

Understanding

High-Efficacy Therapies in MS

A patient-centered guide to the strongest disease-modifying treatments available today

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Today's Roadmap

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And why does it matter?

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IV or subcutaneous, every 6 months

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Disclosures

Financial relationships	*Scientific advising for Genentech (Ocrelizumab) and TG Therapeutics (Ublituximab)*
Off-label use & unpublished data	*Extended interval dosing, wearing off effects, pregnancy uses*
Funding	*Grant applications for educational activities to Biogen, Novartis, Genentech, and TG Therapeutics through the Consortium of MS Centers*

This presentation is for general educational purposes and does not replace individualized medical advice from your own care team.

SECTION 1

What Is High-Efficacy Therapy?

Understanding the landscape before choosing a treatment

The Spectrum of MS Disease-Modifying Therapies

Moderate Efficacy	High Efficacy	Considerations Increase Too
Tecfidera/Vumerity/ Bafiertam, Aubagio, Gilenya, Mayzent	Ocrevus / Zunovo, Briumvi, Kesimpta, Tysabri	Monitoring needs, Risk discussions, Pre-treatment tests

→ Increasing Efficacy, Increasing Monitoring of risks

Why Might Your Doctor Recommend a High-Efficacy Therapy?

Active disease at diagnosis

Multiple lesions on MRI, or relapses that are frequent or severe

High-risk features

Brain or spinal cord lesions that threaten important functions (vision, walking, arms)

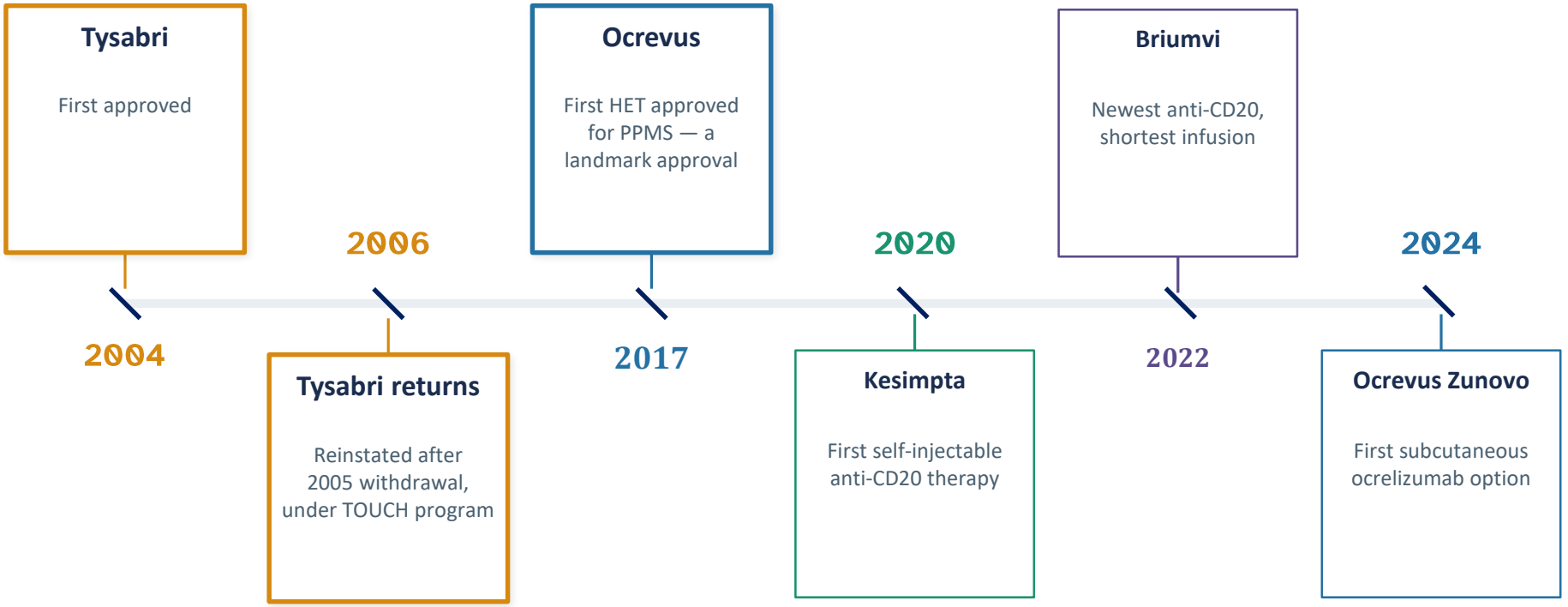
Disease 'breaking through'

New lesions or relapses despite being on a moderate-efficacy drug

Preference for 'treat to target'

A proactive strategy aiming for no evidence of disease activity (NEDA)

Two Decades of High-Efficacy Therapy in MS



Two milestones stand out: Tysabri (2004) proved a highly targeted therapy was possible and reshaped how the field manages risk. Ocrevus (2017) made high efficacy mainstream and was the first drug ever approved for primary progressive MS.

How Do High-Efficacy Therapies Work?

B-Cell Depleting Antibodies

Ocrevus / Zunovo • Briumvi • Kesimpta

Target a protein called CD20 on B cells: immune cells that drive MS inflammation. By removing these B cells from circulation, inflammation in the brain and spinal cord is dramatically reduced.

B cells gradually come back over months, so repeated dosing is needed.

Other Mechanisms

Tysabri

Tysabri works differently: it blocks immune cells from crossing into the brain by targeting a 'doorway' molecule (VLA-4) called alpha-4 integrin.

Because this mechanism doesn't deplete B cells, the safety profile and monitoring needs are quite different from the CD20 therapies.

SECTION 2

Ocrelizumab (Ocrevus & Zunovo)

IV or subcutaneous · every 6 months · approved for RRMS and PPMS

Ocrelizumab (Ocrevus) — IV Formulation

How It's Given

- IV infusion in a clinic or infusion center
- First dose is split: 2 infusions 2 weeks apart
- Then 1 infusion every 6 months
- Each infusion takes ~3.5–4 hours
- Pre-medications given to reduce reactions

How Well It Works

- ~47% reduction in relapses vs placebo (OPERA trials)
- **~95% reduction in Gd+ (active) lesions**
- Only HET approved for primary progressive MS (PPMS)
- Slows disability worsening in PPMS
- Extended duration of effect — more on this later!!
- Delayed time to disability progression
    - However, this effect was not seen when stratified into younger vs older patients

Key Safety Considerations

- Infusion reactions — activation of immune system to remove B cells
    - Antibody & Complement dependent cytotoxicity
- Increased infection risk; avoid live vaccines
- Reactivation of hepatitis B — screen before starting
- Low immunoglobulin levels with long-term use
- PML risk very low (much lower than Tysabri)
- Initially thought to increase breast cancer risk — **DEBUNKED!!**

Ocrevus Zunovo — The Subcutaneous Option

Approved September 2024 — same ocrelizumab molecule, delivered under the skin in about 10 minutes instead of by IV infusion

How It's Given

- Subcutaneous injection in the abdomen, given by a healthcare professional (not self-injected)
- Combined with hyaluronidase to allow rapid absorption of a large volume
- Twice a year, like IV Ocrevus
- Injection itself takes ~15 minutes
- First dose: monitored ~60 min after; later doses ~15 min

How It Compares to IV

- OCARINA II trial: blood levels equivalent to IV Ocrevus
- Same efficacy expected — not a weaker version
- Same indications: relapsing MS and PPMS
- Backed by Ocrevus IV's decade of safety data
- Total visit time much shorter than IV (no multi-hour infusion)

Key Safety Considerations

- Injection reactions (local or systemic) — can occur up to 24 hrs after
- Same infection, hepatitis B, and immunoglobulin precautions as IV
- Pre-medication still required before each dose
- Good option for patients without easy IV access or infusion chair time
- Newer formulation — less long-term SC-specific data than IV

SECTION 3

Ublituximab (Briumvi)

IV infusion · newer CD20 therapy · faster infusion time

Ublituximab (Briumvi) — At a Glance

How It's Given

- IV infusion in a clinic or infusion center
- First dose: 2 infusions at week 0 and week 2
  - May soon be 1 loading infusion soon. **Does this matter to you?**
- Then every 6 months
- Infusion time: ~1 hour (faster than Ocrevus)
- Lower rates of infusion reactions
- Pre-medications given before each infusion

How Well It Works

- ~59% reduction in relapse rate vs teriflunomide (ULTIMATE trials)
- ~97% reduction in Gd+ lesions
- Comparable efficacy to Ocrevus
- Approved for relapsing forms of MS (not PPMS)
- Rapid and deep B-cell depletion
  - 24 hours after first dose: CD19 count 0, usually a few weeks for ocrelizumab
- Interesting wrinkle: wearing off effect?
  - Ongoing clinical trial: Ocrelizumab vs Ublituximab
- Subcutaneous version (dosing every 2-3 months) being tested in Europe

Key Safety Considerations

- Infusion reactions — lower than ocrelizumab
  - Antibody-dependent cellular cytotoxicity
- Increased risk of infections
- Hepatitis B reactivation — screen before starting
- Avoid live vaccines while on therapy
- Low immunoglobulin levels possible over time, but not seen thus far
- Data on very long-term use still accumulating

SECTION 4

Ofatumumab (Kesimpta)

Self-injectable at home · monthly dosing · full B-cell depletion

Ofatumumab (Kesimpta) — At a Glance

How It's Given

- Subcutaneous self-injection (like an EpiPen)
- Loading doses: Weeks 0, 1, 2
- Then monthly injections
- Given at home — no clinic visits for dosing
- Auto-injector pen — relatively easy to use

How Well It Works

- ~50% reduction in relapse rate vs teriflunomide (ASCLEPIOS trials)
- ~94% reduction in Gd+ lesions
- Significant reduction in brain volume loss
- Approved for relapsing forms of MS
- Achieves deep B-cell depletion despite lower dose

Key Safety Considerations

- Injection site reactions (redness, swelling, itch)
- Increased infection risk — upper respiratory most common
  - However, better profile in observational data
- Hepatitis B reactivation — screen before starting
- Avoid live vaccines
- Monitor immunoglobulin levels over time
  - Tends to be stable over time
- Possibly “safer” risk profile to IV anti-CD20s

SECTION 5

Natalizumab (Tysabri)

IV infusion · works differently · very high efficacy for many patients

Natalizumab (Tysabri) — At a Glance

How It's Given

- IV infusion every 4 weeks (standard)
- Extended interval dosing (every 6–8 wks) possible for some
- Infusion takes ~1 hour
- Available via TOUCH prescribing program
- Subcutaneous version (Tyruko) now available

How Well It Works

- ~68% reduction in relapse rate vs placebo (AFFIRM trial)
- ~83% reduction in Gd+ lesions
- Strong effect on disability worsening
- Particularly effective in highly active RRMS
- Works independently of CD20 mechanism

Key Safety Considerations

- PML (brain infection) risk — most important risk
- PML risk tied to JC virus antibody status
- JC antibody index checked regularly
- Risk higher with longer duration & prior immunosuppression
- Extended dosing may lower PML risk
- Rebound activity possible if stopped abruptly

Tysabri: Understanding PML Risk

PML is caused by the JC virus, a common virus most adults have been exposed to.
In people with healthy immune systems, it causes no symptoms. The risk with Tysabri is that it can rarely reactivate in the brain.

JC Negative

No JC antibodies detected

Estimated risk:

Very low (<1 in 10,000)

JC Positive (Low Index, 0.9-1.5)

Antibodies detected, low level

Estimated risk:

Low-moderate (~1 in 1,000 or less)

JC Positive (High Index, 1.5+)

High antibody levels, long use

Estimated risk:

Higher (~1 in 100 to 1 in 50)

✓ JC antibody status is tested every 6 months · Extended interval dosing reduces risk · MRI monitoring is standard

SECTION 6

Comparing Infection Risk

What the clinical trial and real-world data actually show

Why Infection Risk Comes Up With Every High-Efficacy Therapy

All four of these therapies suppress part of the immune system to control MS — so some increase in infection risk is expected. The key is understanding what kind, how much, and how it's monitored.



Mostly Mild Infections

Across anti-CD20 trials, the most common infections are upper respiratory and urinary tract infections — usually managed like any other such infection



Serious Infections Are Rare

Serious infections requiring hospitalization remain uncommon across all four drugs, though risk appears to rise modestly with longer treatment duration



Antibody Levels Matter

With anti-CD20 drugs, low immunoglobulin G (IgG) levels over time are linked to higher infection risk — this is why labs are checked periodically

Infection Risk: What the Trials Showed

Drug	Any Infection (trial data)	Most Common Type	Serious Infections	Distinct Risk to Know
Ocrevus	~58% (OPERA)	Upper respiratory, UTI	Uncommon (~1–2%)	Long-term IgG decline
Briumvi	~56% (ULTIMATE)	Upper respiratory, UTI	Uncommon	Newer drug, less long-term data
Kesimpta	~52% (ASCLEPIOS)	Upper respiratory, injection-site	Uncommon	Similar profile to other anti-CD20s
Tysabri	~53% (AFFIRM)	Upper respiratory, UTI	Uncommon	PML — different category of risk entirely

Figures are approximate "any infection" rates pooled from each drug's pivotal trials and are not from a single head-to-head study — direct cross-trial comparison has real limitations.

Bottom line: overall infection rates are broadly similar across all four drugs — roughly half of patients report some infection over the trial period, almost all mild.

Real-World Data: Duration of Therapy & Infection Risk

What Longer-Term Studies Show

- Real-world cohort studies (anti-CD20 therapies) show serious infections remain rare, but risk rises modestly the longer someone stays on therapy
- Lower IgG (antibody) levels are consistently linked to higher infection risk across multiple studies
- Some studies report low IgG levels (hypogammaglobulinemia) developing in a meaningful minority of patients after several years on anti-CD20 therapy
- Risk factors beyond the drug itself: older age, other medical conditions, and biological sex have all been independently associated with infection risk

How We Monitor & Mitigate This

- Periodic IgG / immunoglobulin level checks
- Vaccination review before starting and ongoing (flu, COVID, pneumococcal)
- Avoiding live vaccines while on active therapy
- Patient education on early signs of infection and when to call
- In select cases, extending the dosing interval to allow partial immune recovery

SECTION 7

Extended Interval Dosing

Can spacing out doses reduce risk while keeping disease control?

What Is Extended Interval Dosing (EID)?

EID means giving a medication less frequently than the standard FDA-approved schedule — for example, every 6 weeks instead of every 4. The goal: maintain disease control while reducing cumulative drug exposure and certain risks.

Best-studied with Tysabri

The largest, most rigorous EID evidence — including a randomized trial — comes from natalizumab

Lower drug exposure

Spacing out doses lowers trough drug levels and may allow partial immune system recovery between doses

Individualized decision

EID is typically considered after a period of stability on standard dosing — not a default starting approach

Tysabri Extended Dosing: The NOVA Trial & Real-World Data

88%

Relative reduction in PML probability with every-6-week vs. every-4-week dosing

TOUCH Registry analysis

~500

Patients randomized in the NOVA trial comparing Q4W vs. Q6W dosing

Phase 3b NOVA trial

No sig. difference

In relapse and MRI outcomes between Q4W and Q6W groups in NOVA

NOVA primary endpoint

Practical takeaway: For patients stable on standard 4-week dosing for ≥1 year, switching to a 6-week interval is a reasonable, evidence-supported option that may lower PML risk without a meaningful drop in efficacy — though it's an individualized discussion, not a universal switch.

Ocrevus Extended Interval Dosing: What Studies Show

Several retrospective studies have looked at delaying the next Ocrevus infusion until B cells start to repopulate ("B-cell-guided" dosing), rather than dosing on a fixed 6-month schedule.

9.9 mo

Median interval between infusions on B-cell-guided EID (vs. 6 mo standard)

Single-center cohort, n=128

0

Clinical relapses occurred in patients switched to B-cell-guided EID

Same cohort, n=113 on EID

↓ Hypo-IgM

Significantly lower rates of low immunoglobulin M with EID vs. standard dosing

Two-center comparison, n=112

Bottom line: this is real, encouraging signal — but it comes from retrospective, single- or two-center cohorts, not a randomized trial like Tysabri's NOVA. It's a reasonable conversation to have, not yet a standard recommendation.

What About Kesimpta and Briumvi?

Kesimpta (Ofatumumab)

- No published studies on extending its dosing interval
- Already dosed monthly at a low, fixed 20mg dose — a different starting point than a 6-month IV drug
- Less an obvious candidate for 'EID' the way Ocrevus or Tysabri are
- An open question for future research, not an active area yet
    - Upcoming clinical trial for every 2 months

Briumvi (Ublituximab)

- No published studies on extending its 6-month maintenance interval
- Current research (ENHANCE trial) is about shortening infusion time and skipping the loading dose — a different question
- Newest of the anti-CD20s, so less long-term data of any kind so far
- Worth revisiting as more real-world experience accumulates

SECTION 8

Comparing the Options

Putting it all together to guide shared decision-making

High-Efficacy Therapies: Side-by-Side Comparison

Drug	Route	Frequency	~MRI activity Reduction	PPMS Approved	Key Risk to Discuss
Ocrevus	IV infusion	Every 6 mo	**~94%***	Yes ✓	Vs. Interferon beta - Infusion rxns, infections
Zunovo	Subcut. infusion	Every 6 mo	**~94%***	Yes ✓	Vs. Interferon beta Injection rxns, infections
Briumvi	IV infusion	Every 6 mo	**~97%**	No	Vs. Teriflunomide Less track record
Kesimpta	Subcut. injection	Monthly	**~94%**	No	Vs. Teriflunomide Duration of effect
Tysabri	IV infusion	Every 4–8 wk	**~92%**	No	Vs. Placebo PML (JC virus)

**vs. interferon beta in head-to-head trials. Other reductions vs. teriflunomide or placebo. Numbers are approximations — individual results vary.*

What Matters Most to You? Questions to Bring to Your Doctor



How do I feel about clinic visits vs. inject at home?



How do I weigh PML risk vs. other types of risk?



Do I want continuous treatment or a variable timing/dosing approach?



What's my family planning situation?



How important is PPMS coverage to me?



Am I willing to do periodic lab monitoring?

What other questions matter to you?

Family Planning & Pregnancy Considerations

These therapies all require discussion about pregnancy planning. None is automatically 'safe' or 'unsafe' — timing and individual circumstances matter greatly. Always discuss with your neurologist and OB.

Ocrevus / Zunovo

Most established safety profile with pregnancy — SOPRANINO & MINORE studies

Stop 1-2 months before conception. Minimal placental transfer. **Established safety with breastfeeding.**

Briumvi

Recommend stopping before conception. Limited pregnancy data compared to Ocrevus — newer drug. Ongoing studies to clarify risk.

Kesimpta

Stop before conception, ideally have been on for 6 consecutive doses before conception. Monthly dosing makes timing more flexible — B cells recover faster between doses.

Tysabri

Can sometimes be continued into early pregnancy. Risk of rebound if stopped suddenly — plan carefully with your neurologist.

Before You Start: What to Expect

1 Blood & urine tests

CBC, liver function, hepatitis B & C, HIV, JC virus antibody, immunoglobulins, and more — depending on the drug

2 Vaccination review

Live vaccines must be given before starting (or timed carefully). Flu and COVID vaccines are recommended once on therapy

3 Baseline MRI

A reference scan to compare against — used to track response after starting treatment

4 Insurance & access

Prior authorization is usually needed. Manufacturer patient assistance programs exist for most of these drugs

5 Consent & education

Detailed discussion of risks and benefits. Many drugs have patient education programs (e.g., TOUCH for Tysabri). **Patient education appt: Deborah Gallaro, RPh**

6 Ongoing monitoring plan

Know your schedule: MRI timing, lab checks, and how to report new symptoms between visits

Key Takeaways

- High-efficacy therapies offer the strongest protection against MS relapses and disability — often 50–70%+ relapse reduction, 95%+ reduction in new MRI activity
- There is no single 'best' drug — the right choice depends on your disease activity, lifestyle, risk tolerance, and family plans
- All of these therapies require pre-treatment testing, monitoring, and regular follow-up — that monitoring protects you
- Weighing risks and benefits is a shared decision — your values matter as much as the clinical data
- It's okay to take time, ask questions, and revisit the decision — we are partners in this process



Questions & Discussion

No question is too small.
*What do **you** want to know from your doctor before starting a new "high-efficacy" therapy?*

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