CLINICAL RESULTS WITH IMMUNOTHERAPY STRATEGIES IN HEMATOLOGICAL MALIGNANCIES

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Dr. Rodríguez-Otero disclosures

- Consulting fees: Janssen, Celgene.
- Speaker’s Bureau: Janssen, Celgene, BMS.
- Research grants: Celgene, BMS.
Four major targets for cancer immunotherapy

- Direct targeting of surface tumor antigens: 
  - Monoclonal antibodies

- Boosting immune effectors: 
  - Adoptive cell therapy

- Activating tumor specific immunity: 
  - Vaccins

- Overcoming inhibitory immune suppression: 
  - Immunomodulators: IMIDs, Checkpoint inh
**Monoclonal antibodies**

- **Direct targeting of surface tumor antigens**
  - *Monoclonal antibodies*

- **Boosting immune effectors:**
  - Adoptive cell therapy

- **Activating tumor specific immunity:**
  - *Vaccins*

- **Overcoming inhibitory immune suppression:**
  - *Immunomodulators: IMIDs, Checkpoint inh*
Immunotherapy has changed the clinical course of Lymphomas


Ratio per 100,000*

15
10
9
NHL mortality
8
7
6
5
4
3
2
1
0

Age adjusted to standard USA population in 2000


Cisplatin (1978)
Etoposide (1983)
Fludarabine (1991)
MabThera® (1997)

90Y ibritumomab tiuxetan (2002)
131I tositumomab (2003)
**Monoclonal antibodies in Multiple Myeloma**

Activation of macrophages
- Antibody-dependent cell-mediated phagocytosis (ADCP)

Activation of natural killer (NK) cells
- Antibody-dependent cellular cytotoxicity (ADCC)

**Direct effects**
- Alterations in intracellular signalling
  - Inhibition of growth factor receptor function
  - Inhibition of adhesion molecule function

**Activation of the complement system**
- Complement-dependent cytotoxicity (CDC)

**Cell death**

**Lysis**

**Signalling cascades**

**Antigen**

**Membrane attack complex**

**C1q**

- Elotuzumab (Anti-SLAMF7)
  - Single Agent[^2]: 26% SD
  - Elo + Ld[^3]: 92% ORR & 33m PFS[^1]
  - Ld +/- ELO[^1]: 19.4 vs 14.9 m[^1]

  - Single agent: 30-35% ORR, PFS 3.7m
  - + Len-Dex: 64-75% ORR (inc. Len ref.)

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[^5]: Sagar Lonial, ASCO 2015, abstract 8512.
[^6]: Martin et al. ASCO 2014; Abstract 8532.
Eloquent-2 (Elo-Ld vs Ld): Extended PFS and TNT

**ORR (ELd vs Ld):** 79% vs 66%.  
**≥VGPR: 32.7% vs 27.9%**

**PFS (19.4 vs 14.9 m)**

- 1-year PFS: 68%
- 2-year PFS: 57%
- 3-year PFS: 41%

**TNT (33 vs 21 m)**

- TNT: 33 vs 21 m  
  HR 0.62 (95% CI 0.50, 0.77)

**27% reduction in the risk of disease progression or death**

Relative improvement in PFS of 44% at 3 years
Anti CD38 antibodies: Mechanisms of Action

Daratumumab

**Direct ON-TUMOR Actions**
- CDC: Complement-dependent cytotoxicity
- ADCC: Antibody-dependent cell-mediated cytotoxicity
- ADCP: Antibody-dependent cellular phagocytosis
- Apoptosis

**IMMUNOMODULATORY Actions**
- Modulation of tumor microenvironment
- Depletion of immuno-suppressive cells
- Increase in cytotoxic & helper T cells

**Myeloma Cell Death**

## Anti CD38 in MM: single agent activity in RRMM

<table>
<thead>
<tr>
<th>Study details</th>
<th>Daratumumab</th>
<th>Isatuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 studies: GEN501, SIRIUS &amp; combined analysis</td>
<td>First in-human, phase 1 dose escalation</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>Pts with rel/ref MM n=148 (SIRIUS n=42 and GEN501 n=106)</td>
<td>Pts with rel/ref MM N=97</td>
</tr>
<tr>
<td>Dose</td>
<td>16 mg/kg</td>
<td>Dose is not yet defined</td>
</tr>
</tbody>
</table>
| Results | • **ORR 31%** *(36% GEN501 & 29% SIRIUS)*  
• Median DOR: 7.6 m  
• 1 year OS: 77% / 69%  
• Median PFS in the combined analysis: 20m.  
• Infusion-related reactions gr 1-2 | • At ≥ 10 mg/kg: **24%**  
• Abnormal CA: 44%  
• Median DOR: 6.6 m  
• IARs: 49%, mostly grade ≤2, 94% during 1\textsuperscript{st} infusion. |

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**Dara/SAAR are CD38 MoAB showing activity as single agents in RRMM patients**

# Anti-CD38 MoAb plus Len/dex in RRMM

## Daratumumab + Len/Dex vs SAR650984 + Len/Dex

<table>
<thead>
<tr>
<th>Target</th>
<th>CD38</th>
<th>CD38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent activity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| **Study details** | Phase 1/2 dose escalation & expansion  
Prior IMiDs: 80%  
Pts ref or intolerant to Len excluded | Phase Ib dose escalation trial  
Pts rel + ref to IMiD:84% |
| **Patients** | n=32 | n=31 |
| **Results** | **ORR 81%**  
(35% CR, 28% VGPR, 19% PR) | **ORR 58%**  
(6% sCR, 23% VGPR, 29% PR)  
PFS 6.2 months |

Plesner et al. ASH 2014 (Abstract 84); ASH 2015 (Abs 507); Martin et al. ASH 2014 (Abstract 83); oral presentation
Daratumumab-Len-Dex (DRd) vs Len-Dex (Rd) in Relapsed MM - Phase III POLLUX trial (569 Patients)

<table>
<thead>
<tr>
<th>Metric</th>
<th>DRd vs Rd</th>
<th>CR (DRd vs Rd)</th>
<th>ORR (DRd vs Rd)</th>
<th>TTP (DRd vs Rd)</th>
<th>DOR (DRd vs Rd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>63% reduction</td>
<td>43% vs 19%</td>
<td>93% vs 76%</td>
<td>NR vs 18.4</td>
<td>NR vs 17.4 m</td>
</tr>
<tr>
<td>ORR</td>
<td>93% vs 76%</td>
<td>43% vs 19%</td>
<td>93% vs 76%</td>
<td>NR vs 18.4</td>
<td>NR vs 17.4 m</td>
</tr>
<tr>
<td>CR</td>
<td>43% vs 19%</td>
<td>93% vs 76%</td>
<td>43% vs 19%</td>
<td>NR vs 18.4</td>
<td>NR vs 17.4 m</td>
</tr>
<tr>
<td>TTP</td>
<td>NR vs 18.4</td>
<td>NR vs 17.4 m</td>
<td>NR vs 18.4</td>
<td>NR vs 17.4 m</td>
<td>NR vs 17.4 m</td>
</tr>
<tr>
<td>DOR</td>
<td>NR vs 17.4 m</td>
<td>NR vs 17.4 m</td>
<td>NR vs 17.4 m</td>
<td>NR vs 17.4 m</td>
<td>NR vs 17.4 m</td>
</tr>
</tbody>
</table>

DVd vs Vd in Relapsed MM - Phase III CASTOR trial
Efficacy data: ORR, PFS and TTP

ORR (DVd vs Vd): 83% vs 63%
CR (DVd vs Vd): 20% vs 9%

**PFS**

- Median PFS: NR
- Median PFS: 7.2 months
- HR: 0.39 (95% CI, 0.28-0.53); \( P < 0.0001 \)

**TTP**

- Median TTP: NR
- Median TTP: 7.3 months
- HR: 0.30 (95% CI, 0.21-0.43); \( P < 0.0001 \)

MoAbs: Futures perspectives

Bispecific T cell engagers:
BCMA – CD3 phase I trials

Conjugated MoAb:
ABBV-838: MMAE-CS1
GSK2857916: BCMA - MMAF
Conjugated antibodies in Hodgkin disease: Brentuximab Vedotin

Naked antibodies failed to induce objective responses

Conjugated antiCD30 + MMAE (antitubulin agent) = Brentuximab Vedotin

ORR 75%; CR rate 34%
Median PFS 5.6 m
Median DOR for patients in CR: 20.5 m

Younes A et al. JCO 2012
Brentuximab Vedotin: Frontline treatment of DLBCL – Randomized phase II trial

Study objectives: ORR, CR, PFS, OS, safety

Pts with CD30-unselected high-intermediate–risk or high-risk untreated DLBCL; ECOG PS 0-2 (N = 53)

| Brentuximab Vedotin 1.2 mg/kg + Standard R-CHOP x 6 (n = 30) |
| Brentuximab Vedotin 1.8 mg/kg + Standard R-CHOP x 6 (n = 23) |

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Pts (N = 51)</th>
<th>BV 1.2 mg/kg + R-CHOP (n = 29)</th>
<th>BV 1.8 mg/kg + R-CHOP (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>80 (66.9-90.2)</td>
<td>79 (60.3-92.0)</td>
<td>82 (59.7-94.8)</td>
</tr>
<tr>
<td>CR</td>
<td>67 (52.1-79.2)</td>
<td>66 (45.7-82.1)</td>
<td>68 (45.1-86.1)</td>
</tr>
<tr>
<td>PR</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Estimated PFS,* %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mos</td>
<td>79</td>
<td>83</td>
<td>75</td>
</tr>
<tr>
<td>12 mos</td>
<td>65</td>
<td>67</td>
<td>61</td>
</tr>
<tr>
<td>PD or death, %</td>
<td>31</td>
<td>24</td>
<td>41</td>
</tr>
</tbody>
</table>

CR rate comparable in ABC vs GCB DLBCL subtypes (69% vs 65%)

BCMA – MMAF for RRMM (GSK2857916)
Phase I dose escalation trial (n=30)

100% IMID refractory and 90% PI refractory
70% with ≥ 5 prior lines of therapy

Maximum % Change in M-Protein or Free Light Chain

ORR = 8/30 (27%; 95% CI: 12.3%, 45.9%)
   • 1 sCR, 3 VGPR, 4 PR
CBR = 11/30 (37%; 95% CI: 19.9%, 56.1%)

Adoptive cell therapy

Direct targeting of surface tumor antigens

Monoclonal antibodies

Boosting immune effectors:

Adoptive cell therapy

Activating tumor specific immunity:

Vaccins

Overcoming inhibitory immune suppression:

Immunomodulators: IMIDs, Checkpoint inh
Adoptive Cell Therapy – Engineered T cells

Specific antitumor T cells

- CAR T cells
- TCR-engineered T cells

Activation and expansion

Genetically engineer cancer-specific T-cells

Fragmentation of tumour sample and isolation of tumour infiltrating lymphocytes

Transfusion into recipient

References:
1. A cloned TCR conferring tumor recognition is inserted into circulating lymphocytes.

2. Genetically inserted TCRs recognized tumor antigens in the groove of a specific MHC molecule.

3. Activation of the T cells is dependent on the TCR, therefor subject of the same counter regulatory pathways.
CARs are engineered fusion proteins that contain an extracellular antigen-binding domain composed of a single chain variable fragment (scFv) derived from an Ab that confers recognition to a tumor-associated antigen, linked in tandem to intracellular signaling motifs capable of T cell activation (CD3z) and costimulatory molecules, like CD28 or CD137. This construct is then transfected or transduced in patient’s autologous T cells.
## CAR T cells vs TCR engineered T cells

<table>
<thead>
<tr>
<th>TCR engineered T cells</th>
<th>CAR T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA - restricted.</strong></td>
<td>Antigen recognition is independent of MHC molecule.</td>
</tr>
<tr>
<td>Accordingly, a limited number of individuals presenting such HLA molecules are eligible for this treatment option.</td>
<td><strong>Not HLA-restricted</strong></td>
</tr>
<tr>
<td><strong>TCR (but not CAR) T cells can recognize intracellular proteins,</strong> providing a broader array of potential therapeutic targets</td>
<td><strong>Only extracellular proteins</strong> can be recognized (like MoAb)</td>
</tr>
<tr>
<td><strong>Activation of the T cells depends on the TCR</strong></td>
<td>Possibility to insert other genes encoding molecules involved in costimulation, survival, proliferation or inflammation allowing the T cell to <strong>avoid inhibitory mechanisms displayed by the tumor</strong></td>
</tr>
<tr>
<td></td>
<td>Massive release of pro-inflammatory cytokines produced by hyperactive CAR T cells.</td>
</tr>
</tbody>
</table>
## Autologous CD19 CAR-T in B-ALL

<table>
<thead>
<tr>
<th>Institution</th>
<th>Constructs</th>
<th>Patients</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC(^1-3)</td>
<td>CAR CD19 <strong>CD28</strong> CD3ζ retrovirus</td>
<td>46 ref B-ALL Cy or Cy-Flu</td>
<td>CR 82% MRD - : 83% 39% relapsed</td>
</tr>
<tr>
<td>FHCRC(^4)</td>
<td>CAR CD19 <strong>41BB</strong> CD3ζ retrovirus 1:1 CD4:CD8 ratio</td>
<td>29 patients Cy or Cy-Flu</td>
<td>CR 83%; 100% in Cy+Flu 70% relapsed in Cy group</td>
</tr>
<tr>
<td>CHOP/U Penn(^5-6)</td>
<td>CAR CD19 <strong>41BB</strong> CD3ζ retrovirus</td>
<td>53 B-ALL ref</td>
<td>ORR 100% MRD - : 85% 38% relapsed</td>
</tr>
<tr>
<td>NCI(^7)</td>
<td>CAR CD19 <strong>CD28</strong> CD3ζ lentivirus</td>
<td>21 patients</td>
<td>CR: 70% MRD - : 60% CR 29%</td>
</tr>
</tbody>
</table>

- ORR ≈ 100%
- CR rates: 70 – 80%
- 40%- 70% relapses

## CD19 CAR-T in Lymphoma presented ASH 2016

<table>
<thead>
<tr>
<th>Abstract #</th>
<th>Institution</th>
<th>Constructs</th>
<th>Lymphoma</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>#3026</td>
<td>Penn</td>
<td>CAR CD19 41BB CD3ζ lentivirus</td>
<td>DLBCL (7 GC, nonGC)</td>
<td>ORR 52% CR 38% (no relapse)</td>
</tr>
<tr>
<td>#1100</td>
<td>Penn</td>
<td>CAR CD19 41BB CD3ζ lentivirus</td>
<td>FL</td>
<td>ORR 79% CR 50%</td>
</tr>
<tr>
<td>#1851</td>
<td>Baylor</td>
<td>CAR CD19 41BB CD3ζ retrovirus, CAR CD19 CD28 CD3ζ retrovirus</td>
<td>DLBCL</td>
<td>ORR 75% CR 50%</td>
</tr>
<tr>
<td>#999</td>
<td>NCI</td>
<td>CAR CD19 CD28 CD3ζ lentivirus humanized</td>
<td>DLBCL, MCL, FL</td>
<td>ORR 85% CR 29%</td>
</tr>
<tr>
<td>#4192</td>
<td>Juno</td>
<td>CAR CD19 CD28 41BB CD3ζ lentivirus 1:1 CD4:CD8 ratio</td>
<td>DLBCL, MCL</td>
<td>ORR 75% CR 66%</td>
</tr>
<tr>
<td>#998</td>
<td>Kite</td>
<td>CAR CD19 CD28 CD3ζ retrovirus</td>
<td>PMBCL, FL</td>
<td>ORR 100%</td>
</tr>
<tr>
<td>LBA-6</td>
<td>Kite</td>
<td>CAR CD19 CD28 CD3ζ retrovirus</td>
<td>DLBCL</td>
<td>ORR 76% CR 47%</td>
</tr>
</tbody>
</table>

- **ORR**: 50 – 100%
- **CR**: ≈ 30 – 65%
CD19-CAR T cells in MM

**Efficacy**

ORR 80%

### Study Design

**Eligibility Criteria**
- Multiple Myeloma
- Progression within one year of prior ASCT
- Age <70
- Fit for 2nd ASCT

**Primary Endpoints**
- Safety (CRS, neurotoxicity)
- Feasibility (manufacturing success)

**Secondary Endpoints**
- CTL019 engraftment and B cell aplasia
- Day 42 and day 100 response
- Progression-free survival (vs. last ASCT)
- Correlation of response to CD19 expression

**Salvage**
- High-dose Melphalan + Auto-SCT
- CTL019 5 x 10^7 cells
- 12-14 DAYS
- FOLLOW FOR PFS

**Day 100 Response**

- VGPR 01
- PD 02
- VGPR 03
- VGPR 05
- VGPR 06
- VGPR 07
- PR 08
- PD 09
- PR 10
- VGPR 12

Days post-ASCT

ASCT #1

ASCT + CTL019
<table>
<thead>
<tr>
<th>Patient</th>
<th>Myeloma type</th>
<th>CAR-BCMA cell dose (T cells/kg)</th>
<th>Response (duration in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>k light chain only</td>
<td>0.3x10⁶</td>
<td>PR (2)</td>
</tr>
<tr>
<td>2</td>
<td>IgA λ</td>
<td>0.3x10⁶</td>
<td>SD (6)</td>
</tr>
<tr>
<td>3</td>
<td>k light chain only</td>
<td>0.3x10⁶</td>
<td>SD (6)</td>
</tr>
<tr>
<td>4</td>
<td>λ light chain only</td>
<td>1x10⁶</td>
<td>SD (10)</td>
</tr>
<tr>
<td>5</td>
<td>IgG k</td>
<td>1x10⁶</td>
<td>SD (4)</td>
</tr>
<tr>
<td>6</td>
<td>IgG λ</td>
<td>1x10⁶</td>
<td>SD (2)</td>
</tr>
<tr>
<td>7</td>
<td>IgG λ</td>
<td>3x10⁶</td>
<td>SD (6)</td>
</tr>
<tr>
<td>8</td>
<td>k light chain only</td>
<td>3x10⁶</td>
<td>VGPR (8)</td>
</tr>
<tr>
<td>9</td>
<td>k light chain only</td>
<td>3x10⁶</td>
<td>SD (10+)</td>
</tr>
<tr>
<td>10</td>
<td>IgA k</td>
<td>9x10⁶</td>
<td>Stringent CR (6+)</td>
</tr>
<tr>
<td>11</td>
<td>IgG λ</td>
<td>9x10⁶</td>
<td>PR (6+)</td>
</tr>
<tr>
<td>12</td>
<td>IgA λ</td>
<td>3x10⁶</td>
<td>SD (2)</td>
</tr>
</tbody>
</table>

BCMA-CAR T cells in MM – UPenn experience

Cohen et al. ASH 2016 Abstract 1147

**Study design**

- **Cohort 1**
  - 1 - 5 x 10^8 CAR+ T cells (n=3-6)
  - Up to n=9

- **Cohort 2**
  - Cytok 1.5 g/m² + 1 - 5 x 10^7 CAR+ T cells (n=3-6)
  - Up to n=9

- **Cohort 3**
  - Cytok 1.5 g/m² + 1 - 5 x 10^8 CAR+ T cells (n=3-6)
  - Up to n=9

**Clinical responses**

**ORR: 44%**

<table>
<thead>
<tr>
<th>Pt</th>
<th>BM PC%</th>
<th>Cytogenetics</th>
<th>CART dose received (% of planned)</th>
<th>CRS grade</th>
<th>Time to 1st response (days)</th>
<th>Best Heme response</th>
<th>PFS (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>70</td>
<td>+11 -17p</td>
<td>2 x 10e8 (40%)</td>
<td>3 (toci)</td>
<td>14</td>
<td>sCR*</td>
<td>12+</td>
</tr>
<tr>
<td>02</td>
<td>60</td>
<td>+1q +4p -17p</td>
<td>5 x 10e8 (100%)</td>
<td>1</td>
<td>14</td>
<td>MR</td>
<td>2</td>
</tr>
<tr>
<td>03</td>
<td>95</td>
<td>t(4;14) -16q</td>
<td>2 x 10e8 (40%)</td>
<td>3 (toci)</td>
<td>15</td>
<td>VGPR*</td>
<td>5</td>
</tr>
<tr>
<td>09</td>
<td>15</td>
<td>t(11;14)-16q</td>
<td>5 x 10e8 (100%)</td>
<td>2</td>
<td>-</td>
<td>SD</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>95</td>
<td>+1q +4p -17p</td>
<td>1.8 x 10e8 (100%)</td>
<td>-</td>
<td>-</td>
<td>PD</td>
<td>0.5</td>
</tr>
<tr>
<td>11</td>
<td>80</td>
<td>t(4;14)-16q</td>
<td>5 x 10e8 (100%)</td>
<td>2</td>
<td>25</td>
<td>MR</td>
<td>2.5</td>
</tr>
<tr>
<td>07</td>
<td>15</td>
<td>+1q, +11, -14, -16</td>
<td>5 x 10e8 (100%)</td>
<td>2</td>
<td>14</td>
<td>uPR**</td>
<td>1.5</td>
</tr>
<tr>
<td>08</td>
<td>80</td>
<td>-1p +1q, -4 -17p</td>
<td>5 x 10e8 (100%)</td>
<td>4 (toci)</td>
<td>-</td>
<td>PD</td>
<td>0.5</td>
</tr>
<tr>
<td>15</td>
<td>90</td>
<td>+1q, t(11;14)</td>
<td>5 x 10e8 (100%)</td>
<td>2 (toci)</td>
<td>14</td>
<td>VGPR*</td>
<td>2+</td>
</tr>
</tbody>
</table>

**Median number of prior lines: 9 (4 – 11)**

- 89% refractory to bortezomib, pomalidomide, carfilzomib.
- 78% refractory to Lenalidomide.
- 44% refractory to Dara.

**Safety:**

- 89% CRS (grade 3-4: 33%)
- Grade 4 PRES Sd
Safety concerns regarding CAR T cell therapy

- CRS
  - 40-100%
  - (severe ≈ 20-30%)
- Allergic reactions
- Off target effects
- Neurologic toxicities
- GVHD
Important Considerations

Target selection
- CAR design
- Optimal dose and conditioning treatment

Patient selection
- Pre or post-allogeneic stem cell transplant
- Manage of toxicities
- Relapse
Activating tumor specific immunity: Vaccines

- Direct targeting of surface tumor antigens
  - Monoclonal antibodies

- Boosting immune effectors:
  - Adoptive cell therapy

- Activating tumor specific immunity:
  - Vaccins

- Overcoming inhibitory immune suppression:
  - Immunomodulators: IMIDs, Checkpoint inh
Dendritic cell vaccines in Multiple Myeloma

- Vaccination combining different **antigen formats and adjuvants** has been investigated in MM (Rosenblatt et al., 2013),

- but active vaccine strategies are hampered by the **insufficient numbers of induced T cells**, their **poor homing to tumor sites**, and the **immunosuppressive tumor microenvironment**.

- Two separate vaccinations approaches: peptide-based (NY-ESO-1, MAGE-AE, WT-1, XBP-1) and dendritic cell fused vaccines (**broad spectrum of MM antigens are presented in the context of dendritic cell mediated costimulation**).

- **Phase I**: RRMM. n=16 patients. Median of prior lines: 4. Well tolerated.

- **ORR**: 11/16: **Stable disease**. Several patients with SD lasting for 12 to 41 months.

- **Phase II** trial in the context of ASCT: CR/VGPR rate 78% early after ASCT. 24% of patients that improve responses.

Checkpoint inhibitors: Overcoming tumor immune suppression

Direct targeting of surface tumor antigens

- Monoclonal antibodies

Activating tumor specific immunity:

- Vaccins

Boosting immune effectors:

- Adoptive cell therapy

Overcoming inhibitory immune suppression:

- Immunomodulators: IMIDs, Checkpoint inh
Immune Checkpoints

Press the gas pedal  Release the brakes

**PD-1: Releasing the brakes**

**PD-1** (Programmed death receptor 1)

- Surface of **ACTIVATED T-cells**.
- **Ligands: PD-L1 & PD-L2**, are expressed on the surface of **APC** and **Tumor cells**.
- **Binding** of PD-L1 or PD-L2 to PD-1 induces **INHIBITION** of T-cell
- **Limit the activity of activated T-cells**

- Cancer cells exploit the PD-1 pathway to create an immunosuppressive milieu\(^1,2,3\).

- Upregulation of PD-L1 expression levels has been described in: melanoma (40-100%), NSCLC (35-95%), MM (93%)\(^4,5\), and linked to poor clinical outcomes\(^4,5\).

- TILs have been shown to express significantly higher levels of PD-1\(^6\).

- The tumor microenvironment secrete proinflammatory cytokines (IFNγ) that upregulate PD-1 on TILs\(^6\).

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Role of PD-1 inhibitors in hematological malignancies

**NIVOLUMAB SINGLE AGENT**
*(Checkmate 039)*

- DLBCL: 36% ORR
- Follicular lymphoma: 40% ORR
- Mycosis Fungoides: 15%
- Peripheral T cell lymphoma: 40%

- **Hodgkin disease (n=23):**
  - 78% prior ASCT
  - 78% relapsed after Brentuximab
  - 87% > 3 prior lines.
  - PFS at 24 weeks: 86%
  - ORR 87% with 22% of CR.

- **In MM: 67% SD**

**PEMBROLIZUMAB SINGLE AGENT** *(KEYNOTE-013)*

- MDS, HL, RRMM and NHL.

Several trials in combination are ongoing

Lesokhin et al. JCO 2016
Clinical differences in responses reflect biological differences in the tumor cell

**Hodgking Lymphoma**

Characterized by high PD-L1 expression and high responsiveness to checkpoint blockade

**Non-Hodgkin Lymphoma**

A diverse group of tumors, characterized by a variable PD-L1 expression relative to HL

*Modified from P Armand, ASH 2016*
Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma.
Checkmate-205B: Nivolumab HL after failure of BV or ASCT

Responses

- All but 1 responder had a reduction of ≥50% from baseline in tumor burden

7 CR
55 PR
18 NR or EE

Median number of prior lines: 4
100% prior ASCT and prior BV and RR cHL
Refractory to BV: 54%

N=80

**ORR: 76%**
Checkmate-205: Nivolumab HL after failure of BV or ASCT

PFS and OS

- Nivo + Brentuximab: ORR 90%, CR 62% (Herrera AF, et al. ASH 2016)
Pembrolizumab in RR HL after BV failure
Response rate and DOR:

Similar results with Pembrolizumab

Armand et al; J Clin Oncol 2016
## Checkpoint Blockade in NHL (Nivolumab)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>n</th>
<th>ORR</th>
<th>Median Follow-up in weeks</th>
<th>Median Response Duration in weeks</th>
<th>Ongoing Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>11</td>
<td>4 (36%)</td>
<td>23</td>
<td>22 (6, 77+)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Follicular NHL</td>
<td>10</td>
<td>4 (40%)</td>
<td>91</td>
<td>NR (27+, 82+)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>CTCL/MF</td>
<td>13</td>
<td>2 (15%)</td>
<td>43</td>
<td>NR (24+, 50+)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>PTCL</td>
<td>5</td>
<td>2 (40%)</td>
<td>31</td>
<td>NR (11, 79+)</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

**Other combinations:**
- R + pidilizumab (R sens pts): ORR 66% / CR 52%
- R + 4-1BB (R / R pts): ORR 21%
Role of PD-1 inhibitors in Multiple Myeloma

- PD-L1 is commonly present (although at low levels)¹ vs only 25% of patients².

PD-L1 expression across all disease stages

Increase PD-1 among Tcells of MRD/RR pts.

Treatment with PD-1 inhibitors in a MM animal model induced prolonged survival.

Lenalidomide reduces PD1 and PD-L1 expression on RR-MM cells

The checkpoint blockade combined with Lenalidomide:
- Higher cytokine production in effector cells in MM Bone Marrow
- Higher cytotoxicity against MM cells

Lenalidomide with Checkpoint Blockade Reverses MDSC Induced Immune Suppression in MM

# Pembrolizumab treatment in RRMM

<table>
<thead>
<tr>
<th>Study design</th>
<th>KEYNOTE-023 (Ph I): PEMBRO-LEN-DEX¹</th>
<th>Ph I/II: PEMBRO – POMA –DEX²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEMBRO 200mg/2QW LEN 25mg 1-21</td>
<td>PEBRO 200mg/2QW POMA 4mg 1-21</td>
</tr>
<tr>
<td></td>
<td>DEX 40mg weekly</td>
<td>DEX 40mg weekly</td>
</tr>
</tbody>
</table>

| Patient population | - N= 62  
|                   | > 2 prior lines RRMM  
|                   | PI & IMID exposure |
|                   | - N= 38  
|                   | >2 prior lines RRMM  
|                   | PI & IMID exposure |

| Refractory status | 75% Len-refractory  
|                  | 63% Bort-refractory  
|                  | 50% double/triple/cuadruple refractory |
|                   | 89% Len-refractory  
|                   | 82% Bort-refractory  
|                   | 70% double-refractory |

| ORR | Efficacy populat. (n= 40): 50% Len-refr (n=29): 38% |
|     | Total (n=45): ORR 65% ≥VGPR: 29% Double refractory (n=32): 68% Median PFS 17.4m |

| Safety | AEs consistent with individual drug safety profiles for approved indications  
|        | IRAEs: no pneumonitis. No colitis. 65% AEs grade 3-5, 33% neutropenia |
|        | Good safety profile  
|        | irAEs: 38%  
|        | Pneumonitis: 14% |

¹San Miguel JF, ASH 2015 oral presentation 505; Mateos MV, ASCO 2016 ²Badros A, ASH 2016, abstract 490
Final remarks

• Clinical success of checkpoint inhibition especially in solid tumors has *relight the interest in immunotherapy against cancer* and this field is now moving forward very rapidly.

• Nevertheless there are still some open questions:

  - It is important to define *target populations* that will benefit most from specific immunotherapeutic strategies as well as

  - *Biomarkers to predict response* to certain treatments such as checkpoint inhibitors, for example.

  - Therapeutic strategies only targeting one pathway are often ineffective or short-lived when treating cancer patients. On this basis, *combinatorial strategies using immunotherapy as a backbone* might revolutionize cancer treatment and hopefully improve patient outcomes.
Thank you for your attention