



Combined Immunosuppression and Radiotherapy in Thyroid Eye Disease CIRTED

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**On behalf of the CIRTED investigators
ABCD Conference 2018**

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You wait ages then....

Articles

Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2 × 2 factorial, double-blind, randomised controlled trial



Rathie Rajendram*, Peter N Taylor*, Victoria J Wilson, Nicola Harris, Olivia C Morris, Marjorie Tomlinson, Sue Yarrow, Helen Garrott, Helen M Herbert, Andrew D Dick, Anne Cook, Rao Gattamaneni, Rajni Jain, Jane Olver, Steven J Hurel, Fion Bremner, Suzannah R Drummond, Ewan Kemp, Diana M Ritchie, Nichola Rumsey, Daniel Morris, Carol Lane, Nachi Palaniappan, Chunhe Li, Julie Pell, Robert Hills, Daniel G Ezra, Mike J Potts, Sue Jackson, Geoffrey E Rose, Nicholas Plowman, Caty Bunce, Jimmy M Uddin†, Richard W J Leef, Colin M Dayan

Articles

Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial



George J Kahaly, Michaela Riedl, Jochem König, Susanne Pitz, Katharina Ponto, Tanja Diana, Elena Kampmann, Elisa Kolbe, Anja Eckstein, Lars C Moeller, Dagmar Führer, Mario Salvi, Nicola Curro, Irene Campi, Danila Covelli, Marenza Leo, Michele Marinò, Francesca Menconi, Claudio Marcocci, Luigi Bartalena, Petros Perros, Wilmar M Wiersinga, for the European Group on Graves' Orbitopathy (EUGOGO)*

Summary

Background European guidelines recommend intravenous methylprednisolone as first-line treatment for active and

Lancet Diabetes Endocrinol 2018

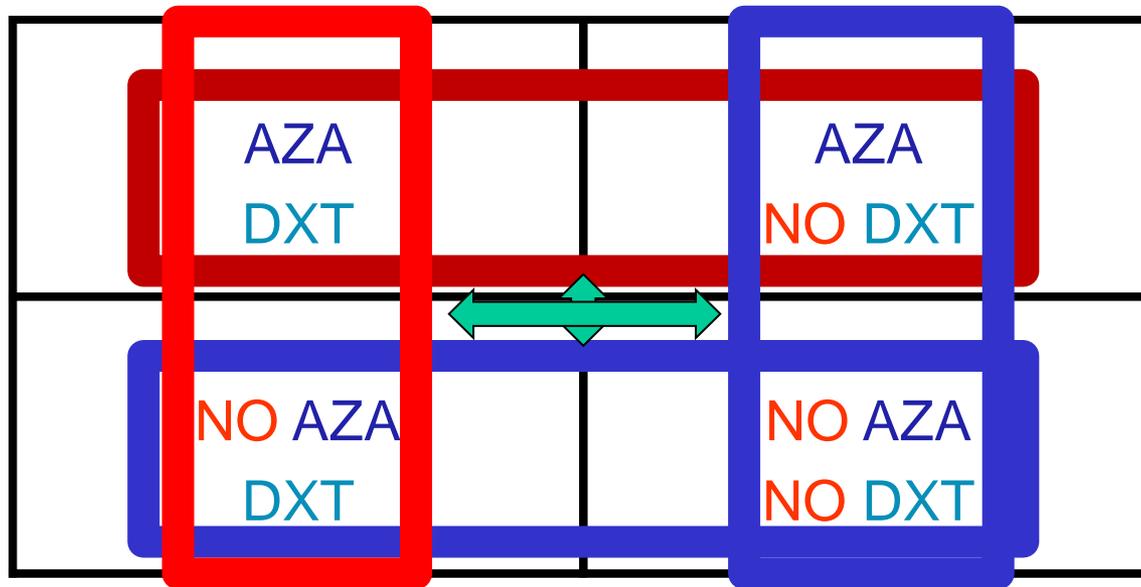
- **Thyroid Eye Disease results in substantial visual dysfunction and psychological morbidity.**
- **Current evidence is conflicting regarding orbital radiotherapy and anti-proliferative immunosuppression.**
- **Furthermore, little is known about clinical outcomes more than 24 weeks after initiating these interventions.**

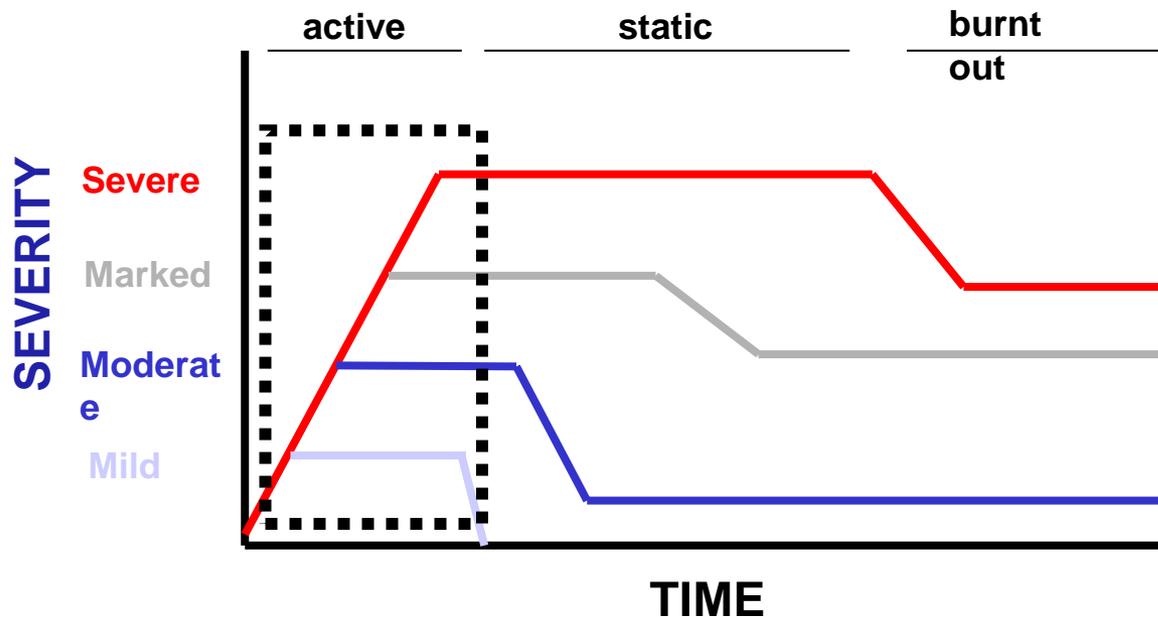


Aims + Methods

- **Undertook a masked factorial randomised control trial.**
- **To assess long-term benefit of low-cost immunosuppression and orbital radiotherapy in the context of concomitant steroid treatment.**
- **Recruited 126 patients.**

FACTORIAL DESIGN





Rundle F, Wilson C. (1945) *Clin Sci*; 5:177-194.

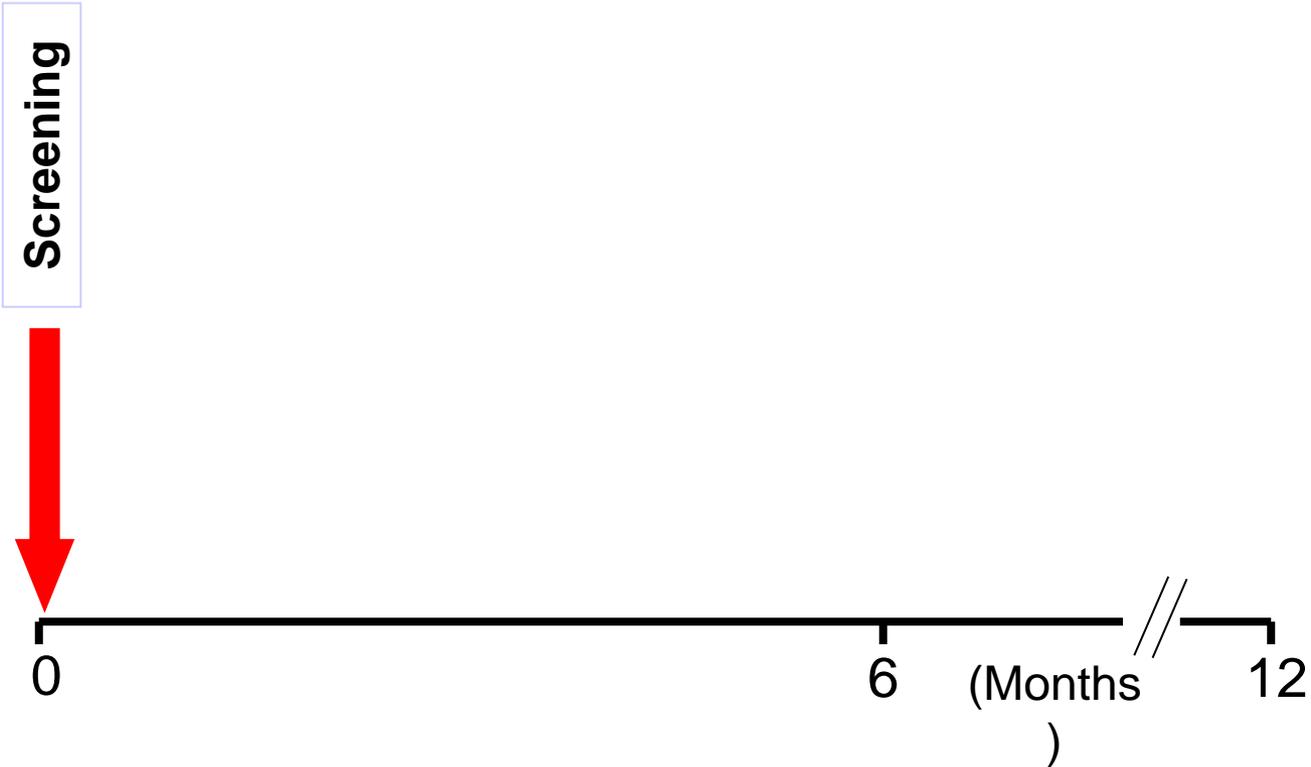
Key Inclusion

CAS ≥ 4 worst eye

OR if less than 6 months duration

**CAS ≥ 2 with a history of proptosis/
motility restriction**

Week - 4



Week - 2

Enrolment



**Start
Prednisolone**

TIME AFTER ENROLMENT	PREDNISOLONE DOSE (mg per day)
1 – 3 days	80
4 – 7 days	60
1 – 2 weeks	40
3 – 6 weeks	30
7 – 10 weeks	20
11 – 14 weeks	15
15 – 18 weeks	10
19 – 20 weeks	7.5
21 – 22 weeks	5
23 – 24 weeks	2.5



Week 0

Randomise

Start Trial Rx

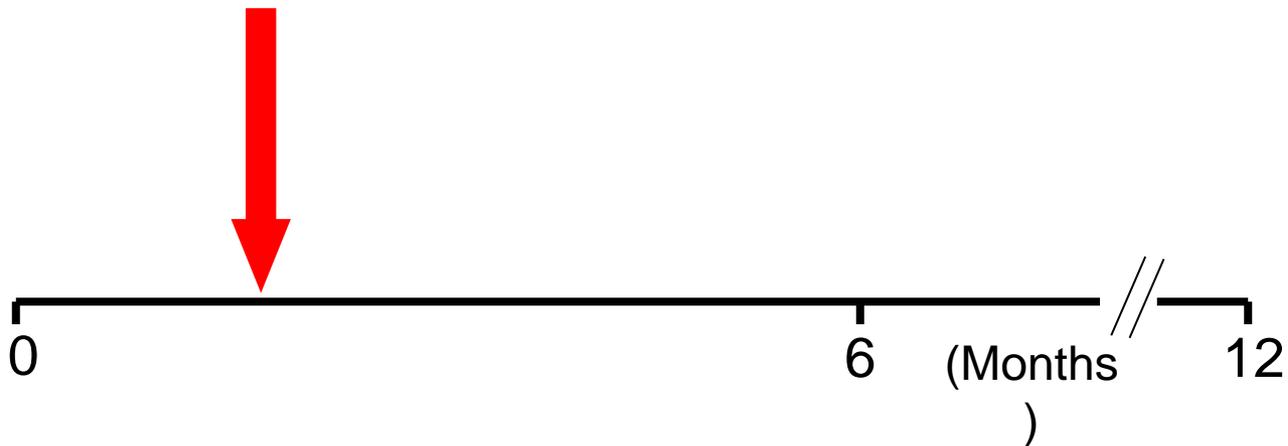
BODY MASS	AZATHIOPRINE STARTING DOSE (Once Daily)	NUMBER OF AZATHIOPRINE 50mg TABLETS (per day)	NUMBER OF PLACEBO TABLETS (per day)
< 50 kg	100 mg	2	2
50 – 79kg	150 mg	3	3
≥ 80 kg	200 mg	4	4



Week 5

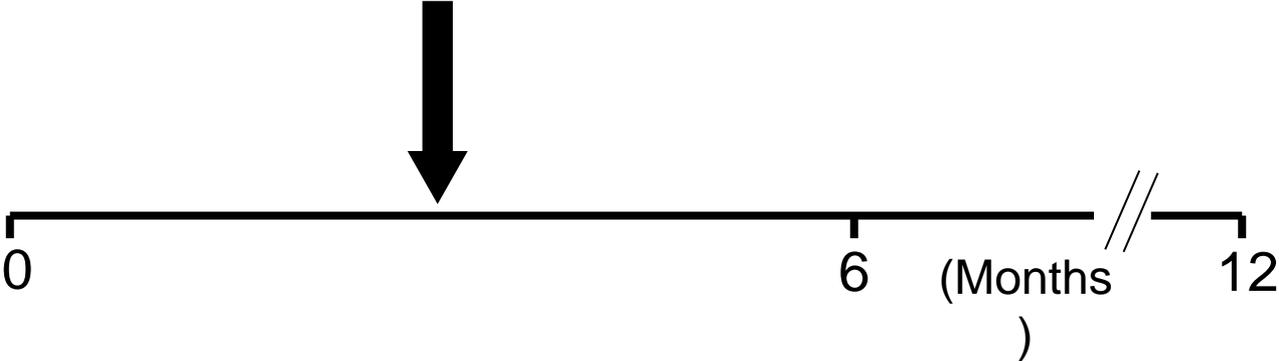
Radiotherap
y

Sham or Active Rx:
12 sessions over 2 – 3 weeks



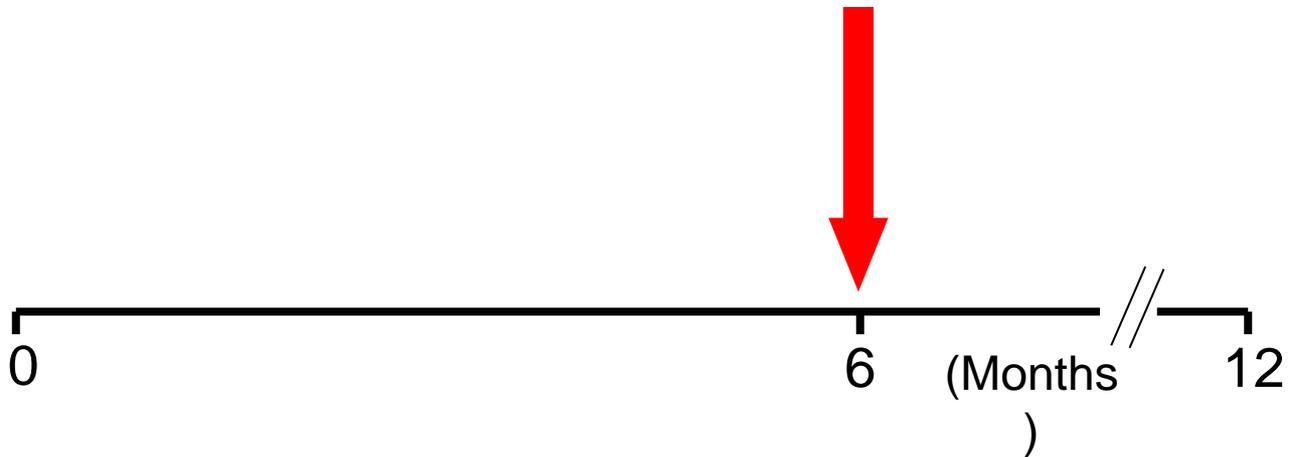
Week 12

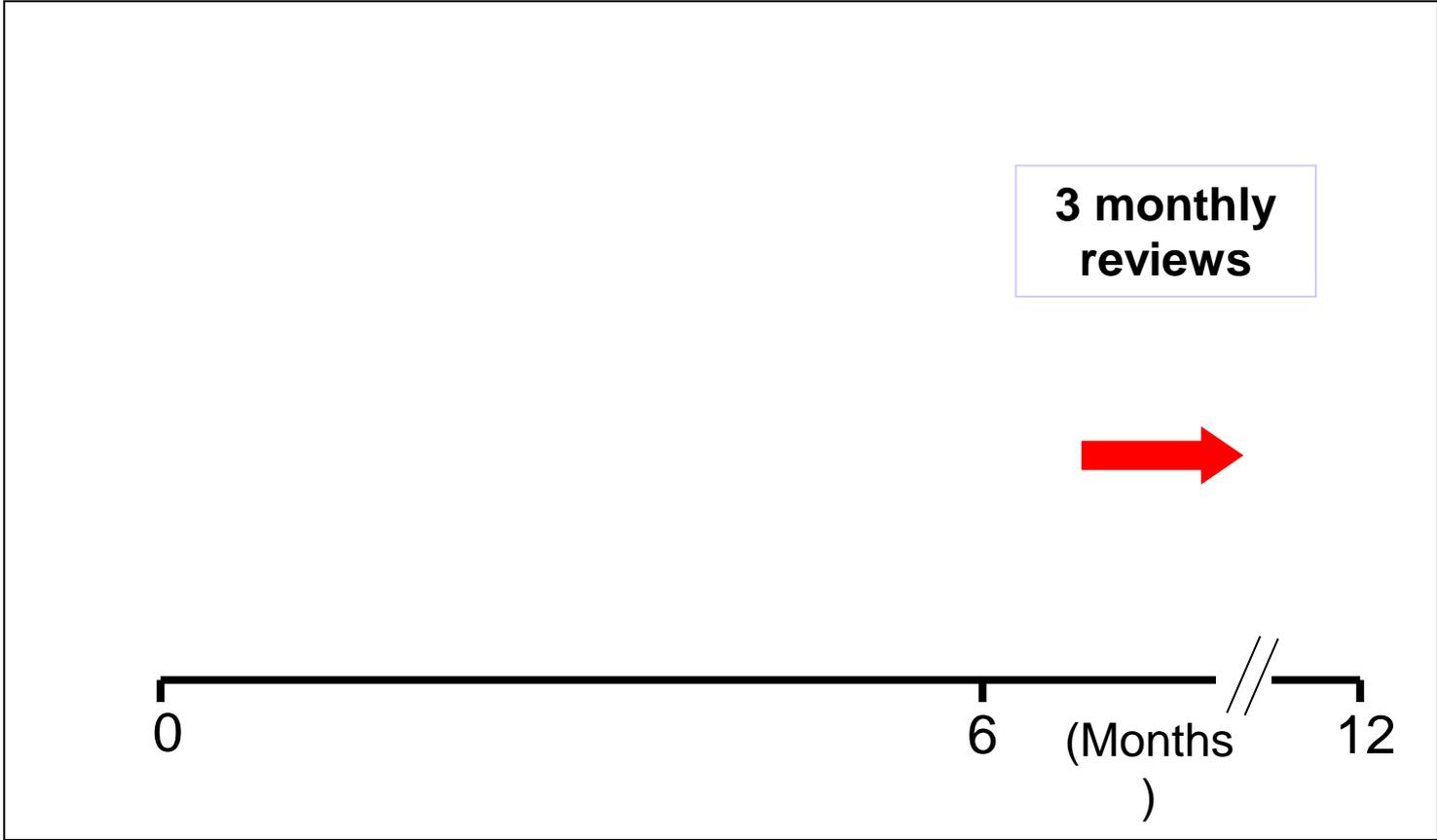
**Short-term
Outcome
Assessment
t**



Week 24

**Stop
Steroids**





Week 48

Trial Exit

Long-term
Outcome
Assessment
t



Major Criteria

- An improvement of ≥ 1 grade in diplopia score
- An improvement of $> 8^\circ$ of eye movement in any direction
- A reduction of ≥ 2 mm in proptosis

Minor Criteria

- A reduction of ≥ 2 mm in lid aperture
- An improvement of ≥ 1 grade in soft tissue involvement
- An improvement in best-corrected visual acuity of ≥ 1 line on the Snellen chart
- Subjective improvement

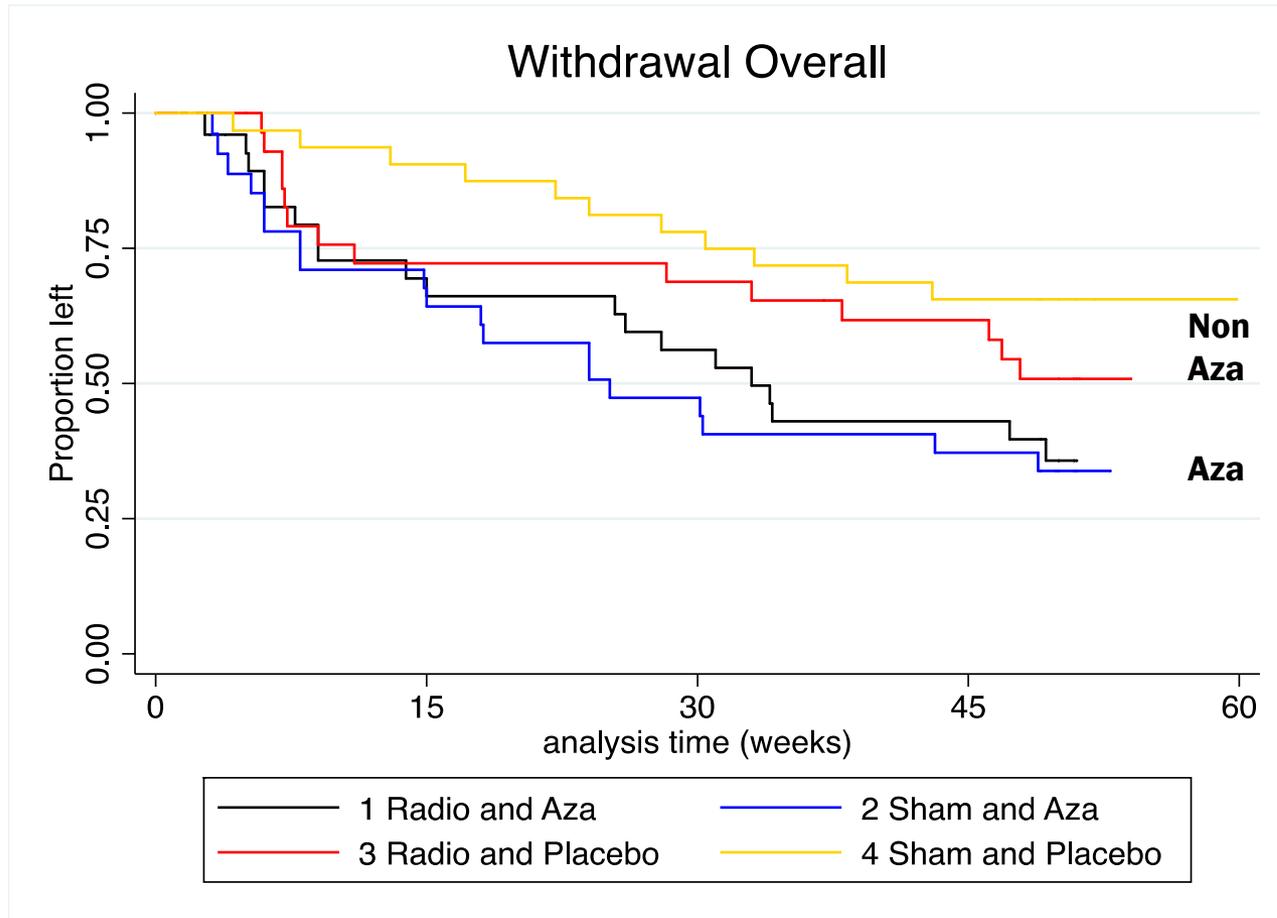
Mourits MP *et al.* (2000) *Lancet*, 355: 1505-1509

Marcocci C *et al.* (2001) *J Clin Endocrinol Metab*, 86(8): 3562-7

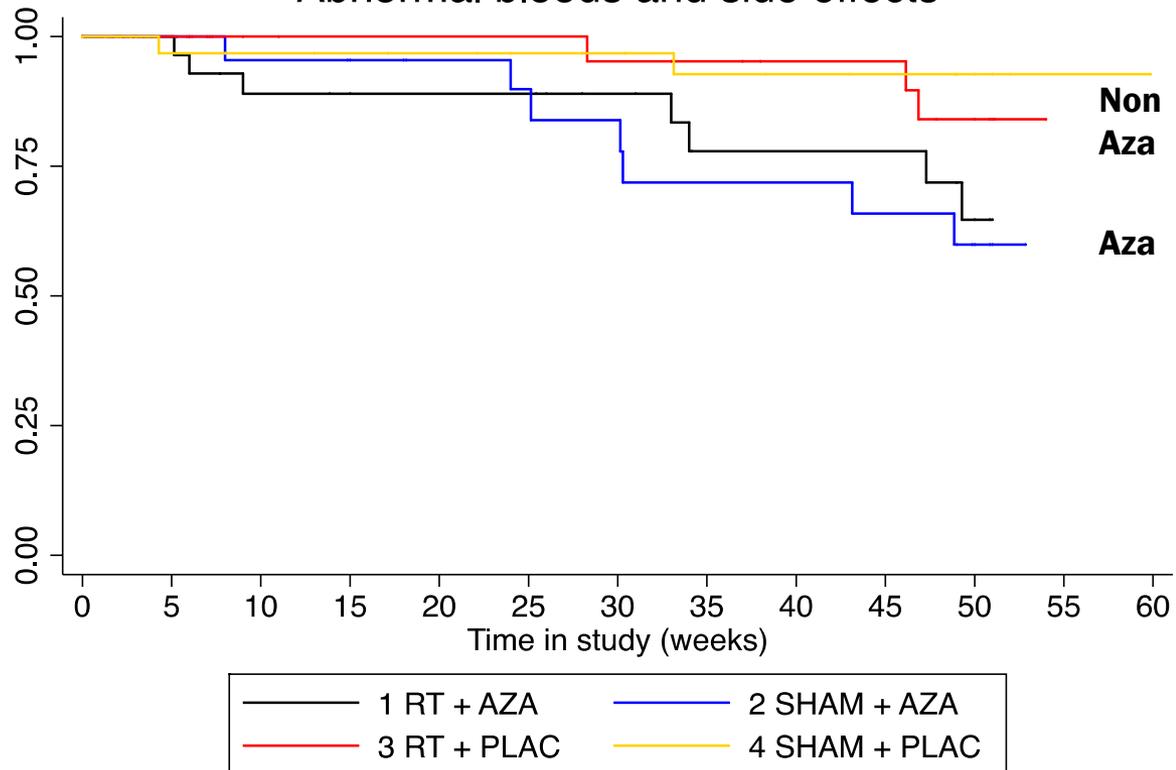
Prummel MF *et al.* (2004) *J Clin Endocrinol Metab*, 89: 15-20

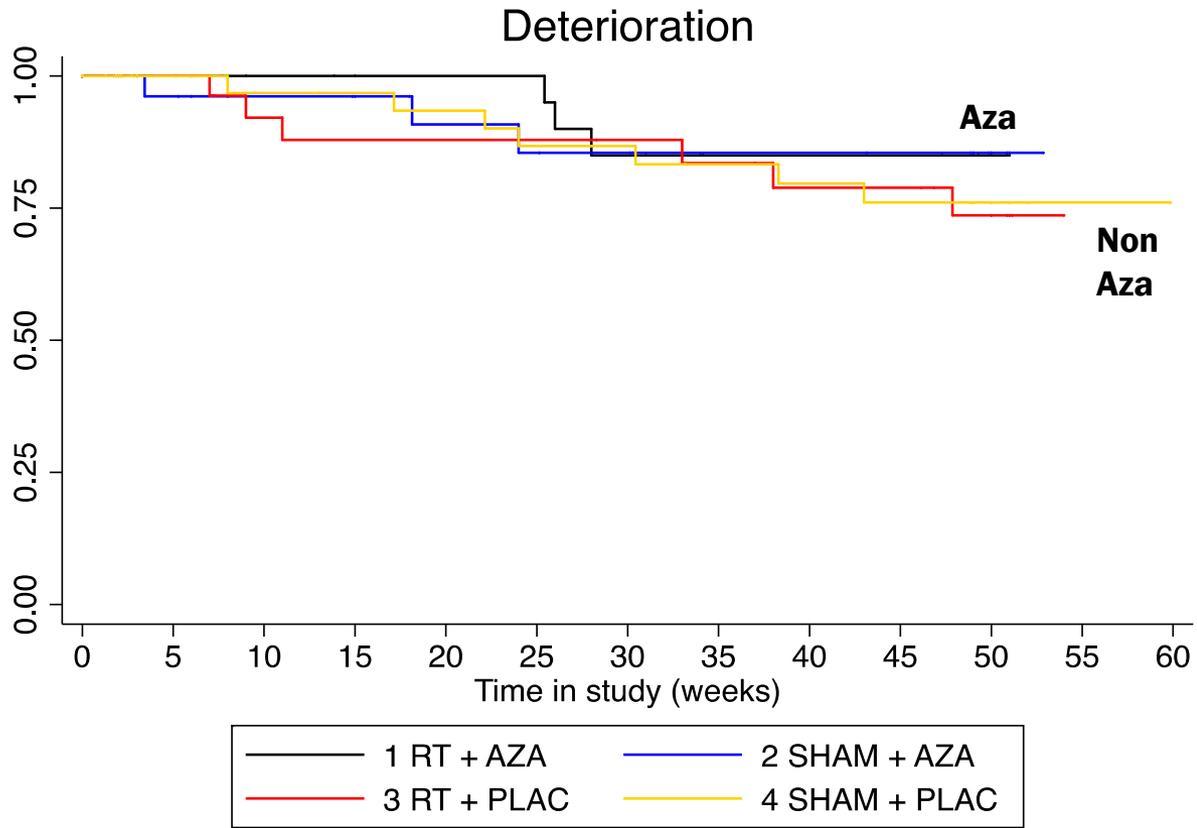
Results

**MOST
CAME
BACK !**

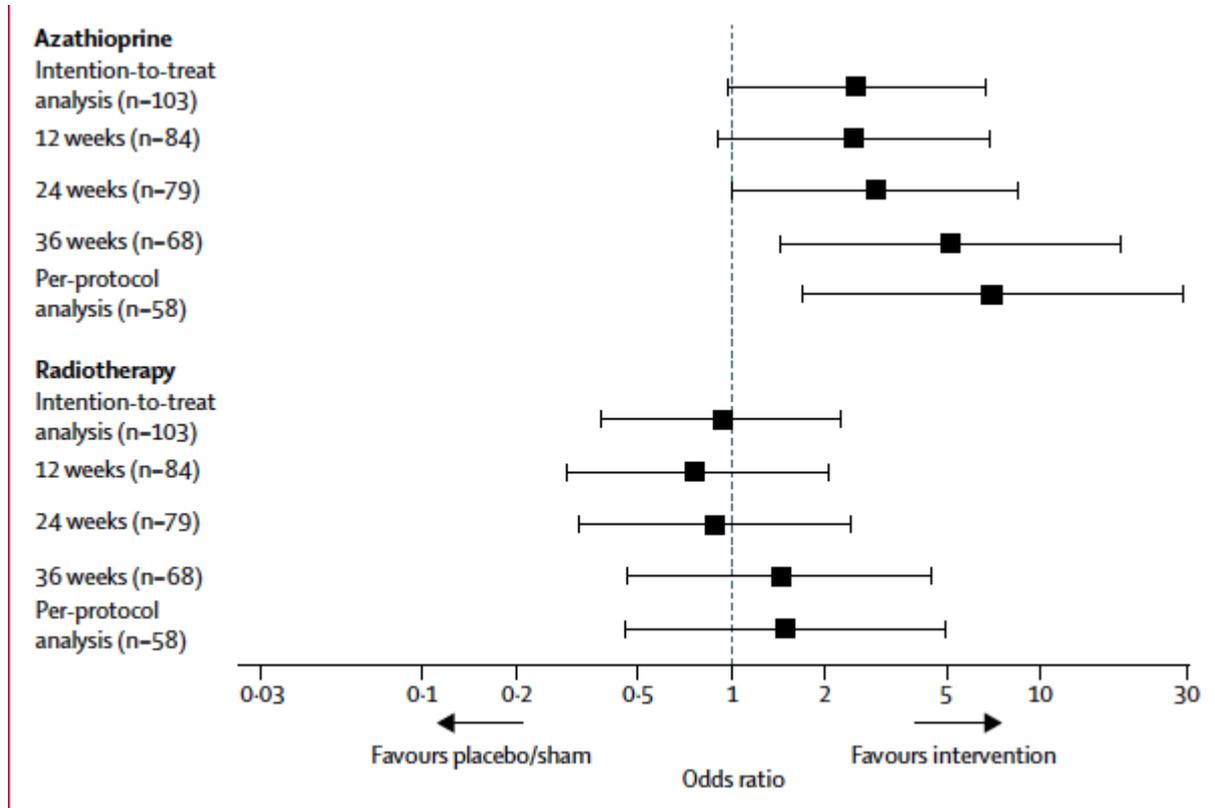


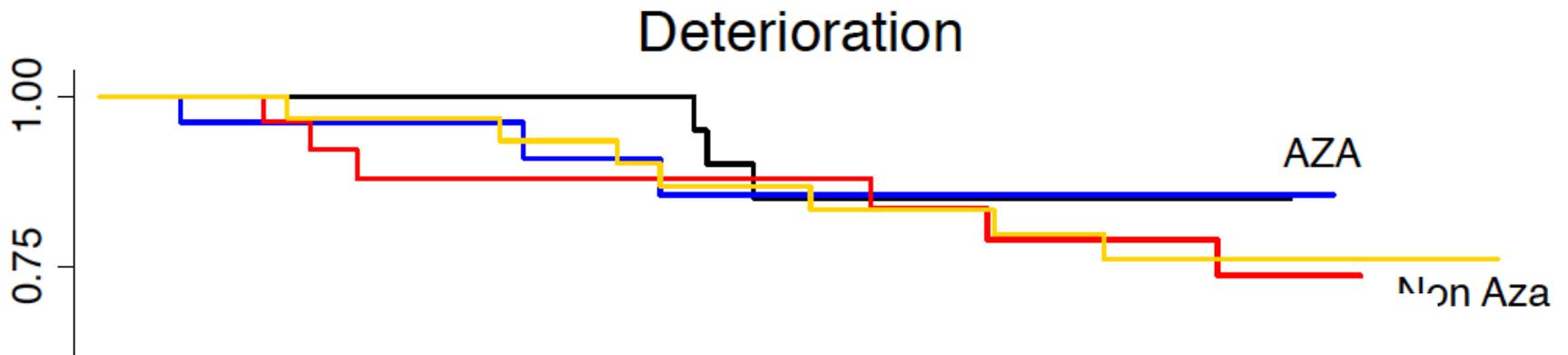
Abnormal bloods and side effects





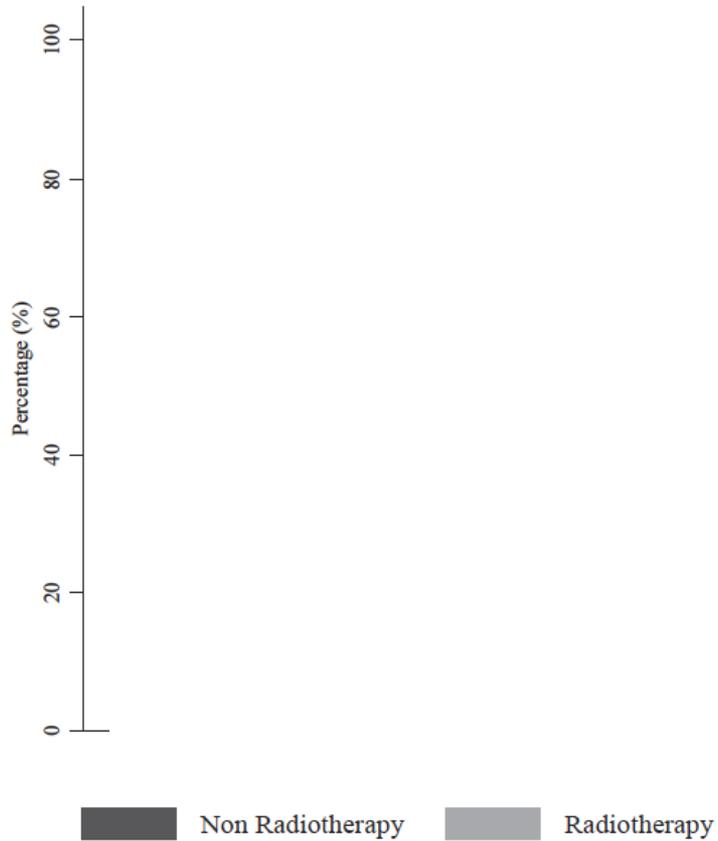
BCCOM



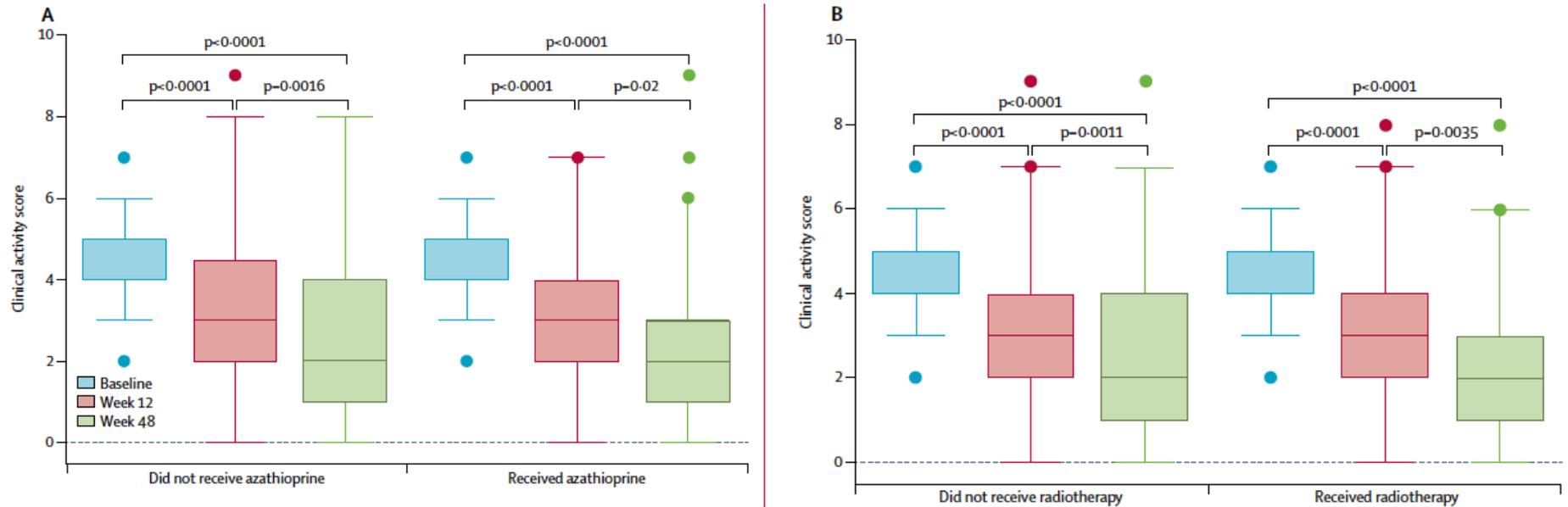


BCCOM Breakdown

Supplementary Figure 3B BCCOM breakdown in terms of improvement or deterioration by Radiotherapy status

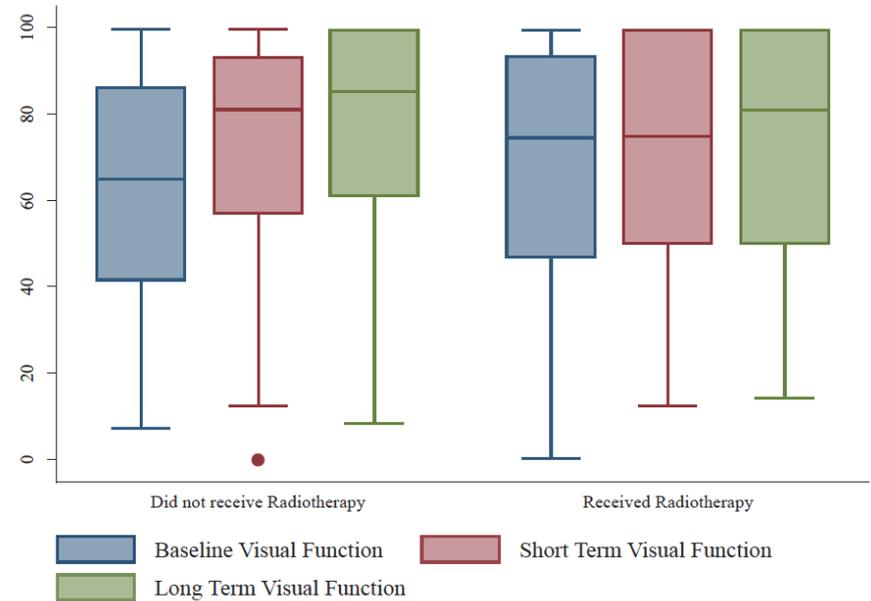
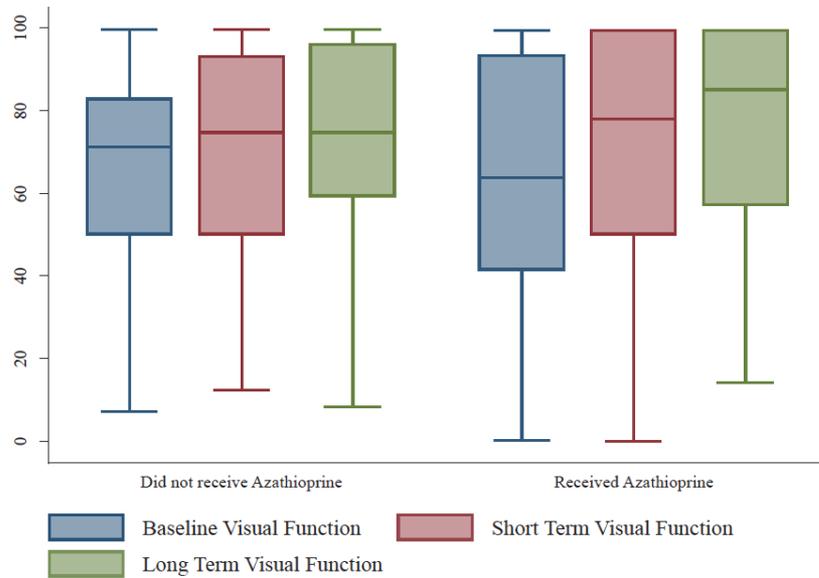


CAS



Overall substantial improvement, but no apparent additional benefit from either azathioprine or radiotherapy.

GOQOL



Overall substantial improvement, but no apparent additional benefit from either azathioprine or radiotherapy.

MINGO

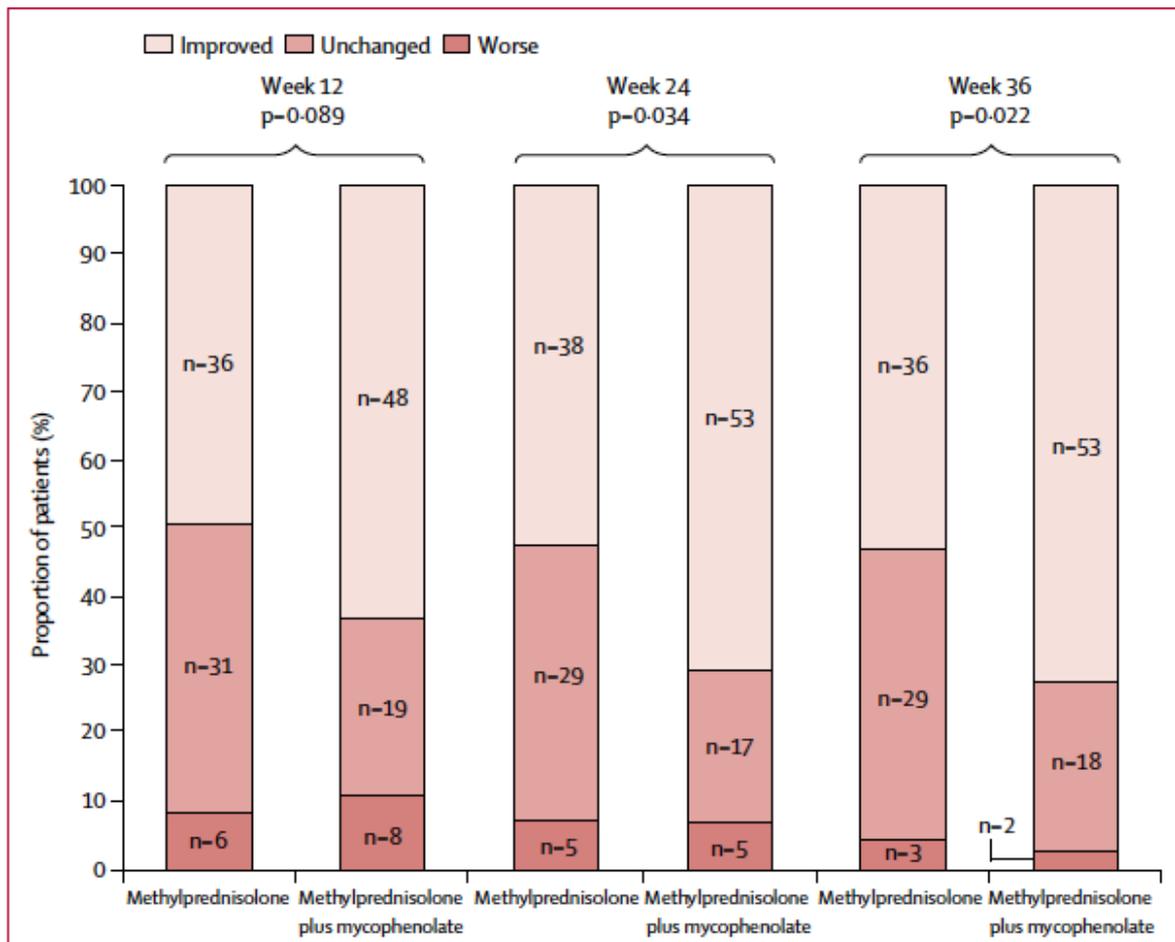


Figure 4: Post-hoc analysis of treatment effect on Graves' orbitopathy compared with baseline

Compared with baseline, percentage of patients with either overall ophthalmic improvement, no change, or worsening disease. p values were calculated with Fisher's exact test as a post-hoc analysis.

- **No radiotherapy group**
- **Mycophenolate MUCH better tolerated.**
- **Also saw benefit (diplopia driven)**
- **Might have observed reduction in rebound but observed less of this phenomenon.**

Conclusion

- **There is no apparent added benefit from radiotherapy when used in combination with high dose steroids.**
- **Azathioprine does appear to have a role if tolerated in preventing relapse after steroid withdrawal.**
- **Similar findings from MINGO study, mycophenolate better tolerated (would use this instead).**
- **Going to meta-analyse these trials.**

Thanks



CIRTED Team

Bristol

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Sue Yarrow
Helen Garrott
Helen Herbert
Andrew Dick
Nichola Rumsey
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