Welcome to the Post Biologic Era

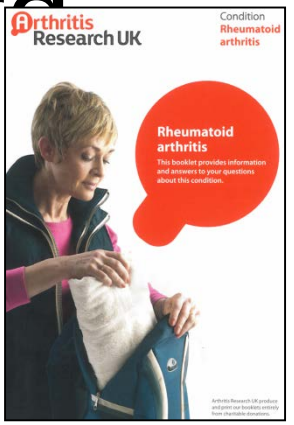
David Walker &

Sandra Robinson

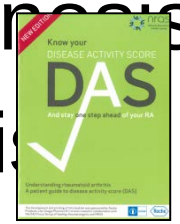
Perspective:

	Waiting Time
1978 SHO Gold & Penicillamine. Erosion pre treatment	13 weeks
1984 SR 20% DMARD Sulphasalazine	13 weeks
1994 Cons 60% DMARD Methotrexate	18 weeks
2002 80% DMARD Leflunomide & TNFi & Rituximab	52 weeks
2012 90% DMARD Tocilizumab & Abatacept	12 weeks
2014 EAC	2 weeks

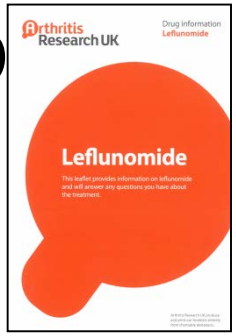
Keeping the patient on board



- Here is a booklet on your diagnosis
- And this is what a DAS score is



- And: I want to s u c D



- And this one….
- And this one….
- r

Healthcare at its very best - with a personal touch

Treat to target

- Fashionable
- Works in studies but some tortology
- Difficult round the fringes: Are you really going to go for a biologic to get from 2.8 to 2.6?
- Negotiating th  nat would you like your DAS

Tolerability/Adherence

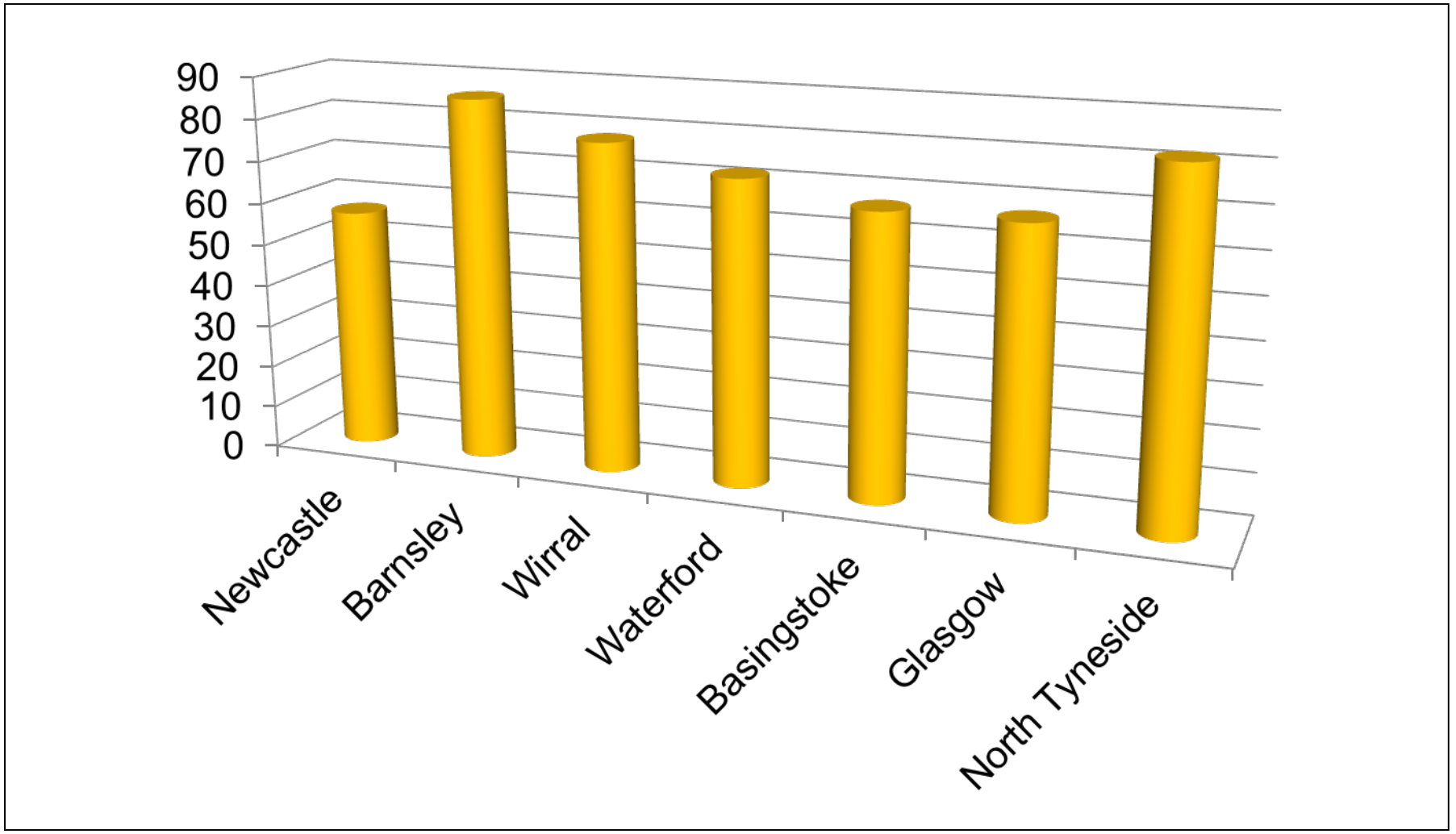
- 56% to 85% of patients on a stable dose of Methotrexate are suffering from side effects.
- 51% would be attracted to a drug regime that did not include Methotrexate.
- Are they taking it?
- Most Nurses believe that patients would not be open about it.
- Most doctors don’t believe that.

Does tolerance have an impact on adherence?

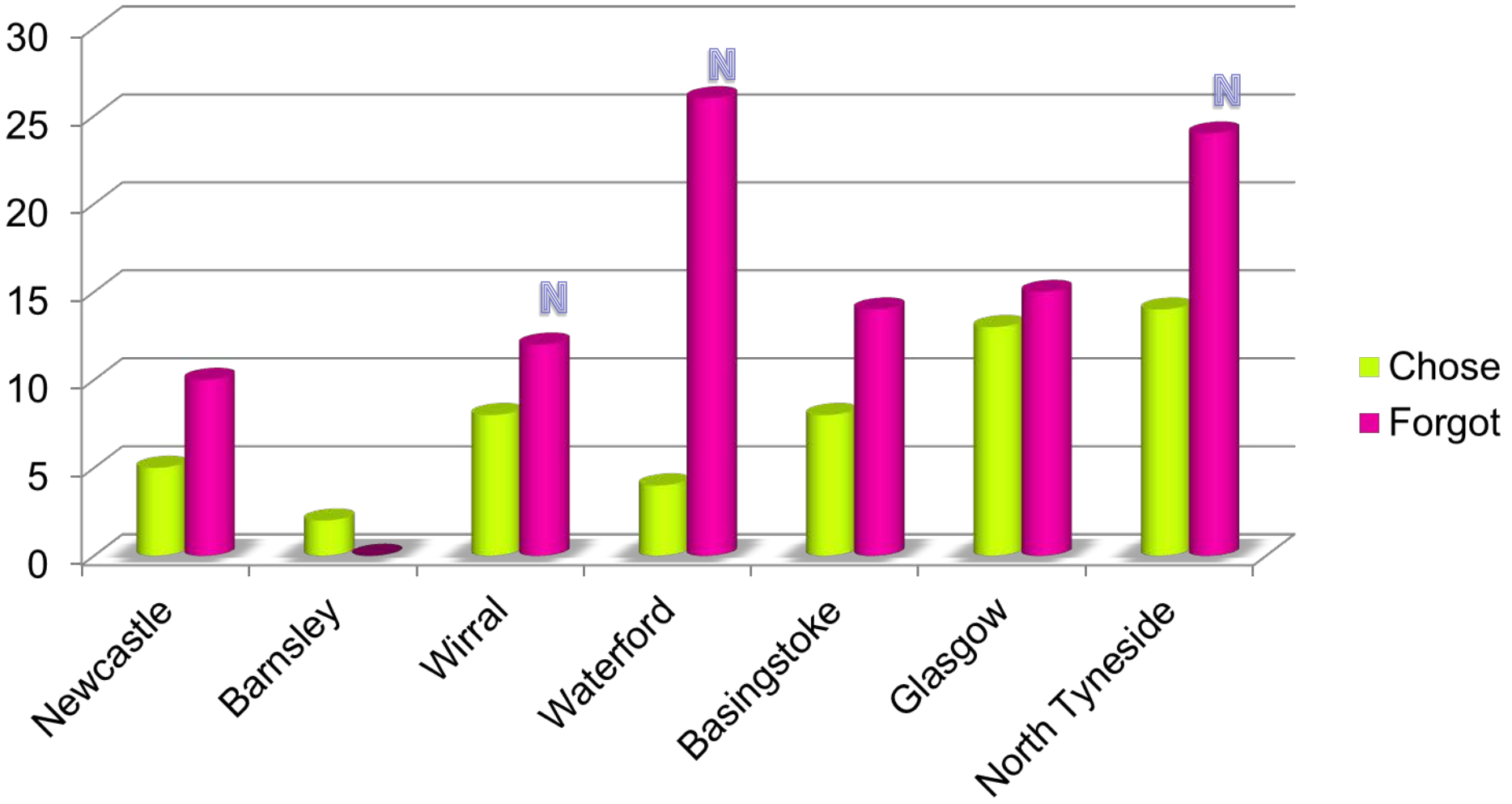
- In 2011 we wondered if there should be a standard for Methotrexate Tolerance
- We asked 100 patients who had never reported side effects if they suffered any
- 56% said yes
- This audit was repeated in 6 centres across the UK

S Robinson; S Gibson; E George; U Martin; P Heslop; H Wrightson, P Prowse; M Kalinowski; D Marshall; M Reed; A Adebajo; D Walker. Tolerability and Adherence problems in patients on a stable dose of Methotrexate: Results of a multi-centre survey. Musculoskeletal Care 2015; 14,152-155.

Total Percentage of Any Side Effects



Chose or forgot to take



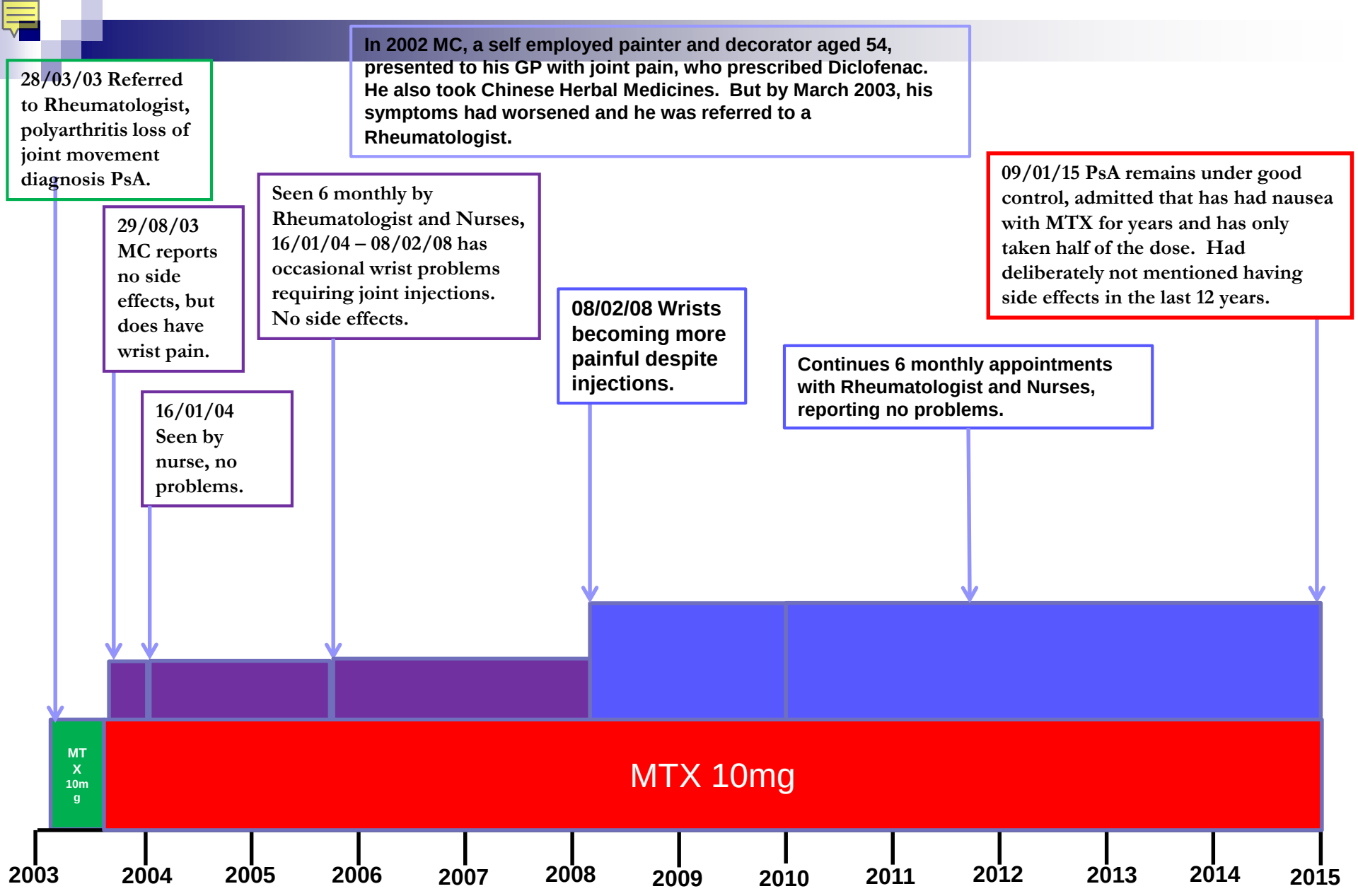
~70% of non-adherence is intentional[1]

Gender	Cognitive ability, depression, social support, coping skills	Concerns about treatment (fear of side effects etc)
Income	Number of medicines, disease seriousness beliefs	Beliefs about illness (cause, timeline)
Age	Health literacy, locus of control	Beliefs about cost of therapy
Race	Self-efficacy, trust in HCP, HCP-patient concordance	Necessity (perceived need) for treatment
Income, personality	Symptom experience	Perceived drug efficacy

1.

Why do Patients not tell us?

- Do not want to disappoint
- Do not think there is anything else they can take
- Are managing their disease and side effects adequately
- To not want to appear to be “breaking the rules”
- Are afraid medication will be stopped


In 2002 MC, a self employed painter and decorator aged 54, presented to his GP with joint pain, who prescribed Diclofenac. He also took Chinese Herbal Medicines. But by March 2003, his symptoms had worsened and he was referred to a Rheumatologist.
28/03/03 Referred to Rheumatologist, polyarthritis loss of joint movement diagnosis PsA.
29/08/03 MC reports no side effects, but does have wrist pain.
16/01/04 Seen by nurse, no problems.
Seen 6 monthly by Rheumatologist and Nurses, 16/01/04 – 08/02/08 has occasional wrist problems requiring joint injections. No side effects.
08/02/08 Wrists becoming more painful despite injections.
Continues 6 monthly appointments with Rheumatologist and Nurses, reporting no problems.
09/01/15 PsA remains under good control, admitted that has had nausea with MTX for years and has only taken half of the dose. Had deliberately not mentioned having side effects in the last 12 years.
MTX 10mg
MTX 10mg
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

What prompted the patient to reveal his partial adherence?

- The Health Care Professional had been chatting to the patient about side effects and revealed that an anaesthetist colleague did not adhere to treatment
- This empowered the patient to reveal his partial adherence to treatment for years
- It was a relief for the patient to be unburdened with this
- The result was that the patient would try to take the medication as prescribed by splitting the dose between two days returning after 3 months for follow up and change of treatment if necessary

The Importance of Identifying Non-Compliance

- **Why Should Non-Adherence be a problem?**
- **May not even be a problem if the patient can manage their disease and remain in remission**
- **Poor disease control which may lead to hospitalisation in some cases**
- **May lead to being prescribed biologics which has increased risk and cost**
- **Poor control of Side Effects**
- **Missing the chance to try something which may work better**
- **May not have an effective partnership for disease management with their Rheumatologist/Nurse**
- **Fundamentally better for us to have accurate information and we can learn from the patient experience**

Adherence and patient education

- Nurses do a lot of the formal patient education
- The most universal and directly necessary education is around DMARD therapy
- The “consultation” involves the transfer of knowledge which is received in the context of the patients experience and beliefs
- The aim is to improve patient concordance

National Survey

- identify the training that rheumatology nurses had received for educating patients about Methotrexate
- identify confidence in different aspects of this role
- evaluate knowledge around clinical situations relevant to Methotrexate use
- identify any need for additional training

Robinson, Sandra, Hassell, Andrew, Ryan, Sarah, Adams, Nicola and Walker, David J. (2017) *A national survey of nurse training: Confidence and competence in educating patients commencing methotrexate therapy.* Musculoskeletal Care, 15 (3). pp. 281-292. ISSN 1478-2189

Training Method

Main Training Method	Number of respondents (n= 73)
Observing – other nurses and self directed	49 (67%)
Observing – Rheumatologists Clinics	8 (11%)
In-house chemotherapy course	7 (9.5%)
In-house competencies	4 (5.5%)
Rheumatology Course	4 (5.5%)
Prescribing Course	1 (1.4%)

Confidence

Confidence Level	Number of Respondents (n = 85)
Very Confident	51 (60%)
Confident	20 (24%)
Somewhat Confident	10 (12%)
Not at all Confident	4 (5%)

Conclusions

- Nurses report confidence to educate patients about Methotrexate but it takes 3 – 12 months for most to achieve this.
- Nurses use a lot of prompts in the form of leaflets and checklists which may inhibit patients from asking questions
- There is no “Gold Standard” training available, nurses have to be self motivated and resourceful in order to increase their education
- Nurses are not taught consultation techniques which involves checking perceived knowledge at intervals

An exploration of the experiences of rheumatology nurses counselling patients on methotrexate therapy
Sandra M. Robinson Sarah Ryan Nicola Adams Andrew Hassell David Walker
30 August 2018 Musculoskeletal Care https://doi.org/10.1002/msc.1361

BIOLOGICS

- Made by living cells
- More like a whisky than a chemical
- Large proteins (antibodies or receptors)
- Directed at components of the inflammatory cascade
- Expensive to make
- Difficult to copy (Bio-similars)

Anomalies:

- Some licenced for use only with Methotrexate
- Rituximab only after TNFi
- NICE can’t go against the licence
- Purchasers take a financial view

Co-morbidities

- If you don’t have anything that stops us treating you, then we have the tools to supress your arthritis.
- Infection risk is the biggest.

Co-Morbidities

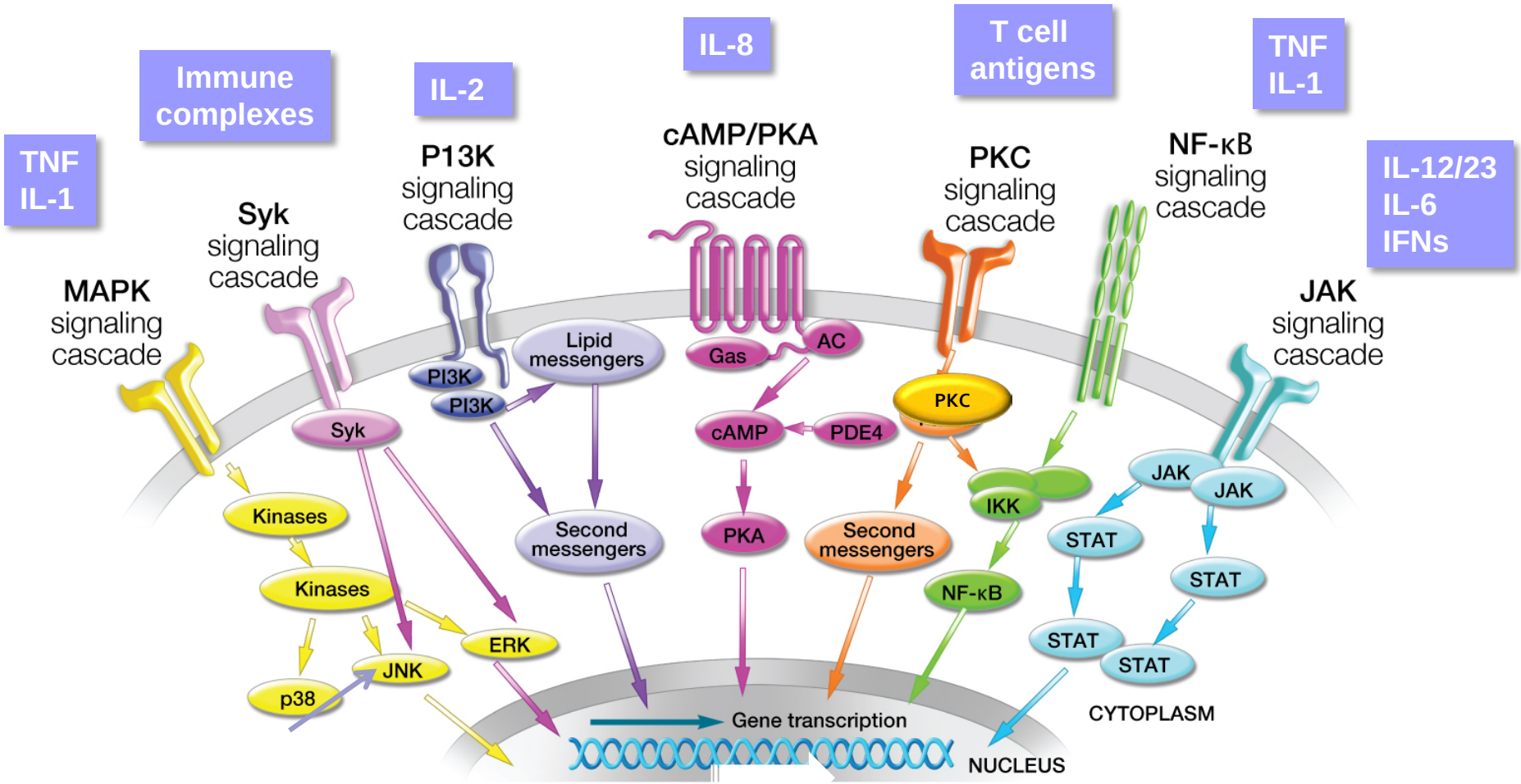
- Interesting register data showing you are 5 x less likely to go into remission if your BMI is over 30!
- You are 2.5 x less likely to go into remission if you smoke!
- Swefot database

Conclusion

- Treatment of RA has improved beyond all recognition, both in strategy for use of conventional DMARDs and use of Biologics.
- Early Arthritis Clinics are here to stay.
- There are huge challenges keeping the patients on board.
- Patients who don’t need treatment tend to do very well on it!

Are we entering a Post Biologic Era?

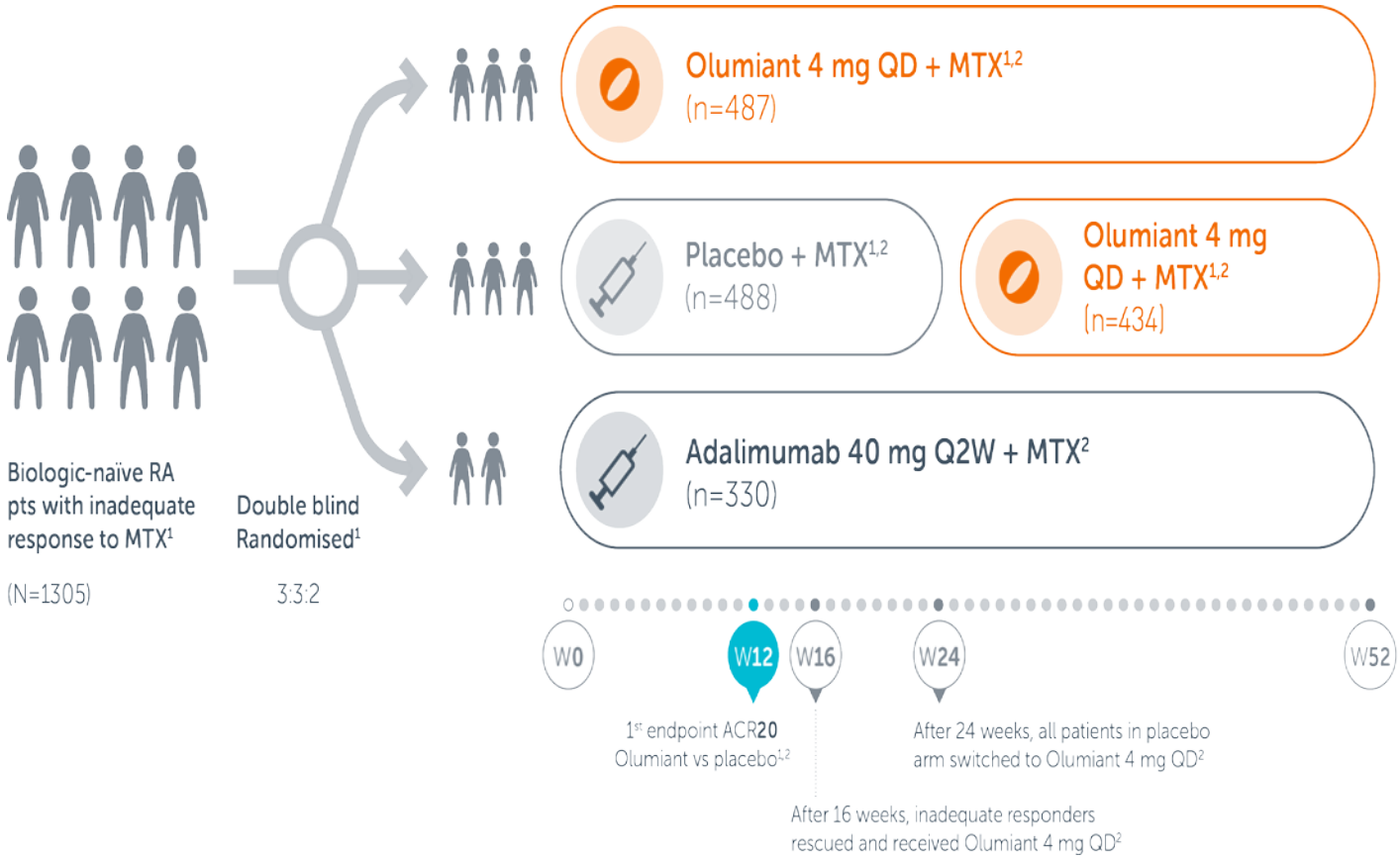
Future therapeutic targets:



1. Mavers M et al. *Curr Rheumatol Rep* 2009;11(5):378–85. 2. Rommel C et al. *Nat Rev Immunol* 2007;7(3):191–201.
3. Taskén K et al. *Physiol Rev* 2004;84(1):137–67. 4. Baier G et al. *Curr Opin Cell Biol* 2009;21(2):262–7.

RA BEAM: Olumiant's head-to-head trial vs adalimumab with background methotrexate (MTX)

In patients with moderate-to-severe RA who have had an inadequate response to MTX (MTX-IR)[1]



PRIMARY ENDPOINT[1]

- W12 ACR20 response

SECONDARY ENDPOINTS[1]

- Change from baseline in:
  - W24 mTSS
  - W12 HAQ-DI
  - W12 DAS28-CRP
- SDAI
- Patient-reported outcomes
- Comparisons at all time points:
  - All outcomes above
  - ACR20 and ACR50 response
  - DAS28-ESR
  - CDAI

1. Taylor P, *et al. N Engl J Med* 2017; 376:652-62. DOI:10.1056/NEJMoa1608345.
2. Taylor P, *et al. N Engl J Med* 2017; 376:652-62. DOI:10.1056/NEJMoa1608345. (Supplementary appendix.)

RA-BEAM: Key inclusion and exclusion criteria

Key inclusion criteria

- Adult-onset RA, defined by ACR/EULAR 2010 criteria
- Inadequate response to MTX
- ≥ 3 erosions*

  * Patients with 1-2 erosions could enroll if rheumatoid factor or anti-citrullinated protein antibody was positive
- Stable background MTX
- ≥ 6/68 tender joints and ≥ 6/66 swollen joints
- hsCRP ≥ 6.0 mg/L

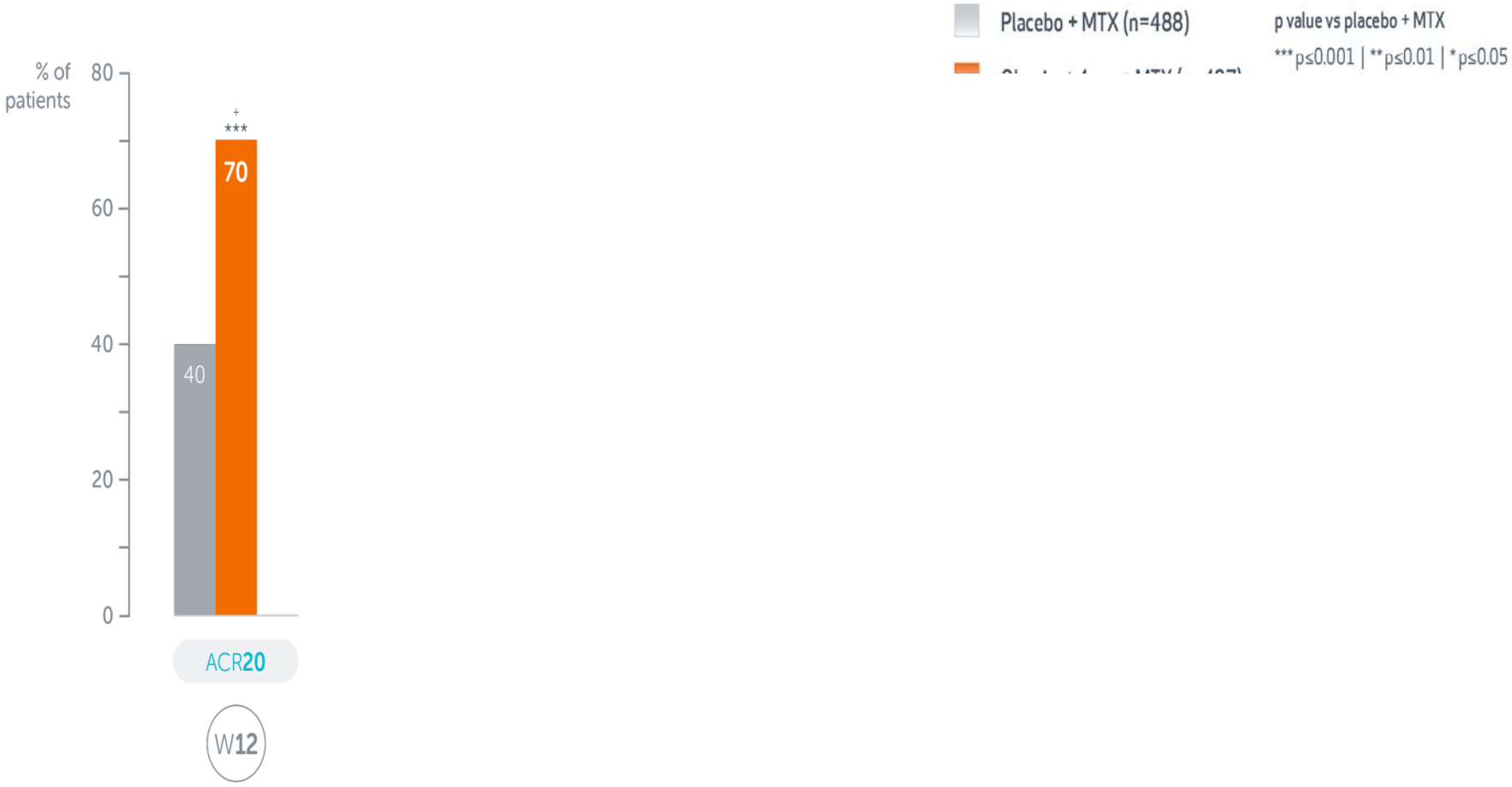
Key exclusion criteria

- Prior biologic DMARD use

Taylor P, *et al. N Engl J Med* 2017; 376:652-62. DOI:10.1056/NEJMoa1608345.

RA-BEAM – ACR20 superiority over placebo

Olumiant achieved its primary endpoint - ACR20 superiority over placebo at Week 12



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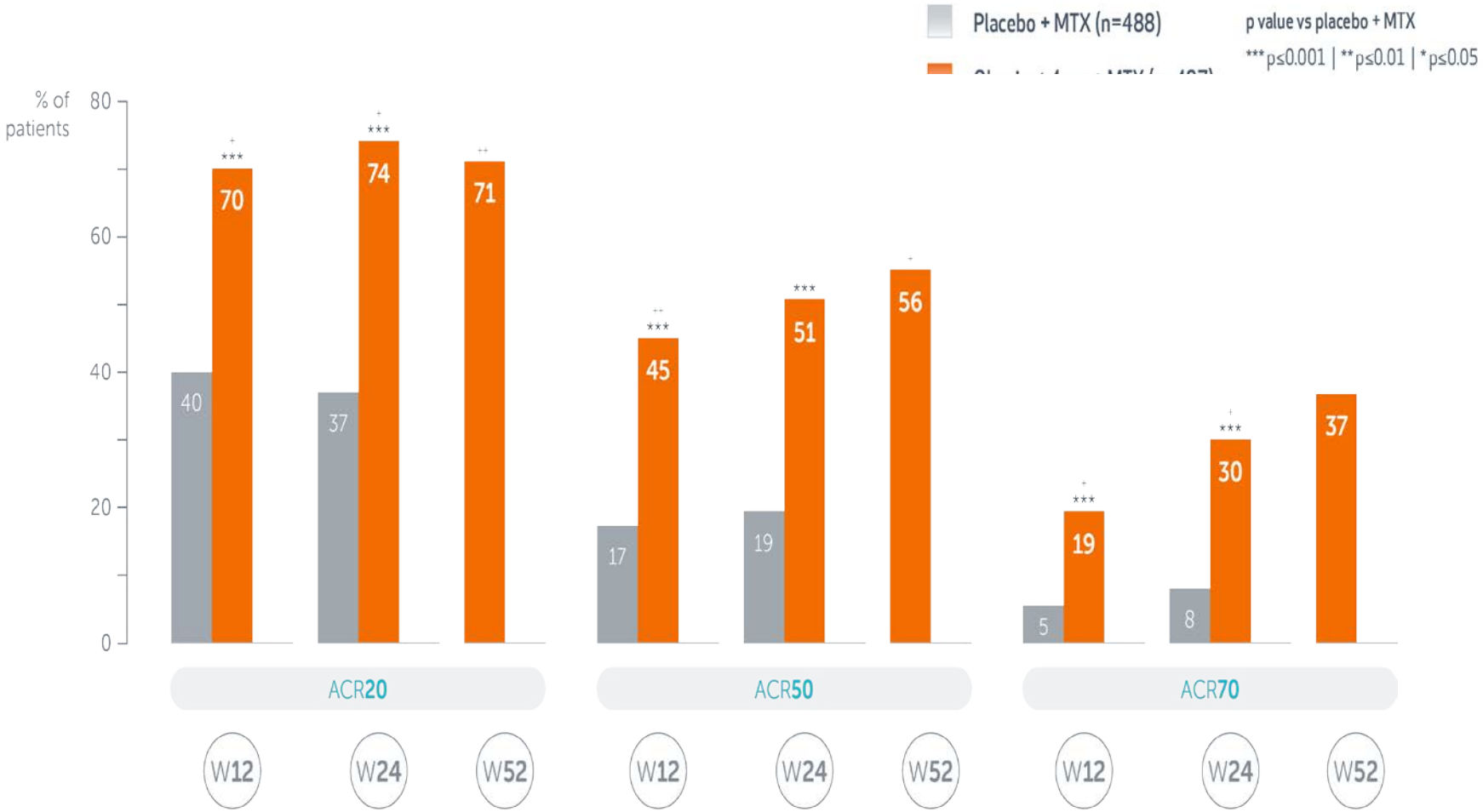
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.(Supplementary appendix.)
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.

RA-BEAM – ACR20 superiority over placebo

Olumiant maintains superior efficacy vs placebo over [illegible]



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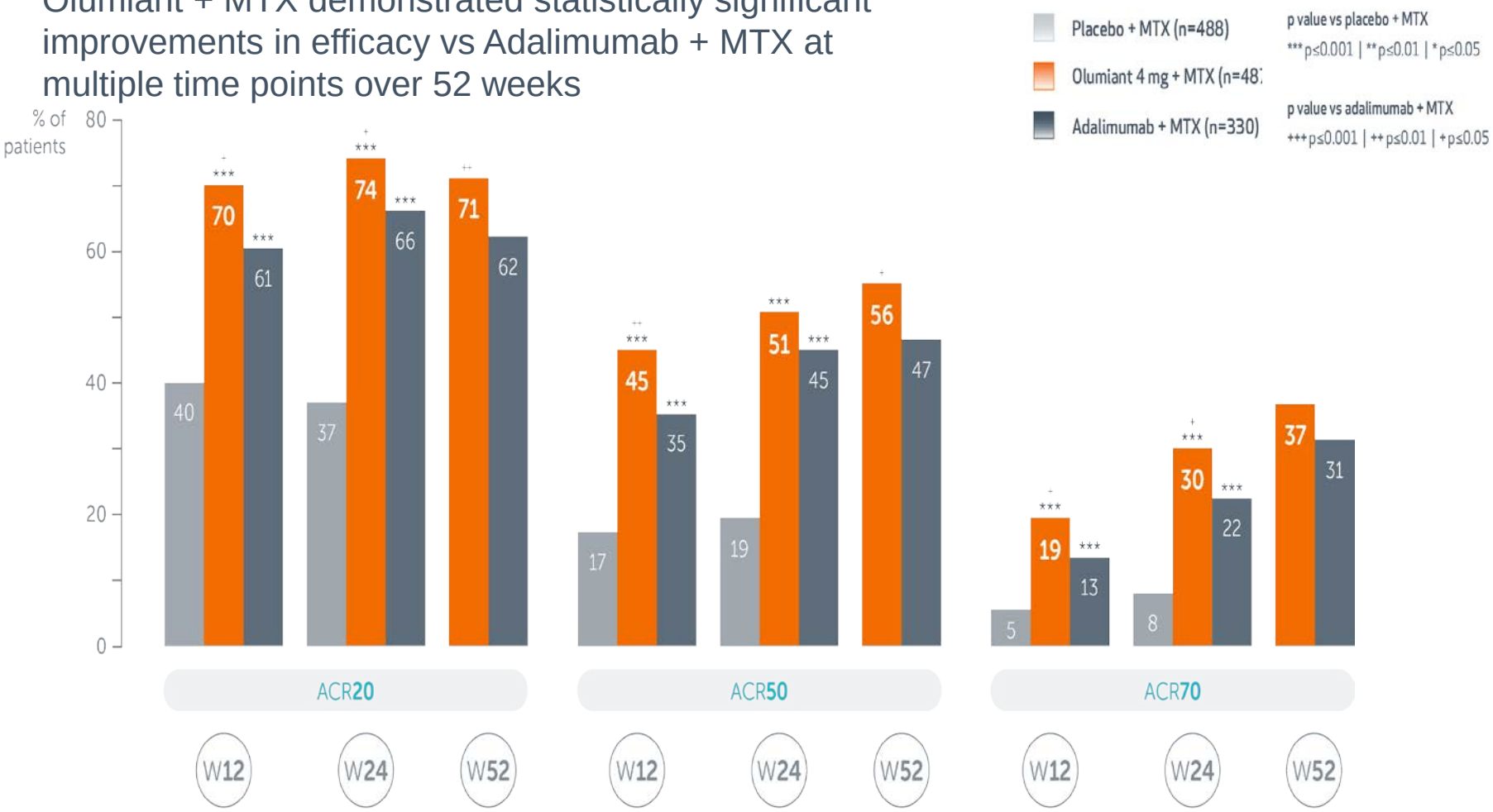
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.

RA-BEAM – ACR 20 superiority over Adalimumab at week 12

Olumiant + MTX demonstrated statistically significant improvements in efficacy vs Adalimumab + MTX at multiple time points over 52 weeks



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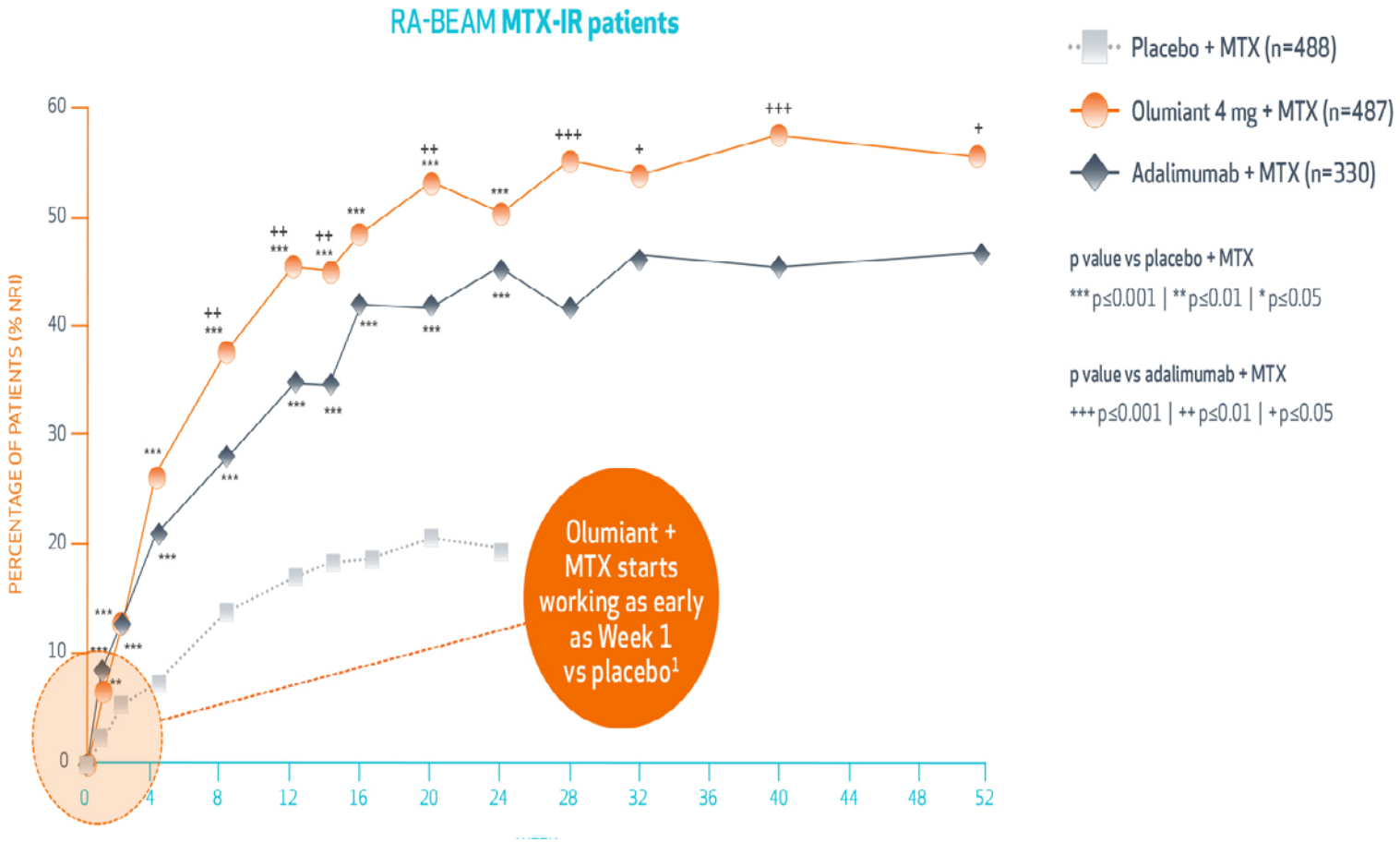
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.

Rapid and sustained response – ACR50

Olumiant + MTX demonstrated statistically significant improvements in ACR50 compared with adalimumab + MTX at multiple time points from Week 8 to Week 52



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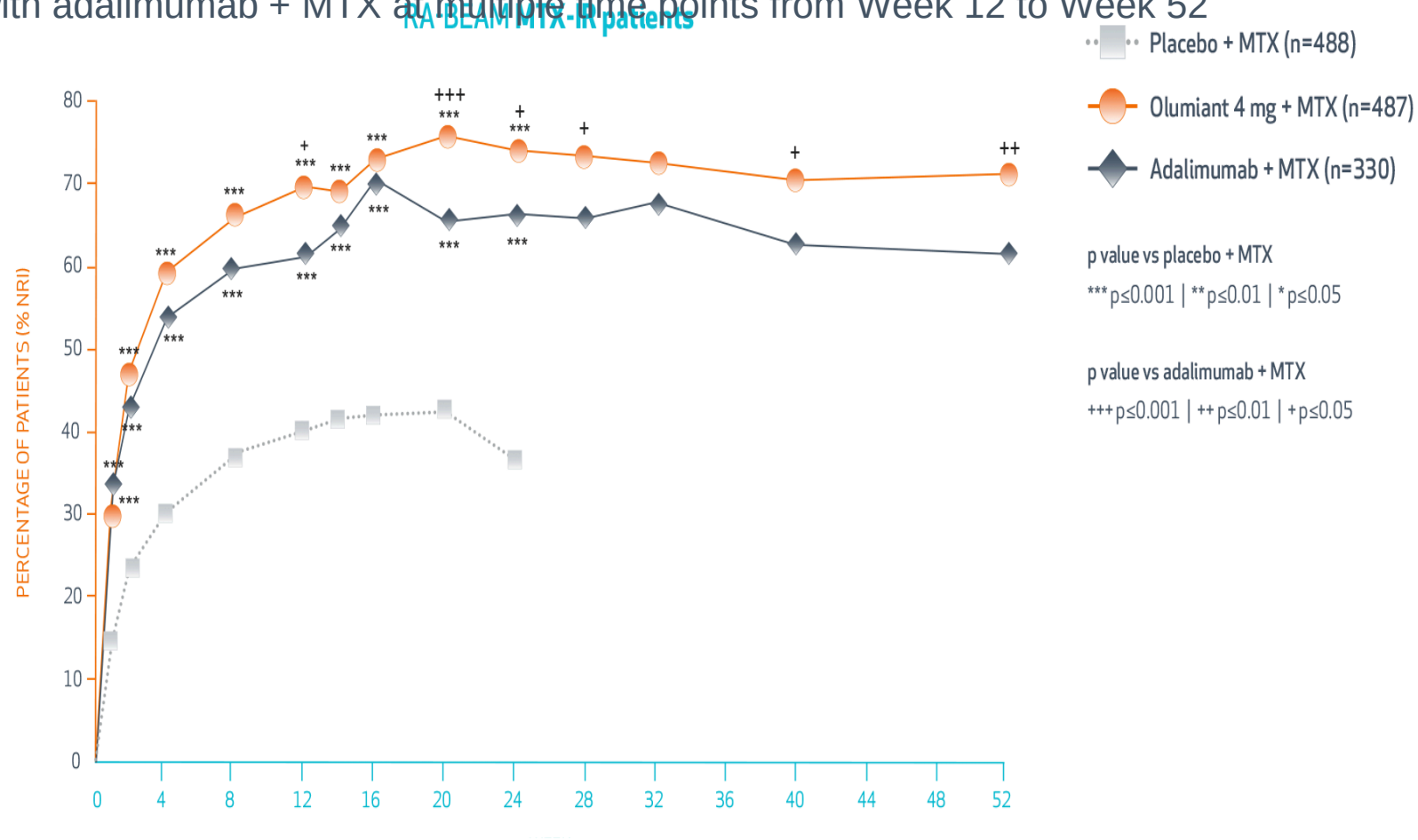
Rapid and sustained response – ACR20

Olumiant + MTX demonstrated statistically significant improvements in ACR20 compared
with adalimumab + MTX at multiple time points from Week 12 to Week 52



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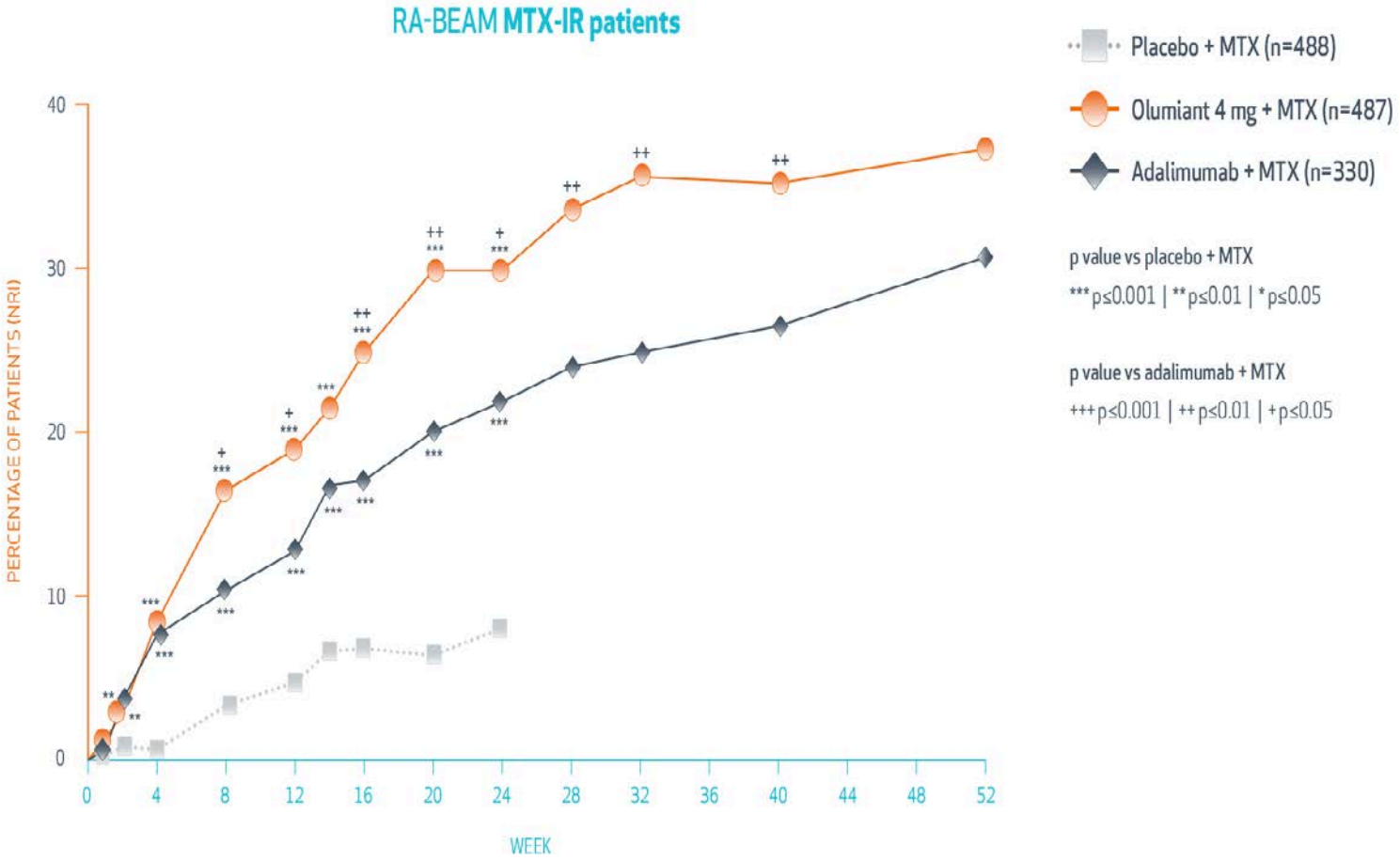
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.(Supplementary appendix.)
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.

Rapid and sustained response – ACR70

Olumiant + MTX demonstrated statistically significant improvements in ACR70 compared
with adalimumab + MTX at multiple time points from Week 8 to Week 40



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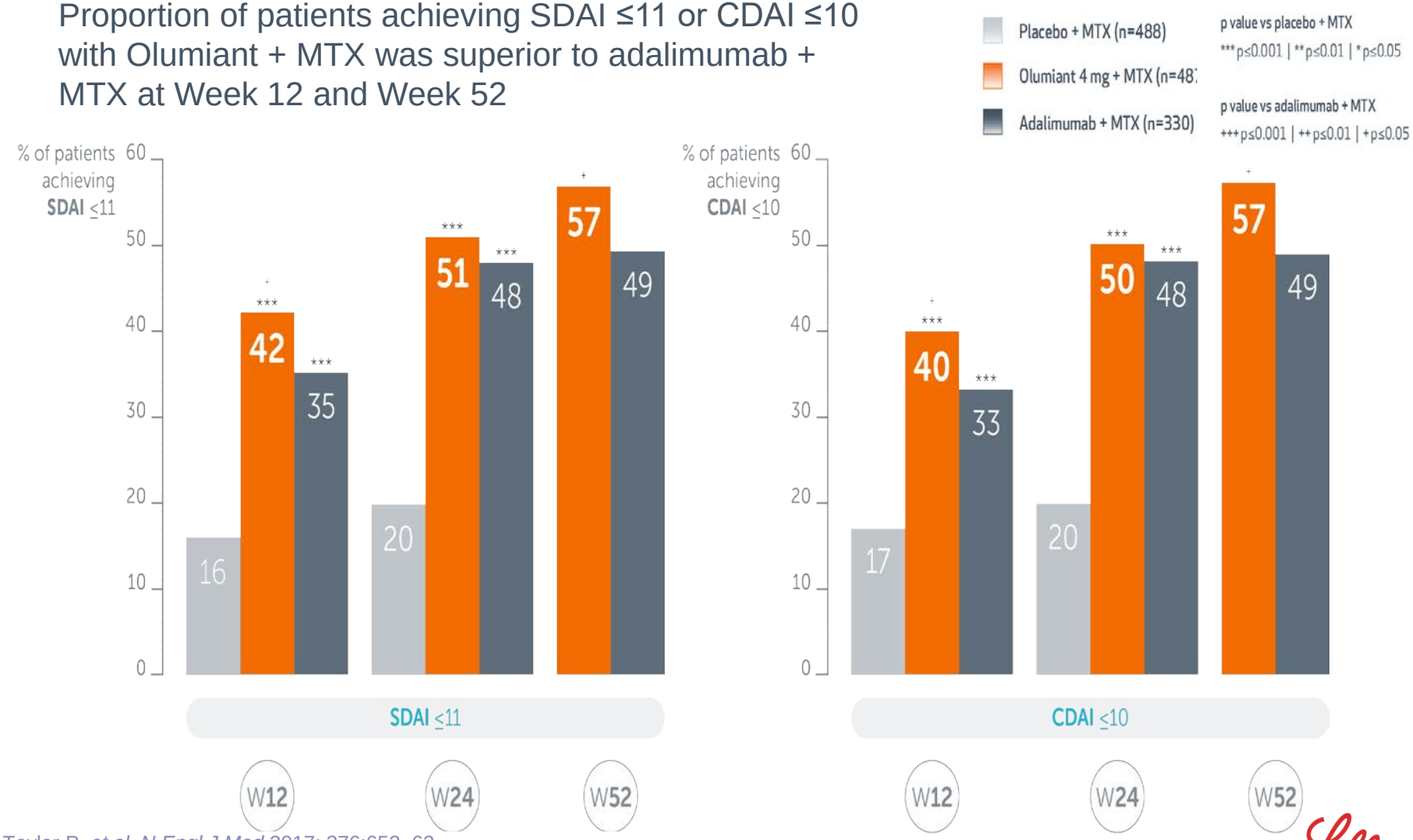
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.(Supplementary appendix.)
Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.

RA-BEAM – Patients achieving SDAI ≤11 or CDAI ≤10

Proportion of patients achieving SDAI ≤11 or CDAI ≤10 with Olumiant + MTX was superior to adalimumab + MTX at Week 12 and Week 52



Taylor P, *et al. N Engl J Med* 2017; 376:652–62. DOI:10.1056/NEJMoa1608345.(Supplementary appendix.)

RA-BEAM: Safety

Adverse event profile

Six placebo-controlled studies were integrated (997 patients on 4 mg Olumiant once daily and 1070 patients on placebo) to evaluate the safety of Olumiant in comparison to placebo for

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Upper respiratory tract infections[a]	Herpes zoster Herpes simplex[b] Gastroenteritis Urinary tract infections	
Blood and lymphatic system disorders		Thrombocytosis >600 x 10^9 cells/L[c]	Neutropaenia <1 x 10^9 cells/L[c]
Metabolism and nutrition disorders	Hypercholesterolaemia[c]		Hypertriglyceridaemia[c]
Gastrointestinal disorders		Nausea	
Hepatobiliary disorders		ALT increased ≥3 x ULN[c]	AST increased ≥3 x ULN[c]
Skin and subcutaneous tissue disorders			Acne
Investigations			Weight increased Creatine phosphokinase increased >5 x ULN[c]

Please consult the summary of product characteristics for further details.

[a]Combined term (acute sinusitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection)

[b]Combined term (eczema herpeticum, herpes simplex, ophthalmic herpes simplex, oral herpes)

[c]Includes changes detected during laboratory monitoring

Olumiant (baricitinib) tablets. Summary of Product Characteristics. Eli Lilly and Company Ltd. 2017.

Adverse events overview: 0-24 Weeks

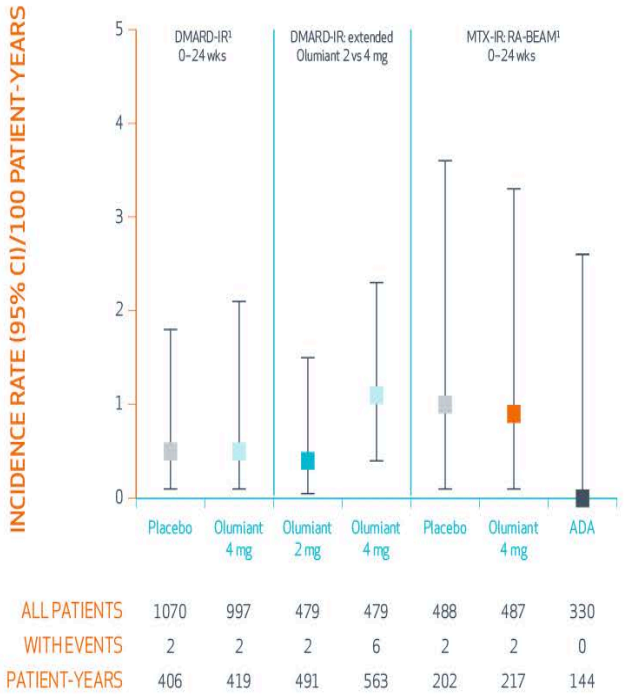
	RA-BEAM[1] (MTX IR)			RA-BUILD[2] (cDMARD IR)			RA-BEACON[3] (TNFi IR)		
% of Patients	PBO[a] N=488	ADA[a] N=330	Bari 4 mg[a] N=487	PBO[b] N=228	Bari 2 mg[b] N=229	Bari 4 mg[b] N=227	PBO[c] N=176	Bari 2 mg[c] N=174	Bari 4 mg[c] N=177
Serious AEs (SAEs)[d]	5	2	5	5	3	5	7	4	10
Serious infections	1	(<1)	1	2	(<1)	2	3	2	3
TEAEs	60	68	71	71	67	71	64	71	77
Discontinuation due to AE	3	2	5	4	4	5	4	4	6
Infections	27	33	36	35	31	42	31	44	40
Herpes zoster	(<1)	1	1	0	2	1	1	1	4
Malignancies, n (%)	3 (<1)	0	2 (<1)	0	0	1 (<1)	0	0	2 (1)
NMSC, n (%)	1 (<1)	0	0	0	0	1 (<1)	0	0	2(1)
MACE	0	0	(<1)	(<1)	0	0	0	0	(1)

[a]Participants taking background MTX therapy throughout the study.
[b]Background cDMARD required unless documented intolerance or contraindication [n=48 (7%)].
[c]Participants taking background cDMARD therapy throughout the study.
[d]SAEs reported using conventional ICH definitions.

1. Taylor PC, et al. *N Engl J Med* 2017;376:652-62
2. Dougados M. et al. *Ann Rheum Dis* 2016;(Ahead of print). doi:10.1136/annrheumdis-2016-210094
3. Genovese MC, et al. *N Engl J Med* 2016;374:1243-52

Olumiant showed no increased risk of malignancy (excluding NMSC) vs placebo or adalimumab + MTX at 24 weeks

Malignancy excluding NMSC[1,2]



Malignancy excluding NMSC incidence rates* and 95% CI by time periods – all patients treated with Olumiant in clinical trials[3]

Olumiant data presented in the above figure is combined data from Phase 2 and 3 placebo controlled studies in RA patients.

Olumiant data presented in above figures is combined data from
Phase 1–3 studies in RA patients. Dose is an average of all exposures.

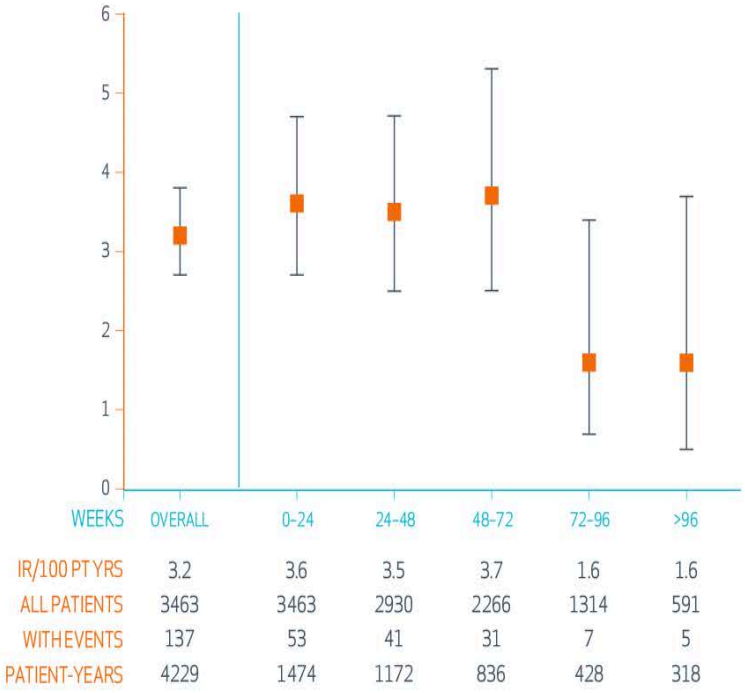
*Incidence rate was calculated as number of patients with event per 100 patient-years of observation time (including follow-up period) with observation time censored at the event start date
CI=confidence interval; IR=incidence rate; PT YRS=patient-years.

Data on file: Olumiant safety information.
Smolen JS, *et al. Ann Rheum Dis* 2016;75:412–3.
Smolen JS, *et al*. Presentation at EULAR, June 8–11, 2016; London, UK.

Olumiant showed no increased risk of serious infections vs placebo or adalimumab + MTX at 24 weeks[1–3]

Serious infection by analysis set[1,2]

Serious infection incidence rates* and 95% CI by time periods – all patients treated with Olumiant in clinical trials[3]



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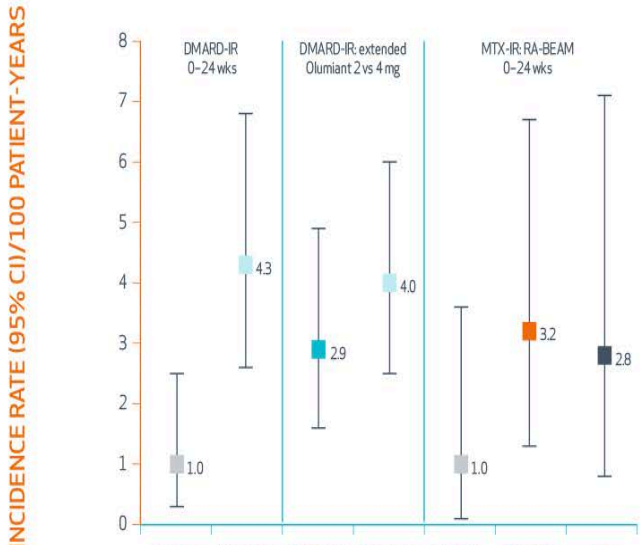
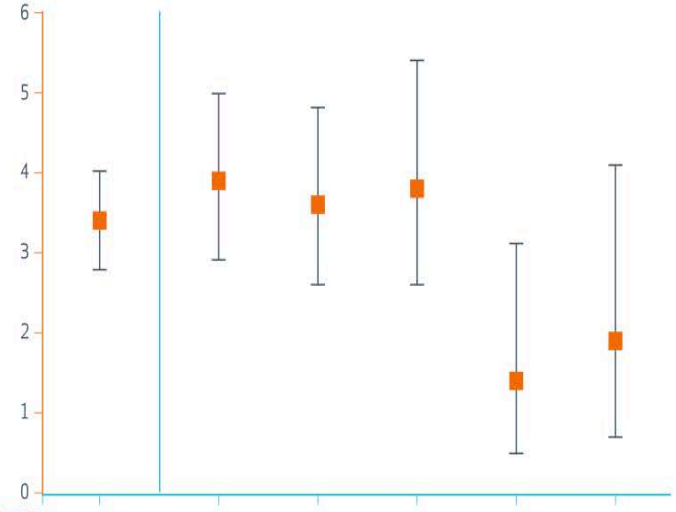
The risk of herpes zoster was increased in patients treated with Olumiant vs placebo[1–3]

Herpes zoster by analysis set[1,2]



	Placebo	Olumiant 4 mg	Olumiant 2 mg	Olumiant 4 mg	Placebo + MTX	Olumiant 4 mg + MTX	ADA + MTX
ALL PATIENTS	1070	997	479	479	488	487	330
WITH EVENTS	4	18	14	22	2	7	4
PATIENT-YEARS	406	417	482	555	202	217	144

Herpes zoster incidence rates* and 95% CI by time periods – all patients treated with Olumiant in clinical trials[3]



WEEKS	OVERALL	0–24	24–48	48–72	72–96	>96
IR/100 PT YRS	3.4	3.9	3.6	3.8	1.4	1.9
ALL PATIENTS	3463	3463	2938	2282	1314	588
WITH EVENTS	143	57	42	32	6	6
PATIENT-YEARS	4241	1476	1178	839	426	322

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Smolen JS, *et al*. Presentation at EULAR, June 8–11, 2016; London, UK.

Effect on Laboratory Values: 0-24 weeks

	RA-BEAM[1] (MTX IR)			RA-BUILD[2] (cDMARD IR)			RA-BEACON[3] (TNFi IR)		
CTCAE grade, n (%)	Pbo[b,c] (N=488)	Bari 4 mg[c] (N=487)	ADA[c] (N=330)	Pbo[b,c] (N=228)	Bari 2 mg[c] (N=229)	Bari 4 mg[c] (N=227)	Pbo (N=176)	Bari 2 mg (N=174)	Bari 4 mg (N=177)
Low hemoglobin count									
Grade 3: ≥6.5 to <8.0 g/dL	1 (<1)	0	1 (<1)	0	1 (<1)	0	0	1 (<1)	0
Low neutrophils count									
Grade 3: <1000 cells/mm^3	0	2 (<1)	0	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	0
Low lymphocytes count									
Grade 3: ≥200 to <500 cells/mm^3	9 (2)	4 (<1)	1 (<1)	2 (<1)	3 (1)	2 (<1)	0	2(1)	0
Elevated ALT									
Grade 3: >5X ULN and ≤20X ULN	5 (1)	3 (<1)	3 (<1)	0	2 (<1)	1 (<1)	0	0	0
Elevated creatinine									
Grade 3: >3X ULN and ≤6X ULN	0	0	0	0	0	2 (<1)	0	0	1(<1)

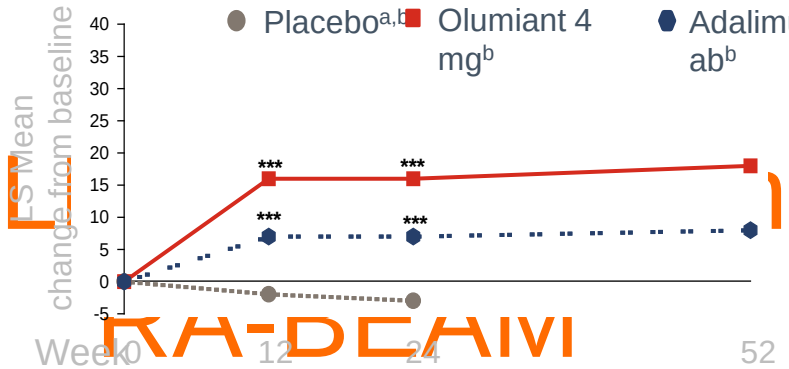
Data in table are n (%) patients, and indicate the worst common terminology criteria for adverse events grade in patients who experienced a treatment-emergent increase in grade at any time during the treatment period, up to the time of rescue. No patient discontinued study drug because of anemia. N = number of patients in the analysis.

Non-rescued PBO patients were switched to bari 4 mg QD at Week 24.

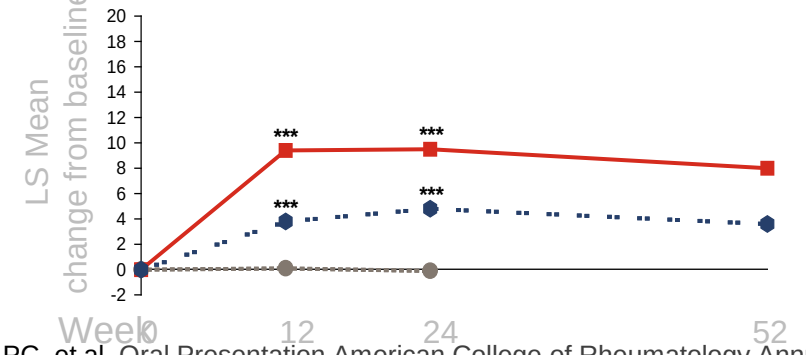
All patients on background MTX.

1. Taylor PC, et al. *N Engl J Med* 2017;376:652-62. Supplementary appendix
2. Dougados M.et al. *Ann Rheum Dis.* ; (Ahead of print). doi:10.1136/annrheumdis-2016-210094. Supplementary appendix
3. Genovese MC, et al. *N Engl J Med* 2016;374:1243-52. Supplementary appendix

LDL (mg/dL)



HDL (mg/dL)



P-values vs. placebo
***p≤.001
**p≤.01
*p≤.05

LDL/HDL ratio (mean)	Placebo (N=487)	Bari (N=484)	ADA (N=330)
Baseline	2.09	2.03	2.03
Week 12	2.04	2.04	2.06
Week 24	2.06	2.07	2.05
Week 52	-	2.12	2.05

[a]Non-rescued PBO patients were switched to bari 4 mg QD at Week 24;

[b]All patients on background MTX

Taylor PC, et al. Oral Presentation American College of Rheumatology Annual Conference, 2015. Baricitinib Versus Placebo or Adalimumab in Patients with Active Rheumatoid Arthritis (RA) and an Inadequate Response to Background Methotrexate Therapy: Results of a Phase 3 Study.

Laboratory Values

Lipids	Increase across parameters; Plateau 12 weeks	• Increase responds to statin. • The effect of these elevations on the cardiovascular system has not been determined - no evident relation with MACE at the time of analysis.
Liver	ALT increase, with cDMARD background	• Most cases of hepatic transaminase elevations were asymptomatic and transient. • Increased similar to those seen with adalimumab. • Pattern and incidence of elevation in ALT/AST remained stable over time.
CPK	Dose-dependent increase	• Most cases were transient and did not require discontinuation. • No confirmed rhabdomyolysis • Elevations observed at 4 weeks and remained stable at higher value thereafter.
Renal	Very small creatinine increase	• Increase at 2 weeks, remained stable thereafter. • May be due to inhibition of creatinine secretion in renal tubules • Estimates of eGFR based on creatinine may be slightly reduced without actual loss of renal function of occurrence of adverse events.

Olumiant (baricitinib) tablets. Summary of Product Characteristics. Eli Lilly and Company Ltd, 2017

Hematology

Hemoglobin[1]

- Hemoglobin < 8 g/dL was reported in less than 1% of patients in clinical trials.

Neutrophils[1, 2]

- Decreases similar to adalimumab.
- No relationship with occurrence of serious infections.

Lymphocytes[1]

- Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L was reported in less than 1% of patients in clinical trials.

Platelets[1]

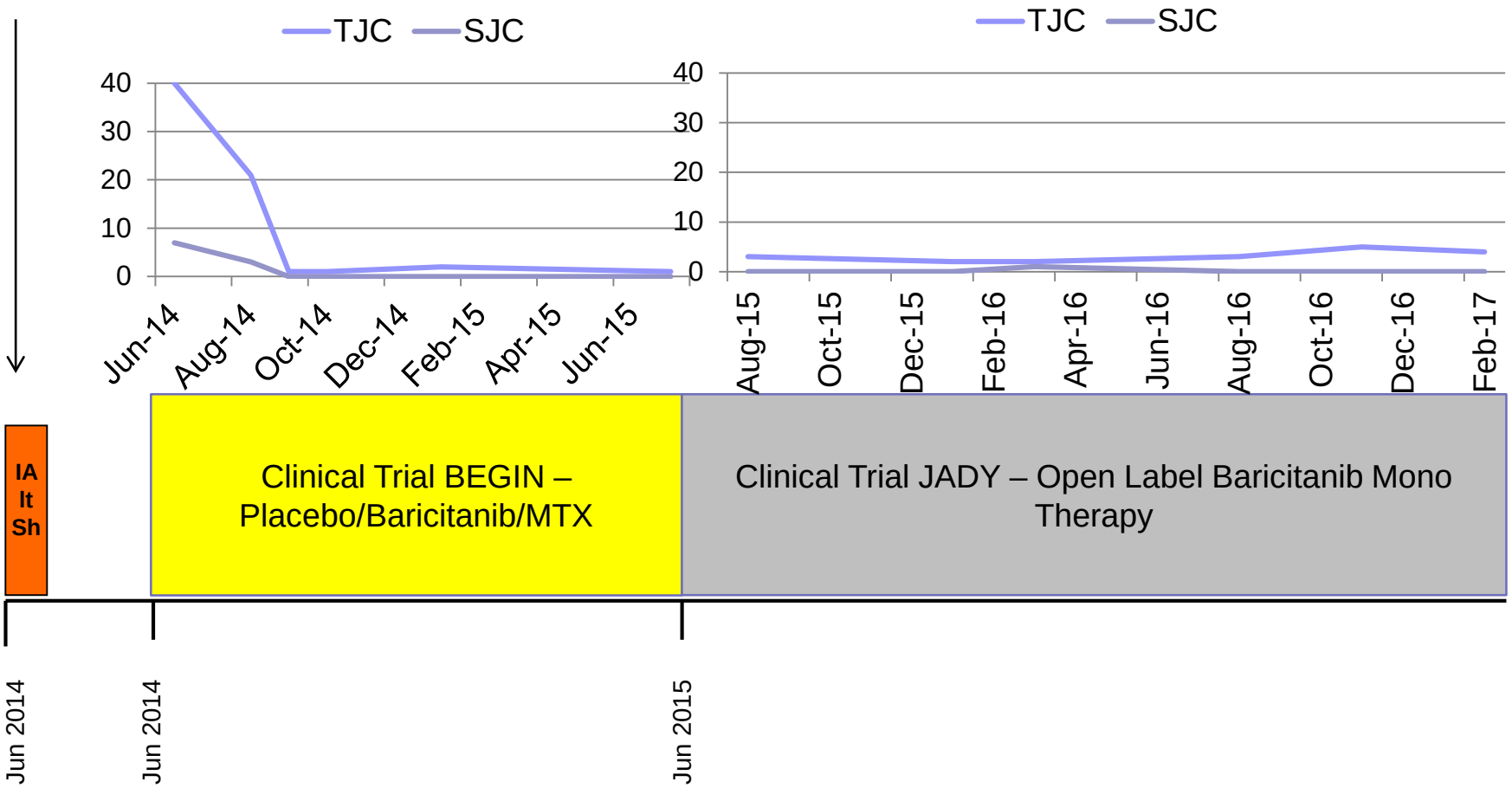
- No association with AE of thrombotic nature.
- Pattern and incidence remained stable at a higher value than baseline over time including in the long term extension study.

1. Olumiant (baricitinib) tablets. Summary of Product Characteristics. Eli Lilly and Company Ltd, 2017
2. Taylor PC, et al. *N Engl J Med* 2017;376:652-62. Supplementary appendix

Practical use of Olumiant

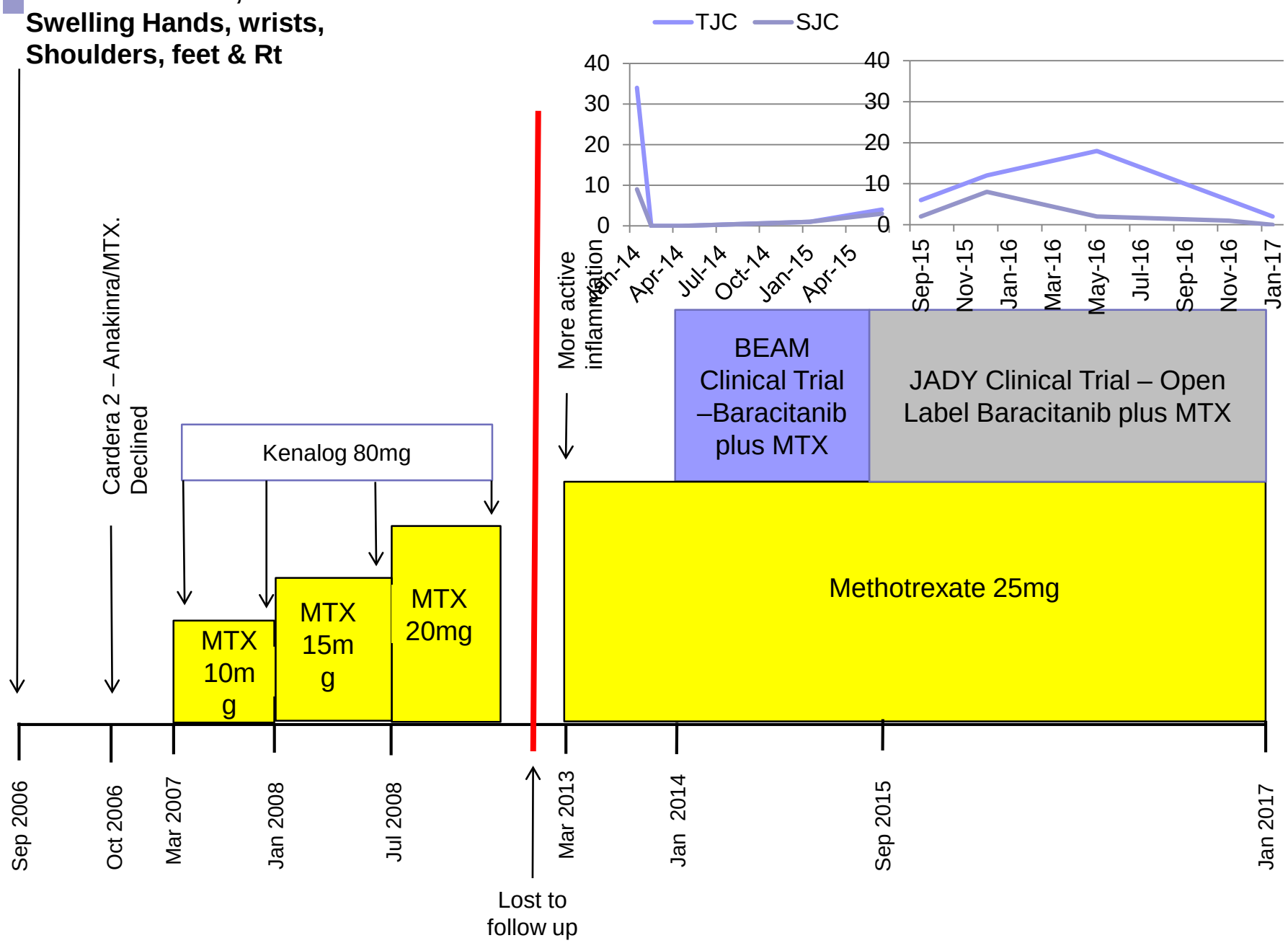
65 ♂ Painter & Decorator, Hx L acromial neuralgia, presents with T & S MCPs & PIPs, EMS > 1hr, Rh F 217.

JR Male, YOB 1948



MM Female, YOB 1942

GP referral- ?RA, Pain & Swelling Hands, wrists, Shoulders, feet & Rt



JD
07/04/45
Civil Servant

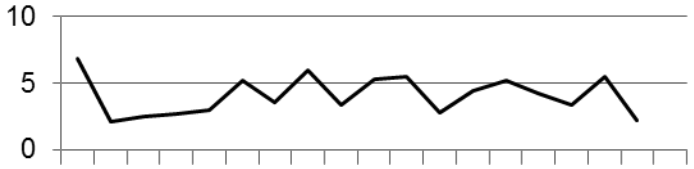
SURGERY

SYNOVECTOMIES
Left Knee
Right Knee
R TKR
L TKR
Wrist Replaced
Trapeziectomy
R Shoulder
MCP
L Shoulder
Forefoot Arthroplasty
R Elbow

STUDIES

SIBSHIP Study
MJR Study
< TRACE RA >

DAS SCORES



Onset Seropositive RA
Symmetrical and Psoriasis

FROBEN AND COPROXAMOL

Penicillamine

GOLD

SZP

MTX 10

15

HUMIRA

ETAN

RITUXIMAB X 3

ABAT

TOC

BARI

3/76 79 82 85 88 91 94 97 2000 2003 2006 2009 2012 2015 2018

Stopped Proteinuria

Stopped Proteinuria

Ineffective

Tolerance

Rash

Psoriasis Worse

Responds in 2 weeks
Improved sicca symptoms
Stopped Drops!

Ineffective