Predicting Responders & Non Responders

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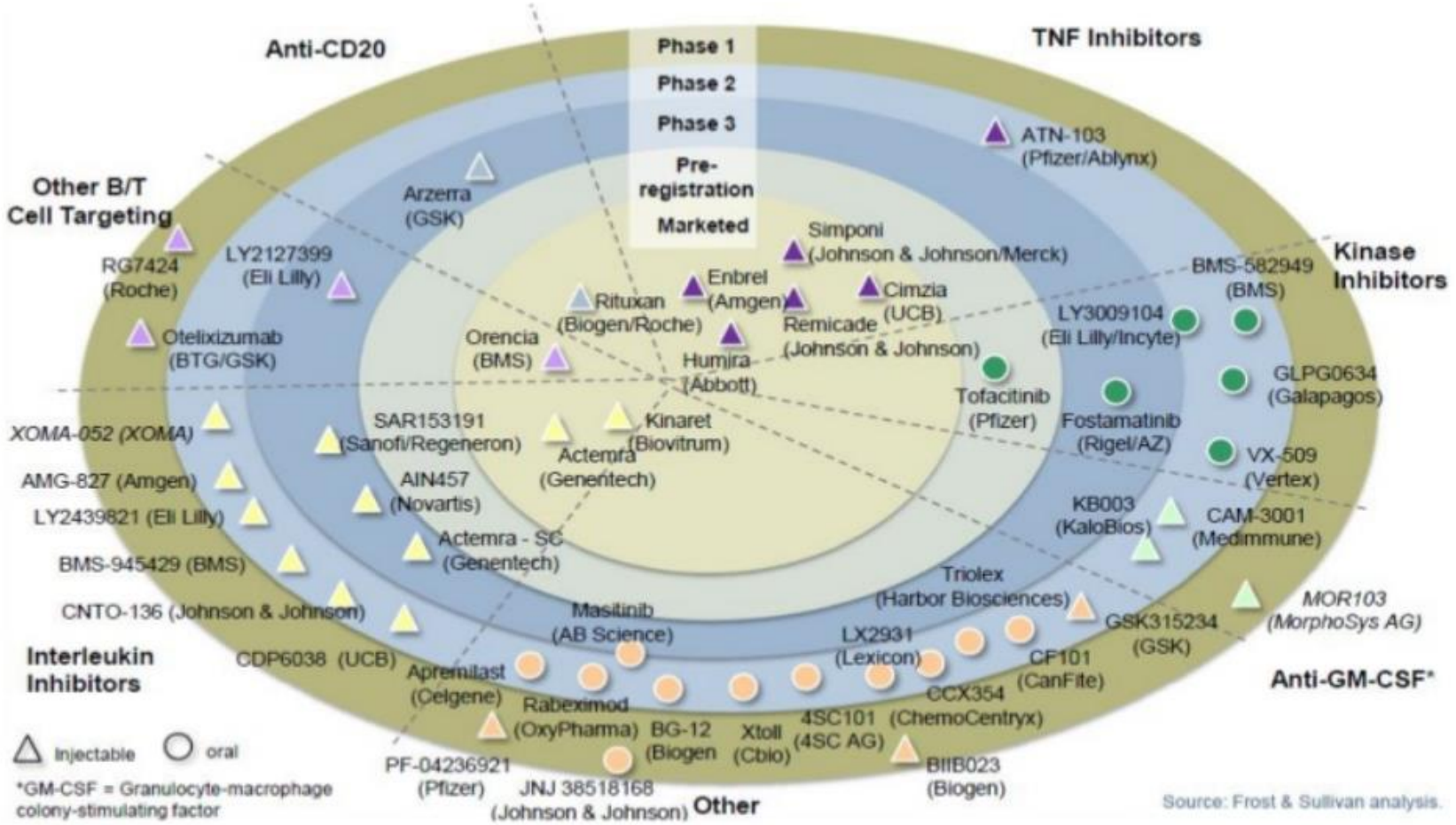
GSK

For the more prevalent Immunology diseases there are multiple treatment options

Biological RA Drugs Under the Development-Competitive Landscape



Year: 2012

Which patient will gain most benefit from which compound?

- Baseline variables?
  - Demographics
  - Disease severity
  - Conmeds
  - Biomarkers
  - PGx
  - Etc.

  - Methodology: subgroup analyses, covariate effects

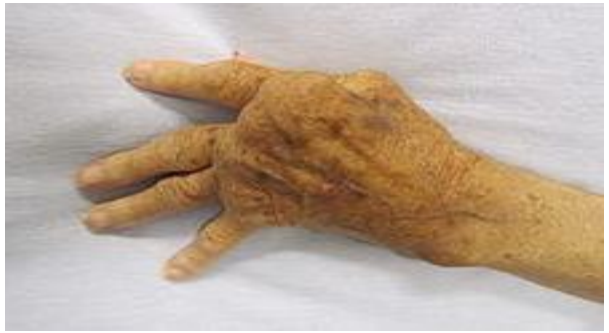
  - Frequently carried out, but not conclusive and very few H2H studies

Give it a try?

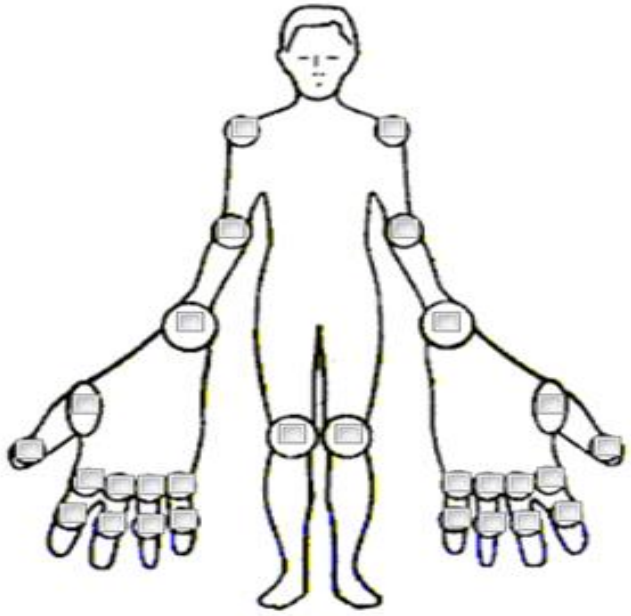
- Working Hypothesis
  - If the medicine doesn't work well in the first few weeks, it probably won't work well in the longer term.
  - How do we best assess that?
    - How well does it need to work in the first weeks?
    - How long do you need to try for?
    - What's the risk?
      - Of stopping when you should have continued.
      - Of continuing when you should have stopped.

Example Background

- Rheumatoid Arthritis
  - Inflammation of joints



- DAS28 Endpoint
  - Continuous score made up of joint counts, inflammatory markers, patient assessment.
  - ≥5.1 indicates active disease
  - ≤3.2 indicates low disease activity (LDA)
  - ≤2.6 remission.

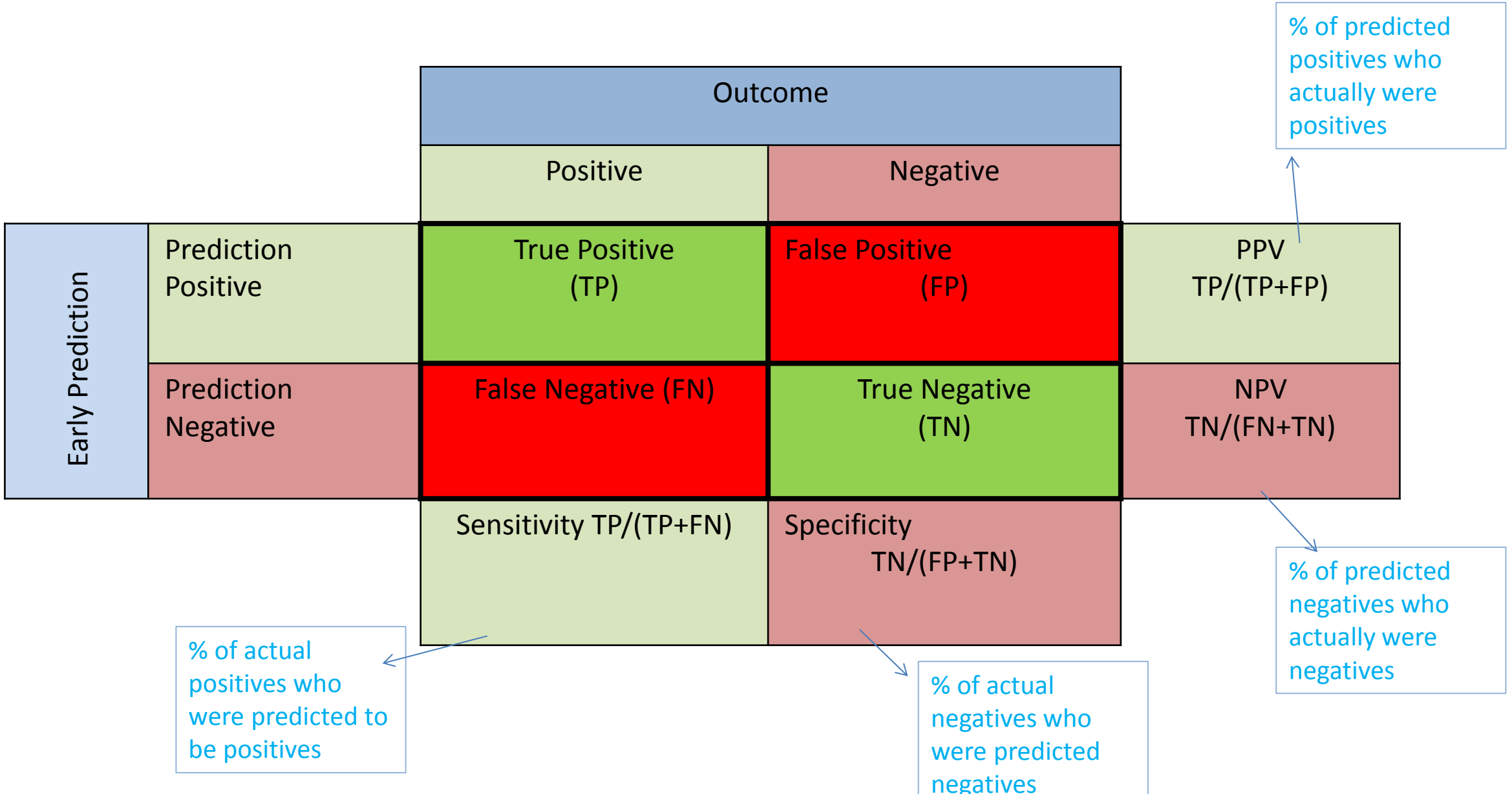


Methodology

- Consider early response like a ‘diagnostic’ test for longer term response/remission.
  - Sensitivity
  - Specificity
  - Positive Predictive Values.
  - Negative Predictive Values
  - False Positive Rate
  - False Negative Rate

Terminology

- Sensitivity
  - Pr(correctly identified as positive).
  - Also called TPR (True Positive Rate)
- Specificity
  - Pr(correctly identified as negative)
  - Equal to 1-FPR (False Positive Rate)
- Positive Predictive Value (PPV)
  - Pr (Being positive if identified as positive)
- Negative Predictive Value (NPV)
  - Pr (Being negative if identified as negative)


Outcome
Positive
Negative
Early Prediction
Prediction Positive
True Positive (TP)
False Positive (FP)
PPV TP/(TP+FP)
Prediction Negative
False Negative (FN)
True Negative (TN)
NPV TN/(FN+TN)
Sensitivity TP/(TP+FN)
Specificity TN/(FP+TN)
% of predicted positives who actually were positives
% of predicted negatives who actually were negatives
% of actual positives who were predicted to be positives
% of actual negatives who were predicted negatives

In example RA endpoint terms

		Low Disease Activity at week 52		
		Yes	No	
Changes in DAS28 at week 4	>=0.6	True Positive (TP)	False Positive (FP)	PPV TP/(TP+FP)
	<0.6	False Negative (FN)	True Negative (TN)	NPV TN/(FN+TN)
		Sensitivity TP/(TP+FN)	Specificity TN/(FP+TN)	

Baricitinib *

		Low Disease Activity at week 24		
		Yes	No	
Changes in DAS28 at week 4	>=0.6	62 (TP)	97 (FP)	159 PPV TP/(TP+FP) = 39%
	<0.6	5 (FN)	31 (TN)	36 NPV TN/FN+TN) =86%
		67 Sensitivity TP/(TP+FN) =93%	128 Specificity TN/(FP+TN) =24%	195

*Kremer et al (2015 ACR abstract)
http://acrabstracts.org/abstract/response-to-baricitinib-at-4-weeks-predicts-response-at-12-and-24-weeks-in-patients-with-rheumatoid-arthritis-results-from-two-phase-3-studies/

Interpretation

- NPV = 86%
  - Exact 95% CI=[70%, 95%]
- PPV = 39%
  - Exact 95% CI= [31%, 47%]
- Misclassification rate = 52%.

- NPV high

  ⇒Few patients with minimal early response(<0.6 improvement in DAS28 at week 4) would reach LDA at week 24.
  - Using this rule, relatively low risk of stopping incorrectly.

- PPV low

  ⇒many patients with early response (≥0.6 improvement in DAS28 at week 4) do not reach LDA at week 24.
  - Using this rule, high risk of continuing incorrectly.
  - Only 24% of non-responders would stop treatment

Are different endpoints better?

Table 2. Predictive Values (%) of Low Disease Activity and Remission After 12 and 24 Weeks of Baricitinib 4 mg Treatment in RA-BUILD[1] and RA-BEACON[2]

Decrease from Baseline to Week 4	LDA (DAS28-ESR ≤ 3.2)		Remission (DAS28-ESR < 2.6)	
	Week 12	Week 24	Week 12	Week 24
RA-BUILD				
DAS28-ESR				
<0.6 (NPV)	92.3	86.1	94.9	91.7
≥0.6 (PPV)	26.8	39.0	11.3	20.1
CDAI				
<6 (NPV)	95.1	94.6	97.0	96.7
≥6 (PPV)	26.5	40.9	10.8	20.1
RA-BEACON				
DAS28-ESR				
<0.6 (NPV)	96.8	96.4	96.8	96.4
≥0.6 (PPV)	15.9	23.2	7.1	12.0
CDAI				
<6 (NPV)	95.1	94.6	95.1	94.6
≥6 (PPV)	15.2	21.6	6.4	11.2

NPV=negative predictive value; PPV=positive predictive value

[1]Dougados M et al, Ann Rheum Dis 2015;74(S2):79
[2]Genovese M et al, Ann Rheum Dis 2015;74(S2):75-76

Kremer et al (2015 ACR abstract)
http://acrabstracts.org/abstract/response-to-baricitinib-at-4-weeks-predicts-response-at-12-and-24-weeks-in-patients-with-rheumatoid-arthritis-results-from-two-phase-3-studies/

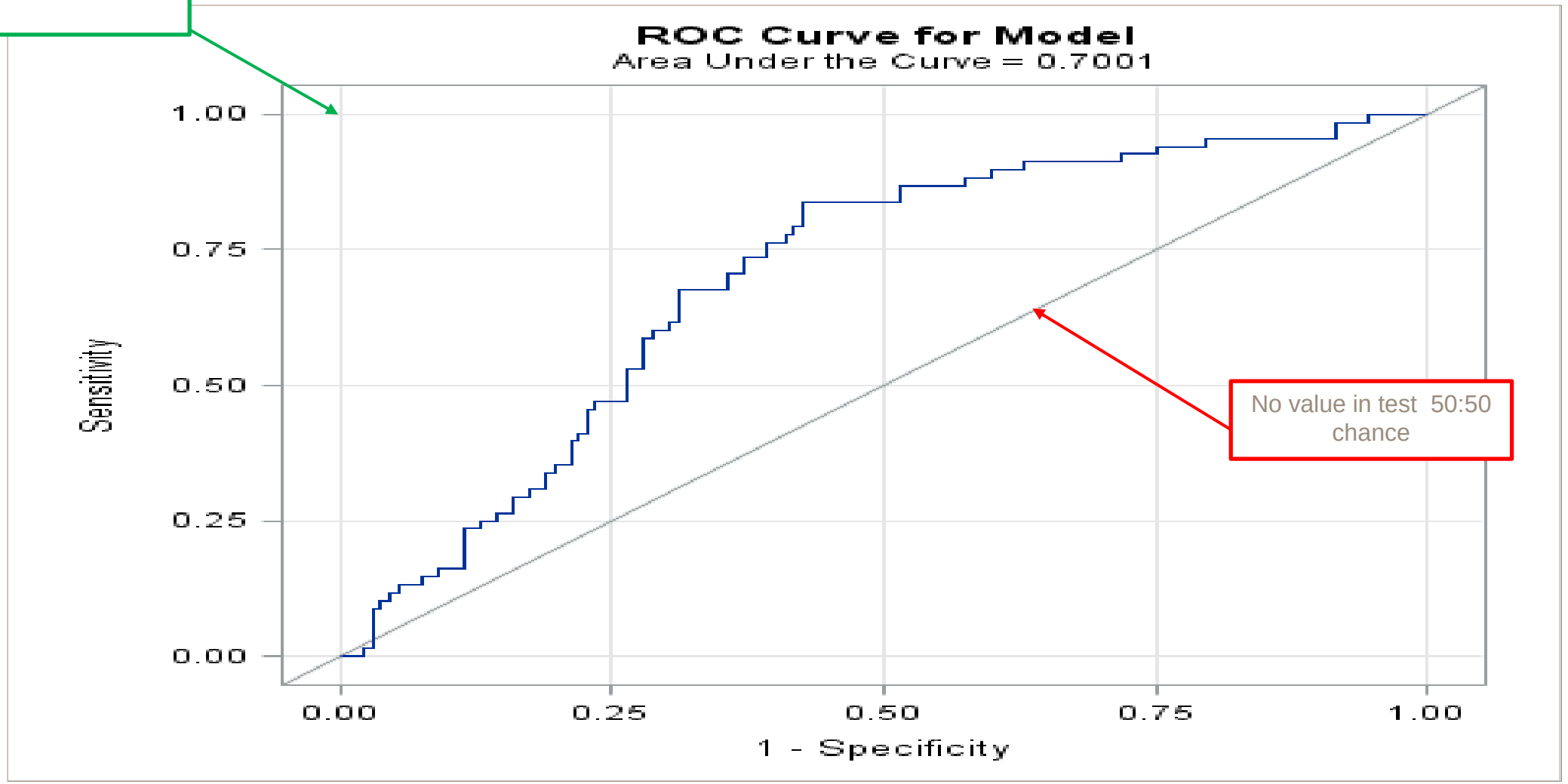
Are different cut points better?

- **Receiver Operating Characteristic Curve** (ROC curve.)
  - Plot of the TPR (sensitivity) vs the FPR (1-specifity) for all different possible cutpoints of the ‘diagnostic’.
  - Shows the trade-off (increase in one is accompanied by decrease in the other)

Simulated Example

		Low Disease Activity at week 24		
		Yes	No	
Changes in DAS28 at week 4	>=0.6	57 (TP)	58 (FP)	115 PPV TP/(TP+FP) = 50%
	<0.6	11 (FN)	74 (TN)	85 NPV TN/FN+TN) = 87%
		68 Sensitivity TP/(TP+FN) =84%	132 Specificity TN/(FP+TN) =56%	200

Simulated Example RoC Curve



'Best Point' assuming equal weight of FPR/TPR, gives DAS28 cut of 0.64

Example from the Literature
(Aletaha et al, Arthritis & Rheumatism 2007)

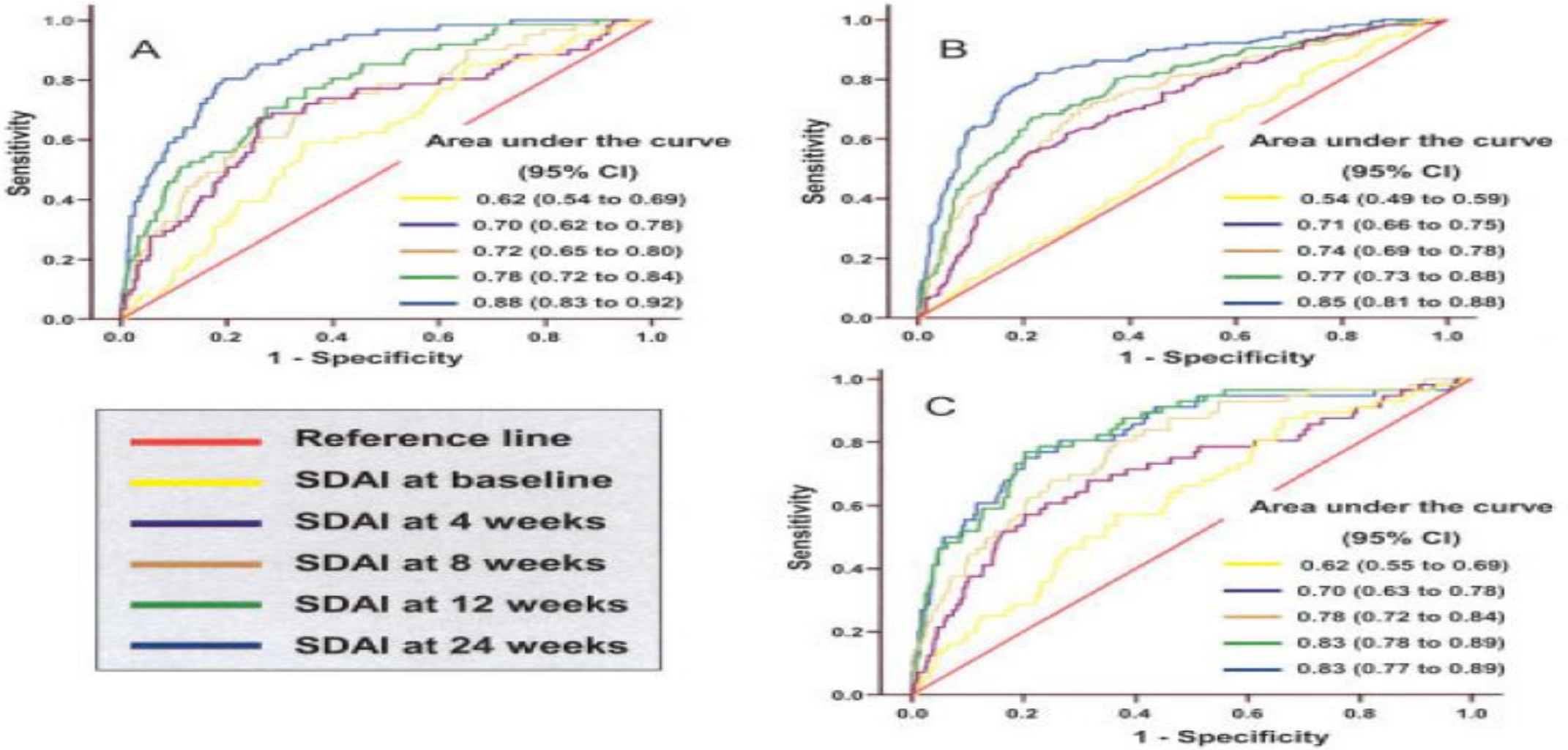
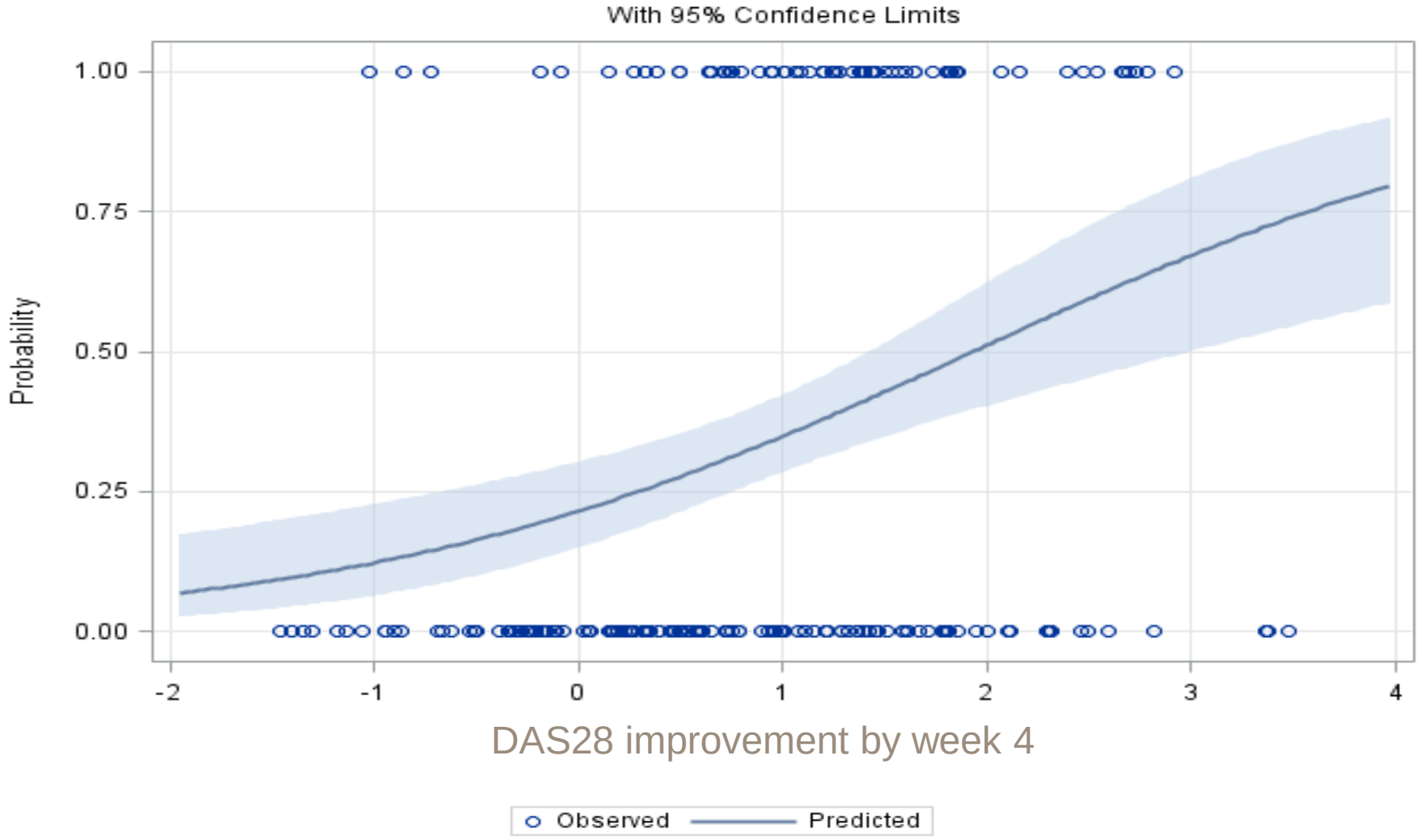


Figure 1. Receiver operating characteristic (ROC) curve analyses for achievement of remission at 12 months in patients with early rheumatoid arthritis (RA) (analysis cohort) and in patients with late RA (validation cohort). **A, Patients with early RA receiving MTX (n 462). B, Patients** with early RA receiving TNF inhibitor plus MTX (n 589). **C, All patients with late RA regardless of treatment (n 763). The increasing area** under the ROC curve (AUC) corresponds to a higher diagnostic test yield; an AUC of 0.5 is a useless test, yielding 1 misclassified patient per 1 correctly classified patient. 95% CI 95% confidence interval; SDAI Simplified Disease Activity Index.

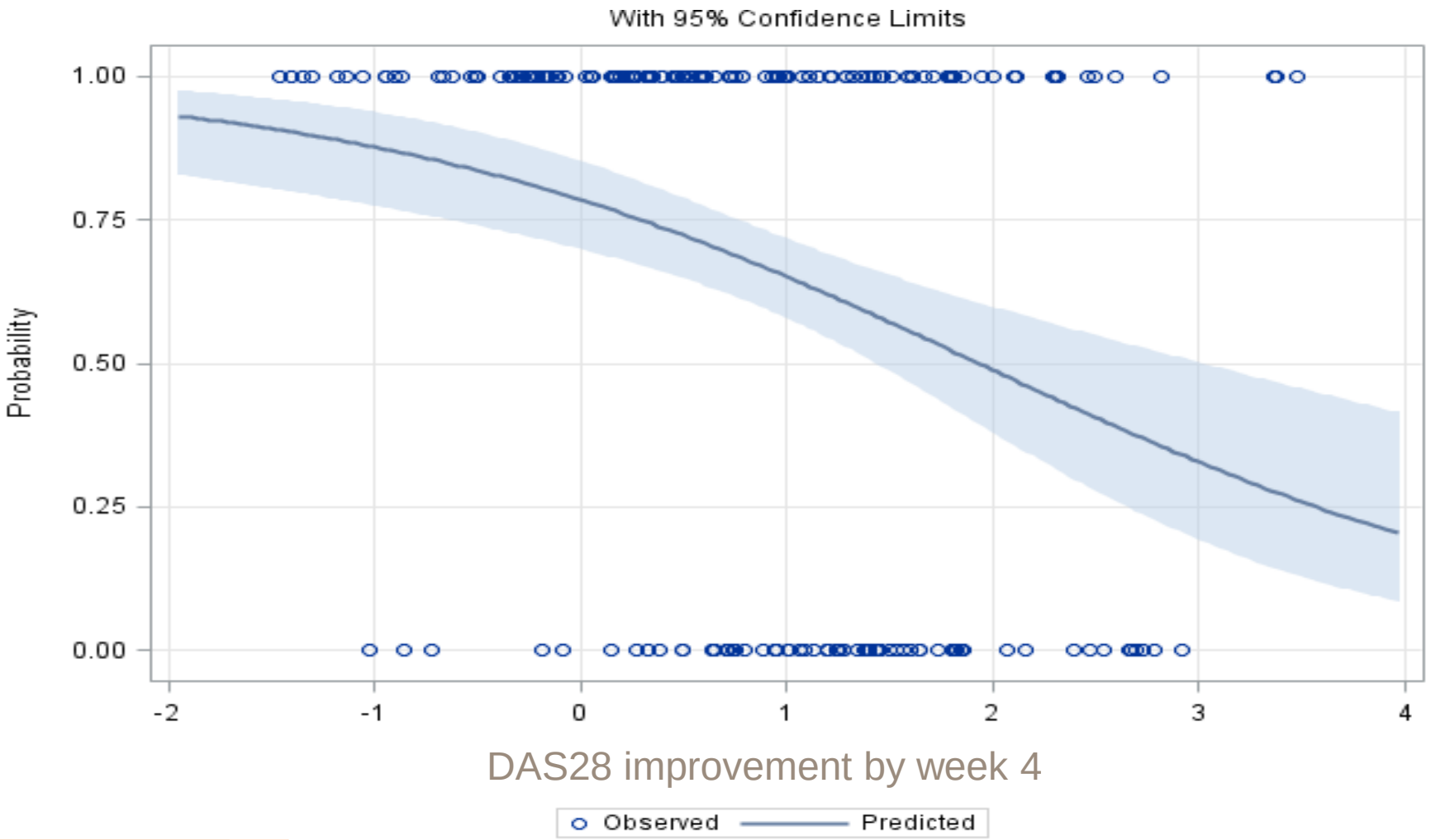
Logistic model

Predicted probabilities for LDA at week 24 by 4 week DAS improvement

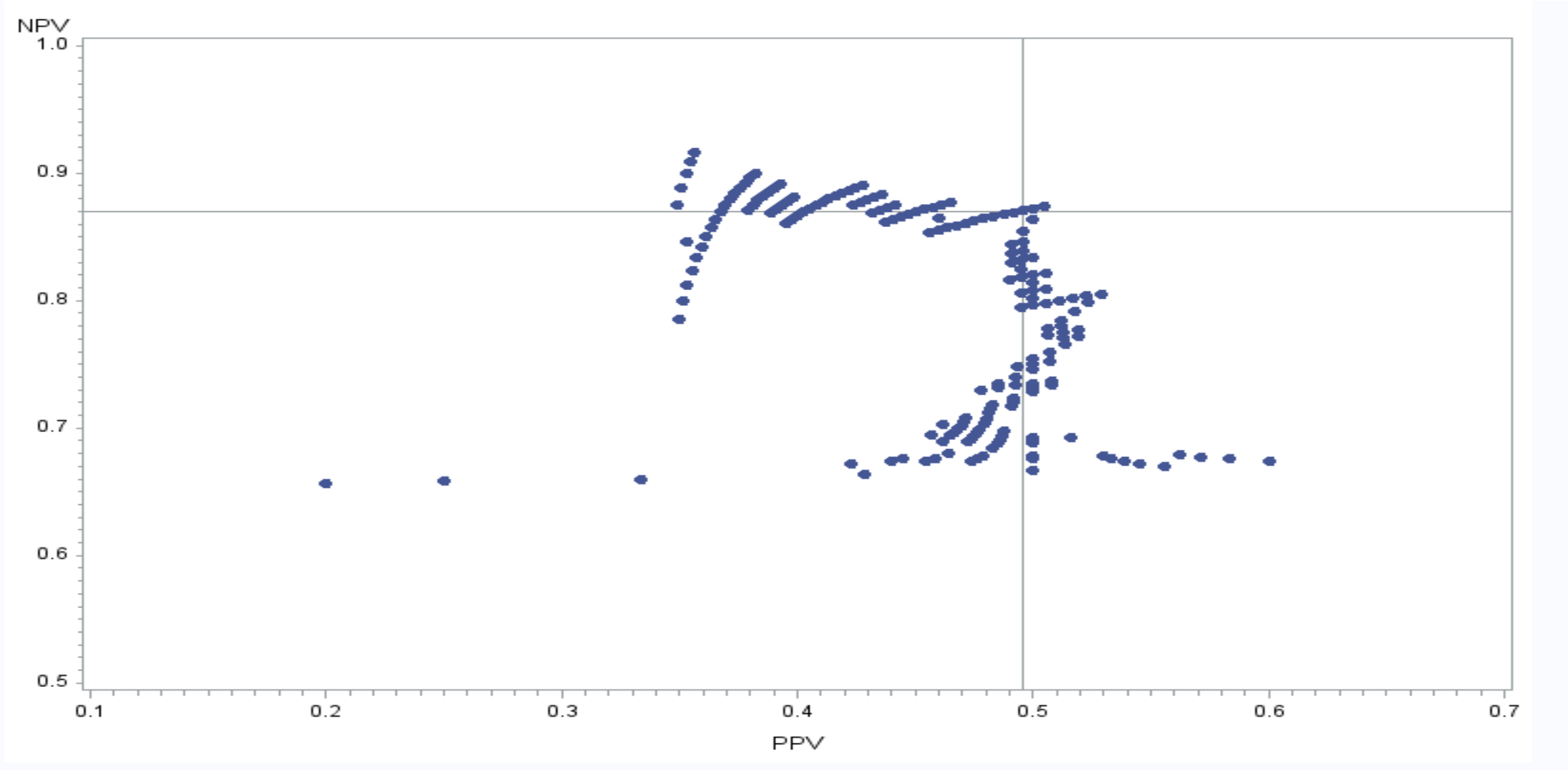


Logistic model

Predicted probabilities for NO LDA at week 24 by DAS improvement



NPV vs PPV



NOTE: 11 obs had missing values.

Lines represent the 0.6 DAS cut point used.

One Step Further

- CART analysis
  - Classification and Regression Trees
  - Optimal recursive splitting of patients into subgroups based on maximum predictive accuracy
    - At each level the patients are split into two group that are most different with respect to the outcome.

- Can consider multiple endpoints, baseline characteristics and timepoints.

Example from literature

Curtis et al Ann Rheum dis 2012.

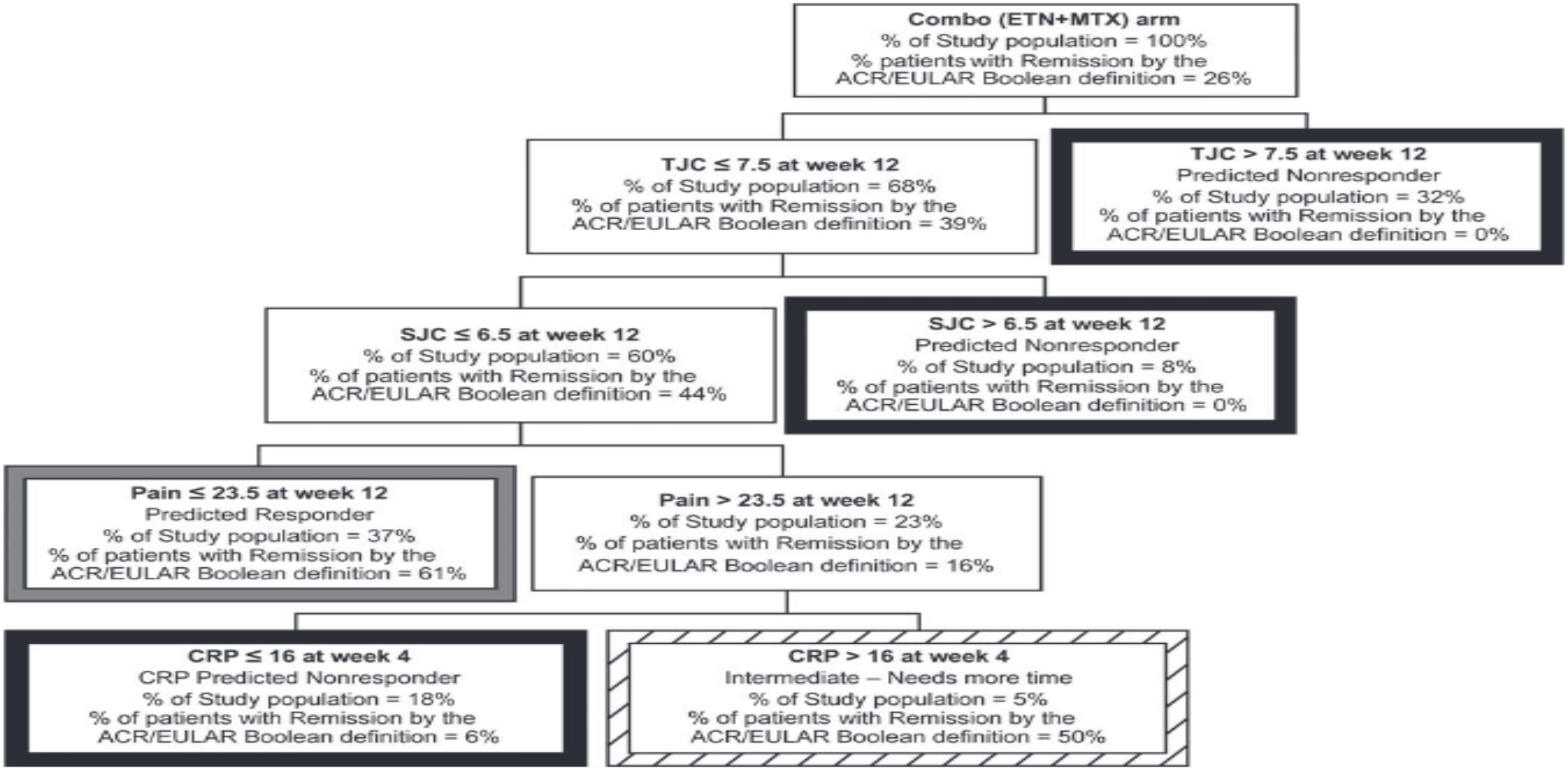


Figure 2 CART decision tree in patients receiving etanercept plus methotrexate with ACR/EULAR remission at 52 or 48 weeks as the outcome variable. Tree nodes of predicted responders, non-responders and patients with indeterminate outcomes are identified by borders of grey, black and diagonal patterns, respectively. ACR, American College of Rheumatology; CART, classification and regression tree; CRP, C-reactive protein (in mg/l); ETN, etanercept; EULAR, European League Against Rheumatism; MTX, methotrexate; SJC, swollen joint count; TJC, tender joint count.

Overall summary of CART output*

		Remission at week 48-52		
		Yes	No	
Prediction from CART analysis	Carry on	48 (TP)	34 (FP)	81 PPV TP/(TP+FP) = 59%
	Stop (black boxes)	2 (FN)	110 (TN)	112 NPV TN/FN+TN)= 98%
		50 Sensitivity TP/(TP+FN) =96%	143 Specificity TN/(FP+TN) =77%	193

**calculated numbers are based on %'s given in paper, so may be slightly out due to rounding.*

Compare to 2 level tree only?*

		Remission at week 48-52		
		Yes	No	
Prediction from CART analysis	Carry on	50 (TP)	66 (FP)	116 PPV TP/(TP+FP) = 43%
	Stop (black boxes)	0 (FN)	77 (TN)	77 NPV TN/FN+TN)= 100%
		50 Sensitivity TP/(TP+FN) =100%	143 Specificity TN/(FP+TN) =54%	193

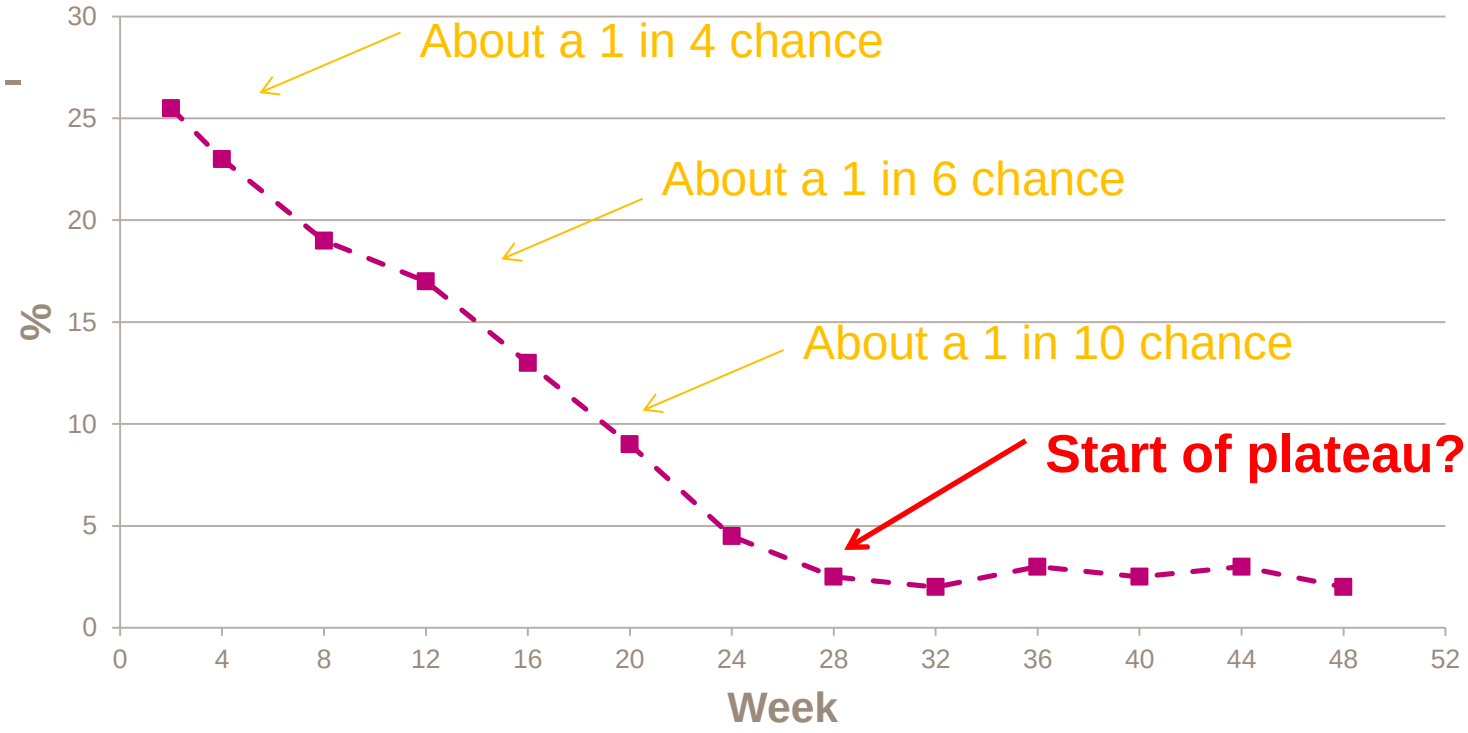
**calculated numbers are based on %'s given in paper, so may be slightly out due to rounding.*

CART approach

- Improvement in accuracy over single DAS28 approach.
- However, complex to generate and to use
  - Especially across multiple time points
  - Consider whether extra steps are worthwhile

Consider Conditional Probabilities to Optimise Duration?

- E.g. Probability of future Remission conditioned on non-response at all timepoints before?



Discussion Points

- The trade off
  - should false positive and false negatives be considered equally?
- Handling missing data
- Different endpoints and timepoints for different compounds.
- Lower hurdles endpoints
  - And therefore higher overall response rates
- Different rules for different patient populations.
- Utility for dose escalation/reduction designs.
- Replication, and potential for labelling.