Principles Of Breast Cancer Therapy

- Kill the cancer cell
  - Chemotherapy
  - Hormone therapy
  - HER2-targeted therapy
- Use the body’s response to kill the cancer
  - Block blood vessel growth
  - Strengthen bone
  - Engage the immune system
Coordinated Immune Responses To Danger

- Stranger Signals
- Danger Signals
- Pattern Recognition Receptors
- Innate Immune Response (1st responders)
- Inflammation
- Adaptive Immune Response (Specialized responders)

C. Pennell, Masonic Cancer Center, UMN
Immune System Constantly Removes Nascent Tumors: **Immune Surveillance**

*Immune Cells*  

*Tumor Cells*
Clinically Apparent Tumors Have Escaped Immune Recognition

Immune Cells

Tumor-induced Immune Suppression

Tumor Cells

C. Pennell, Masonic Cancer Center, UMN
Overcoming Tumor-Induced Immune Evasion: Checkpoint Blockade

Immune Cells

Tumor Cells

Tumor-induced Immune Suppression
How Do T-Cells Recognize Things – The Handshake Is Complex

These Are Not The Cells You’re Looking For

T Cells

Mutation/Antigen

PD-L1

Cancer Cells
Immune Checkpoints = Jedi Mind Trick
Antibodies Disrupt The Trick

**PD-1**
Pembrolizumab
Nivolumab

**PD-L1**
Atezolizumab
Avelumab
Durvalumab

Wolchok Cell 175:1452 2018 PMID: 30500529
<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Population</th>
<th>N</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-012</td>
<td>Pembrolizumab (α-PD-1)</td>
<td>Metastatic TNBC</td>
<td>27</td>
<td>18.5%</td>
</tr>
<tr>
<td>KEYNOTE-086</td>
<td>Pembrolizumab (α-PD-1)</td>
<td>Metastatic TNBC</td>
<td>170 (cohort A) 84 (cohort B)</td>
<td>4.7% 22.6%</td>
</tr>
<tr>
<td>JAVELIN</td>
<td>Avelumab (α-PD-L1)</td>
<td>Metastatic – any subtype</td>
<td>HR+/HER- 72 HR-/HER+ 26 HR-/HER- 58</td>
<td>2.8% 3.8% 8.6%</td>
</tr>
<tr>
<td>Phase Ia trials of Atezolizumab</td>
<td>Atezolizumab (α-PD-L1)</td>
<td>Metastatic TNBC</td>
<td>112</td>
<td>10%</td>
</tr>
</tbody>
</table>

Mutations In Breast Cancer

Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types.
Improving Immunotherapy In Breast Cancer

• Increase tumor cell death
  – Combination with chemotherapy
  – Combination with radiation therapy

• Increase antigenicity of tumor
  – Direct injection into tumor of immune activators

• Increase function of activated T cells
  – Combine checkpoint inhibitors with T cell stimulants
IMpassion130: Results from a global, randomised, double-blind, Phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in treatment-naive locally advanced or metastatic triple-negative breast cancer

Peter Schmid,1 Sylvia Adams,2 Hope S. Rugo,3 Andreas Schneeweiss,4 Carlos H. Barrios,5 Hiroji Iwata,6 Véronique Diéras,7 Roberto Hegg,8 Seock-Ah Im,9 Gail Shaw Wright,10 Volkmar Henschel,11 Luciana Molinero,12 Stephen Y. Chui,12 Roel Funke,12 Amreen Husain,11 Eric P. Winer,13 Sherene Loi,14 Leisha A. Emens15

1Barts Cancer Institute, Queen Mary University of London, London, UK; 2New York University Langone Medical Center, New York, NY, USA; 3University of California San Francisco Comprehensive Care Center, San Francisco, CA, USA; 4University Hospital Heidelberg, Heidelberg, Germany; 5Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; 6Aichi Cancer Center Hospital, Aichi, Japan; 7Department of Medical Oncology, Institut Curie, Paris, France; 8University of São Paulo, São Paulo, Brazil; 9Seoul National University Hospital, Seoul, Korea; 10Florida Cancer Specialists & Research Institute, New Port Richey, FL, USA; 11Roche, Basel, Switzerland; 12Genentech, Inc., South San Francisco, CA, USA; 13Dana-Farber Cancer Institute, Boston, MA, USA; 14Peter MacCallum Cancer Centre, Melbourne, Australia; 15Bloomberg~Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD, USA, now with UPMC Hillman Cancer Center, Pittsburgh, PA USA
Atezolizumab and chemotherapy

- Atezolizumab (anti–PD-L1) monotherapy is approved in the United States, Europe and elsewhere for certain types of metastatic urothelial carcinoma and lung cancer.
- In a Phase I study, atezolizumab monotherapy was active in multiple cancers, including TNBC, with greater activity in patients whose tumours had PD-L1 IC ≥ 1%
- The addition of chemotherapy can enhance atezolizumab’s anti-tumour activity.
  - In a Phase Ib study in mTNBC, concurrent administration of nab-paclitaxel did not inhibit atezolizumab-mediated immunodynamic effects.

DC, dendritic cell.

IMpassion130 study design

Key IMpassion130 eligibility criteria:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

**Atezo + nab-P arm:**
Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle
  + nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

**Plac + nab-P arm:**
Placebo IV
- On days 1 and 15 of 28-day cycle
  + nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

*RECIST v1.1 PD or toxicity*

Primary PFS analysis: ITT population

**Stratified HR = 0.80**
*(95% CI: 0.69, 0.92)*

**$P = 0.0025$**

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (N = 451)</th>
<th>Plac + nab-P (N = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n</td>
<td>358</td>
<td>378</td>
</tr>
<tr>
<td>1-year PFS (95% CI), %</td>
<td>24% (20, 28)</td>
<td>18% (14, 21)</td>
</tr>
</tbody>
</table>

No. at risk:
- Atezo + nab-P: 451, 360, 226, 164, 77, 34, 20, 11, 6, 1, NE
- Plac + nab-P: 451, 327, 183, 130, 57, 29, 13, 5, 1, NE


NE, not estimable. Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

Primary PFS analysis: PD-L1+ population

Stratified HR = 0.62
(95% CI: 0.49, 0.78)

\[ P < 0.0001 \]

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (n = 185)</th>
<th>Plac + nab-P (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n</td>
<td>138</td>
<td>157</td>
</tr>
<tr>
<td>1-year PFS (95% CI), %</td>
<td>29% (22, 36)</td>
<td>16% (11, 22)</td>
</tr>
</tbody>
</table>


Data cutoff: 17 April 2018.

Atezolizumab Approved for Some Patients with Triple-Negative Breast Cancer

On March 8, the Food and Drug Administration (FDA) granted an accelerated approval for the immunotherapy drug atezolizumab (Tecentriq) in combination with chemotherapy for the initial treatment of some women with advanced triple-negative breast cancer.

F刑侦 also approved a companion diagnostic test called the VENTANA PD-L1 (SP142) Assay, which must be used to identify patients with triple-negative breast cancer who are candidates for treatment with this immunotherapy-chemotherapy combination.

“It was very clear from the trial results that the patients who benefited from the combination therapy were those with PD-L1-positive tumors,” said Leisha A. Emens, M.D., Ph.D., of the University of Pittsburgh Medical Center Hillman Cancer Center and Magee Women’s Hospital, one of the trial’s lead investigators.

In triple-negative breast cancer, PD-L1 is expressed mainly on immune cells that infiltrate tumors, Dr. Emens said, noting that this provided part of the rationale for testing an immunotherapy drug plus chemotherapy in patients.
Immune Cells Are Blinding Themselves!
Checkpoint Inhibitors To Date

• Atezolizumab (Tecentriq™) plus nab-paclitaxel (Abraxane™) approved for PD-L1+ metastatic TNBC
  • Specific testing (Ventana PD-L1) required
  • Positive test is ≥1% in **infiltrating immune cells**
• Pembrolizumab (Keytruda™) approved for
  • Tumors with evidence of increased **mutations** (DNA Damage Repair Deficiency)
    • Microsatellite instability-high (MSI-H)
      • Molecular testing (Foundation, Tempus, Caris, etc)
    • Mismatch Repair Deficient (dMMR)
      • Tumor staining for protein expression
• Many ongoing clinical trials testing new combination including ER+ and HER2+ tumors
How Do Mutations Enhance Immune Responses?

Trastuzumab Resistance Because Of Poor Binding To Immune Cells?


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SOPHIA Primary PFS Analysis: A Phase 3 Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies

Hope S. Rugo, MD, 1 Seock-Ah Im, MD, PhD, 2 Gail S. Wright, MD, FACP, FCCP, 3 Santiago Escrivá-de-Román, MD, 4 Michelino De Laurentiis, MD, PhD, 5 Javier Cortes, MD, PhD, 6 Shakeela W. Bahadur, MD, 7 Barbara B. Haley, MD, 8 Raul H. Oyola, MD, 9 David A. Riseberg, MD, 10 Antonino Musolino, MD, PhD, MSc, 11 Fatima Cardoso, MD, 12 Giuseppe Curigliano, MD, PhD, 13 Peter A. Kaufman, MD, 14 Mark D. Pegram, MD, 15 Sutton Edlich, 16 Shengyan Hong, PhD, 16 Edwin Rock, MD, PhD, 16 William J. Gradishar, MD, 17 on behalf of the SOPHIA Study Group

1University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 2Seoul National University Hospital Cancer Research Institute, Seoul, Korea; 3Florida Cancer Specialists & Research Institute, New Port Richey, FL, USA; 4Vall d’Hebron Institute of Oncology, Barcelona, Spain; 5National Cancer Institute Fondazione Pascale, Naples, Italy; 6IOB Institute of Oncology, Madrid & Barcelona; Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 7Bannerer MD Anderson Cancer Center, Gilbert, AZ, USA; 8University of Texas Southwestern Medical Center, Dallas, TX, USA; 9Northwest Georgia Oncology Centers, Marietta Cancer Center, Marietta, GA, USA; 10Mercy Medical Center, Baltimore, MD, USA; 11University Hospital of Parma, Parma, Italy; 12Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 13University of Milan, European Institute of Oncology, Milan, Italy; 14University of Vermont Cancer Center, Division of Hematology/Oncology, Burlington, VT, USA; 15Stanford Women’s Cancer Center, Palo Alto, CA, USA; 16MacroGenics, Inc., Rockville, MD, USA; 17Northwestern University, Chicago, IL, USA
Margetuximab: Fc-engineered to Activate Immune Responses

### Trastuzumab

**Fab:**
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival

**Fc:**
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

### Margetuximab<sup>1,2</sup>

**Fab:**
- Same specificity and affinity
- Similarly disrupts signaling

**Fc engineering:**
- ↑ Affinity for activating FcγRIIIA (CD16A)
- ↓ Affinity for inhibitory FcγRIIB (CD32B)

### Margetuximab Binding to FcγR Variants:

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Receptor</th>
<th>Allelic Variant</th>
<th>Relative Fc Binding</th>
<th>Affinity Fold-Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating</td>
<td>CD16A</td>
<td>158F</td>
<td>Lower</td>
<td>6.6x ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>158V</td>
<td>Higher</td>
<td>4.7x ↑</td>
</tr>
<tr>
<td></td>
<td>CD32A</td>
<td>131R</td>
<td>Lower</td>
<td>6.1x ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131H</td>
<td>Higher</td>
<td>↔</td>
</tr>
<tr>
<td>Inhibitory</td>
<td>CD32B</td>
<td>232I/T</td>
<td>Equivalent</td>
<td>8.4x ↓</td>
</tr>
</tbody>
</table>

PFS Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS (95% CI), Months</th>
<th>HR by Unstratified Cox Model</th>
<th>95% CI</th>
<th>Unstratified Log-Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n=536</td>
<td>Margretuximab + Chemotherapy: 5.8 (5.52–6.97)</td>
<td>0.78 (0.61–0.99)</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 4.9 (4.17–5.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine, n=143</td>
<td>Margretuximab + Chemotherapy: 8.3 (5.55–11.50)</td>
<td>0.77 (0.47–1.26)</td>
<td>0.302</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 5.5 (4.17–8.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eribulin, n=136</td>
<td>Margretuximab + Chemotherapy: 6.0 (3.81–8.05)</td>
<td>0.66 (0.42–1.05)</td>
<td>0.080</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 4.2 (3.38–5.55)</td>
<td></td>
<td></td>
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<tr>
<td>Gemcitabine, n=66</td>
<td>Margretuximab + Chemotherapy: 5.4 (4.07–11.01)</td>
<td>0.58 (0.29–1.18)</td>
<td>0.128</td>
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<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 3.5 (1.45–7.16)</td>
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<td></td>
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<tr>
<td>Vinorelbine, n=191</td>
<td>Margretuximab + Chemotherapy: 5.6 (4.24–6.97)</td>
<td>0.90 (0.60–1.35)</td>
<td>0.606</td>
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<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 5.1 (3.42–6.67)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;2 metastatic sites, n=254</td>
<td>Margretuximab + Chemotherapy: 6.3 (5.42, 8.08)</td>
<td>0.63 (0.44–0.89)</td>
<td>0.009</td>
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<tr>
<td>≤2 metastatic sites, n=282</td>
<td>Trastuzumab + Chemotherapy: 4.2 (3.38, 5.55)</td>
<td></td>
<td></td>
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<tr>
<td>Hormone Receptor+, n=200</td>
<td>Margretuximab + Chemotherapy: 5.8 (4.80, 7.23)</td>
<td>0.58 (0.39–0.86)</td>
<td>0.007</td>
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<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 4.2 (2.83, 5.55)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hormone Receptor+, n=334</td>
<td>Margretuximab + Chemotherapy: 5.7 (5.52, 8.18)</td>
<td>0.88 (0.64–1.19)</td>
<td>0.393</td>
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<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 5.5 (4.24, 7.03)</td>
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<td></td>
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</tr>
<tr>
<td>HER2 IHC 3+, n=291</td>
<td>Margretuximab + Chemotherapy: 6.9 (5.55, 8.31)</td>
<td>0.64 (0.46–0.90)</td>
<td>0.011</td>
<td></td>
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<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 5.6 (3.98, 5.85)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HER2 ISH amplified, n=245</td>
<td>Margretuximab + Chemotherapy: 5.5 (4.01, 6.60)</td>
<td>1.01 (0.71–1.42)</td>
<td>0.972</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 4.6 (4.07, 5.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;60 years, n=170</td>
<td>Margretuximab + Chemotherapy: 6.9 (5.52, 10.51)</td>
<td>0.58 (0.36–0.92)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 5.6 (4.14, 5.85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤60 years, n=366</td>
<td>Margretuximab + Chemotherapy: 5.6 (4.24, 6.97)</td>
<td>0.87 (0.66–1.16)</td>
<td>0.337</td>
<td></td>
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<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 4.6 (4.01, 5.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior (neo)adjuvant Tx: yes, n=303</td>
<td>Margretuximab + Chemotherapy: 6.3 (5.55–8.05)</td>
<td>0.67 (0.48–0.93)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 5.4 (4.01–5.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior (neo)adjuvant Tx: no, n=233</td>
<td>Margretuximab + Chemotherapy: 5.6 (3.71–6.97)</td>
<td>0.99 (0.68–1.42)</td>
<td>0.935</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + Chemotherapy: 4.9 (4.07–7.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hormone receptor positive=ER+ and/or PgR+; hormone receptor negative=ER- and PgR-; IHC=immunohistochemistry; ISH=in situ hybridization; Tx=treatment.
October 2018 Interim OS* for ITT vs CD16A-158F Carriers

158 (41%) of 385 events needed for final OS analysis

**ITT population, n=536**

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=266)</th>
<th>Trastuzumab + Chemotherapy (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of events</strong></td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td><strong>Median OS (95% CI)</strong></td>
<td>18.9 months (16.16–25.07)</td>
<td>17.2 months (15.80–33.31)</td>
</tr>
<tr>
<td><strong>HR by stratified Cox model, 0.95</strong></td>
<td>(95% CI, 0.69–1.31)</td>
<td></td>
</tr>
</tbody>
</table>

**CD16A/FF or FV, n=437 of 506 (86%)**

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=221)</th>
<th>Trastuzumab + Chemotherapy (n=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of events</strong></td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td><strong>Median OS (95% CI)</strong></td>
<td>23.6 months (16.56–NA)</td>
<td>16.9 months (15.41–20.53)</td>
</tr>
<tr>
<td><strong>HR by unstratified Cox model, 0.82</strong></td>
<td>(95% CI, 0.56–1.17)</td>
<td></td>
</tr>
</tbody>
</table>

---

Margetuximab 266 241 209 174 125 85 57 42 29 17 8 3 1 0 Margetuximab 221 207 179 147 104 69 46 34 24 15 7 2 1 0
Trastuzumab 270 237 194 163 122 92 63 37 24 14 6 3 2 1 0 Trastuzumab 216 189 153 130 95 71 48 26 17 10 4 2 1 0

*First interim overall OS analysis at time of PFS analysis (Oct 10, 2018) was immature with 41% of 385 deaths needed for final OS analysis; stopping boundary was not crossed.

Second interim OS analysis will occur after 270 deaths. Final OS analysis will occur after 385 deaths. NA=not achieved.
Making Antibodies Better - Using Existing Antibodies And Someone Else’s NK Cells

**FATE NK-100 Phase 1 Trial**
- Tumor is HER2 or EGFR positive
- Antibodies used are Herceptin™ or Erbitux™
- NK cell donor must be CMV+ and HLA-haploidentical
- Open at UMN (Manish Patel), UCSD, Ohio State, Baylor Scott and White
Overcoming Tumor-Induced Immune Evasion: Immune Cell Expansion

Engineer & Expand Immune Cells ex vivo (CAR-T; NK)

Tumor-Induced Immune Suppression

Tumor Cells
Making Antibodies Better – Attach Them To Your Immune Cells – CAR-T cells

- Variable domain of an antibody are engineered to serve as a T-cell receptor
- Chimeric Antigen Receptor T cells (CAR-T) can recognize and kill cells
- CAR-T effective in B-Cell malignancies (leukemia)
- HER2 CAR-T toxic in some reports, but safe in others

The Immune System

Cells
- Very efficient vs. tumors
- Can multiply
- Migrate actively
- HARD TO GENERATE

Antibodies
- Readily synthesized
- Very specific
- CANNOT MIGRATE
- LIMITED EFFICACY

Cancer Cell

Nabil Ahmed, MD, MPH
Baylor College of Medicine
CAR
Cancer Cell

CAR T cell
CAR T cell
CAR-T Production Is Technically Complex

Case Report of a Serious Adverse Event Following the Administration of T Cells Transduced With a Chimeric Antigen Receptor Recognizing ERBB2

Richard A Morgan¹, James C Yang¹, Mio Kitano¹, Mark E Dudley¹, Carolyn M Laurencot¹ and Steven A Rosenberg¹

¹Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

In an attempt to treat cancer patients with ERBB2 overexpressing tumors, we developed a chimeric antigen receptor (CAR) based on the widely used humanized monoclonal antibody (mAb) Trastuzumab (Herceptin). An optimized CAR vector containing CD28, 4-1BB, and CD3ζ signaling moieties was assembled in a γ-retroviral vector and used to transduce autologous peripheral blood lymphocytes (PBLs) from a patient with colon cancer metastatic to the lungs and liver, refractory to multiple standard treatments. The gene transfer efficiency was high, with a mean of 78% of the transduced cells expressing surface CAR. However, the CAR T cells caused a serious adverse event characterized by fever, chills, dyspnea, hypotension, and hypoxia, which required aggressive supportive care and eventually resulted in the patient’s death. This case highlights the importance of careful monitoring and risk management in the clinical use of CAR T cell therapy.
HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma
A Phase 1 Dose-Escalation Trial

Nabil Ahmed, MD, MPH; Vita Brawley, BS; Meenakshi Hegde, MD; Kevin Bielamowicz, MD; Mamta Kalra, PhD;
Daniel Landi, MD; Catherine Robertson, BS; Tara L. Gray, LVN; Oumar Diouf, MS; Amanda Wakefield, BS;
Alexia Ghazi, DO; Claudia Gerken, MS; Zhongzhen Yi, PhD; Aidin Ashoori, BS; Meng-Fen Wu, MS; Hao Liu, PhD;
Cliona Rooney, PhD; Gianpietro Dotti, MD; Adrian Gee, PhD; Jack Su, MD; Yvonne Kew, MD, PhD;
David Baskin, MD; Yi Jonathan Zhang, MD, PhD; Pamela New, MD; Bambi Grilley, RPh, MS; Milica Stojakovic, PhD;
John Hicks, MD, PhD; Suzanne Z. Powell, MD, PhD; Malcolm K. Brenner, MD, PhD; Helen E. Heslop, MD;
Robert Grossman, MD, PhD; Winfried S. Wels, PhD; Stephen Gottschalk, MD

CONCLUSIONS AND RELEVANCE Infusion of autologous HER2-CAR VSTs is safe and can be associated with clinical benefit for patients with progressive glioblastoma. Further evaluation of HER2-CAR VSTs in a phase 2b study is warranted as a single agent or in combination with other immunomodulatory approaches for glioblastoma.
Trispecific Killer Engagers – TriKEs: The Superglue Of Immune Engagers?

**TriKE-Mediated Killing**

NK Cell

CD16

IL15rα

Immunological Synapse

CD33

Redirected Lysis

Tumor Cell

**Figure A**

Day 14 Image

Day 21 Image

**Table**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Luminescence (Counts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL-60-luc</td>
<td>400</td>
</tr>
<tr>
<td>HL-60-luc + NK + 1633</td>
<td>300</td>
</tr>
<tr>
<td>HL-60-luc + NK + 161533</td>
<td>200</td>
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</table>

University of Minnesota discovery is now a first-in-human clinical trial for leukemia

September 19, 2019

Designer molecule will activate the patient's own immune cells to attack cancer

MINNEAPOLIS, MN- September 19, 2019 - The discovery of tri-specific natural killer engagers (TriKE™), a combination protein that bridges an immune cell and a tumor cell to drive tumor cell killing power exponentially, has led to a new Phase I, first-in-human study to treat leukemia. The study is opening exclusively at the University of Minnesota Medical Center, and is being sponsored by GT Biopharma, Inc.
Immunotherapy For Breast Cancer

• Multiple strategies are under study
  – Vaccines
  – Immuno-stimulants (engineered antibodies, interleukin 15, etc.)
  – Checkpoint inhibitors
  – Checkpoint activators
  – Engineered T cells
  – Novel engagers
  – Combinations of conventional and new immune oncology drugs

• Determining biomarker predictors of immune sensitivity necessary

• Strategies to increase immune “cold” tumors needed
Thanks!

- Patients
- Scientists
- Clinicians
- Elected officials
- Advocates

Knowing how it could change the lives of canines everywhere, the dog scientists struggled diligently to understand the Doorknob Principle.