Table 1. Impact of serologic features on markers of active SLE

	Subset	N	Mean/Median C3	p value	Mean/Median C4	p value	% with Low C3/C4	p value	% DNA +	p value
Baseline N=1019	ALL	1019	1056		186		39.2%		35.8%	
	ENA+	670	990	**	162	**	42.1%	#0.001	43.6%	#0.001
	ENA-	349	1130	0.001	210	0.001	23.8%		30.7%	
	DNA+	399	890	**	130	**	63.9%	#0.001	-	na
	DNA-	620	1130	0.001	210	0.001	22.9%		-	
	ENA+ DNA-	378	1117	**	198	**	25.9%	**	-	na
	ENA- DNA-	242	1211	0.001	237	0.001	18.2%	0.001	-	
Screen N=783	ALL	783		***		***	32.1%		24.9%	
	ANA neg	190	1230	<0.001	230	<0.001	15.3%	#0.073	7.4%	#0.026
	ANA=1:80	74	1130		228		25.7%	comp	17.6%	comp
	ANA=1:160	104	1110		210		25.0%	ns	19.2%	ns
	ANA=1:320	97	1110		190		29.9%	ns	22.7%	ns
	ANA=1:640	104	960		152		47.1%	#0.006	34.6%	#0.019
	ANA=1:1280	88	924		160		45.4%	#0.015	35.2%	#0.019
	ANA=1:2560	52	920		160		48.1%	#0.016	44.2%	#0.002
	ANA≥1:5120	74	959		135		45.9%	#0.016	48.6%	#0.001
	ANA - ENA +	61	1122	*	203	**	21.3%	ns	13.1%	ns
	ANA - ENA -	129	1254	0.007	258	0.001	12.4%		4.7%	
	ANA≥1:80 or DNA+	607	1020	**	170	**	37.7%	#0.012	-	na
	DNA+ or ENA+ or ANA≥1:640	318	940	0.001	152	0.001	46.5%		-

Figure 1 %Variable. domain glycosylation of matched paired samples before and after disease onset.

Conclusion: Our analysis revealed that ACPA IgG molecules can harbor V-domain glycans already relatively long time before disease onset. An increase in ACPA V-domain glycosylation, presumably due to the generation of de-novo N-glycosylation sites or the expansion of N-glycosylation site-bearing clones was associated with an increase in ACPA levels. These results suggest that ACPA-expressing B cells gain a selective advantage through the generation V-domain N-glycosylation in parallel with rising ACPA-levels in serum in the phase prior to the development of arthritis.

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OP0334

WHAT SEROLOGIC PROFILING PROVIDES OPTIMAL ENTRY CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS CLINICAL TRIALS?

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Background: A major concern for SLE clinical trials is the possibility that some patients who technically meet entry criteria may not have active disease. Antinuclear antibody (ANA) is known to lack specificity for SLE, permitting inclusion of

inappropriate patients. Typically, ANA≥1:80 and/or positive anti-double stranded DNA (DNA) are required screening elements, but lately other autoantibody variables have been utilized.

Objectives: To examine serologic features that promote entry of active SLE patients into trials while supporting reasonable recruitment rates.

Methods: Serologic features of 1411 individual subjects who had full laboratory data at screening (N=783) and/or baseline (N=1019) in 4 phase 2 multicenter SLE trials were examined. Complement levels, percent of patients with low C3 or C4, and elevated DNA were used as markers of active disease. Serological profiles consistent with active SLE were tested on screened population for effects on potential screen failure rates.

Results: Of 1019 patients who qualified for the studies (baseline population), 399 (39.2%) were positive for DNA and 670 (65.8%) had anti-Extractable Nuclear Antibodies (ENA). Patients with positive DNA or ENA (even in absence of DNA) had lower complement levels and were more likely to have low C3/C4. (Table 1)

In patients at screening, higher titers of ANA were associated with lower complement levels and higher rates of patients with low C3/C4 and elevated DNA. ENA impacted complement levels even in the absence of ANA. Compared to traditional entry criteria (ANA≥1:80 and/or DNA), patients defined by positive DNA or ENA or ANA≥1:640 had significantly lower complement levels and greater rates of low C3/C4, suggesting a more active patient population. (Table 1)

*t test **ranks ***one way ANOVA on ranks #chi square (comp=comparator) na=not applicable ns=not significant. Data not adjusted for multiple comparisons
Compared to a 22.5% screen failure rate with the typical requirement for ANA≥1:80 or DNA, testing DNA or ENA or low C3/C4 as entry criteria resulted in 30.7% exclusion. Adding high titer (≥1:640) ANA as an additional optional criterion would decrease the screen failure to 25.7%. (Table 2)

Table 2. Impact of serological profiles as entry criteria on potential screen failure rate (N = 783)

Entry Criteria	N	Screen Failure Rate
ANA≥1:80 or DNA	607	22.5%
ANA≥1:80 or DNA or anti-Smith	614	21.6%
DNA or ENA	495	36.8%
DNA or ENA or low C3/C4	543	30.7%
DNA or ENA or ANA≥1:640	552	29.5%
DNA or ENA or low C3/C4 or ANA≥1:640	582	25.7%

Conclusion: The following entry criteria may help increase the likelihood that trial subjects have active SLE: **ANA≥1:640, or DNA, or ENA, or low C3 or C4.** To the extent that a modest loss of recruitment increases the probability of entering true, active SLE patients, these alternative constructs should be considered in future SLE trials.

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Lessons learned from checkpoint inhibitors

OP0335

A PROSPECTIVE CLINICAL AND MRI STUDY OF IMMUNE CHECKPOINT INHIBITOR (ICI)-INDUCED MUSCULOSKELETAL MANIFESTATIONS MYO-FASCIITIS AND NOT SYNOVITIS IS THE PROMINENT IMAGING FINDING

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Background: Immune check point inhibitors (ICI) were a breakthrough in cancer therapeutics. These agents target certain "brakes" of the immune system aiming at activating T cells to fight cancer. Taking into account their mechanism of action it is no surprise that they have been associated with immune related adverse events

Objectives: To assess the prevalence, clinical and imaging characteristics of ICI-induced musculoskeletal manifestations in a prospective manner

Methods: This is a prospective, clinical and MRI study conducted from Jan 2016 to Oct 2018. All patients treated with ICI who developed musculoskeletal manifestations were referred to the Rheumatology Department and subjected to a full clinical assessment and laboratory workup. An MRI of the involved area(s) was performed within one week of the initial clinical evaluation. In 2 patients MRI was not performed due to claustrophobia (n=1) and presence of non compatible metal implant (n=1).

Results: During the study period a total of 130 patients were treated with ICI. Of those, 10 (7.7%) developed ICI-induced musculoskeletal manifestations. They suffered from lung (n=4), bladder (n=3), renal cancer (n=2) or melanoma (n=1) and received treatment with nivolumab (n=7), pembrolizumab (n=1), durvalumab (n=1) and atezolizumab (n=1). They were mostly male (n=8) with a mean $\pm$ SEM age of 66.7 ± 2.6 years. The median (range) time from ICI treatment since development of symptoms was 2.5 (1-22) months. Autoantibodies (RF/ACPA/ANA) were negative in all patients and only 3/10 had a mild/moderate increase of inflammatory markers at disease onset. Three different patterns of musculoskeletal manifestations were found: i) Prominent joint involvement (n=3). Areas involved were the small joints of the hands (n=2) and knee/ankle (n=1). The MRI of the latter patient depicted not only synovitis but also myositis of the muscles surrounding the involved joints, ii) Prominent "periarticular" involvement (n=4). These patients had diffuse swelling of the hands (n=4) feet (n=3) or knees (n=1). Joints retained a good and relatively painless range of motion. MRI depicted mild synovitis with more prominent myositis and/or fasciitis in the surrounding tissues in all cases, iii) Myo-fasciitis (n=3). In all 3 such cases the involved area was the knee. Clinically, these patients presented with pain in the knee and either no objective signs of arthritis (n=2) or swelling with non inflammatory synovial fluid. MRI depicted myo-fasciitis of the surrounding muscles in all cases; a partial tear of the quadriceps tendon was also found in the patient with knee swelling. Overall, symptoms were mild/moderate and responded well to treatment (low dose steroids in 6 and NSAIDs/analgesics in 4) with no need for ICI discontinuation.

Conclusion: In our cohort ICI-induced musculoskeletal manifestations were not uncommon and developed in 7.7% of patients. Imaging evidence of myo-fasciitis was found in all patients indicating that the muscle/fascia is more frequently involved than the synovium. Our clinical and imaging data point to the direction that ICI-induced musculoskeletal manifestations mostly involve periarticular structures and associate mainly with myo-fasciitis and not synovium based pathology

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OP0336

COMMONLY USED DRUGS IN RHEUMATOLOGY MAY ALTER ANTI-TUMORAL RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoint inhibitors (ICIs) are revolutionizing the treatment of some advanced cancers. Gut microbiota has emerged as an important component of anti-tumoral response and can also be related to the occurrence of immune-related adverse events (irAEs). It has recently been shown that antibiotic treatment given at the initiation of ICI therapy had a dramatic impact on microbiota that compromised the anti-tumoral effect of ICIs (1).

Objectives: To evaluate whether co-medications known to have a potential impact on gut microbiota may alter ICI efficacy and/or irAE occurrence when given at ICI onset.

Methods: This was a retrospective cohort study including all cancer patients who received ICIs at our institution from May 2015 to September 2017. Co-medications given to the patients within one month before or one month after the first administration of ICI were extracted from medical records on the basis of a predefined list of medications known to impact gut microbiota. The tumour response, occurrence of irAEs and patient outcomes were assessed on a regular basis. Overall survival (OS) has been considered from the start of ICI therapy.

Results: 635 patients (70% male, mean age 64.5 years) were included, of whom 293 had melanoma, 150 had advanced non-small cell lung cancer and 83 had renal carcinoma. A previous autoimmune disorder was present in 8% of patients, mainly rheumatic and endocrine diseases. Psychotropic drugs (41.1%), proton pump inhibitors (PPIs) (37.3%), angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) (32%), glucocorticoids (GC) (24.2%), antibiotics (21.4%), statins (20.8%) and morphine (20.6%) were the most co-prescribed medications. Baseline GC use, when ≥ 10 mg of prednisone equivalent, was associated with a significant decrease in OS (median 4.5 months versus 24.3 months; $p < 0.0001$) and a less frequent tumour response (55% versus 73%; $p = 0.0001$). When given after ICI onset for the management of irAEs, GC did not influence ICI efficacy (Figure A). Baseline PPIs use also altered both OS (median 10.9 versus 24.3 months; $p < 0.0001$) and tumour response (62% versus 71%; $p = 0.02$) (Figure B). We confirmed the detrimental impact of antibiotics when given at ICI onset, and also found worse outcomes for patients receiving baseline psychotropic drugs (median OS 9.3 versus 19.4 months; $p = 0.0001$). No significant difference was observed with baseline use of NSAIDs, aspirin, statins and ARBs/ACE. Furthermore, co-medication with antibiotics, GC, PPIs, morphine, NSAIDs, aspirin and psychotropic drugs was associated with decreased occurrence of irAEs.

Conclusion: As many of these treatments are used by rheumatologists, one should be aware of their potential detrimental effect when used at ICI initiation, that sometimes could have been avoided.

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