>20%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Grade 3 pneumonitis: 14.9%

Ahn ELCC 2016, Gibbons ELCC 2016
Overlapping toxicities: hepatic

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.*

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT–AST Elevation</th>
<th>Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab</th>
<th>Treatment</th>
<th>Time to Resolution of ALT–AST Elevation</th>
<th>Toxicity Relapse with Repeated Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>4 days</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>36 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>Second cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>10 days</td>
<td>NA</td>
</tr>
<tr>
<td>16±</td>
<td>1</td>
<td>13 days</td>
<td>Vemurafenib and ipilimumab permanently discontinued</td>
<td>20 days</td>
<td>NA</td>
</tr>
</tbody>
</table>

Importance of carefully conducted trials to determine the optimal dose, schedule, and sequence of molecular targeted therapy in combination with immune checkpoint inhibitors

Ribas NEJM 2013
## Immune modulating effects of chemotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Promotes ICD, stimulates expansion Treg</td>
</tr>
<tr>
<td>Carboplatin/cisplatin</td>
<td>Downregulates PD-L2</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Depletes circulating Treg</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Increases CTL/Treg ratio</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Promotes ICD, expands MDSC</td>
</tr>
<tr>
<td>5FU + RT</td>
<td>Increases TILs</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>Expands circulating MDSCs</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>Depletes circulating MDSCs</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Depletes circulating Treg</td>
</tr>
<tr>
<td>Gem/ Cisplatin</td>
<td>Depletes circulating Treg</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Favors tumor infiltration by NK cells and CTLs</td>
</tr>
</tbody>
</table>
Combination chemotherapy + IO


• Chemotherapy may have several immunologic effects:
  • Downregulate suppressive immune cells
  • Induce ICD
  • Enhance presentation of tumour antigens
  • Activate dendritic cells
  • Enhance effector T-cell function
  • Induce PD-L1 expression on tumour cells
Carboplatin/pemetrexed + pembro v carboplatin/pemetrexed (Keynote 021G)

<table>
<thead>
<tr>
<th></th>
<th>Chemo/pembro</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR:</td>
<td>55%</td>
<td>29%</td>
</tr>
<tr>
<td>Time to response:</td>
<td>1.5m</td>
<td>2.7m</td>
</tr>
<tr>
<td>DoR:</td>
<td>NR</td>
<td>16.2m</td>
</tr>
<tr>
<td>PFS:</td>
<td>13.0m</td>
<td>8.9m</td>
</tr>
</tbody>
</table>

Pembro + CT
CT Alone

Median PFS, mos
HR (95% CI)
P value

Pembro + CT
CT Alone

Median OS, mos
HR (95% CI)
P value

Langer Lancet Oncol 2016, Papadimitrakopoulou ASCO 2017
Adverse events: more with pembro+ chemo combination

But still tolerable

<table>
<thead>
<tr>
<th>TRAE, n (%)(^1)</th>
<th>Pembro + chemo (N=59)</th>
<th>Chemo alone (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median treatment (mths)</td>
<td>8.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Any</td>
<td>55 (93)</td>
<td>56 (90)</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>23 (39)</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>6 (10)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Led to death</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

- The most common TRAEs in the pembrolizumab group were fatigue (64%), nausea (58%), and anaemia (32%)
- The most common TRAEs in the chemotherapy group were anaemia (53%), nausea (44%) and fatigue (40%)

Chemotherapy/ paclitaxel/ atezolizumab/ bevacizumab

Basel, 20 November 2017

Phase III IMpower150 study showed Roche’s TECENTRIQ (atezolizumab) and Avastin (bevacizumab) plus chemotherapy significantly reduced the risk of disease worsening or death in the initial treatment of people with a type of advanced lung cancer.

- Data will be submitted to health authorities globally, including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the Phase III IMpower150 study met its co-primary endpoint of progression-free survival (PFS) and demonstrated that the combination of TECENTRIQ* (atezolizumab) and Avastin* (bevacizumab) plus chemotherapy (paclitaxel and carboplatin) provided a statistically significant and clinically meaningful reduction in the risk of disease worsening or death (PFS) compared to Avastin plus chemotherapy in the first-line treatment of people with advanced nonsquamous non-small cell lung cancer (NSCLC). Initial observations for the co-primary endpoint of overall survival (OS) are encouraging. These data are not fully mature and the next OS analysis is expected in the first half of 2018. Safety for the TECENTRIQ and Avastin plus chemotherapy combination appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination.
IO+ radiotherapy

Radiation enhances anti-tumor immunity via immunogenic cell death with downstream activation of DC and T cells & CTL infiltration
PACIFIC: Phase III, Randomized, Double-blind, Placebo-controlled Study

Co-primary endpoints:
- PFS (BICR)
- OS

Secondary endpoints:
- ORR
- DoR
- Safety, tolerability
- PROs

Stage III unresectable NSCLC
No PD after platinum CT-RT x2+
WHO PS=0-1

1-42 days post CT-RT

Durvalumab 10mg/kg q2w for 12 months (n=476)

2:1 randomization, stratified by age, sex, smoking history

Placebo 10mg/kg q2w for 12 months (n=237)

Results of planned interim analysis of PFS
Study remains blinded to OS

Antonia NEJM 2017
• Sequencing of RT/ immunotherapy: IO before/during
• RT dose & fractionation
• Patient selection
### Selected ongoing studies

<table>
<thead>
<tr>
<th>Phase</th>
<th>Condition</th>
<th>Treatment</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>GBM</td>
<td>Nivo/RT vs TMZ/RT</td>
<td>NCT02617589</td>
</tr>
<tr>
<td>II</td>
<td>GBM</td>
<td>Durvalumab</td>
<td>NCT02336165</td>
</tr>
<tr>
<td>III</td>
<td>NSCLC III post CT/RT</td>
<td>Cis/Eto/ EBRT then +/- Nivo</td>
<td>NCT02768558</td>
</tr>
<tr>
<td>II</td>
<td>NSCLC III post CT/RT</td>
<td>Nivo</td>
<td>NCT02434081</td>
</tr>
<tr>
<td>II</td>
<td>NSCLC</td>
<td>SABR then Pembro v pembro</td>
<td>NCT02492568</td>
</tr>
<tr>
<td>II</td>
<td>HNSCC</td>
<td>Cis/ RT/ Pembro</td>
<td>NCT02641093</td>
</tr>
<tr>
<td>II</td>
<td>Bladder</td>
<td>Pembro/CT/RT</td>
<td>NCT02662062</td>
</tr>
<tr>
<td>II</td>
<td>Rectal</td>
<td>Pembro/chemo/RT</td>
<td>NCT02586610</td>
</tr>
</tbody>
</table>
An expanding number of immunotherapy-based combination studies ongoing...

Gergely et al. Nature 2017
Challenges for combination therapies

What is the impact of targeted, conventional and immune-based therapies on immune system?

How to optimise the efficacy, toxicity and tolerability of combination therapy?

How to better prioritise resources for numerous combination therapies?

How to select combinations for further development?

Analysis of pre-and on-treatment clinical samples (tumor, blood)

Collaborative efforts between academia, industry, and regulatory authorities

Well designed pre clinical and clinical studies for optimal treatment dosing and sequence
Tailoring cancer immunotherapy based on PD-L1 & TIL status in tumor microenvironment

Teng Cancer Res 2015
Selecting the optimal combinations

Through analysis of serial tumor samples

Results can

1. Inform target discovery and the development of better preclinical models
2. Identify appropriate therapeutic combinations to further develop clinically.

Immune excluded:
Accumulation of CD8+ T cells

Immune desexed:
T cells but not infiltrated

CD8+ T cells absent from tumor and periphery:
Increase/activate T cells
Vaccines, αCI
viruses, chen targeted thei

ICI, IDOi, aOX40, aTIGIT,
αCEA/FAP IL-2v, αCSF-1R,
TCBs

Chen, Mellman Immunity 2013, Sharma CCR 2016
Does preclinical testing help?

Concurrent OX-40 + anti PD-1
- Increased CTLA-4 and TIM-3 expression
- Reduced CD4+ and CD8+ T-cell proliferation

Sequential OX-40, antiPD-1
- Tumor shrinkage, longer survival

Messenheimer CCR 2017
Conclusion

- Immune checkpoint inhibitors is an ideal backbone for combination
- Multiple efforts to combine agents from different classes underway
- Aim: convert “cold” tumor to T cell inflamed tumor
- Innovative study designs, novel clinical endpoints
- Rational selection given limited resources
- Correlative studies key to understanding
- Awareness of adverse events
Thank you for your attention