PD-1/PD-L1 inhibitors in hematological malignancies, with focus on Lymphoid Malignancies

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DISCLOSURE SLIDE

Nothing to Declare
Introduction

Immune checkpoints are molecules that remove inhibitory pathways that block effective anti-tumor T cell responses

2 main inhibitory pathways

a. PD-1 receptor with its two ligands (PD-L1/PD-L2)
   i. Against PD-1 receptor: Nivolumab, pembrolizumab
   ii. Against the ligands (PD-L1/PD-L2): Durvalumab, atezolizumab

b. CTLA-4 checkpoint receptor and B7 molecules
   i. Ipilimumab (Yervoy)
FDA approval for Hodgkin’s Lymphoma
Aberrancies in immune checkpoint molecules in lymphomas

- **CTLA4-CD28 gene fusion** reported in several types of T cell lymphomas, AITL
  - Transform inhibitory signals into stimulatory signals for T cell activation
  

- **PD-L1 expression** can be induced by **extrinsic signals** (e.g., IFN-γ) secreted from tumor-infiltrating lymphocytes (TILs) or by **intrinsic signals**

- **4 mechanisms of intrinsic signals** reported in lymphoid malignancies:
  - CNAs and/or translocations involving 9p24.1/PD-L1/PD-L2 (HL, PCNSL, PMBCL, PTL)
  - **EBV infection**: LMP1 activates the JAK/STAT pathway and the transcription factor AP-1 (EBV+DLBCL, ENK/TL)
  - **PD-L1 3’-untranslated region (UTR) disruption** in ATLL
  - **Constitutive activation of the JAK/STAT pathway**: ENK/TL extranodal, ALCL, MF
Hodgkin lymphoma (HL)

- Characterized by presence of Reed–Sternberg (RS) cells residing in the extensive inflammatory surroundings.
- PD-L1 and PD-L2 are expressed on the surface of malignant cells:
  - 65–100% of cHL
  - 54% NLPHL
- Amplification of the chromosomal region 9p24.1 (contains the genes encoding PD-L1, PD-L2 and JAK2) results in increased expression of these proteins on RS cells
- JAK2–STAT signaling promotes further increased expression of PD-L1 by augmenting transcription of the PDL1 gene

Regulation of PD-L1 and PD-L2 expression in Hodgkin lymphoma

- EBV infection
- Genetic amplification at the PD-L1 / PD-L2 locus on chromosome 9p24.1
- 9p24.1 amplicon also induces JAK2 & JAK-STAT activity further induces PD-1 ligand transcription

PD-1 Blockade with Nivolumab in R/R Hodgkin's Lymphoma

Pivotal Phase 1 trial

- Major inclusion criteria:
  - R/R HL with at least one lesion measuring more than 1.5 cm
  - Previous treatment with at least one chemotherapy regimen, and no ASCT within the previous 100 days.

- Study design:
  - Phase 1 study
  - Dose of 3 mg/kg chosen for the expansion cohorts
    - Given at wk 1, wk 4, and then every 2 wks until PD or CR or for a maximum of 2 years

In a subgroup of 10 pts with available tumour samples, 100% had *PDL1* and *PDL2* amplifications identified by FISH as well as increased expression of PD-L1 and PD-L2 detected using IHC.
# Efficacy

The ORR was 87%, with 4 patients (17%) having a CR and 16 patients (70%) having a PR. After a median f/U of 40 weeks, the median OS was not reached.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=23)</th>
<th>Failure of both ASCT and BV</th>
<th>No ASCT and Failure of BV</th>
<th>No BV Treatment (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response - no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>0</td>
<td>3 (60)</td>
</tr>
<tr>
<td>PR</td>
<td>16 (70)</td>
<td>12 (80)</td>
<td>3 (100)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (13)</td>
<td>2 (13)</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Objective response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>13</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Percent of patients (95% CI)</td>
<td>87 (66-97)</td>
<td>87 (60-98)</td>
<td>100 (29-100)</td>
<td>80 (28-99)</td>
</tr>
<tr>
<td>PFS at 24 wk - % (95% CI)</td>
<td>86 (66-950)</td>
<td>85 (52-96)</td>
<td>Not calculated</td>
<td>80 (20-97)</td>
</tr>
<tr>
<td>OS - wk</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Phase 2 Study of Nivolumab in Patients With cHL (CheckMate 205)

Brentuximab Vedotin (BV) History

Cohort A
Failed ASCT and naïve to BV
n = 63

Cohort B
Failed BV after ASCT
n = 80

Cohort C
BV before, after or before and after ASCT
N = 100

Screening

Nivolumab 3mg/kg every 2weeks

Treatment until disease progression or intolerable toxicity

Follow up

Chen R et al. JCO 2017;19:2125-2132
Patients with cHL after failure of both ASCT and subsequent BV treatment (Cohort B)

**Efficacy**

<table>
<thead>
<tr>
<th>Response</th>
<th>IRRC (n=80)</th>
<th>Investigator (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>53 (66.3%), 54.8–76.4</td>
<td>58 (72.5%), 61.4–81.9</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>7 (8.8%)</td>
<td>22 (27.5%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>46 (57.5%)</td>
<td>36 (45.0%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18 (22.5%)</td>
<td>18 (22.5%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (7.5%)</td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>3 (3.8%)</td>
<td>1 (13%)</td>
</tr>
</tbody>
</table>

At 6 months, PFS rate was 76.9% (95% CI 64.9–85.3) and OS rate was 98.7%
FISH analyses revealed polysomy 9 in 16%, copy gain of PD-L1/PD-L2 in 58%, & amplification of PD-L1/PD-L2 in 27% of cases (Fig 2A)

RS cells with higher-level 9p24·1 genetic alterations exhibited increased PD-L1/PD-L2 expression (Fig 2B)

CR cases were more likely to have higher level 9p24·1 alterations (Fig 2C)

All patients with CR had PD-L1 H-scores in the 3rd or 4th quartiles; those with PD had PD-L1 H-scores in the 1st quartile (Fig 2D)

PD-L1 H-score: % malignant cells with positive staining multiplied by average intensity of positive staining
CML 2017: Nivolumab Shows Durable Response in R/R cHL, regardless of Brentuximab Vedotin History

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>63</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Median Follow up</td>
<td>19 months</td>
<td>23 months</td>
<td>16 months</td>
</tr>
<tr>
<td>ORR</td>
<td>65%</td>
<td>68%</td>
<td>73%</td>
</tr>
<tr>
<td>CR</td>
<td>29%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Median Duration of response</td>
<td>20 months</td>
<td>16 months</td>
<td>15 months</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.3 months (95% CI, 11.1-22.4)</td>
<td>14.7 months (95%CI, 10.5 - 19)</td>
<td>11.9 months (95%C1, 11.1 - 18.4)</td>
</tr>
</tbody>
</table>

Across cohorts, the median overall survival was not reached, and 40% of patients remained on treatment.
Failed ASCT and subsequent BV Resistant to salvage chemotherapy and BV, and thus ineligible for ASCT Failed ASCT but had not received BV after transplantation

Screening

pembrolizumab 200 mg intravenously every 3 weeks

- Treatment for max. 24 mos. or until PD, intolerable toxicity.
- Patients in CR could stop after a minimum of 6 mos. treatment, with ≥ 2 doses received after documented CR.

Follow up

Chen R et al. JCO 2017;19:2125-2132
Efficacy

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Blinded Independent Central Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/R HL after ASCT and BV</td>
<td>69</td>
<td>ORR: 73.9% CR: 21.7% PR: 52.2% SD: 15.9% PD: 7.2%</td>
</tr>
<tr>
<td>Ineligible for ASCT because chemoresistant to salvage chemo + BV</td>
<td>81</td>
<td>ORR: 64.2% CR: 24.7% PR: 39.5% SD: 12.3% PD: 21.0%</td>
</tr>
<tr>
<td>R/R HL after ASCT but no BV</td>
<td>60</td>
<td>ORR: 70.0% CR: 20.0% PR: 50.0% SD: 16.7% PD: 13.3%</td>
</tr>
</tbody>
</table>

- High response rates were achieved with patients with chemoresistant or primary refractory disease
- At 6 months, the OS rate was 99.5%, and the PFS rate was 72.4%.

Chen R et al. JCO 2017;19:2125-2132
Safety

- Most common grade 3 or 4 treatment related adverse events (TRAE) were neutropenia (2.4%), dyspnea (1%), and diarrhea (1%)

- Immune-mediated adverse events and infusion-related reactions were reported in 28.6%, most commonly hypothyroidism

- Nine patients (4.3%) discontinued because of TRAEs
  - myocarditis, myelitis, myositis, pneumonitis, infusion-related reactions, cytokine release syndrome

- 26 patients (12.4%) experienced TRAEs resulting in treatment interruptions.

- Two patients died during F/U
  - septic shock and acute GVHD (not considered treatment related)

Chen R et al. JCO 2017;19:2125-2132
Distribution of the three PD-L1 expression scores (tumor cell staining intensity, membrane staining of tumor cells, and histiocyte staining) and response to pembrolizumab

A  Staining intensity

90.4% had the highest tumor intensity staining

B  Membrane staining

88.1% were 100% PD-L1+ by membrane staining

C  Histiocyte score

71.8% had maximum PD-L1+ histiocyte staining

Although PD-L1 positivity not required for accrual to this study, majority were PD-L1+ pos

Clinical activity was seen across all groups
Algorithm for the treatment of cHL patients who relapse after ASCT.

Lapo Alinari, and Kristie A. Blum
Blood 2016;127:287-295
Efficacy and tolerability of nivolumab after allogeneic transplantation for relapsed Hodgkin lymphoma

- Retrospective study of 20 pts treated with nivolumab after allo-HCT relapse
- GVHD occurred in 6 pts (30%) after nivolumab initiation
  - All 6 patients had prior history of acute GVHD
  - 2 patients died as a result of GVHD
- ORR was 95%
- At a median follow-up of 370 days:
  - 1-year PFS rate was 58.2% (95% CI, 33.1%-76.7%)
  - 1-year OS survival rate was 78.7% (95% CI, 52.4%-91.5%)
- More data needed to determine the safety of PD-1/LI inhibitor but appear effective with an acceptable safety profile.

# Nivolumab + Brentuximab/Ipilimumab combinations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>Prelim Results</th>
</tr>
</thead>
</table>
| Herrera AF et al. Blood 2016;128:1105 | Phase 1/2 study of Brentuximab + Nivolumab in R/R HL                  | ORR 100% (6/6)  
CR 50% (3/6)               |
| *Diefenbach CS et al. Blood 2016;128:1106 | Phase 1 Study of ipilimumab and/or nivolumab +Brentuximab in R/R HL | ORR 100% (8/8)  
CR 62.5% (5/8)               |
| Ansell S et al. Blood 2016;128:183 | Phase 1 study of ipilimumab + nivolumab in R/R hematologic malignancies | ORR 74% (23/31)  
CR 19% (6/31)               |

*Its safety profile was acceptable without grade 4 immune AEs*
Diffuse large B-cell lymphoma (DLBCL)

• In an analysis of 1253 DLBCL samples, 11% are PD-L1 + (≥ 30% of malignant cells express PD-L1).

• PD-L1 expression is most frequently found in non-GCB DLBCL (87%, 110/123) and PMBL (42.9%, 3/7).

Tumour PD-L1 positivity associated with B symptoms, IPI high risk group and inferior outcome

PD-1–PD-L1 axis may be crucial to the outcomes of a subset of patients with DLBCL, specifically those with ABC-subtype disease.

Primary Mediastinal B Cell Lymphoma (PMBCL)

**PD-1 and PD-1 ligand expression in PMBCL.**

- 9p24.1 amplification detected in 63% of PMBCL samples\(^1,2\)
- Chromosomal rearrangements involving 9p24.1 are detected in 20% of PMBCL samples\(^3\)
- Structural rearrangements involving *JAK2*, *CIITA* (encoding a MHC class II transactivator), and *REL* (encoding a subunit of NF-κB) have also been found in PMBCL\(^4\)

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# Preliminary Results of Immune Check Point Inhibitors in DLBCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesokhin Am et al. JCO 2016;34:2698-704</td>
<td>Phase 1b Nivolumab in patients with R/R hematologic malignancy</td>
<td>DLBCL, 11</td>
<td>4 (36%)</td>
<td>2 (18%)</td>
<td>2 (18%)</td>
<td>Median PFS 7 wks (95% CI 6 to 29)</td>
</tr>
<tr>
<td>Ansell S et al. Blood 2016; 128:183.</td>
<td>Phase 1 Nivolumab + ipilimumab for R/R hematologic malignancies</td>
<td>DLBCL, 10 FL, 5</td>
<td>3 (20%)</td>
<td>0</td>
<td>3 (20%)</td>
<td>Median PFS 1.5 mos. Median OS 2.9 mos</td>
</tr>
<tr>
<td>Zinzani PL</td>
<td>Phase 1b Pembrolizumab in R/R PMBL</td>
<td>16</td>
<td>7 (41%)</td>
<td>2 (13%)</td>
<td>5 (31%)</td>
<td>Median PFS not reached at median F/U 11.3 mos</td>
</tr>
</tbody>
</table>
Restoring Antitumor Immunity via PD-1 Blockade After ASCT for DLBCL

- International phase II study of pidilizumab (anti–PD-1 antibody) in pts with chemosensitive DLBCL undergoing ASCT (n=72)
- Pts received 3 doses of pidilizumab beginning 1 to 3 months after AHSCT
- 35 pts have measurable disease post-HSCT and before the 1st dose of pidilizumab
  ✓ 12/35 (34%) achieved a CR by CT criteria after pidilizumab treatment,
  ✓ 6/35 (17%) achieved a PR
  ✓ ORR rate of 51%.

• Use of pidilizumab improved the 16-mos. PFS (72% versus 52%) and OS (85% versus 60%) compared to historical control

• The post-ASCT state, which is characterized by both minimal residual disease and remodelling of the immune system, might be the ideal setting for ICP blockade.

Primary CNS Lymphoma (PCNSL) and Primary Testicular Large B cell Lymphoma (PTL)

• >50% of the PCNSLs and PTLs harbored 9p24.1 alterations (CNAs and translocations)
  ✓ Translocations identified are identical to those detected in patients with PMBCL
    e.g. juxtaposition of the super-enhancer for the Igλ gene proximal to the 5’-untranslated region (UTR) of PDL2

• Studies evaluating ICP inhibitors in PCNSL and PTL ongoing
Follicular Lymphoma (FL)

- PD-L1 is rarely expressed on FL tumor cells
- FL microenvironment contains many types of T cells that can express PD-1, including CD4+ Th1 cells, CD8+ CTLs, and Treg cells
- Data regarding the prognostic impact of PD-1/PD-L1 expression in FL conflicting:
  - Technical issues (IHC may not accurately discriminate the relative T-cell subsets that are PD-1 positive)
  - Differential use of Rituximab in tested cohorts
- Nonetheless, early studies suggest some clinical activity of ICP inhibitors in FL

Gravelle P et al. Oncotarget 2017; 8: 44960–44975
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesokhin AM et al. J Clin Oncol 2016; 34:2698–704</td>
<td>Phase Ib Nivolumab in patients with R/R hematologic malignancy</td>
<td>FL, 10</td>
<td>4 (10%)</td>
<td>1 (10%)</td>
<td>3 (30%)</td>
<td>Median PFS (wks), NR (7 to NR)</td>
</tr>
<tr>
<td>Westin JR et al. Lancet Oncol 2014; 15:69–77</td>
<td>Phase 2 Pidilizumab + Rituximab in relapsed FL</td>
<td>29</td>
<td>19 (66%)</td>
<td>15 (52%)</td>
<td>4 (14%)</td>
<td>With median F/U of 15.4 mos, median PFS is 18.8 mos for all and NR for 19 responders</td>
</tr>
</tbody>
</table>

Response rates to pidilizumab seem better than re-treatment with rituximab monotherapy

Chronic lymphocytic leukaemia

- Limited data on the clinical efficacy of PD-1/PD-L1 inhibitors in CLL or SLL
- Phase 2 study with pembrolizumab in 25 pts with RR CLL, including 9 with Richter syndrome (RS)
- 60% received prior ibrutinib
- Results:
  - ✓ No response in CLL pts without RS
  - ✓ Among pts with RS, CR, 11% and PR, 33%
  - ✓ 6-month OS rates: RS, 73% and CLL, 59%
- Pembrolizumab has substantial therapeutic activity in RS but not appear to have clear activity in CLL

Ding W et al. Blood 2016; 128:4392
T Cell Lymphoma

- **AITL and TFH lymphomas**
  - From a diagnostic point of view, PD-1 expression is usually observed
  - PD-L1 expression rarely observed on tumor cells
- **In ALCL**, PD-L1+ cases varying from 34 to 100% of the analyzed cases
  - Plausibly due to activation of the STAT3 by the nucleophosmin- fusion protein
- **In PTCL-NOS**, up to 30% are PD-L1+
- **In ATLL**, up to 10% are PD-L1+ due to structural variation at 3’UTR
- **In cutaneous T cell lymphoma**, PD-L1 overexpression observed in MF/SS, possibly in part due to activation of JAK/STAT
  - PD-L1 expression reported in 60 to 100% of ENK/T cell lymphoma due to EBV infection, JAK/STAT activation and endogenous genetic events
# T Cell Lymphoma

<table>
<thead>
<tr>
<th>Tumor</th>
<th>OR, No. (%)</th>
<th>CR, No. (%)</th>
<th>PR, No. (%)</th>
<th>SD, No. (%)</th>
<th>Median PFS, Weeks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell lymphoma (n = 23)</td>
<td>4 (17)</td>
<td>0</td>
<td>4 (17)</td>
<td>10 (43)</td>
<td>10 (7 to 33)</td>
</tr>
<tr>
<td>MF (n = 13)</td>
<td>2 (15)</td>
<td>0</td>
<td>2 (15)</td>
<td>9 (69)</td>
<td>10 (7 to 35)</td>
</tr>
<tr>
<td>PTCL (n = 5)</td>
<td>2 (40)</td>
<td>0</td>
<td>2 (40)</td>
<td>0</td>
<td>14 (3 to NR)</td>
</tr>
<tr>
<td>Other CTCL (n = 3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7 (6 to NR)</td>
</tr>
<tr>
<td>Other non-CTCL (n = 2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (50)</td>
<td>10 (2 to 18)</td>
</tr>
</tbody>
</table>

Expression of PD-L1 in advanced stage ENK/T cell lymphoma is associated with better prognosis (N=73)

- PD-L1 positivity showed no relationship with clinico-pathological features.
- PD-L1+ ENKTL associated with better 5-yr OS
  - Independent predictor for longer OS in patients with advanced stage ENKTL.

Expression of PDL1 in ENK/TL is not associated with survival outcome (N= 76)

- PD-L1 expression in tumor cells and infiltrating immune cells were 79.7 % and 78.5 %, respectively

<table>
<thead>
<tr>
<th>PDL1 expression</th>
<th>0</th>
<th>1+</th>
<th>2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor cells</td>
<td>20.3%</td>
<td>72.2%</td>
<td>7.6%</td>
</tr>
<tr>
<td>infiltrating immune cells</td>
<td>21.5%</td>
<td>65.8%</td>
<td>12.7%</td>
</tr>
</tbody>
</table>

PD-L1+ on EBER-positive tumor cells

PD-L1 is upregulated by EBV-driven LMP1 through NF-κB pathway and correlates with poor prognosis in ENK/TL

- PD-L1 expression positively correlated with LMP1, probably mediated by the MAPK/NF-κB pathway.

- ENK/TL cases had a significantly higher level of serum soluble PD-L1 than healthy individuals

- Expression level of PD-L1 in tumor tissues positively correlated with pretreatment serum concentration of soluble PD-L1

• Pretreatment serum PD-L1 $\geq 3.4$ ng/ml is an independent adverse prognostic factor for PFS and OS in multivariate analysis

\[ \text{Log-rank test } P < 0.001 \]

• Multivariate analysis found a PD-L1 expression of $\geq 38\%$ an independent adverse prognostic factor for PFS and OS

\[ \text{Log-rank test } P < 0.001 \]
PDL1 and its soluble form are highly expressed in ENK/TL

- N = 17
- PD-L1 positivity defined as >10% of the CD56+ tested positive for PD-L1
- Concentration of soluble PD-L1 (sPD-L1) in the sera of ENKT/L patients and healthy volunteers were measured.
- PD-L1 found on all malignant cells and tumor-infiltrating macrophages

Arrows indicate colocalization of CD56 and PD-L1

• Level of sPD-L1 was higher in patients compared to normal volunteers.

• Levels of serum sPD-L1 in patients correlated with the expression of PD-L1 in malignant cell.

• High-sPD-L1 group showed significantly worse prognosis than the low-sPD-L1 group.

Oncogenic activation of STAT3 pathway drives PD-L1 in ENK/L

Lim ST et al. JCO 2017; 35:15
PD1 blockade with pembrolizumab was a potent strategy for NK/T-cell lymphomas failing L-asparaginase regimens

- 7 patients with relapsed/refractory NK/TL
  - Failed L-asparaginase regimens and allogeneic HSCT in 2 cases
  - Treated with the PD1 antibody pembrolizumab.
  - After a median of 7 (range, 2-13) cycles of pembrolizumab and median follow up of 6 (range, 2-10) months, 5 CR patients remained in remission.
  - Expression of the PD1 ligand was strong in 4 patients (3 achieving CR) and weak in 1 (achieving PR).

Kwong et al. Blood 2017
Multiple Myeloma

- Initial studies suggest no activity with the single-agent PD-1 inhibitor
- However, significant efficacy seen in combination with an immunomodulatory agent (IMiDs)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>SD</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansell S et al. Blood 2016 128:183;</td>
<td>Phase 1. Nivolumab + Ipilimumab for R/R hematologic malignancies</td>
<td>7 pts with MM</td>
<td>0</td>
<td>0</td>
<td>14% (1/7)</td>
<td>none responded, similar to Nivo as single agent</td>
</tr>
<tr>
<td>Mateos M-V et al. JCO.2016.34.15_sup pl.8010</td>
<td>Phase 1. Pembrolizumab + lenalidomide for R/R multiple myeloma</td>
<td>51 (40 evaluable)</td>
<td>50% (20/40)</td>
<td>3% (1/40)</td>
<td>48% (19/40)</td>
<td>Response noted in lenalidomide refractory cases</td>
</tr>
<tr>
<td>Badros A. Blood 2017 130:1189-1197</td>
<td>Pembrolizumab + pomalidomide in R/R multiple myeloma</td>
<td>48</td>
<td>60% * (29/48)</td>
<td>6% (3/48)</td>
<td>23% (11/48)</td>
<td>73% refractory to both a proteasome inhibitor and an IMiD and 70% with prior ASCT.</td>
</tr>
</tbody>
</table>

* PD-L1 expression on MM cells associated with a trend toward a higher rate of very good partial (VGPR) in PD-L1–positive pts compared with negative and weakly positive pts (54% vs 20%)
Acute Myeloid Leukemia

- Data from clinical trials using PD-1/PD-L1 inhibitors in AML patients limited.
- Hypomethlyating agents (e.g. 5-azacitidine) used to treat AML can induce up regulation of PDL1
  - possible synergistic effect of checkpoint inhibitors with these classes of drugs

Induction of PD-L1, PD-L2, PD-1 and CTLA4 expression in leukemia cell lines treated with hypomethylating agent

Phase IB/II study: Nivolumab + AZA relapsed AML

- N = 51
- 35 pts are evaluable for response:
  - 6 (18%) CR/ CRi (CR with insufficient recovery of counts)
  - 9 (26%) had 50% BM blast reduction
  - Response was durable with no relapses among pts who achieved CR/Cri
  - Median OS of 9.3 mos. compares favorably to historical data with AZA-based salvage protocols

Naval Daver et al. Blood 2016;128:763
Myelodysplastic Syndromes

• PD-1, PD-L1, PD-L2 and CTLA4, are aberrantly upregulated in 8 to 34% of bone marrow CD34+ cells from patients with myeloid leukemias.
• There was a trend towards increased expression in MDS
• The relative expression of PD-L1 from PBMNC was significantly higher in MDS (P=0.018) and CMML (P=0.0128) compared with AML.

<p>| ≥ 2 fold expression of PDL1, PDL2, PD1 and CTLA4 in bone marrow CD34+ cells |
|-----------------------------|------------------|----------------|-----------------|------------------|</p>
<table>
<thead>
<tr>
<th>MDS</th>
<th>cMML</th>
<th>AML</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=69</td>
<td>N=46</td>
<td>N=9</td>
<td>N=124</td>
</tr>
<tr>
<td>PDL1</td>
<td>36%</td>
<td>32%</td>
<td>25%</td>
</tr>
<tr>
<td>PDL2</td>
<td>12%</td>
<td>14%</td>
<td>33%</td>
</tr>
<tr>
<td>PD1</td>
<td>8%</td>
<td>26%</td>
<td>22%</td>
</tr>
<tr>
<td>CTLA4</td>
<td>6%</td>
<td>14%</td>
<td>0%</td>
</tr>
</tbody>
</table>

# ICP inhibitor in MDS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Manero G et al. Blood 2016; 128:345.</td>
<td>Phase 1b Keynote-013, MDS pts after hypomethylating agent failure</td>
<td>28</td>
<td>4% (1/27)</td>
<td>0</td>
<td>4% (1/27)</td>
<td>52% (14/27) of patients had stable disease.</td>
</tr>
<tr>
<td>AZA + Novo as 1st frontline</td>
<td></td>
<td>13</td>
<td>69% (9/13)</td>
<td>15% (2/13)</td>
<td>0</td>
<td>Tolerable safety profile and clinical activity</td>
</tr>
<tr>
<td>Nivo after hypomethylating agent</td>
<td></td>
<td>15</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>No activity, enrollment closed</td>
</tr>
<tr>
<td>Ipi after hypomethylating agent</td>
<td></td>
<td>9</td>
<td>22% (2/9)</td>
<td>0%</td>
<td>22% (2/9)</td>
<td>Induce responses in previously treated pts</td>
</tr>
</tbody>
</table>
Summary

- Blockade of the PD-1/PD-L1 axis translated into promising results in cHL at present
- ICP inhibitors are partially effective in treatment of DLBCL, FL and several types of T-NHL (SS, MF, PTCL)
- ICP inhibitors may be the turning point in the treatment of NK/T cell lymphoma
- Monotherapy with ICP inhibitor is unsatisfactory on CLL although modest activity observed in CLL in RS
- Monotherapy with ICP inhibitor is unsatisfactory in MM
  - A combinational approach needed to improve outcomes, especially with immunomodulatory drugs (lenalidomide, pomalidomide)
- In AML and MDS patients, ICP inhibitors are administered in combination with 5-azacitidine based on preclinical evidence of a potential synergistic effect.
- Data on ALL and CML limited
- Optimal sequencing of chemotherapy
- Use with antibody conjugates, e.g. Bredtuximab with ICP inhibitor
- Use it post ASCT

- Small molecules that upregulate immune receptors/ligands, or immunomodulation (HDAC inhibitors, lenalidomide)
- Ibrutinib and idelalisib, which may have off target effects on T cell cells
- Block downstream signaling induced by ICPs, e.g. MTOR inhibitor

• Inhibit more than one Checkpoint
• Block an inhibitory signal and simultaneously give and activating signal
• Use with a different immune activator: CART, BITE
Thank You