Checkpoint Inhibitors in Lymphoma

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Professor of Medicine, Weill Medical College of Cornell University
There are currently 75 prospective clinical trials open at MSKCC studying checkpoint inhibitors in solid and liquid tumors

Please only open studies where there are prospective biopsies being done!
Hodgkin Lymphoma
HL by the Numbers

Optimal Upfront Treatment
8000 pts

Favorable ES
1000
100 Fail

Unfavorable ES
2500
300 Fail

Unfavorable ES with Bulk
1000
200 Fail

Favorable AS
2500
500 Fail

Unfavorable AS
1000
300 Fail

700 Pts ≥ 70 years
No standard TX

TREATMENT FAILS IN 1400 PATIENTS
Relapsed/Refractory HL: 1400 pts/year

Salvage therapy (1-2)

PET neg.
- 70% success
  - 980 pts
  - 735 Pts Cured with ASCT
  - 245 pts Treatment Failure

PET pos. PR
- 15% success
  - 210 pts
  - 110 pts Treatment Failure
  - 100 pts Cured with ASCT

No Response
- 15% failure
  - 210 pts

Allo vs CPI
555 pts

Cured with ASCT
Epidemiology of Hodgkin lymphoma in USA

- **81,080** estimated lymphoma cases in 2016
- Close to **8,350** in the USA diagnosed with Hodgkin lymphoma annually
  - Approximately **1,200** will die from the disease
  - Over **210,000** patients have a history of HL

**Age Distribution (Bimodal Distribution):**
- 34 yrs: 32%
- 20 yrs and >55 yrs: 28%

- Higher survival rate but an increased incidence of long-term health complications for older patients (>60 years old)
- No standard treatment exists for older patients (>60 years old)
Why is this topic so important?

The cure rate of relapsed/refractory HL is > untreated ABC-DLBCL

Bobby Jones said I never learned anything from a golf match I won
We must get it correct this time!
Composition of the microenvironment in B cell lymphomas

- Follicular Lymphoma
- Burkitt Lymphoma
- Hodgkin Lymphoma
- DLBCL

Tumour cells:
- CD4+ T cells
- T_{FH} cells
- FOXP3+ T cells
- T_{FR} cells

T cell subsets:
- T_{H1} cells
- T_{H2} cells
- CD8+ T cells

Other immune cells:
- B cells
- Mast cells
- Plasma cells
- Eosinophils
- Macrophages
- Follicular dendritic cells
- Blood vessel
- Stromal cell

Legend:
Composition of the microenvironment in cHL

Follicular Lymphoma

Burkitt Lymphoma

Hodgkin Lymphoma

DLBCL

<table>
<thead>
<tr>
<th>Tumour cells</th>
<th>T cell subsets</th>
<th>Other immune cells</th>
<th>Stromal cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T cells</td>
<td>$T_H^1$ cells</td>
<td>$B$ cells</td>
<td>Follicular dendritic cells</td>
</tr>
<tr>
<td>$T_{FH}$ cells</td>
<td>$T_H^2$ cells</td>
<td>Mast cells</td>
<td>Blood vessel</td>
</tr>
<tr>
<td>FOXP3+ T cells</td>
<td>CD8+ T cells</td>
<td>Plasma cells</td>
<td>Macrophages</td>
</tr>
<tr>
<td>$T_{FR}$ cells</td>
<td></td>
<td>Eosinophils</td>
<td>Stromal cell</td>
</tr>
</tbody>
</table>
Targeting PD1/PDL1 Pathway in Hodgkin Lymphoma

Adapted from Stathis & Younes: Ann Oncology 2015
### HLA expression on HRS cells in classical Hodgkin lymphoma at diagnosis

Antigen loss is even greater in the second-line setting

<table>
<thead>
<tr>
<th>HLA expression</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12%</td>
</tr>
<tr>
<td>Only HLA class I lost</td>
<td>18%</td>
</tr>
<tr>
<td>Only HLA class II lost</td>
<td>24%</td>
</tr>
<tr>
<td>Both HLA antigens lost</td>
<td>46%</td>
</tr>
</tbody>
</table>
Incidence plots and mutation types for recurrent mutations in HRS cells

MHC II (HLA-DR) and failure-free survival

![Image of MHC II (HLA-DR) and failure-free survival graph]

- HLA II positive: 82%
- HLA II negative: 65%
- P = 0.001

Hazard ratio: 2.00 (95% CI: 1.19-3.45); p = 0.01

Gains and amplifications of the PD-L1/2 locus in classic Hodgkin lymphoma (n = 20)

Twa et al, Blood 123: 2062-5 (2014); Twa et al, J Pathol 2015
PD-L1 Almost Universally Expressed on RS Cells Through 9p24.1 Amplification or EBV

Patterns of PD-L1 expression in HL
Does immune checkpoint blockade in HL work by the expected mechanism?

PD-L1 expression or HLA-DR?

CD8 T cells and/or PD1+ cells

Mutational load or CN gains of 9p24

Mutational load in HL is minimal, but CN gains of 9p24 are common

Most cases express the ligands, but MHC class I or II loss by HRS cells occurs in most cases (but may be expressed more frequently at relapse?)

Almost no PD-1+ T cells in cases of classical HL
Do we have reliable biomarkers for selecting patients for immune checkpoint blockade in HL?

Melanoma-specific MHC-II expression represents a tumour-autonomous phenotype and predicts response to anti-PD-1/PD-L1 therapy

Predictive Biomarkers for PD-1 Axis Therapies: The Hidden Treasure or a Call for Research

PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations
Mechanism of Nivo/Pembro in HL?

- Very few PD-1⁺ T cells in HL biopsies

- Most cases of HL with FISH data show a good correlation between 9p24 amplification and expression of the ligands PD-L1 and/or PD-L2

- Both 9p24 gain/amplification may be enriched for in the relapsed/refractory setting?

- HRS cells show frequent loss of HLA class I and II, so difficult to reconcile the arguments in favor of immune checkpoint blockade mediated by “releasing the hounds”
Known biomarkers of response to anti-PD-1 therapy in HL

- **Evidence of T-cell activation**
  - Increase in T and NK cells in the peripheral blood
  - Increased IFN-\(\gamma\) response signature
  - Decreased Treg:Teff ratio
  - Decreased PD-1 expression

- These did not correlate with response to therapy

Merryman et al, *Blood* 2017
Known biomarkers of response to anti-PD-1 therapy in HL

• Evidence of T-cell activation

• **Alterations in HRS cells**
  - PD-L1 expression
  - JAK/STAT activation

• All patients on both a phase I and phase II study of nivolumab had nuclear pSTAT3 suggestive of constitutive JAK/STAT activation

Peripheral Blood Immunophenotyping

- PB samples baseline and cycle 7 (n=9)
- Change in circulating lymphocyte subsets by flow
NanoString Analyses

- Baseline FFPE tumor biopsies (n=19)
- 680 immune-related gene platform

<table>
<thead>
<tr>
<th>IFN-γ</th>
<th>Expanded Immune</th>
<th>T-Cell Receptor Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDO1</td>
<td>CD3D</td>
<td>NKG7</td>
</tr>
<tr>
<td>CXCL10</td>
<td>IDO1</td>
<td>HLA-E</td>
</tr>
<tr>
<td>CXCL9</td>
<td>CIITA</td>
<td>CXCR6</td>
</tr>
<tr>
<td>HLA-DRA</td>
<td>CD3E</td>
<td>LAG3</td>
</tr>
<tr>
<td>STAT1</td>
<td>CCL5</td>
<td>TAGAP</td>
</tr>
<tr>
<td>IFNG</td>
<td>GZMK</td>
<td>CXCL10</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>STAT1</td>
</tr>
<tr>
<td></td>
<td>HLA-DRA</td>
<td>GZMB</td>
</tr>
<tr>
<td></td>
<td>CXCL13</td>
<td>IL2RG</td>
</tr>
</tbody>
</table>
## NanoString Analyses

**Baseline FFPE tumor biopsies (n=19)**

**680 immune-related gene platform**

<table>
<thead>
<tr>
<th>Signature</th>
<th>Direction</th>
<th>Signed Rank Test Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expanded Immune Score</td>
<td>Positive</td>
<td>0.0028</td>
</tr>
<tr>
<td>TCR Score</td>
<td>Positive</td>
<td>0.0038</td>
</tr>
<tr>
<td>IFN-γ Score</td>
<td>Positive</td>
<td>0.0052</td>
</tr>
</tbody>
</table>
Unanswered questions regarding the MOA of anti-PD-1 therapy in HL

1. Does anti-PD-1 therapy activate anti-tumor immunity in HL, and if so, what is the effector cell?
   - CD4+ T cells?
   - NK Cells?

2. Do immunosuppressive features of either R-S cells or the HL microenvironment predict response to anti-PD-1 therapy?
   - PD-L1 expression/genetic amplification
   - MHC-I and MHC-II expression
   - R-S cell mutational burden
   - Regulatory T-cells
Patients eligible for or receiving anti-PD-1 therapy

Multiple core biopsies

FFPE sections

Single cell sorting

T-cells
- Immunophenotype
- Gene expression
- Clonality

HRS cells
- PD-L1/2 expression
- MHC-I/II expression
- Mutational and neoantigen burden
- Gene expression

Microenvironment
- PD-L1/2 expression
- NK cell infiltration
- Treg infiltration
- Gene expression
Longer term results with antibodies blocking PD-1 signaling
Longer term Follow up of Phase 1 trial of Pembrolizumab (KEYNOTE-013)

Enrollment: Dec 2013 - Sep 2014

Data cut off: Nov 17, 2014
Median duration of follow-up: 5 months
Moskowitz CM et al., ASH 2014

Data cut off: Oct 27, 2015
Median duration of follow-up: 19 months
Armand P et al, ASH 2015

Data cut off: Sep 27, 2016
Median follow-up: 29 months
Armand et al. ASH 2016 abstract #1108
# Keynote 013 - Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>All Patients N = 31</th>
<th>Prior ASCT, BV Post ASCT n = 16</th>
<th>ASCT Ineligible, Failed BV n = 8</th>
<th>Prior ASCT, BV Pre ASCT n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI</td>
<td>n (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>18 (58%)</td>
<td>39-76</td>
<td>11 (69%)</td>
<td>41-89</td>
</tr>
<tr>
<td>CR</td>
<td>6 (19%)</td>
<td>8-38</td>
<td>3 (19%)</td>
<td>4-46</td>
</tr>
<tr>
<td>PR</td>
<td>12 (39%)</td>
<td>22-58</td>
<td>8 (50%)</td>
<td>25-75</td>
</tr>
</tbody>
</table>

Data cutoff date: September 27, 2016

Armand et al. ASH 2016 abstract #1108
Keynote 013 – Durability of Responses
Change From Baseline in Target Lesions

Change From Baseline In Target Lesions (%)

Time Since Initiation of Treatment (months)

Best Overall Response

Data cutoff date: September 27, 2016

Armand et al. ASH 2016 abstract #1108
Longer Term Follow up of Pembrolizumab Phase 2 trial (KEYNOTE-087)

Cohort 1 (N = 69)†
Patients following R/R cHL who progressed after ASCT and subsequent BV therapy

Cohort 2 (N = 81)†
Patients following R/R cHL who failed salvage chemotherapy, ineligible for ASCT‡ and failed BV therapy

Cohort 3 (N = 60)†
Patients following R/R cHL who failed ASCT and not treated with BV after transplantation

Pembrolizumab 200 mg Q3W

Response assessed according to Revised Response Criteria for Malignant Lymphomas (Cheson 2007)

Survival Follow-Up

CT scans repeated Q12W
PET repeated at W12, W24, to confirm CR or PD, and as clinically indicated

• **Primary end point:** Overall response rate (ORR; blinded independent central review)
• **Secondary end points:** ORR (investigator review), DOR, PFS, OS

†Patients in all cohorts had to have ECOG PS 0-1
‡Unable to achieve a CR or PR to salvage chemotherapy

Moskowitz et al. ASH 2016 abstract #1107
### Keynote 087: ORR by Cohort (BICR)

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progressed after ASCT and subsequent BV therapy</td>
<td>Failed salvage chemotherapy, ineligible for ASCT and failed BV therapy</td>
<td>Failed ASCT and not treated with BV after transplantation</td>
</tr>
<tr>
<td></td>
<td>N = 69</td>
<td>N = 81</td>
<td>N = 60</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>n (%)</td>
<td>95% CI†</td>
<td>n (%)</td>
</tr>
<tr>
<td>Complete remission‡</td>
<td>51 (73.9)</td>
<td>61.9-83.7</td>
<td>52 (64.2)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>36 (52.2)</td>
<td>39.8-64.4</td>
<td>32 (39.5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (15.9)</td>
<td>8.2-26.7</td>
<td>10 (12.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (7.2)</td>
<td>2.4-16.1</td>
<td>17 (21.0)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>2 (2.9)</td>
<td>0.4-10.1</td>
<td>2 (2.5)</td>
</tr>
</tbody>
</table>

*Data cutoff: September 25, 2016*

Moskowitz et al. ASH 2016 abstract #1107
### Keynote 087: ORR by Blinded Central Review: Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>Primary Refractory Disease (n = 73)</th>
<th>Relapsed After ≥3 Lines of Therapy (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI ‡</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58 (79.5)</td>
<td>68.4-88.0</td>
</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (23.3)</td>
<td>14.2-34.6</td>
</tr>
<tr>
<td><strong>Partial remission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 (56.2)</td>
<td>44.1-67.8</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (5.5)</td>
<td>1.5-13.4</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (11.0)</td>
<td>4.9-20.5</td>
</tr>
<tr>
<td><strong>Unable to determine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (4.1)</td>
<td>0.9-11.5</td>
</tr>
</tbody>
</table>

†These subgroups are not mutually exclusive
‡Based on binomial exact confidence interval method

Data cutoff: September 25, 2016

Moskowitz et al. ASH 2016 abstract #1107
Longer term Follow up Phase 2 Study of Nivolumab (CheckMate 205): Cohorts A and B

- Phase 2 study conducted in Europe and North America

**Cohort A**
- **n = 63**
- BV naïve post-ASCT

**Cohort B**
- **n = 80**
- BV treated post-ASCT
- FDA approval May 2016

**Nivolumab 3 mg/kg IV Q2W**
- Treatment until disease progression or unacceptable toxicity

Patients could elect to discontinue nivolumab and proceed to allogeneic (allo)-HSCT

**Primary Endpoint**
- ORR by IRRC

**Additional endpoints**
- Duration of response
- Duration of CR/PR
- PFS by IRRC
- OS
- Safety

**ASH 2016**
- Primary disclosure
- Minimum follow-up 9 months

### Best Overall Response

**Cohort A: Nivolumab in BV-Naïve Post-ASCT Patients**

<table>
<thead>
<tr>
<th>IRRC assessed</th>
<th>Cohort A (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>43 (68)</td>
</tr>
<tr>
<td>95% CI</td>
<td>55, 79</td>
</tr>
<tr>
<td><strong>CR, n (%)</strong></td>
<td>14 (22)</td>
</tr>
<tr>
<td><strong>PR, n (%)</strong></td>
<td>29 (46)</td>
</tr>
<tr>
<td><strong>SD, n (%)</strong></td>
<td>13 (21)</td>
</tr>
<tr>
<td><strong>PD, n (%)</strong></td>
<td>7 (11)</td>
</tr>
</tbody>
</table>

Timmerman et al. ASH 2016 abstract #1110
Duration of Response by Best Response

*Cohort A: Nivolumab in BV-Naïve Post-ASCT Patients*

**Database lock**  Jun 2016

**Median**

- **duration of follow-up, mo**  14  (1–20)
- **Median DOR, mo**  NR  (NR, NR)

**No. of patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Durable responses in both complete and partial responders

Timmerman et al. ASH 2016 abstract #1110
Duration of Response by Best Response
*Cohort B: Nivolumab After BV Post-ASCT*

![Graph showing probability of response over months with data for CR, PR, and OR responses across different months.]

**Database lock**
- Oct 2015
- Apr 2016

**Median follow-up, mo**
- 9 (range 2–12)
- 15 (range 2–19)

**ORR, n (%)**
- 53 (66)
- 54 (68)

**Median DOR, mo**
- 8 (95% CI 7, NR)
- 13 (95% CI 9, NR)

**Median DOCR, mo**
- 5 (95% CI NR, NR)
- NR (95% CI 5, NR)

**Median DOPR, mo**
- 8 (95% CI 7, NR)
- 13 (95% CI 8, NR)

*Timmerman et al. ASH 2016 abstract #1110*
Novel combinations for relapsed and refractory HL patients
Nivolumab and Ipilimumab
Two immune checkpoint inhibitors

CTLA-4 blockade (ipilimumab)
- APC–T-cell interaction
- CTLA-4 is expressed on T cells and inhibits T-cell activation
- Ipilimumab disrupts the CTLa-4 pathway, thus inducing anti-tumor immunity

PD-1 blockade (nivolumab)
- Activation (cytokine secretion, lysis, proliferation, migration to tumor)
- Tumor microenvironment
- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
- Nivolumab disrupts PD-1 pathway signaling and restores anti-tumor T-cell function

Ansell et al. ASH 2016 abstract #183
**HL: Best Overall Response**

<table>
<thead>
<tr>
<th></th>
<th>HL (N = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Complete response</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Partial response</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Relapsed or progressive disease</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>Median duration of OR, months (range)</strong></td>
<td>NR (0.0+, 13.4+)</td>
</tr>
<tr>
<td><strong>Transplant naïve</strong>&lt;sup&gt;b&lt;/sup&gt; (n = 18)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>12 (67)</td>
</tr>
</tbody>
</table>

Change in tumor burden, HL

- Responders (n = 23)
- Non-responders (n = 8)

Change from baseline in target lesions tumor burden (%)

Time since first treatment date (weeks)

1st occurrence of new lesion

Off treatment

Ansell et al. ASH 2016 abstract #183
Brentuximab vedotin (BV) plus nivolumab as First Salvage Therapy

Brentuximab vedotin disrupts the microtubule network and triggers an immune response through the induction of endoplasmic reticulum stress.

Nivolumab targets the programmed death-1 (PD-1) immune checkpoint pathway and restores antitumor immune responses.

- Both agents are well tolerated with high single-agent response rates in patients with R/R HL (BV=72% ORR, 33% CR; Nivo=73% ORR, 28% CR)
- Together, they could yield improved CR rates and improved durability of responses, and potentially lead to better long-term outcomes

Herrera et al. ASH 2016 abstract #1105
• Target enrollment: ~55 patients

• Patients were treated in 21-day cycles for up to 4 cycles (12 weeks)
  • During Cycle 1, BV was administered on Day 1 and Nivo on Day 8
  • During Cycles 2-4, dosing of both drugs occurred on Day 1 of each cycle
  • After completion of the Cycle 4 response assessment, patients were eligible to undergo ASCT

• Investigator assessment of lymphoma response and progression was per the Lugano Classification Revised Staging System for malignant lymphoma (Cheson et al., 2014)
# Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease status at study entry</strong></td>
<td></td>
</tr>
<tr>
<td>Primary Refractory</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Relapsed, remission duration ≤ 1 year</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Relapsed, remission duration &gt; 1 year</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>4 (10)</td>
</tr>
<tr>
<td><strong>Prior chemotherapies</strong></td>
<td></td>
</tr>
<tr>
<td>ABVD</td>
<td>38 (90)</td>
</tr>
<tr>
<td>AVD or ABVE-PC</td>
<td>4 (10)</td>
</tr>
<tr>
<td>BEACOPP or Stanford V</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

- 42 patients (52% F, 48% M) with a median age of 37 years have been enrolled

\(^a\) Two patients received AVD after discontinuing ABVD due to AEs, and 1 patient received BEACOPP after discontinuing ABVD due to inadequate interim response.
BV + Nivolumab: Adverse Events

- AEs occurring in ≥ 10% of patients (N=42) post-ASCT\(^a\) were all Grade 1 or 2 in severity with the exception of one Grade 3 urticaria event

- AEs occurring in ≥ 50% of patients post-ASCT (N=6) included anemia (G3), vomiting (G1), diarrhea (G1), febrile neutropenia (G3), and neutropenia (G4)

- One patient with treatment-related serious adverse event after Cycle 1 BV: dehydration (G3), asthenia (G1), hypercalcemia (G2), malaise (G2), nausea (G1)

---

\(^a\) Includes 1 occurrence of Grade 3 urticaria, \(^*\) One PT of IRR not reported as associated with infusion
**BV + Nivolumab: Infusion-Related Reactions (IRRs)**

IRRs observed in 38% of patients: most common were flushing, nausea (14% each); chest discomfort, dyspnea, urticaria (12% each); cough, and pruritus (10% each)

A protocol amendment was instituted requiring premedication with low-dose corticosteroids (hydrocortisone 100 mg or equivalent) and antihistamine at Cycles 2-4

Premedication regimen including low-dose corticosteroid did not impact the rate or severity of IRRs, however no patients discontinued treatment due to an IRR

<table>
<thead>
<tr>
<th>Cycles</th>
<th>BV</th>
<th>Nivo</th>
<th>IRRs Pre-Amendment</th>
<th>IRRs Post-Amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>BV</td>
<td>Nivo</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>BV</td>
<td>Nivo</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>BV</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>BV</td>
<td></td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

% of Doses with IRRs
BV + Nivolumab: Tumor Response per Investigator

ORR (26/29) = 90%
95% CI: 72.6, 97.8

CmR (18/29) = 62%
95% CI: 42.3, 79.3

Deauville score (N=29)

<table>
<thead>
<tr>
<th>Score</th>
<th>n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CmR</td>
<td>1</td>
<td>8 (28)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6 (21)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Missin</td>
<td>1</td>
<td>1 (3)</td>
</tr>
<tr>
<td>PmR</td>
<td>4</td>
<td>6 (21)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2 (7)</td>
</tr>
<tr>
<td>NmR</td>
<td>5</td>
<td>1 (3)</td>
</tr>
<tr>
<td>PmD</td>
<td>5</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*Cycle 2 SPD reported for 1 patient
BV+Nivolumab for Relapsed Patients
E4412 Schema: (Arms D-F)

Arm Y: Dose Level -1
Nivolumab 1mg/kg IV day 1 of cycles 1-46
Brentuximab vedotin 1.2 mg/kg IV day 1 of cycles 1-16

Arm D: Dose Level 1 (N=3)
Nivolumab 3 mg/kg IV day 1 of cycles 1-46
Brentuximab vedotin 1.2 mg/kg IV day 1 of cycles 1-16

Arm E- Dose Level 2 (N=7)
Nivolumab 3 mg/kg IV day 1 cycles 1-46
Brentuximab vedotin 1.8 mg/kg IV day 1 of cycles 1-16

Arm F- Phase I Expansion Cohort (N=9)
Nivolumab 3 mg/kg IV day 1 cycles 1-46
Brentuximab vedotin 1.8 mg/kg IV day 1 of cycles 1-16

Diefenbach et al. ASH 2016 abstract #1106
## E4412 Patient Demographics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Relapsed HL (N = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, yr (range)</td>
<td>40 (21-70)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (47)</td>
</tr>
<tr>
<td>Baseline ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (57)</td>
</tr>
<tr>
<td>1</td>
<td>6 (32)</td>
</tr>
<tr>
<td>2</td>
<td>2 (11)</td>
</tr>
<tr>
<td>B symptoms, n (%)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Number of prior systemic therapies, mean (range)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>Prior transplant, n (%)</td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Prior Brentuximab, n (%)</td>
<td>4 (21)</td>
</tr>
</tbody>
</table>
• Elevated hepatic enzymes most common: transient primarily cycle 1 no impact on treatment
• Peripheral sensory neuropathy common in BV re-treatment patients
### Best comparison phase II studies, ASCT and BV failure

<table>
<thead>
<tr>
<th></th>
<th>Pembro</th>
<th>Nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>69</td>
<td>80</td>
</tr>
<tr>
<td>Age</td>
<td>34 (19-64)</td>
<td>37 (28-48)</td>
</tr>
<tr>
<td>Prior Tx</td>
<td>4 (2-12)</td>
<td>4 (3-15)</td>
</tr>
<tr>
<td>Prior BV</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Prior auto-SCT</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>72%</td>
<td>66%</td>
</tr>
<tr>
<td>CR (IR)</td>
<td>22%</td>
<td>9%</td>
</tr>
<tr>
<td>CR (doc)</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>PR</td>
<td>51%</td>
<td>58%</td>
</tr>
<tr>
<td>SD</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>POD</td>
<td>6%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Moskowitz et al, *ISHL* 2016
I have some reservations on the Pembrolizumab label

• There is an implication that patients with primary refractory, transplant-eligible disease can receive this therapy prior to salvage chemotherapy

• This would be a MISTAKE in clinical judgement

• As far as I know, no patient has been cured with a CPI

• Reserve Pembrolizumab for HL having a poor response to salvage chemotherapy or for ASCT failures
Phase 1b Study of Pembrolizumab in Patients with Relapsed/Refractory PMBCL: Results from the Ongoing KEYNOTE-013 Trial

Pier Luigi Zinzani,1 Vincent Ribrag,2 Craig H. Moskowitz,3 Jean-Marie Michot,2 John Kuruvilla,4 Arun Balakumaran,5 Yayan Zhang,5 Patricia Marinello,5 Sabine Chlosta,5 Eric Gustafson,5 Margaret A. Shipp,6 Philippe Armand6

1Institute of Hematology “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy; 2Institut Gustave Roussy, Villejuif, France; 3Memorial Sloan Kettering Cancer Center, New York, NY, USA; 4Princess Margaret Cancer Centre, Toronto, ON, Canada; 5Merck & Co., Inc., Kenilworth, NJ, USA; 6Dana-Farber Cancer Institute, Boston, MA, USA
Relapsed/Refractory PMBCL

- 80% of PMBCL patients are cured with standard frontline therapy
- ~200 patients/year in the US are diagnosed with rrPMBCL, with a poor prognosis and limited treatment options (no standard of care)
- Overall response rate in rrPMBCL is ≤25% and 2-year OS is 15%
- New treatment options are needed, but small patient numbers limit ability to conduct clinical trials
- PMBCL frequently harbors amplification/translocations involving the 9p24.1 locus, leading to PD-L1 and PD-L2 overexpression
- Pembrolizumab is an anti–PD-1 antibody that helps restore antitumor immune surveillance

Phase 1b KEYNOTE-013 Study

**Overall Study**
MDS  
MM  
Classical HL  
NHL  
PMBCL  
- Relapsed/refractory  
- ASCT failure/ineligible  
- ECOG PS 0-1  
- Adequate organ function  
- No autoimmune disease  
- No pneumonitis

Pembrolizumab IV  
10 mg/kg Q2W OR  
200 mg Q3W

- **CR**
  - Discontinuation allowed after ≥24 wk

- **PR or SD**
  - Treat for 24 mo or PD or Intolerable toxicity

- **PD**
  - Discontinue (option to continue until PD confirmed)

**PET/CT scans at weeks 6 and 12**
then Q9W per IHP 2007 criteria
Phase 1b KEYNOTE-013 Study

- **Primary endpoints**
  - Safety
  - Overall response rate

- **Key secondary endpoints**
  - Complete remission rate
  - Duration of response
  - Biomarkers

- **Safety population**: all patients who received ≥1 dose of study drug

- **Efficacy population**: all patients with (a) ≥1 dose of study drug and (b) ≥1 post-baseline tumor assessment or disease progression before the first tumor assessment
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>30.5 years (22-62)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (61)</td>
</tr>
<tr>
<td>1</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Bulky lymphadenopathy, a n (%)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>&lt;3 lines, n (%)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>≥3 lines, n (%)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Prior autologous stem cell transplantation, n (%)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Transplant ineligible, n (%)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Prior radiation, n (%)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Prior rituximab, n (%)</td>
<td>18 (100)</td>
</tr>
</tbody>
</table>
# Treatment-Related Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Safety population (N = 18)</th>
<th>All AEs n (%)</th>
<th>Grade 3 or 4 AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any related AE</td>
<td>11 (61)</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

## Related AEs in ≥2 patients (≥1 patient for grade 3 or 4)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Grade 3 or 4 AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Venoocclusive liver disease</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

### No discontinuations due to AEs

### No treatment-related deaths

### Serious AEs (none deemed related to treatment by investigator): bacterial pneumonia (n=2), pneumonia, persistent cough, chest pain exacerbation (n=1 each)

### Immune-related AEs: grade 2 aggravated diarrhea, grade 2 radiation pneumonitis (n=1 each)

Data cutoff May 27, 2016.
## Best Overall Investigator-Assessed Response (Efficacy Population)

<table>
<thead>
<tr>
<th>Efficacy population (N = 17)</th>
<th>Number of patients</th>
<th>% (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>7</td>
<td>41 (21-64)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>2</td>
<td>12 (2-33)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6</td>
<td>35 (17-58)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>18 (5-40)</td>
</tr>
<tr>
<td>No assessment(^a)</td>
<td>1</td>
<td>6 (0-25)</td>
</tr>
</tbody>
</table>

\(^a\) Patients with progressive disease had not been treated with prior targeted therapies.
Best Percentage Change From Baseline in Tumor Size (Evaluable Patients)

81% of patients (13/16) had reduction in target lesions

-50% decrease
Patient Case – Complete Response

- 49-year old woman
- PMBCL diagnosis

Previously treated with:
- R-CHOP
- R-DHAC
- ASCT
- Radiation
- EZH2 histone methyltransferase inhibitor
- Methotrexate + R-GEMOX

Baseline

9 Weeks Post-Baseline

Images courtesy of Jean-Marie Michot and Vincent Ribrag, Institut Gustave Roussy, Villejuif, France.
**Treatment Exposure and Response Duration**
(Evaluable Patients)

- **Median follow-up duration:**
  11 mo (range: 3-27)

- **6/7 (86%) responses ongoing**
  at time of analysis

- **Median response duration:**
  not reached (range: 2-23 mo)

- Two patients reached the maximum 2 years of treatment and remain in remission (follow-up: 25.4 mo, 23.8 mo)

**Weeks**
Conclusions

• Conventional therapy for rrPMBCL often yields poor outcomes, highlighting need for new treatment options

• Pembrolizumab treatment was associated with manageable safety profile, promising response rate, and long-lasting remissions in heavily pretreated patients with rrPMBCL

• KEYNOTE-170: global, multicenter phase 2 study evaluating safety and efficacy of single-agent pembrolizumab in larger cohort of rrPMBCL (NCT02576990)
Some of our new studies
New study: ABVD and nivolumab

Stage III/IV disease
9p24.1 amplification, enriched in ASHL and associated with PFS

Roemer et al, J Clin Oncol 2016
Cohort A
Age <60, stage III/IV
Phase I schema
Cohort A
Age <60, stage III/IV
Phase II schema

ABVDx2 cycles → PET
Deauville 1-3

PET

Deauville 4-5

AVDx4

Nivox8 doses
New study: LAG 3 and Anti-PD1

DLBCL
LAG-3 (Lymphocyte activation gene-3) checkpoint pathway

LAG-3 is an inhibitory receptor that binds to MHC class II

- Expressed on activated CD4 and CD8 T-cells, γδ T cells, NK, pDCs, B, NKT, and Treg cells
- Often co-expressed with PD-1 on antigen-experienced T cells
- Expression is increased in tumors compared to normal tissues

—Blocking LAG-3 enhances T-cell function

- Increases T cell proliferation, proinflammatory cytokine production and expression of effector molecules

Freeman, Nat Imm, 2012
**Why Study anti-Lag3 in combination with anti-PD-1?**

- REGN3767 (anti-LAG-3) + REGN2810 (anti-PD-1) has encouraging efficacy in mouse models

**Addition of Anti-hLAG-3 Enhances Efficacy of Anti-hPD-1 REGN2810 and Improves Survival of Tumor-Bearing Mice**

- Dual humanized PD1\textsubscript{hum/hum}/LAG-3\textsubscript{hum/hum}
- Treatment days are indicated by arrows

- **Two-way ANOVA (Dunnett’s multiple comparison test),** \(p<0.01\), \(p<0.05\)

- **log-rank (Mantel Cox) test, with Bonferroni adjustment for multiple comparisons,** \(\ast\ast\ast p<0.0001\), \(\ast\ast p<0.01\)

- IgG control (25 mpk), anti-LAG-3 (25 mpk), anti-PD-1 (REGN2810; 10 mpk), anti-PD-1 + anti-LAG-3

- n=6 mice/group (IgG control)
- n=12 mice/group (a-PD-1, a-LAG-3)

- IgG control, anti-LAG-3, anti-PD-1, anti-PD-1 + anti-LAG-3

- Percent survival

- Days after implantation

- Percent tumor-bearing

- Percent tumor-free

- Days after implantation

- REGN in-house data
LAG-3 (Lymphocyte activation gene-3) checkpoint pathway

LAG-3 is an inhibitory receptor that binds to MHC class II

- Expressed on activated CD4 and CD8 T-cells, γδ T cells, NK, pDCs, B, NKT, and Treg cells
- Often co-expressed with PD-1 on antigen-experienced T cells
- Expression is increased in tumors compared to normal tissues

- Blocking LAG-3 enhances T-cell function
  - Increases T cell proliferation, proinflammatory cytokine production and expression of effector molecules

Freeman, Nat Imm, 2012
Dual targeting of LAG-3 & PD-1 with blocking antibodies may be more effective than either single agent in tumor & pathogen infection models.
Efficacy Assessments by CT/MRI Q6 weeks (cycles 1-8) or Q9 weeks (cycles 9-17)

Obtain archived tumor tissue for histological confirmation of malignancy

On trial biopsy: at baseline, D29, and at PD

Efficacy Assessment C5D1 by FDG-PET/CT (DLBCL)
Total number of patients for the study, and to be enrolled at MSKCC

- 3 DLBCL cohorts, 9-15 patients per cohort = 27-45
- 4 sites participating, none strong in NHL, so MSKCC expected to have the majority of patients
New study: Nivolumab and IBrutinib

Richter’s transformation
PCI32765-LYM-1002: Study Design
Nivolumab + Ibrutinib in relapsed B-cell malignancies

Part A n=18
(Dose Optimization)

Part B (n=30 in each cohort)
(Expansion Cohort: Two-stage design)

A-1
I: 420 mg, po, qd
N: 3mg/kg, i.v., q14d

A-2
I: 560 mg, p.o., qd
N: 3 mg/kg, i.v., q14d

B 1: I: 420 mg/qd PO + N: 3 mg/kg/q14d
B1: CLL (del 17p or del 11q)

B 2 and B 3: I: 560 mg/qd PO + N: 3 mg/kg/q14d
B2: Follicular Lymphoma
B3: DLBCL
Favorable Relapse of HL
ESHL, treated with < 6 cycles of chemotherapy alone and relapsed or refractory early stage disease
   RAPID failures for example
     Where ISRT is commonly administered
Simon 2-Stage Design
   CR rate will increase from 20% with pembrolizumab alone to 50% with the use of pembrolizumab + ISRT
Have we forgotten about allogeneic stem cell transplantation in the new era of CPI?

Let’s remember that the CPI have not cured anyone yet with HL!
The issues

- 3 yr. PFS with allogeneic transplant varies in 2016 but ranges from 30-50%

- No patient in the US will be BV naive if an allogeneic transplant is required

- Should an allogeneic transplant be offered to any patient that has not received a CPI?

- Should an allogeneic transplant only be considered in patients that have disease progression on CPI?

- Should CPI be a bridge to allo in all cases?
  - Should only patients that have < CR be referred for an allo?
  - Should only patients with a CR be referred for an allo?
Safety and Efficacy of Allogeneic Hematopoietic Stem Cell Transplant Following PD-1 Blockade in Relapsed/Refractory Lymphoma

Reid W. Merryman, MD¹, Haesook T. Kim, PhD², Pier Luigi Zinzani, MD, PhD³, Carmelo Carlo-Stella, MD⁴,⁵, Stephen M Ansell, MD⁶, Miguel-Angel Perales, MD⁷, Abraham Avigdor, MD⁸, Ahmad S. Halwani MD⁹, Roch Houot, MD, PhD¹⁰,¹¹, Tony Marchand, MD¹⁰, Nathalie Dhedin, MD¹², Willy Lescaut, MD¹³, Anne Thiebaut-Bertrand, MD¹⁴, Sylvie François, MD¹⁵, Aspasia Stamatoullas-Bastard, MD¹⁶, Pierre-Simon Rohrlitch, MD¹⁷, Hélène Labussière Wallet, MD¹⁸, Luca Castagna, MD⁴,⁵, Armando Santoro, MD⁴,⁵, Veronika Bachanova, MD, PhD¹⁹, Scott C. Bresler, MD, PhD¹⁹, Amitabh Srivastava, MD²⁰, Harim Kim²¹, Emily Pesek¹, Marie Chammas¹, Carol Reynolds, PhD¹, Vincent T. Ho, MD¹, Joseph H. Antin, MD¹, Jerome Ritz, MD¹, Robert J. Soiffer, MD¹, and Philippe Armand, MD, PhD¹.
• 39 patients
• All received prior CPI
• cGVHD-41% at 1 yr.
• 1 yr. cumulative incidence of relapse is only 14%
• Only 4 patients died from TRM
My current strategy for ASCT failures which is subject to change

• If disease is nodal only and stage I/II, and pt is RT naïve: radiotherapy with curative intent

• Advanced stage
  – HLA typing and refer for a potential allogeneic stem cell transplantation
  – Start CPI
    • If CR is achieved continue for another 3 months and if CR is maintained stop therapy and monitor, restart if HL progression and refer back for allo consideration
    • If a PR is achieved continue therapy based upon clinical situation, (PR can convert to CR), however refer back to transplant physician for repeat evaluation and further discussions
    • If stable disease is achieved, a CR will not happen, continue therapy until definitive disease progression and then start MOPP vs. clinical trial, and refer back for allo consideration if a PR is achieved
Hodgkin Lymphoma: A Model of Success in Oncology
I am honored to be studying this disease and taking care of the patients

• First hematologic malignancy, London (Hodgkin 1832)
• First cured with radiotherapy, Toronto (Peters 1950)
• First prospective randomized trials, Stanford (Kaplan 1960)
• First advanced-stage cancer cured with combination chemotherapy (MOPP),
  – NCI (DeVita 1967)
• First cases of secondary leukemia and solid tumors (early 1970’s)
• First disease cured with immunotherapy?
Case 1: FV

66-year-old female
Relapsed/Refractory Hodgkin lymphoma
Oncology History

- Diagnosed with stage IIIA mixed cellularity HL in 1972.
  - treated with splenectomy and cobalt radiation
- Early 2010: developed anorexia, weight loss, fevers, sweats, rash, and pruritus
- 3/6/2010: biopsy of right groin LN consistent with mixed cellularity Hodgkin lymphoma, stage IIIB
  - treated with ABVD x 6 cycles -> CR
- Early 2011: developed left posterior cervical LN. Biopsy confirmed recurrent disease, stage IIIA
  - Received ICE x 4 months (no. of cycles unknown), complicated by bilateral PE
  - Did not go to transplant
FV Oncology History

• Late 2012: recurrent disease
  – treated with EVAC x 4; critical illness following cycle 4 with pneumonia/meningitis

• 5/15/2012 - 5/24/2013: Brentuximab vedotin

• 9/2014 – 4/2015: CUDC (dual HDAC & PI3K Inhibitor) on protocol
Oncology History cont’d

- 11/24/15: Initiated Pembrolizumab 200mg q 3 weeks on Phase 2 clinical trial
- 10/21/16: POD, but continued tx on study
- 1/2017: further POD → off study
FV Pembrolizumab

- Received 19 doses
  - Tx discontinued due to disease progression
- Toxicities related to treatment: hypothyroidism, rash
Case 2: YM

48-year-old female
Relapsed/refractory Hodgkin lymphoma
YM Oncology History

- March 2010 dx with stage IIA nodular sclerosing Hodgkins lymphoma
- 5/6/10 BM Bx without involvement
- She received 5 cycles of ABVD followed by IFRT to bilateral neck, supraclavicular fossa, mediastinum.
- Restaging at completion of treatment demonstrated residual disease
- 11/4/10 right level 4 LN bxs with atypical lymphoid proliferation, compatible with residual classical Hodgkin lymphoma.
- late 2011 ICE chemotherapy
- Feb 2012 autologous SCT (conditioning regimen unknown).
YM Oncology History, Cont’d

• Upon first restaging post-transplant, the patient had refractory disease.
• 7/3/12 R cervical LN bx: classical Hodgkin Lymphoma, CD30+
• July 2013: initiated brentuximab. Imaging after two cycle demonstrated VGPR. However, at the next restaging, she had progressive disease.
• Therapy was changed to Gemcitabine, Navelbine, and Doxil. She received 6 cycles, completed 7/24/13.
• PET/CT 8/23 revealed CR.
  – Her sister, who is HLA-matched was pregnant at that time. She delivered in December 2013. Patient refused cord blood transplant as alternative
YM Oncology History, cont’d

• PET on 1/14/14 revealed hypermetabolic thoracic and abdominal lymphadenopathy suspicious for malignant involvement
• 3/31/14 initiated pembrolizumab 10mg/kg on phase I clinical trial
• 6/20/14 PET/CT CR
• Second restaging 10/17/14 NED. CT 6/25/15 NED
• 10/16/2015 dose #50 pembrolizumab on study → study end
• 2/2017 NED
YM - Pembrolizumab

- Received 50 doses over 2 year period of time
  - Tx discontinued due to finite dosing schedule per protocol
- Toxicities related to treatment: none.
# Lymphoma Disease Management Team

## Lymphoma Service
- Connie Batlevi
- Philip Caron
- Pamela Drulinksy
- John Gerecitano
- Audrey Hamilton
- Paul Hamlin
- Steve Horwitz
- Andrew Intlekofer
- Anital Kumar
- Matt Matasar
- Alison Moskowitz
- Craig Moskowitz
- Ariela Noy
- Lia Palomba
- Carol Portlock
- David Straus
- Santosh Vardhana
- Anas Younes, Chief
- Andrew Zelenetz

## Radiation Oncology
- Joachim Yahalom

## Lymphoma Transplant Program
- Matt Matasar
- Craig Sauter
- Craig Moskowitz
- Juliet Barker
- Gunjan Shah
- Miguel Perales
- Sergio Giralt

## Hematopathology
- Ahmet Dogan, Chief
- Maria Arcila
- Caleb Ho
- Oscar Lin
- Peter Maslak
- Chris Park
- David Park
- Filiz Sen
- Mariko Yabe

## Nuclear Medicine
- Heiko Schoder, Chief
- Neetha Pandit-Tasker
- Jorge Carasquillo

## Radiology
- James Caravelli
- Jurgen Rademaker
- Gary Ulaner
SAVE THE DATE

MSK SYMPOSIUM ON LYMPHOMA
STATE-OF-THE-ART IN BIOLOGY, THERAPY AND PATIENT CARE

May 5-6, 2017

Memorial Sloan Kettering Cancer Center
Zuckerman Research Center
417 East 68th Street
New York, NY 10065

Course Director
Anas Younes, MD, Chief, Lymphoma Service
Development of Anti-PD1/PDL1-Based Therapy

- **Ibrutinib**
- **Revlimid**
- **Brentuximab Vedotin**
- **PI3Ki/mTORi**
- **Urelumab (4-1BB)**
- **Ipilimumab (CTAL4)**
- **a-CD20**
- **Chemo therapy**