Disclosures

Lucas McCarthy, MD has nothing to disclose
Outline

• Currently available DMTs
  • Use, safety, tolerability and effectiveness

• New updates on current DMTs

• New DMTs approved or pending approval
  • Daclizumab (Zinbryta) and Ocrelizumab

• Conclusions, Personalized Treatments
## MS Disease Modifying Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPAXONE (Glatiramer Acetate)</td>
<td>1997</td>
</tr>
<tr>
<td>GLATOPA (Glatiramer Acetate)</td>
<td>2015</td>
</tr>
<tr>
<td>BETASERON (Interferon Beta-1b)</td>
<td>1993</td>
</tr>
<tr>
<td>AVONEX (Interferon Beta-1a)</td>
<td>1996</td>
</tr>
<tr>
<td>REBIF (Interferon Beta-1a)</td>
<td>2002</td>
</tr>
<tr>
<td>EXTAVIA (Interferon Beta-1b)</td>
<td>2009</td>
</tr>
<tr>
<td>PLEGRIDY (Peginterferon Beta-1a)</td>
<td>2014</td>
</tr>
<tr>
<td>GILENYA (Fingolimod)</td>
<td>2010</td>
</tr>
<tr>
<td>AUBAGIO (Teriflunomide)</td>
<td>2012</td>
</tr>
<tr>
<td>TECFIDERA (Dimethyl Fumarate)</td>
<td>2013</td>
</tr>
<tr>
<td>NOVANTRONE (Mitoxantrone)</td>
<td>2000</td>
</tr>
<tr>
<td>TYSABRI (Natalizumab)</td>
<td>2004 / 2006</td>
</tr>
<tr>
<td>LEMTRADA (Alemtuzimab)</td>
<td>2014</td>
</tr>
<tr>
<td>ZINBRYTA (Daclizumab)</td>
<td>2016</td>
</tr>
</tbody>
</table>
With 14 Approved DMTs for MS, plus many off-label therapies

How do we decide what to use?
MS DMT – One Physician’s Perspective

## Injectable Medications: Modest Efficacy and Strong Safety Profile

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>How Given</th>
<th>How Often</th>
<th>Injection Reactions</th>
<th>Flu-like Symptoms</th>
<th>Blood Testing Required</th>
<th>Refrigeration Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex</td>
<td>Into Muscle (Deepest)</td>
<td>4x / Month</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (1 week outside)</td>
</tr>
<tr>
<td>Rebif</td>
<td>Under Skin</td>
<td>12x / Month</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (1 month outside)</td>
</tr>
<tr>
<td>Betaseron</td>
<td>Under Skin</td>
<td>12x / Month</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Plegridy</td>
<td>Under Skin</td>
<td>2x / Month (least often)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (1 month outside)</td>
</tr>
<tr>
<td>Copaxone</td>
<td>Under Skin</td>
<td>30x / Month or 12x / Month</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes (1 month outside)</td>
</tr>
<tr>
<td>Glatopa*</td>
<td>Under Skin</td>
<td>30x / Month (most often)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes (1 month outside)</td>
</tr>
</tbody>
</table>

*There have not been large scale human trials of Glatopa specifically (FDA approved via Biosimilar to Copaxone)
# Oral MS Medications

**Moderate Efficacy, Convenience, Some Safety Concerns**

<table>
<thead>
<tr>
<th></th>
<th>Gilenya</th>
<th>Aubagio</th>
<th>Tecfidera</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>Once Daily</td>
<td>Once Daily</td>
<td>Twice Daily</td>
</tr>
<tr>
<td><strong>Relapse Reduction</strong></td>
<td>54% 🌟🌟🌟🌟🌟</td>
<td>31% 🌟🌟🌟🌟</td>
<td>51% 🌟🌟🌟🌟🌟</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Headache, Nausea, Diarrhea, Abdominal Pain, Respiratory Changes, Infections, Back Pain, Hypertension</td>
<td>Headache, Diarrhea, Nausea, Hair thinning, Tingling</td>
<td>Flushing, Abdominal pain, Diarrhea, Nausea, Vomiting, Rash</td>
</tr>
<tr>
<td><strong>Serious Risks</strong></td>
<td>Slow heart rate, Arrhythmia, Congestive heart failure, Macular edema, Rare viral brain infections (HSV, VZV, PML)</td>
<td>Liver damage, Birth defects, Transient kidney failure, Nerve damage, skin reactions</td>
<td>Rare viral brain infection cases (PML)</td>
</tr>
<tr>
<td><strong>Year Approved</strong></td>
<td>2010</td>
<td>2012</td>
<td>2013</td>
</tr>
</tbody>
</table>

*compared with Placebo in separate trials, not directly comparable
Gilenya Updates – improved tolerability?

AAN 2016 Platform – Volmer et al. Rocky Mountain MS Center

271 patients – Gilenya, 342 patients – Tecfidera
Followed for 2 years, retrospectively collected data

• Less Relapses with Gilenya - 8.9% vs. 12.9%
• Less Discontinuation with Gilenya - 34.3% vs. 47.1% (p=0.002)
  • GI problems lead to 23.9% Gilenya and 80.5% Tecfidera discontinuations
Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial

Fred Lublin*, David H Miller*, Mark S Freedman, Bruce A C Cree, Jerry S Wolinsky, Howard Weiner, Catherine Lubetzki, Hans-Peter Hartung, Xavier Montalban, Bernard M J Uitdehaag, Martin Merschhemke, Bingbing Li, Norman Putzki, Fonda C Liu, Dieter A Häring, Ludwig Kappos, on behalf of the INFORMS study investigators†

## Table 3. Incidence rates for specific AEs and SAEs in the LC and CC

<table>
<thead>
<tr>
<th>Important identified risk (AEs/SAEs)</th>
<th>Long-term Cohort (N=1655)</th>
<th>Core Cohort (N=1212)</th>
<th>IRR*† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AE n (IR)</td>
<td>SAE n (IR)</td>
<td>AE n (IR)</td>
</tr>
<tr>
<td>Bradyarrhythmia post-first dose</td>
<td>274 (4.0)</td>
<td>19 (0.2)</td>
<td>157 (9.9)</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>79 (1.0)</td>
<td>1 (0.01)</td>
<td>27 (1.5)</td>
</tr>
<tr>
<td>Herpes zoster infections</td>
<td>83 (1.1)</td>
<td>7 (0.09)</td>
<td>18 (1.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>238 (3.3)</td>
<td>2 (0.02)</td>
<td>94 (5.5)</td>
</tr>
<tr>
<td>Infections</td>
<td>1302 (63.3)</td>
<td>80 (1.0)</td>
<td>797 (91.6)</td>
</tr>
<tr>
<td>Opportunistic</td>
<td>7 (0.09)</td>
<td>2 (0.02)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gastrointestinal candidiasis</td>
<td>1 (0.01)</td>
<td>1 (0.01)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Herpes zoster disseminated</td>
<td>1 (0.01)</td>
<td>1 (0.01)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>2 (0.02)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>1 (0.01)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2 (0.02)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leukopenia &amp; Lymphopenia</td>
<td>377 (5.8)</td>
<td>6 (0.07)</td>
<td>79 (4.6)</td>
</tr>
<tr>
<td>Liver transaminase elevation</td>
<td>334 (4.9)</td>
<td>4 (0.05)</td>
<td>197 (12.2)</td>
</tr>
<tr>
<td>Macular edema</td>
<td>11 (0.1)</td>
<td>3 (0.04)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Reproductive toxicity</td>
<td>64 (0.8)</td>
<td>12 (0.15)</td>
<td>21 (1.2)</td>
</tr>
</tbody>
</table>

LONGTERMS Study
Cohen et al. AAN 2016
Tecfidera Updates

Lymphopenia Rates
- ~30% relative reduction in lymphocyte counts from baseline
- 5-6% develop severe lymphopenia (< 500 cells/uL)
- Nadir of lymphopenia typically around 9 months
- More lymphopenia in the elderly and with baseline low counts

Combined analysis of DEFINE / CONFIRM / ENDORSE trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;40</td>
</tr>
<tr>
<td>ALC &lt;0.5 x 10⁹/L persisting for ≥6 months, % (95% CI) [n/N]</td>
<td>0.9% (0.5–1.6) [12/1323]</td>
</tr>
</tbody>
</table>

Fox et al. AAN 2016; Wenten et al. AAN 2016
## Oral MS Medications

### Moderate Efficacy, Convenience, Some Safety Concerns

<table>
<thead>
<tr>
<th></th>
<th>Gilenya</th>
<th>Aubagio</th>
<th>Tecfidera</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Lag</strong></td>
<td>After lab tests, heart and eye exams and first dose monitoring</td>
<td>After lab tests</td>
<td>After lab tests and titration</td>
</tr>
</tbody>
</table>
| **Baseline Testing** | Blood Work  
Electrocardiogram (EKG)  
Eye Exam  
Skin Exam (optional)  
6+ hour first-dose monitoring | Blood Work  
Blood Work | Blood Work |
| **Follow-up Monitoring** | Blood work  
Repeat eye exam at 3 months  
Consider follow-up EKG, skin exam | Blood work  
- LFT’s q1 month x 6 months  
- CBC w/diff q6-12 months | Blood work  
- CBC w/diff q6-12 months |

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# Oral MS Medications

## Personalized Options To Discuss

<table>
<thead>
<tr>
<th>Gilenya</th>
<th>Aubagio</th>
<th>Tecfidera</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prefer once daily dosing</td>
<td>- Prefer once daily dosing</td>
<td>- Ok with BID dosing</td>
</tr>
<tr>
<td>• Better Tolerability?</td>
<td>- No liver disease</td>
<td>- Normal lymphocyte counts</td>
</tr>
<tr>
<td>• No significant Heart Disease</td>
<td>- Not planning pregnancy</td>
<td>- Prefer quick to start (titration)</td>
</tr>
<tr>
<td>• Not on anti-arrhythmics</td>
<td>- Ok for Monthly lab tests x6</td>
<td></td>
</tr>
<tr>
<td>• No significant Asthma or COPD</td>
<td>- Prefer quickest to start</td>
<td></td>
</tr>
<tr>
<td>• Low risk for macular edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Slower start – need for ophtho, EKG, +/- derm, and first-dose observation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Infusion MS Medications

## Highest Efficacy, Higher Safety Concerns

<table>
<thead>
<tr>
<th></th>
<th>Novantrone</th>
<th>Tysabri</th>
<th>Lemtrada</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year Approved</strong></td>
<td>2000</td>
<td>2004 / 2006</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Every 3 months</td>
<td>Every 4 weeks</td>
<td>Once per year x 2+</td>
</tr>
<tr>
<td><strong>Approved Use</strong></td>
<td>Relapsing Remitting MS, Secondary Progressive MS*</td>
<td>Relapsing Remitting MS</td>
<td>Relapsing Remitting MS</td>
</tr>
<tr>
<td><strong>Relapse Reduction</strong></td>
<td>54% vs. Placebo</td>
<td>68% vs. Placebo</td>
<td>55% reduction vs. Avonex</td>
</tr>
<tr>
<td><strong>Serious Risks</strong></td>
<td>Cardiotoxicity, Acute Leukemia, Amenorrhea</td>
<td>Highest risk for PML, Liver damage, Skin cancer</td>
<td>ITP, Autoimmune Thyroiditis, Bone Marrow Suppression, Viral infections, PJP pneumonia, Lymphoma</td>
</tr>
</tbody>
</table>

*Manufacturer Recommendation: 3rd Line - For patients who failed 2 or more other MS treatments*
Cases of PML in MS Patients:

**Tysabri** – 617 cases in ~150,000 patients

**Gilenya** – 3 cases* in ~160,000 patients

**Tecfidera** – 4 cases+ in ~180,000 patients

* Lymphocyte counts all < 0.7 x 10^9/L for >6 months

*1 RRMS only; 1 NMO case; 1 RRMS w/ prior Tysabri use

Biogen Update 1/2016; Neuroinfectious Disease, Continuum. 2015.
Risk is based on 3 factors

- Exposure to JC Virus, and JC Virus antibody index level
- Prior immune suppressive medication use (e.g. Mitoxantrone, Methotrexate, Cyclophosphamide…)
- Duration of Tysabri use (longer = higher risk)
# PML risk on Tysabri for MS

<table>
<thead>
<tr>
<th>JCV Ab Index</th>
<th>Duration of Tysabri Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 Years</td>
</tr>
<tr>
<td>≤ 0.9</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>≤1.1</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>≤1.3</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>≤ 1.5</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1 in 1,000</td>
</tr>
</tbody>
</table>

*No Prior Immunosuppression

PML risk on Tysabri for MS


Years on Tysabri

*No Prior Immunosuppression
JCV Ab Negative – False Security?

JCV Ab Testing

- 2.5% false negative rate
- 3 cases of PML in JCV Ab negative
- up to 12% JCV annual conversion rate on Tysabri

---

Clinical/Scientific Notes

Natalizumab-related PML 2 weeks after negative anti-JCV antibody assay

Marie-Sarah Gagne Brosseau, MD, Gary Stobbe, MD and Annette Wundes, MD

Published online before print January 6, 2016, doi: http://dx.doi.org/10.1212/WNL.0000000000002330

Neurology 10.1212/WNL.0000000000002330

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1 Gorelik et al. Ann Neurol. 2010  
2 Gange Brosseau et al. Neurology 2016  
MS DMT – One Physician’s Perspective

Safer
More Effective

Risky
Less Effective

Pending DMTs – What’s Next?
FDA approves Zinbryta to treat multiple sclerosis

The U.S. Food and Drug Administration today approved Zinbryta (daclizumab) for the treatment of adults with relapsing forms of multiple sclerosis (MS). Zinbryta is a long-acting injection that is self-administered by the patient monthly.

"Zinbryta provides an additional choice to patients who may require a new option for treatment," said Billy Dunn, M.D., director of the Division of Neurology Products in the FDA’s Center for Drug Evaluation and Research.
Pending DMTs – Daclizumab

• What is Daclizumab (Zinbryta)?

• What are the benefits / risks?

• When will it be available?

• What does this add to this list of current DMTs?
Daclizumab – What is it?

- Daclizumab (ZINBRYTA) high-yield process SC self injection
- Humanized monoclonal antibody to interleukin-2 (IL-2) receptor subunit (CD25)
- CD25 is expressed highly on proinflammatory effector T-cells
- Modulates IL-2 signaling without causing general lymphopenia
  - Decreases abnormally-activated T-cells
  - Decreases pro-inflammatory lymphoid tissue inducer cells
  - Increases CD56 natural killer (NK) cells
Daclizumab – What is it?

CD56+ NK Cells (increase)

Treg Cells (decrease)

Fam et al. AAN 2016

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Daclizumab – What is it?

Total Lymphocyte Counts - stable

Error bars represent standard error of the mean (SEM)

Fam et al. AAN 2016
Daclizumab – What is it?

Timeline:

1997 - Dazclizumab approved for renal transplant organ rejection (Hoffman La-Roach),
2009 – no longer marketed due to commercial reasons
2011 – SELECT trial results – phase IIb – Daclizumab vs. Placebo
2012 – SELECTION extension trial results – 2 year follow-up
2014 – DECIDE trial results – phase III – Daclizumab vs. Avonex
2016 – FDA Approved for RRMS on 5/27/16
Daclizumab – What is it?

- Does not affect influenza vaccine-induced antibody responses or expansion of memory B cells
- Does not cause overall lymphopenia or significant CD4/CD8 ratio changes
- Does not affect the activity of cytochrome P450 enzymes
- Used in >50,000 transplant patients for graft rejection (IV form) with favorable adverse event profile\(^1,2\)

\(^1\)Sandrini S. Clin Transplant 2005  \(^2\)Milo, R. Ther Adv Neurol Disord. 2014
Daclizumab Trials

**SELECT Trial**

- 600+ RRMS q4 week Daclizumab 300mg, 150mg or Placebo
- 1 year duration
- ARR 0.23, 0.21 vs. 0.46 – 54% relative reduction
- Sustained Disability – HR 57% relative reduction at 3 months
Daclizumab Trials - SELECT

A

% Relapse Free

Proportion of patients relapse free

Placebo
Daclizumab HYP 150 mg
Daclizumab HYP 300 mg

Number at risk
Placebo 196
Daclizumab HYP 150 mg 201
Daclizumab HYP 300 mg 203

B

% With Disability Progression

Proportion of patients with confirmed disability progression

Placebo
Daclizumab HYP 150 mg
Daclizumab HYP 300 mg

Time on study (weeks)

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Daclizumab Trials - SELECTION

SELECTION - extension of SELECT trial

- 517 RRMS, q4 week Daclizumab 300mg or 150mg (no placebo)
- 1 year extension, 2 years total duration
- Primary outcome – safety
  - 1 death due to autoimmune hepatitis (unclear association)
Daclizumab Trials - DECIDE phase 3 trial

DECIDE Trial – active comparator

• 1800+ RRMS
• Daclizumab 150mg q4 week vs. Avonex q1 week
• 2-3 year follow-up
• ARR 0.22 vs. 0.39 – 45% relative reduction
• Sustained Disability – 16% vs. 20% (non-significant)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Daclizumab</th>
<th>Avonex</th>
<th>% Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.22</td>
<td>0.39</td>
<td>45%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of new or newly enlarged T2 lesions</td>
<td>4.3</td>
<td>9.4</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disability progression confirmed at 12 wk* (%)</td>
<td>16</td>
<td>20</td>
<td>16%</td>
<td>0.16</td>
</tr>
<tr>
<td>Disability progression confirmed at 24 wk (%)</td>
<td>13</td>
<td>18</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>MSFC score (mean change from baseline)</td>
<td>0.091</td>
<td>0.055</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No evidence of disease activity (NEDA) (%)</td>
<td>22</td>
<td>13</td>
<td>9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*12 wk disability progress - primary disability outcome (NS)

Daclizumab – DECIDE phase 3 trial

% Free from Relapse
HR 0.59 (95% CI 0.50 – 0.69), p = <0.001

% With Confirmed Disability Progression
HR 0.84 (95% CI 0.66 – 1.07), p = 0.16

Daclizumab – Risks

Serious Adverse Events

- 15% vs. 10% total in Daclizumab 150mg vs. Avonex
- More infections and more serious infections
- More significant transaminitis
- More cutaneous reactions
- One death due to autoimmune hepatitis
- Similar tolerance – discontinuation rate = 15% vs. 9%

Daclizumab – Serious Adverse Events

- **Infections**
  - 5% serious infections vs. 2% in Avonex (DECIDE)
  - 2% serious infections vs. 0% in Placebo (SELECTION)
    - Similar rates of HSV and VZV, no PML or encephalitis cases

- **Transaminitis**
  - >3x ULN 10% vs. 9% Daclizumab vs. Avonex
  - >5x ULN 6% vs. 3% Daclizumab vs. Avonex

- **Cutaneous Reactions**
  - 17 – 22% any reaction (SELECTION)
  - Serious in 2% (14 cases) Daclizumab vs. <1% (1 case) Avonex
    - Dermatitis, angioedema, DRESS, psoriasis...

- **Autoimmunity**
  - SELECTION trial 300mg Daclizumab x 2 years (not approved dosing)
    - 1 death with Autoimmune Hepatitis, 2 cases of Ulcerative Colitis, 1 Grave’s disease, 1 Glomerulonephritis, 8 lymphadenopathy/lymphadenitis
FDA Approved 5/27/2016 for RRMS

BOXED WARNING

“Zinbryta should generally be used only in patients who have had an inadequate response to two or more MS drugs because Zinbryta has serious safety risks, including liver injury and immune conditions.”

- similar to Alemtuzimab

Prescribed under a Risk Evaluation and Mitigation Strategy (REMS) program

- similar to Tysabri and Alemtuzimab.

FDA News Release, May 27, 2016

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504000.htm
Daclizumab – What is it?

• What is Daclizumab?
• What are the benefits / risks?
• When will it be available?
• What does this add to this list of current DMTs?
Dacizumab – What does this add?

• **FDA Recommendation:**
  - 3rd Line DMT – after failing 2-3 other DMTs due to safety profile
  - Similar to Alemtuzimab

• **Convenience**
  - Self-Administered subcutaneous, Once Monthly

• **Close Monitoring and Safety Issues**
  - Monthly LFT’s with each dosing recommended by FDA, REMS program

• **Strong Efficacy**
  - 43% ARR reduction vs. Avonex
  - Similar to 49% ARR reduction with Alemtuzimab vs. Rebif (CARE-MS 1)
Pending DMTs – What’s Next?

Ocrelizumab

- Humanized CD20 antibody (similar to Rituximab)
- Infusions q6 months in trials (2x infusions 2 weeks apart)
- 3 completed Phase 3 trials
- Expected FDA Application for PPMS and RRMS (“early 2016”)
- Will be expedited FDA review through “Breakthrough Therapy” designation for PPMS
**Ocrelizumab – Trials Summary**

**OPERA 1 and OPERA 2 - RRMS**
- Pooled Data
- 1,656 RRMS, randomized, active comparator (Rebif), 2 years
- Reductions: 50% ARR, 40% Disability Progression, 80% T2 Lesions

**ONTARIO - PPMS**
- 732 PPMS, randomized, placebo controlled, 5 years
- Reductions: 24% Disability Progression, 29% 25ft Walk, 17.5% Brain Volume Loss

*Full Data not yet published.*

Presented at ECTRIMS 2015: Hauser et al. ECTRIMS 2015; Montalban et al. ECTRIMS 2015
Annualized Relapse Rate
• Ocrelizumab: 46-47% reduced vs. Rebif (OPERA 1 + 2)
• Alemtuzimab: 49-55% reduced vs. Rebif (CARE-MS 1 + 2)

6 month Sustained Disability Progression
• Ocrelizumab: 37-43% reduced vs. Rebif (OPERA 1 + 2)
• Alemtuzimab: 30-42% reduced vs. Rebif (CARE-MS 1 + 2)

*Not able to directly compare these due to differences in trials
OPERA 1 + 2 presented at ECTRIMS 2015. Not yet published.
Ocrelizumab – Safety

Any Adverse Effects
• 34% Infusion Reactions vs. 9.7% Rebif (OPERA 1+2)
• 39% Infusion Reactions vs. 25% Placebo (ONTARIO)

Serious Adverse Effects
• 6.9% vs. 8.7% Rebif (OPERA 1+2)
• 20% Serious Infections vs. 22% in Placebo (ONTARIO)

*Full Data not yet published.
Presented at ECTRIMS 2015: Hauser et al. ECTRIMS 2015; Montalban et al. ECTRIMS 2015
Personalized treatment for MS?

Can we predict who will most benefit from which DMT?

Is there a place for initial early aggressive MS therapy with second or third line DMTs?
MS Medications: How To Treat?
Escalation vs. Induction

**Escalation**
- Start with safe, first-line medication, increase if unresponsive
- Most common method and well studied

**Induction**
- Start with aggressive, typically 2nd or 3rd line medication
- Consider de-escalating if stable after some time
AAN 2016 Controversy Talk

Timothy Vollmer, MD — UC Denver, Rocky Mountain MS Center
Brian Weinshenker, MD — Mayo Clinic

“Maintaining Cognitive Reserve”
“Preventing Serious Adverse Effects”
“Preventing Brain Atrophy”
“Long Term DMT Effects Not Well Known”
“Early New Lesions Predict Future Disability”
MS Treatment – Escalation

MS Diagnosis

Relapse

Relapse

Relapse

Relapse

Physical Functioning

MRI Lesions

Pre-Clinical

TIME

Secondary Progressive

Escalating DMT Treatments:

First-Line Med  Second-Line  Third Line

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Could we do better?

Goal is to accurately predict response to first-line therapy

Start best first-line drug for each patient to maximize benefit and reduce risk
MS Treatment – Early Aggressive Treatment

MS Diagnosis

- Pre-Clinical
- MRI Lesions
- Early Aggressive DMT: Second / Third-Line Med
- First-line

Physical Functioning

TIME

Relapse

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**MS Aggressive 1st Line Therapy - Tysabri?**

- **Newly diagnosed RRMS patient**
  - Check JCV serum antibody status
  - **JCV Ab positive**
    - Prior immunosuppression
      - **Yes**
        - Do not consider NTZ first line.
      - **No**
        - JCV Ab Index
          - ≤1.5
            - Consider NTZ first line. Monitor with MRI brain for asymptomatic PML lesions every 3–4 months. Repeat JCV Index every 3–6 months.
          - >1.5
            - Consider other DMT options. Consider NTZ first-line use only for a limited time (12–24 months) in patients with aggressive MS disease courses.
  - **JCV Ab negative**
    - Consider NTZ first line. 
    - Monitor JCV Ab status for seroconversion every 3–6 months.
How to predict MS patient prognosis or response to therapy?
How to predict MS patient prognosis or response to therapy?

**Known Risk Factors for More Aggressive MS**

Younger age at onset
Male gender
Non-white ethnicity
Earlier since diagnosis
Cigarette smoking
Low Vitamin D level
Many active lesions on MRI
High number of prior relapses
Spinal fluid inflammatory markers
Comorbid Depression, Stress, or Cognitive Impairment
MS Personalized Risk Predictions
3 Best Predictive Factors

Clinical Relapses

Disability Progression (EDSS, MSFC)

MRI Activity

Proposed MS Treatment Algorithm

1st Line Treatments
- Treatments
- High Risk Changes

2nd Line Treatments
- Stable
- Escalate
- De-escalate

3rd Line or Experimental Treatments
- More High Risk Changes
- Escalate

Overly Simplified

Proposed MS Treatment Algorithm

1st Line Treatments

- High Risk Changes
  - Continue or Switch

2nd Line Treatments

- De-escalate

Stable

- Continue

3rd Line or Experimental Treatments

- Escalate
  - More High Risk Changes
  - Continue or Switch

Thank you!

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