Universitätsspital Basel

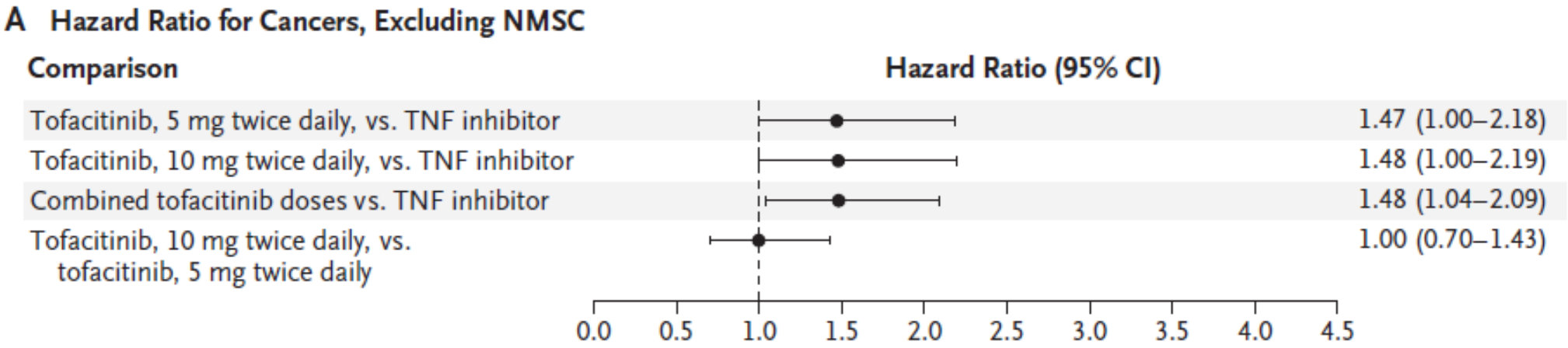
Rheumatoide Arthritis

EULAR Highlights

Diego Kyburz
Rheumatologie
Universitätsspital Basel

Focus on cancer risk in RA

- Tofacitinib with increased risk vs TNF-Inhibitor (ORAL Surveillance)



Ytterberg et al, NEJM 2022

Cancer incidence in RA in real-world

- German registry study: Methods

  - Data from the German register RABBIT, a prospective longitudinally followed cohort of RA patients (start in 05/2001)
  - Selection of patients without cancer history with treatment episodes started between 01/2017 and 12/2022
  - All patients vs. patients selected according to Oral Surveillance criteria: age ≥ 50 years and ≥1 cardiovascular risk factor (hypertension, chronic heart disease, diabetes, hyperlipoproteinaemia, smoking)
  - Incidence rates and extended Cox regression analysis

Schaefer et al, EULAR OP0218

Cancer incidence in RA in real-world

- Patient characteristics: all patients

	JAKi n=3071	TNFi n=3780	ABA n=789	RTX n=852	IL6i n=1198	csDMARD n=3282
Age (years)	60.0	57.3	59.7	61.2	58.6	60.8
Men	23%	26%	25%	30%	25%	26%
Disease duration (years)	12.6	9.4	11.9	15.4	11.0	11.3
Seropositivity	79%	74%	82%	92%	79%	74%
# previous b/tsDMARDs	2.3	0.9	2.4	3.0	2.3	1.6
DAS28-ESR	4.1	4.3	4.4	3.7	4.2	3.7
Glucocorticoids ≥10 mg/d	9%	9%	10%	7%	9%	6%
% of full physical function	65.6	69.5	63.1	64.6	65.6	68.7
# comorbidities	2.5	2.1	2.8	2.8	2.2	2.4
Current smokers	26%	26%	27%	22%	27%	26%
Ever smokers	59%	58%	65%	63%	59%	60%
Treated in clinic	18%	14%	26%	32%	17%	17%

Schaefer et al, EULAR OP0218

Cancer incidence in RA in real-world

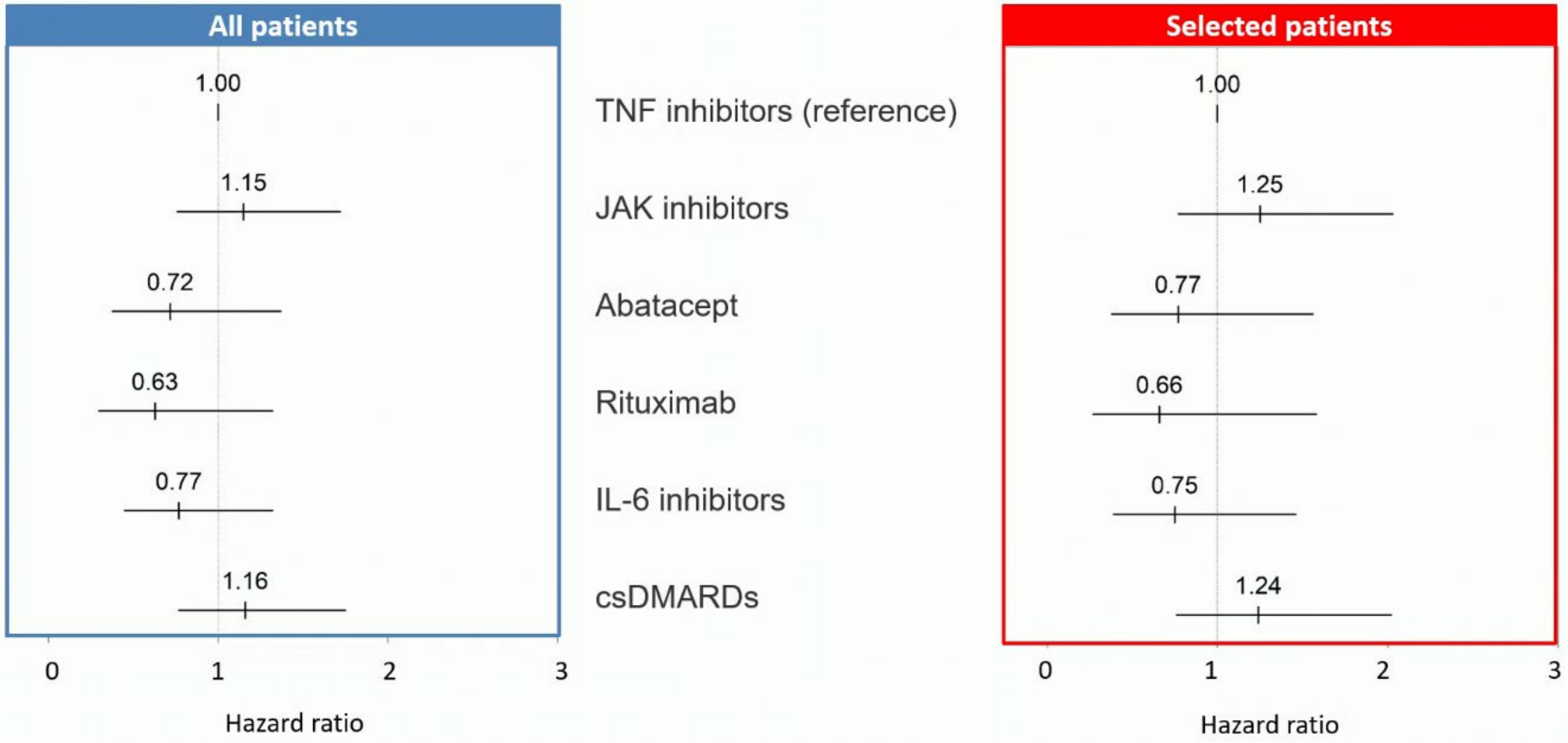
- Patient characteristics: selected patients (like ORAL surveillance)

	JAKi n=1841	TNFi n=2014	ABA n=469	RTX n=496	IL6i n=661	csDMARD n=1979
Age (years)	64.5	63.8	65.0	65.7	63.5	65.8
Men	26%	29%	29%	35%	28%	28%
Disease duration (years)	13.5	10.2	13.0	15.8	11.8	12.0
Seropositivity	79%	74%	82%	90%	78%	74%
# previous b/tsDMARDs	2.4	0.9	2.4	3.0	2.3	1.6
DAS28-ESR	4.3	4.5	4.5	3.8	4.4	3.8
Glucocorticoids ≥10 mg/d	10%	10%	10%	8%	10%	6%
% of full physical function	61.7	64.9	59.5	61.6	61.2	64.7
# comorbidities	3.2	2.9	3.7	3.8	3.1	3.3
Current smokers	35%	37%	36%	29%	36%	33%
Ever smokers	64%	66%	71%	67%	64%	64%
Treated in clinic	18%	12%	28%	31%	18%	16%

Schaefer et al, EULAR OP0218

Cancer incidence in RA in real-world

- Results: adjusted regression analysis



Schaefer et al, EULAR OP0218

Cancer incidence in RA in real-world

eular 23
EUROPEAN CONGRESS OF RHEUMATOLOGY
31 MAY – 3 JUNE

- Conclusion

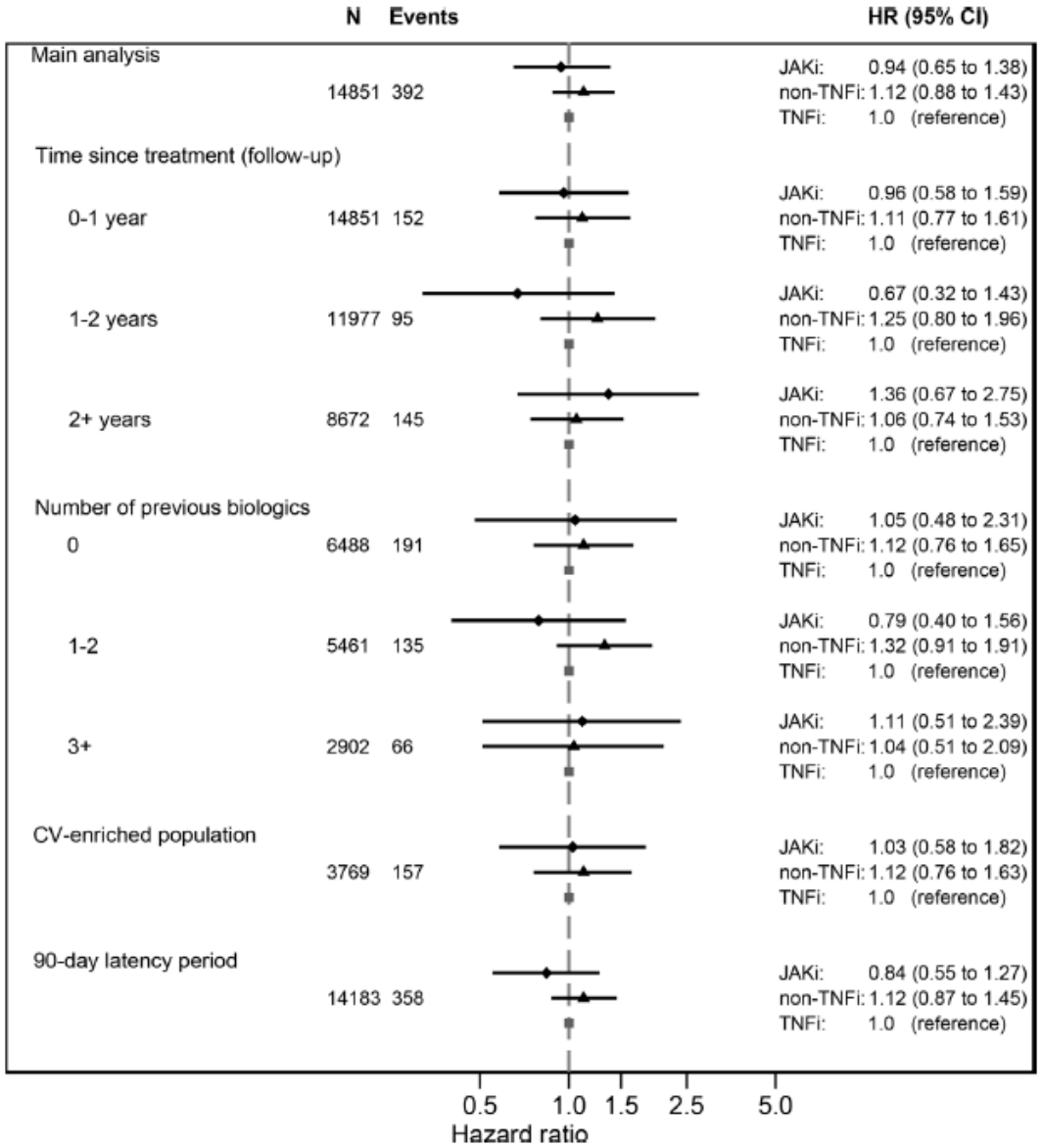
- **Incidence rate of malignancies** in patients receiving **JAKi was numerically higher**
  - **than incidence rate for TNFi**
  - **than incidence rate for tofacitinib in ORAL Surveillance**
- **No evidence of an increased relative risk of malignancies in any DMARD group compared to TNFi** when they are prescribed in daily rheumatological care, neither in all patients or in those selected according to ORAL Surveillance criteria

Schaefer et al, EULAR OP0218

Universitätsspital Basel

Cancer incidence in RA in real-world

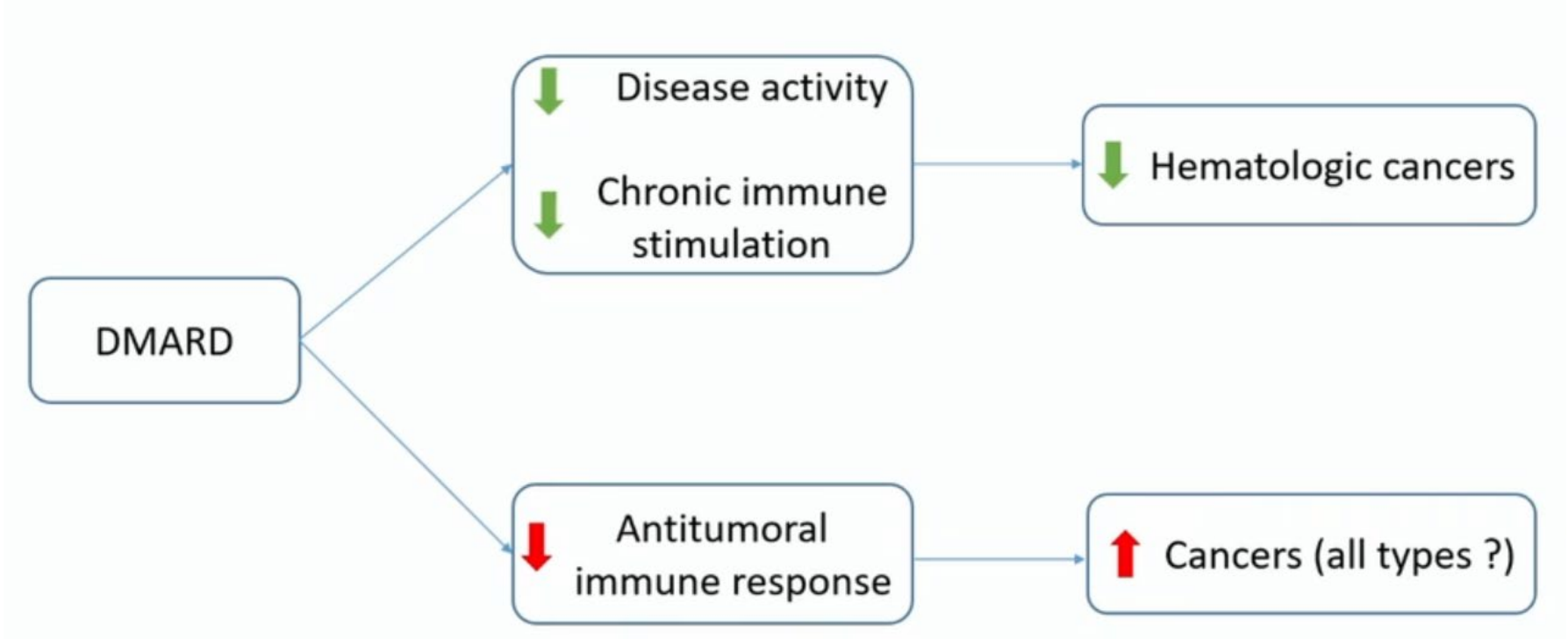
- Swedish ARTIS registry



Huss et al, Ann Rheum Dis 2023

Cancer risk in RA

- Most studies so far focused on the risk related to DMARDs



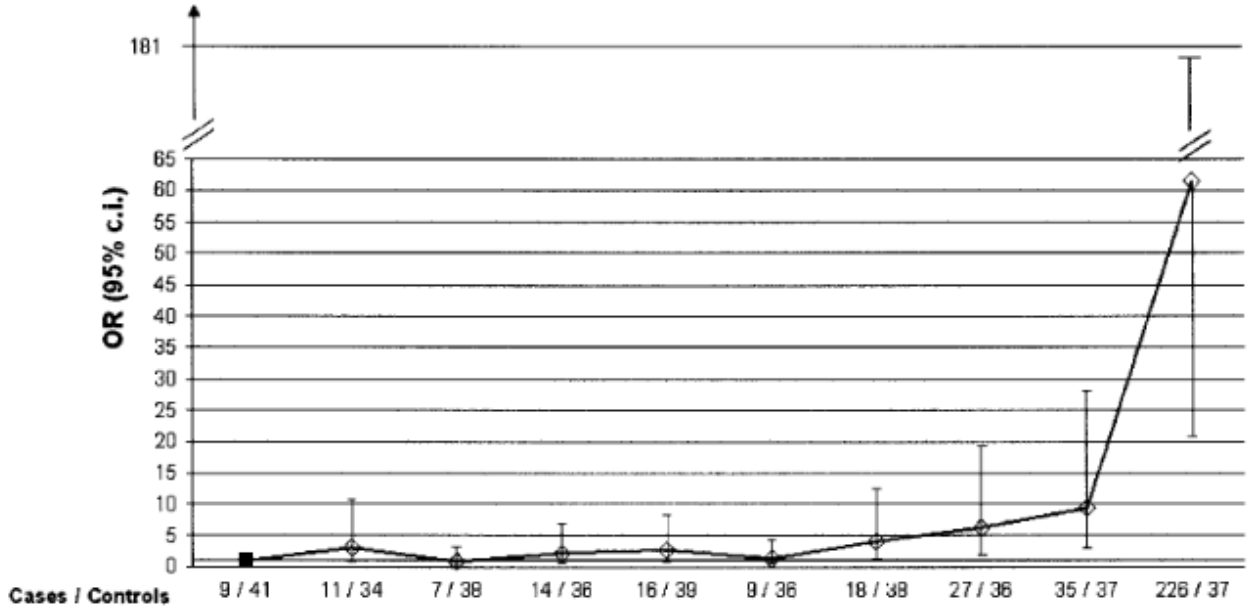
Beydon et al, EULAR OP0044

Cancer risk in RA

ARTHRITIS & RHEUMATISM
Vol. 54, No. 3, March 2006, pp 692–701
DOI 10.1002/art.21675

Association of Chronic Inflammation, Not Its Treatment, With Increased Lymphoma Risk in Rheumatoid Arthritis

Eva Baecklund,[1] Anastasia Iliadou,[2] Johan Askling,[2] Anders Ekbom,[3] Carin Backlin,[4] Fredrik Granath,[2] Anca Irinel Catrina,[2] Richard Rosenquist,[4] Nils Feltelius,[5] Christer Sundström,[4] and Lars Klareskog[2]



Baecklund et al, Arthritis Rheum 2006

Cancer risk in RA

- Is the cancer risk increased in RA patients compared to the general population?

Objectives

Principal :

- Compare global and site-specific cancer risk in RA patients to the general population

Secondary :

- Compare cancer risk in RA patients to the general population, according to treatment

Beydon et al, EULAR OP0044

Cancer risk in RA

- French study using claims data from French health care database

Inclusion criteria

- Aged 20 years or older
- Without cancer history
- With a diagnostic of RA defined as :
  - CIM-10 M05 or M06 code
  - With at least one DMARD dispensation

Events

- All-cancer (except NMSC)
- Site-specific cancer

Studied population

SNDS
Système national des données de santé

French universal healthcare database

2010 – 2019 (+1 yr follow-up)

Reference population

FRANCIM registry

Beydon et al, EULAR OP0044

Cancer risk in RA

- Patient characteristics and treatment

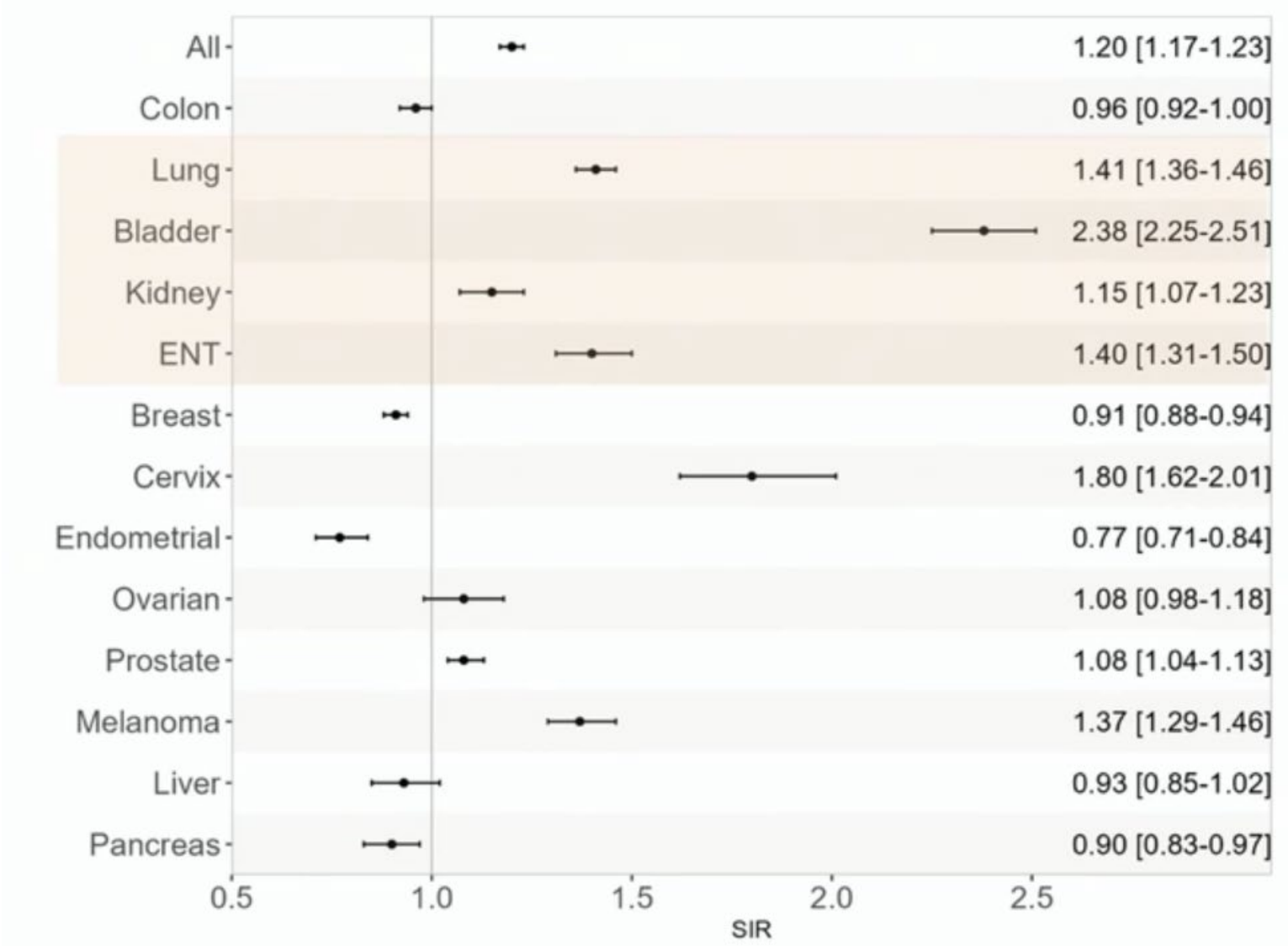
RA patients characteristics	
Subjects (n)	257 074
Female, n (%)	189,335 (73.7%)
Male, n (%)	67,739 (26.3%)
Person-years, n (PY)	2,098,239
Age at inclusion (median [IQR])	58.3 (48.0-68.7)
Follow-up duration (median, IQR)	8.7 (4.8-11.9)
Cancers per subject (n, %)	
0	234,550 (91.2%)
1	19,682 (7.7%)
≥ 2	2,342 (1.0%)

Subject exposed (N)	
csDMARD alone	236,265
TNFi	65,997
Anti-IL6R	14,985
Rituximab	13,398
Abatacept	14,532
JAKi	7,062

Beydon et al, EULAR OP0044

Cancer risk in RA

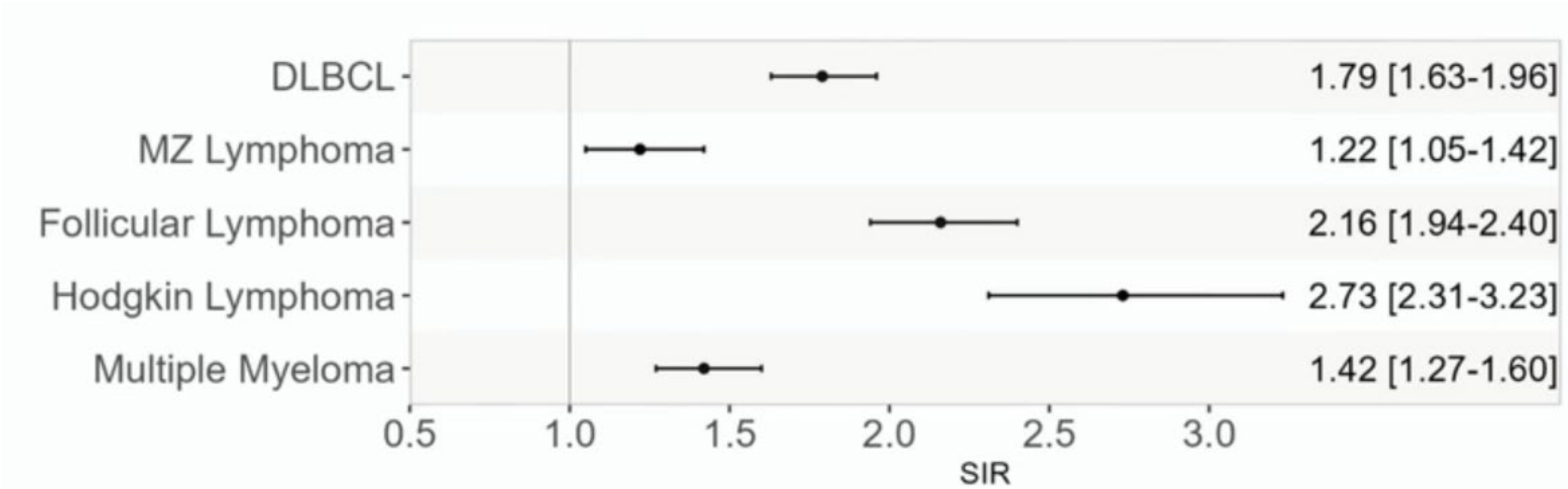
- Results



Beydon et al, EULAR OP0044

Cancer risk in RA

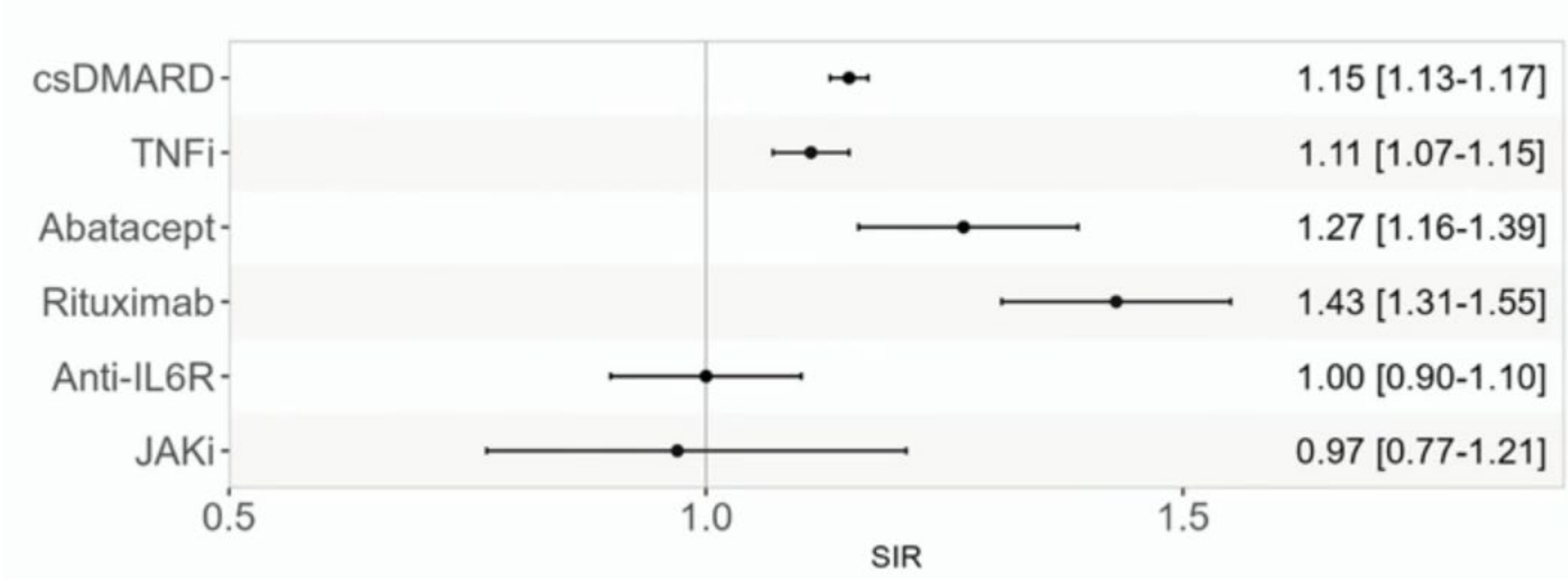
- Results: hematological cancer



Beydon et al, EULAR OP0044

Cancer risk in RA

- Results: cancer risk and DMARD use



Beydon et al, EULAR OP0044

Cancer risk in RA

- Results: hematological cancer risk and DMARD use

CANCERS	csDMARD	TNFi	Abatacept	Rituximab	Anti-IL6R
DLBCL	1.89 [1.68-2.12]	1.54 [1.15-2.05]	3.16 [1.87-5.35]	2.27 [1.22-4.23]	1.32 [0.59-2.94]
MZ Lymphoma	1.10 [0.90-1.36]	1.57 [1.07-2.31]	1.99 [0.82-4.79]	**2.87 [1.36-6.03]**	0.39 [0.05-2.77]
Follicular Lymphoma	2.28 [1.99-2.61]	2.14 [1.61-2.86]	0.98 [0.31-3.04]	**2.61 [1.30-5.24]**	0.31 [0.04-2.19]
Hodgkin Lymphoma	2.62 [2.09-3.29]	2.88 [1.92-4.30]	1.10 [0.15-7.88]	**6.44 [2.89-14.39]**	1.80 [0.45-7.25]
Multiple Myeloma	1.20 [1.06-1.37]	1.10 [0.80-1.50]	2.22 [1.26-3.92]	**8.81 [6.61-11.74]**	2.21 [1.25-3.90]

Indication bias for rituximab probable

Beydon et al, EULAR OP0044

Cancer risk in RA: summary

- Cancer incidence in RA increased
  - Smoking related cancers, also bladder cancer
  - Cervix and prostate cancer increased
  - Increased risk of hematological cancers (decrease over time ?)

- Some cancers with lower incidence
  - breast, endometrial, pancreatic cancer
  - RA risk factors may be protective

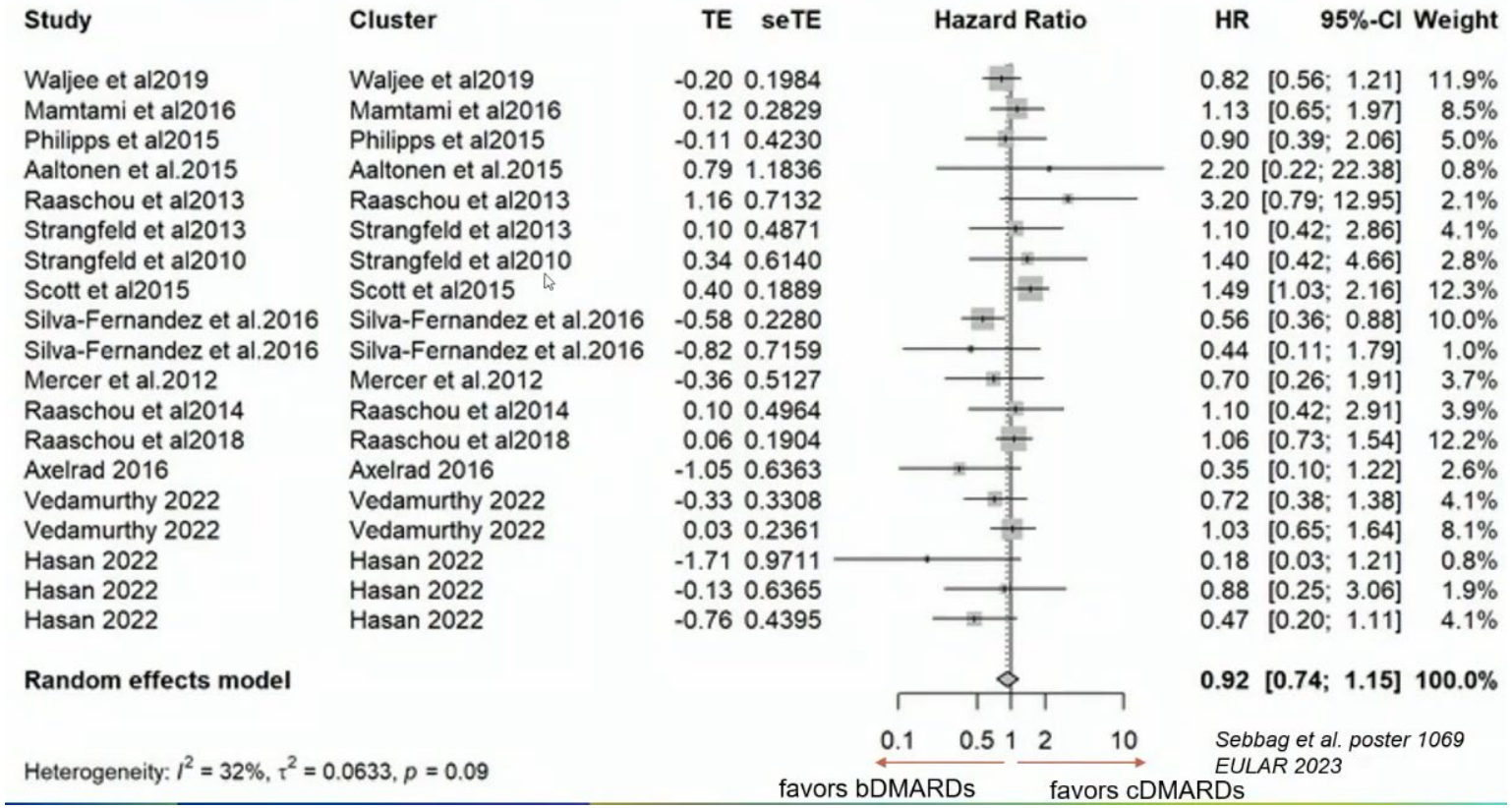
Beydon et al, EULAR OP0044

DMARD therapy in patients with history of cancer

EULAR points to consider

- Kein erhöhtes Risiko für bDMARD vs csDMARD

Systematic literature review : patients with history of cancer treated with c/b/tsDMARDs



Gottenberg et al, EULAR OP0045

DMARD therapy in patients with history of cancer

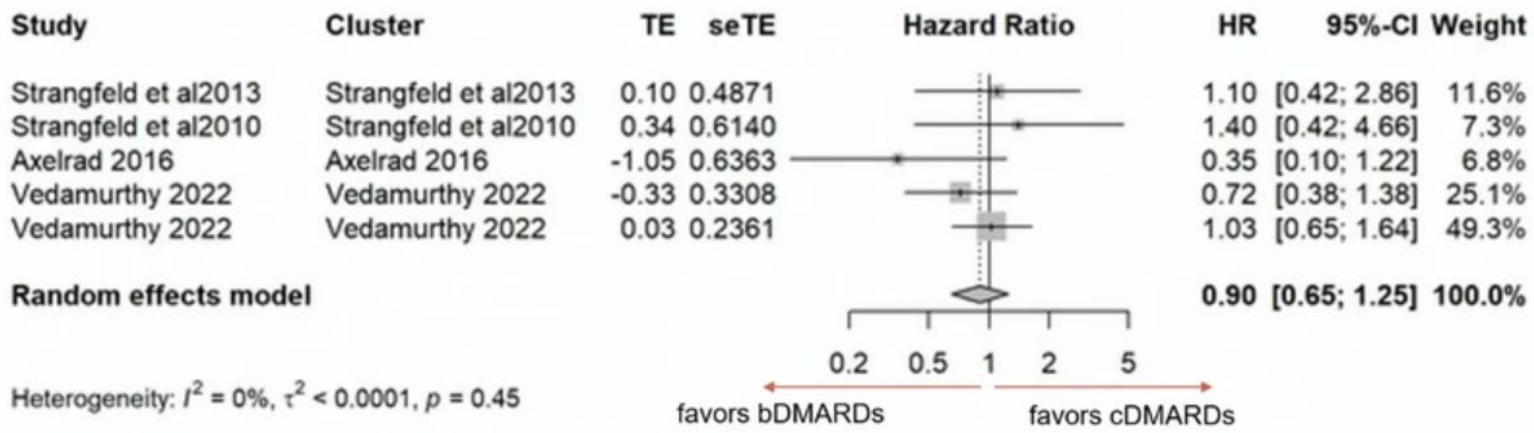
EULAR points to consider

- Cancer in remission. How long to wait with DMARD treatment?

PTC 4. Appropriate targeted anti-rheumatic treatment can be initiated without delay in patients with a cancer in remission

- Level of agreement : 9.4 (0.9)

Meta-analysis of risk of new cancer when bDMARDs are initiated within 5 years after cancer diagnosis (but where cancer is in remission)



Sebbag et al, poster 1069, EULAR 2023,

Gottenberg et al, EULAR OP0045

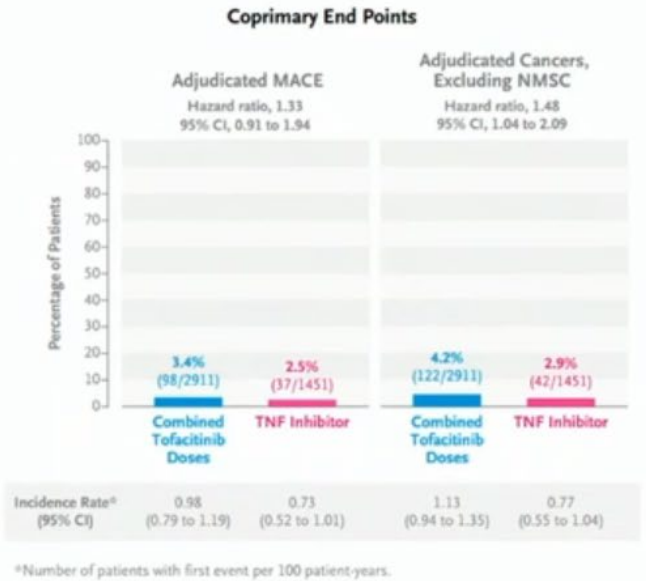
DMARD therapy in patients with history of cancer

EULAR points to consider

- Use of JAKi ?

PTC 5. In patients with a history of cancer, JAK inhibitors and Abatacept may be used with caution, and only in the absence of therapeutic alternatives

- Level of agreement : 8.9 (1.1)
- PTC based on emerging evidence in patients with no prior history of cancer
- Considering tofacitinib, ORAL surveillance trial, a randomized controlled study comparing the occurrence of MACEs and cancers between tofacitinib and anti-TNF (adalimumab or etanercept), reported a significant increase in the incidence of cancer



CONCLUSIONS

Risks of MACE and cancers were higher with tofacitinib than with TNF inhibitors among patients with rheumatoid arthritis; noninferiority of tofacitinib was not shown for these end points.

Ytterberg N Engl J Med. 2022

Gottenberg et al, EULAR OP0045

DMARD therapy in patients with history of cancer

EULAR points to consider

- Abatacept ?

  - Considering abatacept in patients with RA and no history of cancer, literature includes 6 observational studies showing in 5/6 a mild but significant increase of incidence of cancer

Study	Type of cancer	Adjusted HR (95% CI) / bDMARDS unless specifed
Ozen et al.	Overall malignancy	1.89 (0.93, 3.82)
Montastruc et al.	Overall malignancy	1.17 (1.06, 1.30) 1.20 (1.03, 1.39)
Simon et al.	Overall malignancy	1.02 (1.09, 1.16)
De Germay et al.	Melanoma	reported odds ratio, 1.58 (1.17, 2.08)
Wadstrom et al.	Squamous cell skin cancer	2.12 (1.14, 3.95) compared with anti-TNF
Huss et al.	Total malignancy	1.8 (1.2, 2.6) compared with b/ts DMARD naive after 2-5 years of active treatment

Ozen, Arthritis Res Ther 2019, Montastruc et al. Rheumatology 2019, Simon et al. Arthritis Res Ther 2019, de Germay et al. Rheumatology 2020, Wadstrom, et al. JAMA Int Med 2017, Huss et al, Rheumatology 2022

Gottenberg et al, EULAR OP0045

DMARD therapy in patients with history of cancer

EULAR points to consider

eular 23
EUROPEAN CONGRESS OF RHEUMATOLOGY
31 MAY – 3 JUNE

PTC 6. When targeted antirheumatic therapy is indicated in patients with a history of solid cancer, anti-cytokine bDMARDs may be preferred over other treatment options

PTC 7. When targeted anti-rheumatic therapy is indicated in patients with a history of lymphoma, B cell depleting therapy may be preferred over other treatment options.
Level of agreement 9.3 (1.1)

PTC 8. In patients with a malignancy not in remission and an active inflammatory arthritis, the decision to start targeted anti-rheumatic therapy should be based on a shared decision between the patient, the specialist caring for cancer and the rheumatologist.
Level of agreement 9.8 (0.5)

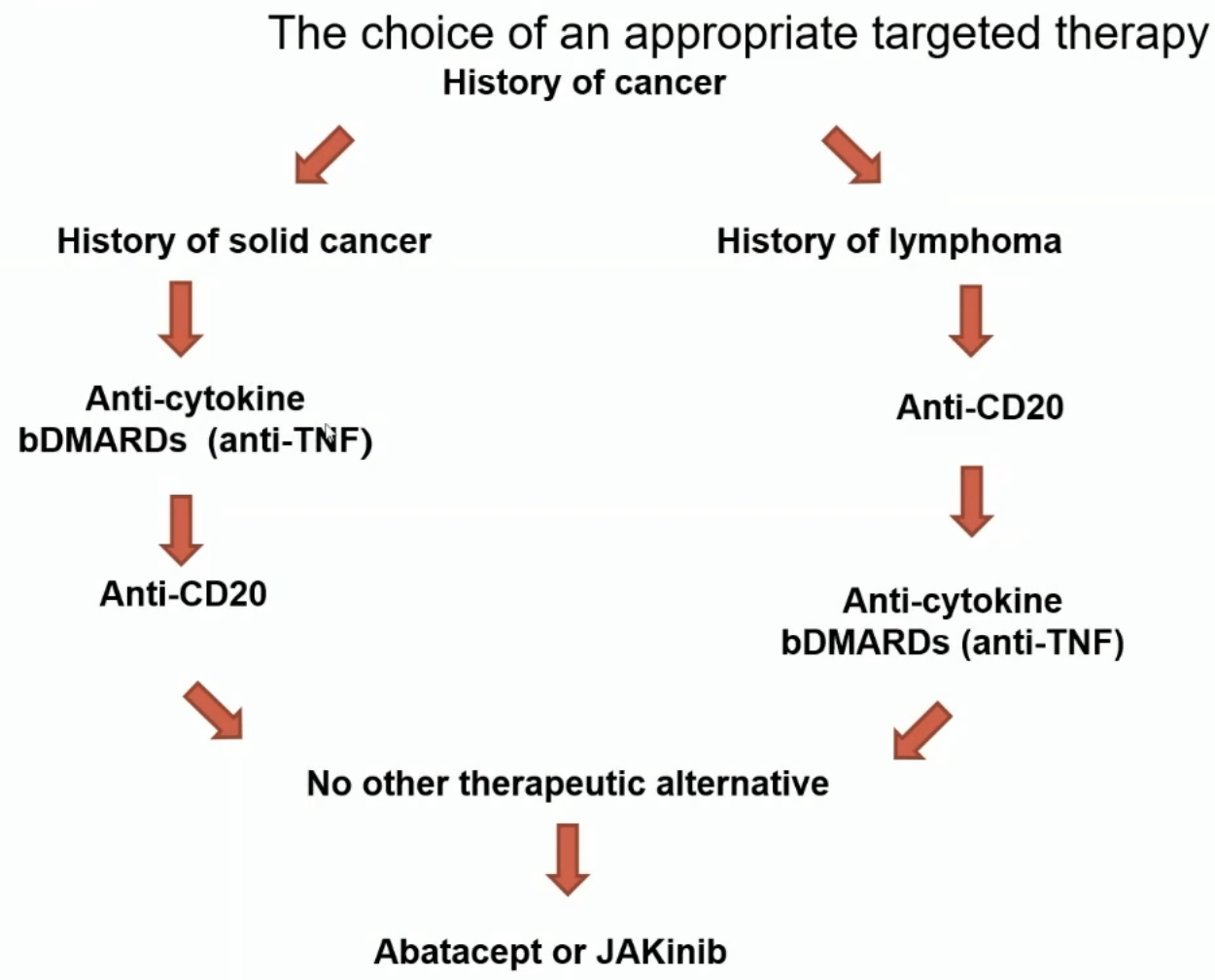
Gottenberg et al, EULAR OP0045

Universitätsspital Basel

DMARD therapy in patients with history of cancer

EULAR points to consider

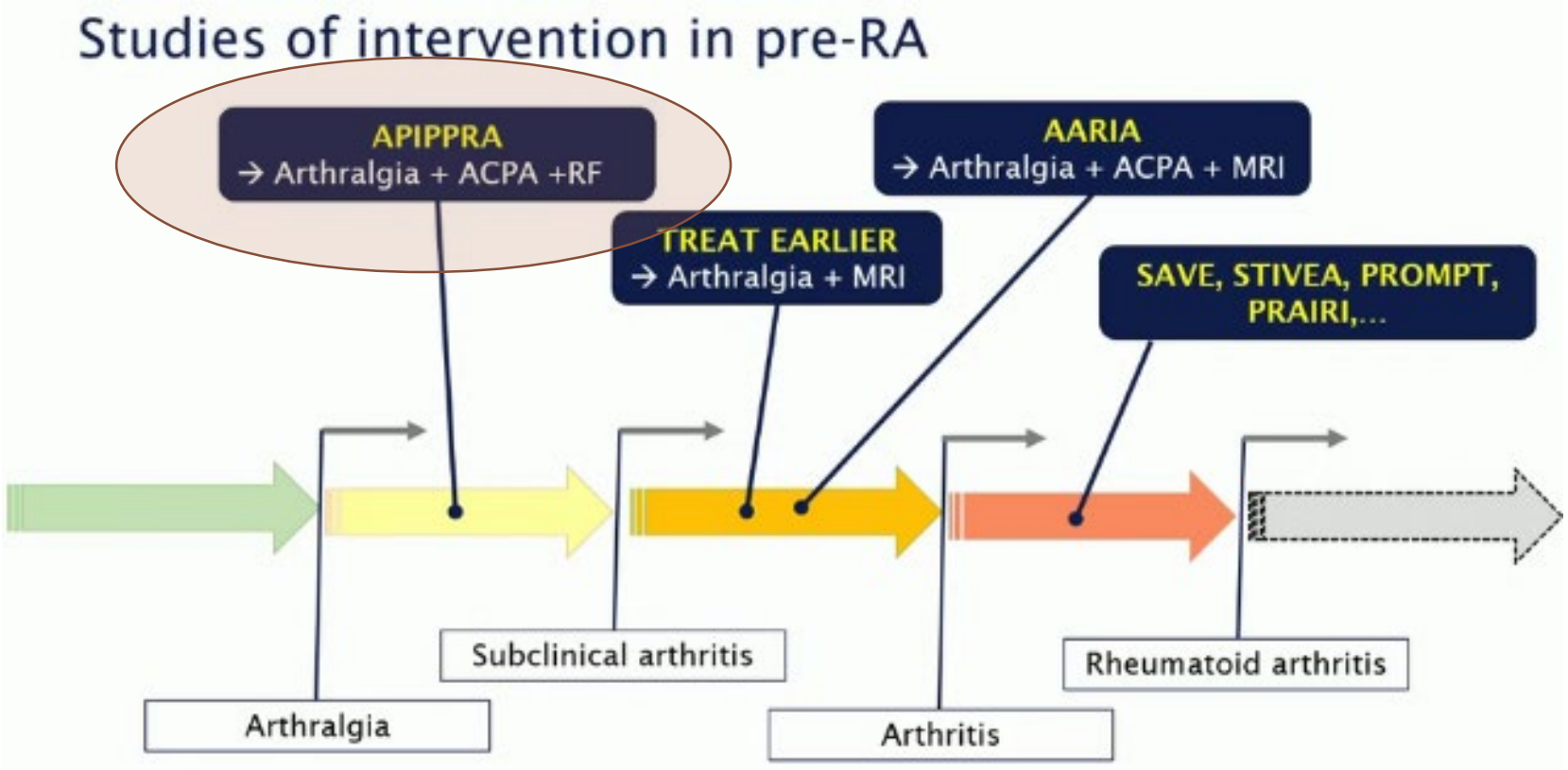
- Recommendations



Gottenberg et al, EULAR OP0045

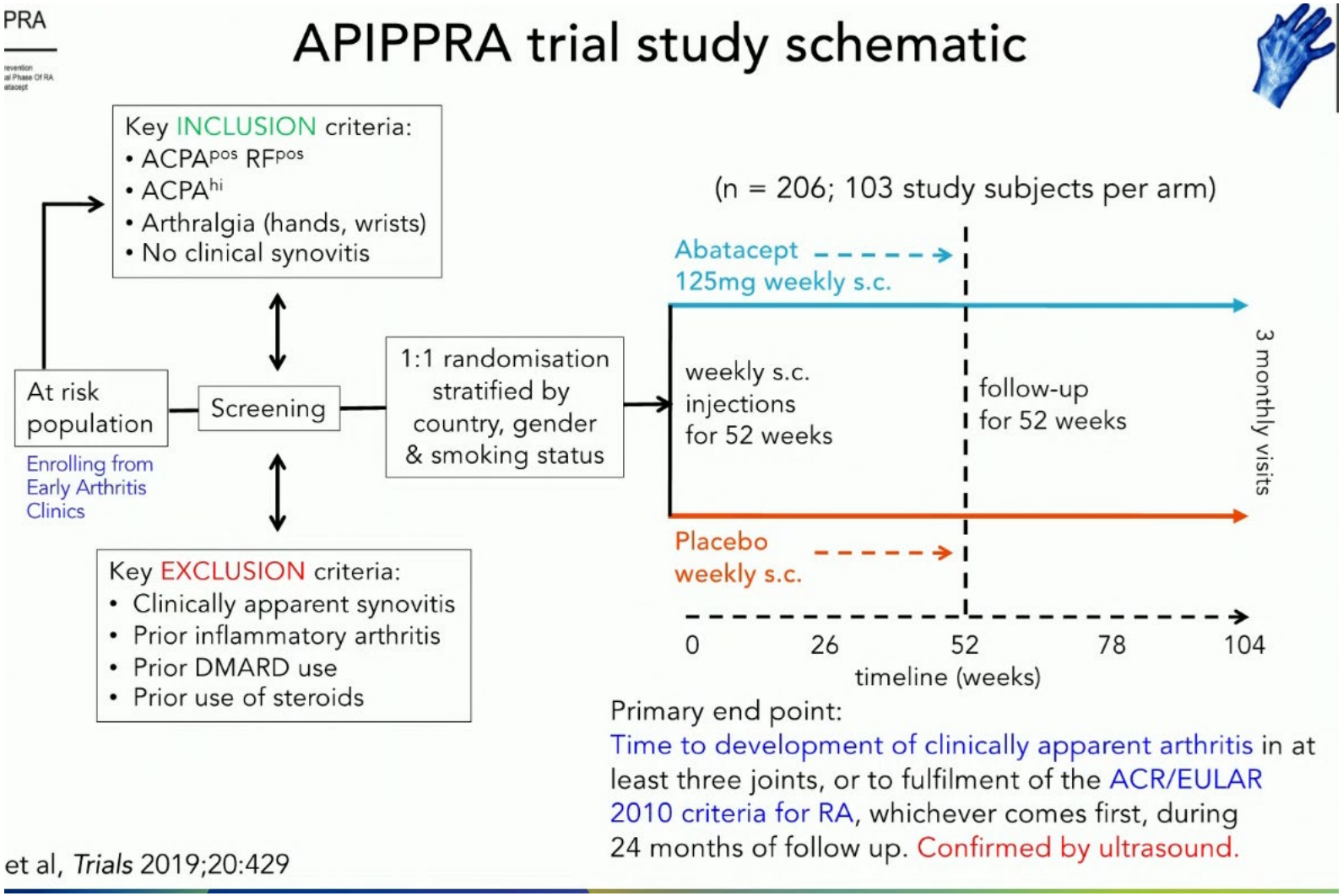
Early treatment for RA

- Patients with arthralgia but no synovitis: prevention possible ?



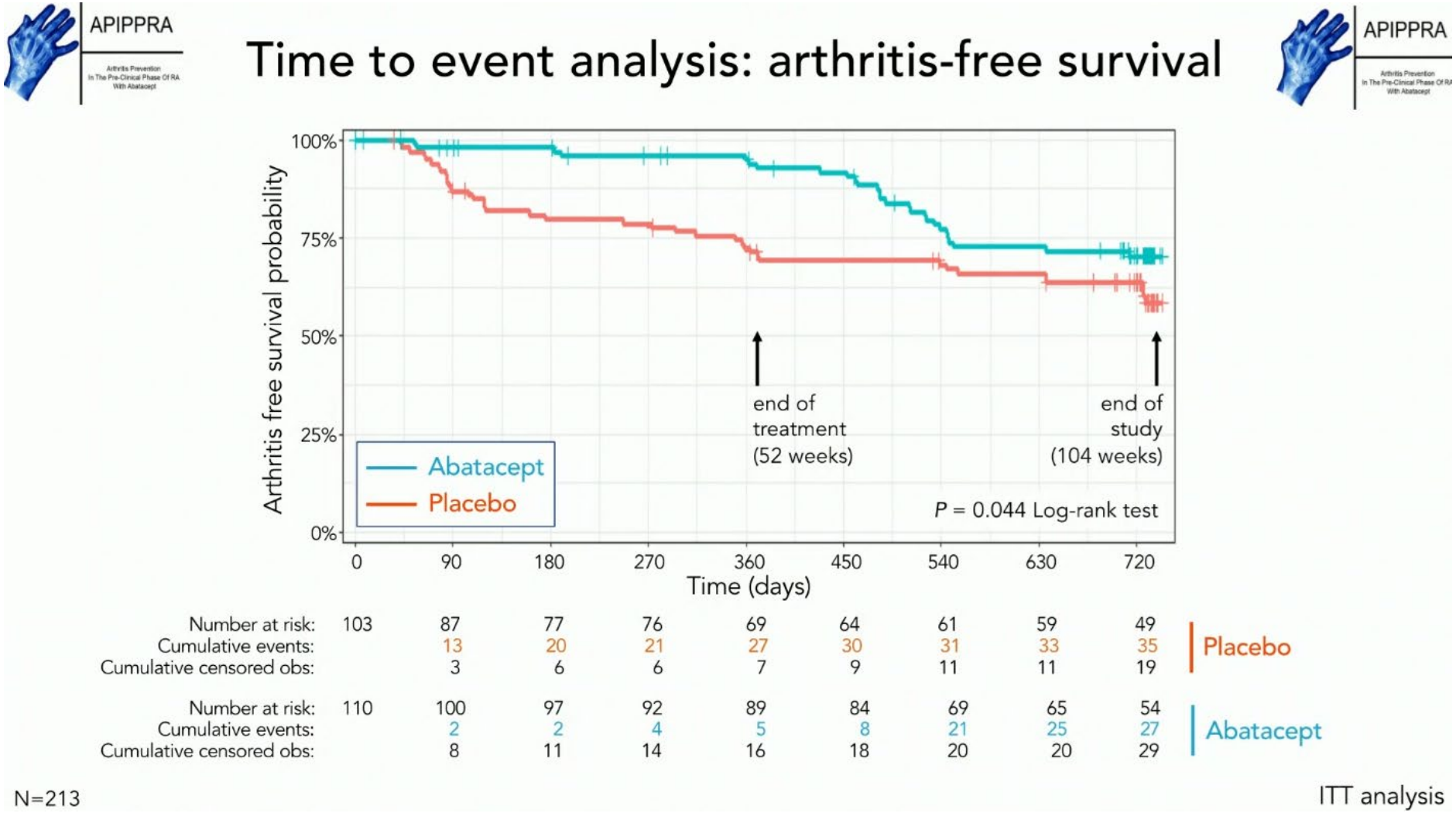
Aletaha, EULAR plenary lecture

APIPPRA Study



Cope et al, EULAR OP0130

APIPPRA: RA prevention ?



Cope et al, EULAR OP0130

APIPPRA: RA prevention ?

Summary statistics

	End of treatment (52 weeks)		End of study (104 weeks)	
	Placebo (N=103)	Abatacept (n=110)	Placebo (N=103)	Abatacept (n=110)
Primary endpoint (%)	30 (29.1%)	7 (6.4%)	38 (36.9%)	27 (24.5%)
Hazards Ratio Cox-regression model	0.2 [95% CI 0.09 – 0.45] *P* = 0.0002		0.61 [95% CI 0.37 – 0.99] *P* = 0.003	
Restricted mean survival time between arms (days)	52.7 [95% CI 27.8 – 77.6] *P* < 0.001		99.2 [95% CI 37.5 - 160.9] *P* = 0.002	

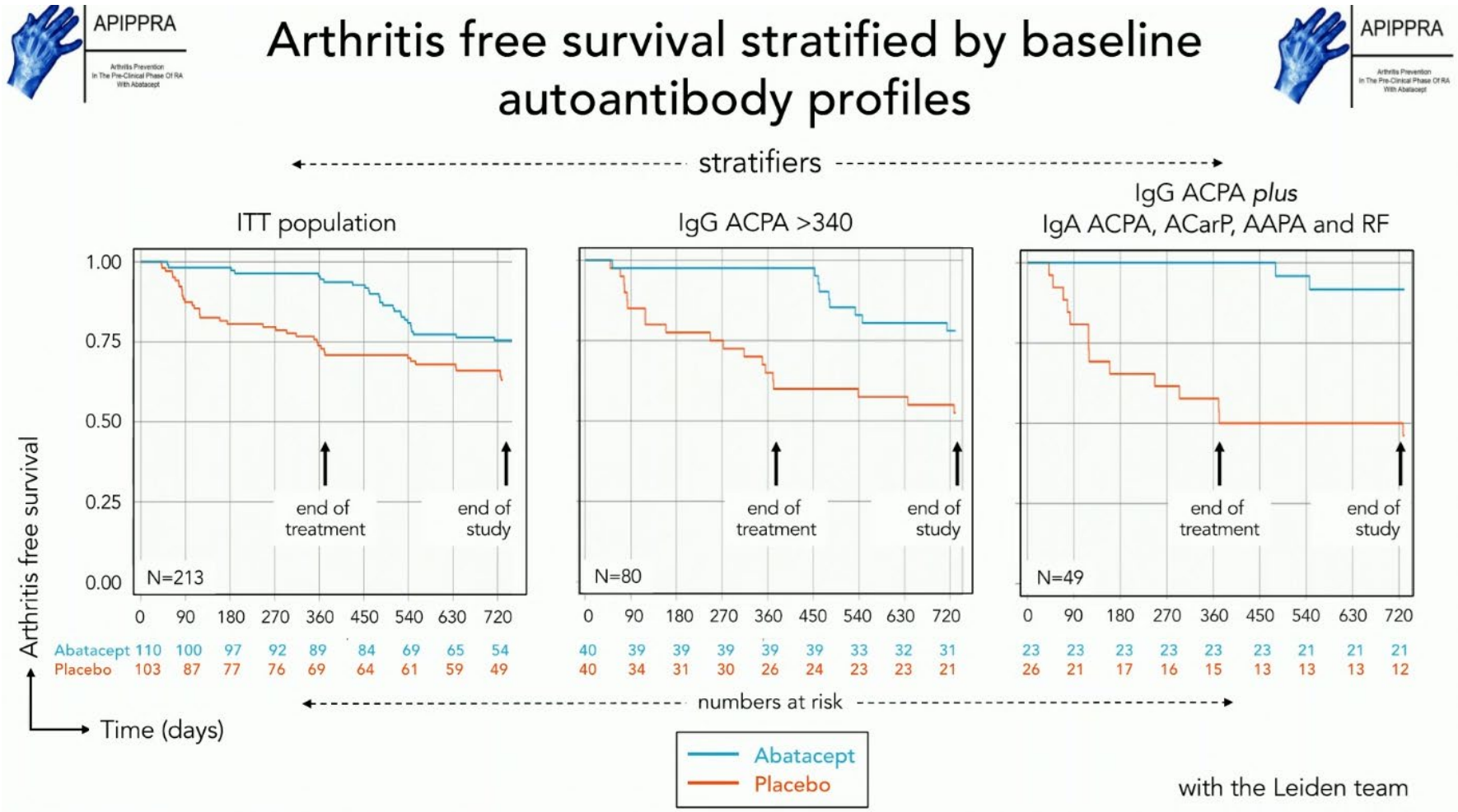
Note: there is non-proportionality of the hazards across the 104 weeks most likely because treatment is stopped at 52 weeks

N=213

ITT analysis

Cope et al, EULAR OP0130

APIPPRA: RA prevention ?



Cope et al, EULAR OP0130

APIPPRA: RA prevention ?

- Pre-RA trials are feasible
- No new safety signals
- Abatacept reduced the rate of progression to RA at 12 months
- Survival curves converge during year 2
- Certain subpopulations may benefit more

Cope et al, EULAR OP0130

Universitätsspital Basel

Vielen Dank für die Aufmerksamkeit