CLINICAL DATA SHEET

Type I Interferon (IFN-1) Gene Expression Assay

>30 Rigorous Studies Conducted at Centers of Excellence Validating the Clinical Utility of IFN-1

Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials

Vital EM, Merrill JT, Morand EF, et al. Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials. Ann Rheum Dis. 26 Jan 2022.

Background: Systemic Lupus Erythematosus (SLE) is a variable disease influenced by a number of patient demographic and clinical characteristics. Individual patient variables can influence disease course and response to therapy. In the TULIP-1 and TULIP-2 trials, treatment with standard therapy plus anifrolumab showed a general benefit to patients with a high IFN-1 gene signature. The purpose of this study was to determine the efficacy and safety of anifrolumab treatment across multiple SLE patient subgroups, using data collected from the TULIP clinical trials. Methods: This study was based on a post hoc analysis of pooled data from two 52-week phase III, placebo-controlled, double-blind trials (TULIP-1 & TULIP-2). The TULIP trials evaluated the efficacy of IV-administered 300mg anifrolumab treatment versus placebo in patients with autoantibody-positive, moderate-to-severe SLE. Clinical outcomes were determined for each of several pre-determined patient subgroups: IFN-1 (high/low), age, sex, BMI, race, geographic region, onset age, glucocorticoid use, disease activity and serological markers (anti-dsDNA antibodies, low C3, and low C4).

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Results: Data was collected from 726 patients that received either 300mg anifrolumab (360 patients) or a placebo (366 patients). Of this patient pool, 600/726 (82.6%) were IFN-1 high. IFN-1 high patients had more active disease at baseline and were more likely to demonstrate abnormal serological markers than IFN-1 low patients. Across the entire patient population, a greater percentage of patients treated with anifrolumab achieved a British Isles Lupus Assessment Groupbased Composite Lupus Assessment (BICLA) response at 52 weeks. The BICLA response experienced by the entire patient population was similar to the level of most independent patient subgroups. Patient subgroups with notably larger treatment differences between anifrolumab and placebo treatment included those with IFN-1 high status (18.2%), patients with abnormal serological markers at baseline (23.1%), and Asian patients (29.2%). Safety evaluation showed similar results across all patient subgroups.

Conclusions: Analysis of pooled TULIP trial data showed that benefits associated with anifrolumab treatment were observed across most patient subgroups when compared to the population as a whole. (There were a few subsets with limited data, however, that may warrant additional study.) Overall, **IFN-1 high patients and patients with abnormal baseline serological markers showed the greatest benefit from treatment with anifrolumab versus placebo. Only the IFN-1 high patients had a statistically significant benefit from the therapy and the IFN-1 high patients achieve benefit on the basis of both SRI-4 and BICLA** (Table 1). Anifrolumab safety profiles were similar among most subgroups studied. This study suggests that anifrolumab is likely to have a consistent benefit across patient subgroups with moderate-to-severe SLE.

Table 1: Primary and secondary outcomes in patients with SLE by IFNGS in pooled data from the TULIP-1 and TULIP-2 trials.

	All Patients			IFNGS-High			IFNGS-Low		
	Placebo (n=366)	Anifrolumab 300 mg (n=360)	Difference (95% CI), nominal p value*	Placebo (n=302)	Anifrolumab 300 mg (n=298)	Difference (95% CI), nominal p value*	Placebo (n=64)	Anifrolumab 300 mg (n=62)	Difference (95% CI), nominal p value*
End point	**n/N (%)**		**Percentage points**	**n/N (%)**		**Percentage points**	**n/N (%)**		**Percentage points**
BICLA response, week 52	112/366 (30.8)	171/360 (47.5)	16.6 (9.7 to 23.6), <0.001	88/302 (29.4)	142/298 (47.6)	18.2 (10.5 to 25.8), <0.001	24/64 (37.5)	29/62 (46.8)	9.3 (−8.0 to 26.5), 0.292
SRI(4) response, week 52	147/366 (40.1)	188/360 (52.2)	12.1 (4.9 to 19.3), <0.001	118/302 (39.0)	160/298 (53.7)	14.7 (6.8 to 22.6), <0.001	29/64 (45.3)	28/62 (45.2)	−0.2 (−17.5 to 17.2), 0.986
Sustained GC taper, weeks 40–52†	147/366 (40.1)	188/360 (52.2)	12.1 (4.9 to 19.3), <0.001	118/302 (39.0)	160/298 (53.7)	14.7 (6.8 to 22.6), <0.001	29/64 (45.3)	28/62 (45.2)	−0.2 (−17.5 to 17.2), 0.986
≥50% reduction in CLASI- A score, week 12‡	24/94 (24.9)	49/107 (46.0)	21.0 (8.1 to 34.0), 0.001	23/81 (27.9)	47/93 (50.5)	22.6 (8.4 to 36.9), 0.002	1/13 (8.3)	2/14 (15.0)	6.7 (−26.3 to 39.6), 0.692
≥50% reduction in active (swollen and tender) joints, week 52§	71/190 (36.8)	81/164 (49.4)	12.6 (2.4 to 22.9), 0.016	61/157 (38.4)	64/129 (49.7)	11.3 (−0.2 to 22.8), 0.054	10/33 (30.4)	17/35 (48.5)	18.1 (−5.0 to 41.3), 0.125
≥50% reduction in active (swollen and tender) joints, week 52§	0.67	0.51	0.75 (0.60 to 0.95), 0.017	0.77	0.54	0.70 (0.54 to 0.90), 0.005	0.49	0.55	1.12 (0.62 to 2.01), 0.705
FACIT- F response, week 52**	97/366 (26.5)	124/360 (34.3)	7.8 (1.0 to 14.5), NA	78/302 (25.9)	102/298 (34.1)	8.2 (0.8 to 15.6), 0.030	19/64 (29.7)	22/62 (35.5)	5.8 (−10.7 to 22.3), 0.491
SF- 36 MCS response, week 52††	75/366 (20.3)	96/360 (26.5)	6.1 (−0.1 to 12.4), NA	57/302 (18.7)	81/298 (26.9)	8.2 (1.4 to 15.0), 0.018	18/64 (28.1)	15/62 (24.2)	−3.9 (−19.7 to 11.8), 0.624
SF- 36 PCS response, week 52‡‡	95/366 (26.1)	118/360 (32.8)	6.7 (0.0 to 13.5), NA	77/302 (25.7)	98/298 (33.0)	7.3 (−0.1 to 14.6), 0.053	18/64 (28.1)	20/62 (32.3)	4.1 (−12.2 to 20.5), 0.620

For additional references, please see page 8.

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Increased Risk of Progression to Lupus Nephritis for Lupus Patients with Elevated Interferon Signature

Arriens C et al, Increased Risk of Progression to Lupus Nephritis for Lupus Patients with Elevated Interferon Signature [abstract], Arthritis Rheumatol. 2019; 71 (suppl 10).

Background: The interferon (IFN) signature in SLE is well established, distinguishing lupus patients from healthy controls. Additionally, within lupus patients, higher levels of IFN-responsive gene expression associate with higher disease activity, elevated autoantibodies, greater number of SLE criteria, and higher damage indices. Despite these associations in SLE patients, an individual's IFN signature lacks responsiveness to acute changes in disease activity in longitudinal analyses. This stability is more reflective of a continuous trait, likely the result of known interferon pathway genetic associations. Elevated levels of IFN have been noted in lupus nephritis, which occurs in approximately half of SLE patients and is a major cause of morbidity and early mortality. Delay in diagnosis of lupus nephritis results in prolongation of renal inflammation, and often irreversible kidney damage.

The ability to predict patients at greater risk of lupus nephritis may improve surveillance, reduce time to diagnosis and treatment, and potentially result in improved outcomes in lupus nephritis. We evaluated the prognostic significance of an individual having an elevated IFN-signature trait and progression to lupus nephritis.

Methods: The study included 201 lupus patients, all meeting both the ACR 1997 and SLICC 2012 classification criteria for SLE from a single institution. The open cohort had a median follow-up time of 14.14 years [IQR 10.96, 19.83]. Stored whole blood RNA (PAXgene) samples from the earliest longitudinal timepoint on these 201 patients were assessed for interferon signatures using an IFN-responsive four gene expression assay (Autoimmune Profile Assay, DxTerity Diagnostics) to define an individual's overall IFN-signature trait. Lupus nephritis status was defined by the date of attainment of the renal component of the SLICC SLE classification criteria. Cox proportional hazards modeling was utilized to determine the contribution of IFN signature trait, age at SLE diagnosis, gender, and race to the development of lupus nephritis.

Results: The cohort of 201 SLE patients included 58 patients who developed lupus nephritis and 113 with a high IFN signature trait. Characteristics of the complete group, as well as IFN-signature subgroups, are displayed in Table 2. High IFN signature trait was an independent predictor for earlier time to development of nephritis (Hazard Ratio 3.36, p=0.0008) after adjusting for age at SLE diagnosis, gender, and race (Figure 1). In our Cox proportional hazards model, younger age at diagnosis of SLE, male gender, and nonwhite race were also associated with higher likelihood of nephritis development. Racial subgroup analyses found that high IFN signature remained a significant predictor of earlier nephritis when evaluating either non-white patients (Hazard Ratio 3.41, p=0.021) or white patients (Hazard Ratio 2.97, p=0.031), adjusting for age at SLE diagnosis and gender.

Conclusions: **Assessment of an individual's interferon signature phenotypic trait at the time of SLE diagnosis may be a useful tool.**

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Table 2

Variable	All		IFN High		IFN Low	
Total (n,%)	201	100%	113	56.22%	88	43.78%
Demographics						
Female (n,%)	180	89.11%	99	87.61%	81	92.05%
Race						
White/Caucasian	13	6.44%	12	10.62%	1	1.14%
Black/African American	47	23.27%	29	25.66%	18	20.45
Hispanic/Latino	23	11.39%	17	15.04%	6	6.82%
Native American	23	11.36%	17	15.05%	6	6.82%
White/Caucasian	95	47.03%	38	33.62%	57	64.77%
Age at SLE Diagnosis (median, IQR)	32.00	[23.00-43.00]	27.65	[22.00-37.00]	37.5	[26.00-44.25]
Lupus Nephritis (n,%)	**58**	**28.86%**	**48**	**42.48%**	**10**	**11.36%**

Figure 1 Hazard Ratio (HR)

HR non-white patients = 3.41
p = 0.021

HR white patients = 2.97
p = 0.031

HR cohort = 3.36
p = 0.0008

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Activation of the Interferon-α Pathway Identifies a Subgroup of Systemic Lupus Erythematosus Patients with Distinct Serologic Features and Active Disease

Kirou KA et al, Activation of the Interferon-α pathway identifies a subgroup of Systemic lupus erythematosus patients with distinct Serologic Features and active disease, Arthritis Rheum 52:1491–503 (2005).

Objective: Gene-expression studies have demonstrated increased expression of interferon (IFN)–inducible genes (IFIGs) in peripheral blood mononuclear cells (PBMCs) of many patients with systemic lupus erythematosus (SLE), with a predominant effect of type I IFN. This study examined the hypothesis that increased disease severity and activity, as well as distinct autoantibody specificities, characterize SLE patients with activation of the type I IFN pathway.

Methods: Freshly isolated PBMCs from 77 SLE patients, 22 disease controls, and 28 healthy donors were subjected to real-time polymerase chain reaction for 3 IFIGs that are preferentially induced by IFNα, and the data were used to derive IFNα scores for all individuals. Expression of IFIGs was significantly higher in SLE patients compared with disease controls or healthy donors. SLE patients with high and low IFNα scores were compared for clinical manifestations of disease, disease severity, disease activity, serologic features, and potential confounders, by bivariate and multivariate analyses.

Results: SLE patients with a high IFNα score had a significantly higher prevalence of renal disease, a greater number of American College of Rheumatology criteria for SLE, and a higher Systemic Lupus International Collaborating Clinics damage index (SDI) score than did SLE patients with low IFNα scores. Patients with high scores showed increased disease activity, as measured by lower C3 levels, hemoglobin levels, absolute lymphocyte counts, and albumin levels, and a higher anti–double-stranded DNA (dsDNA) titer, erythrocyte sedimentation rate, and SLE Disease Activity Index 2000 score. The presence of antibodies specific for Ro, U1 RNP, Sm, and dsDNA, but not phospholipids, was significantly associated with a high IFNα score. Logistic regression analysis confirmed that renal disease, higher SDI scores, low complement levels, and presence of anti–RNA binding protein (RBP) autoantibodies were associated with a high IFNα score.

Conclusions: Activation of the IFNα pathway defines a subgroup of SLE patients whose condition is characterized by increased disease severity, including renal disease, increased disease activity, reflected in complement activation, and autoreactivity to RBP for development of lupus nephritis.

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Sub-setting systemic lupus erythematosus by combined molecular phenotypes defines divergent populations in two phase III randomized trials

Petri M, et al, Sub-setting systemic lupus erythematosus by combined molecular phenotypes defines divergent populations in two phase III randomized trials, Rheumatology 2021;60:5390-5396 doi:10.1093/rheumatology/keab144.

Background: Heterogeneity of SLE patients is a major challenge, this paper used 4 biomarkers (IFN-1 high/low, anti-dsDNA (+/-), C3 and C4 (low/normal) to subset SLE patients.

Methods: Re-analysis of clinical data of 1747 patients from two randomized phase III Illuminate (tabalumab) clinical trials based on IFN-1, anti-dsDNA, C3 and C4. Correlations with clinical manifestations, medications, and patient geography were made (Table). Defined SLE (+) group (n=1500) as IFN-1 (high) or anti-dsDNA (+) and C3 or C4 (low) and compared with SLE(-) group (n=247) defined as IFN-1 (low), anti-dsDNA (-) and C3 and C4 normal.

Table 3

	SLE(+) (*n* = 1500)	SLE(-) (*n* = 247)	*P*-value
Mean SLEDAI	10.7	8.3	<0.001
SLEDAI >10	934 (62.3)	69 (27.9)	<0.001
SLEDAI organ system			
Immunological	1186 (79.1)	13 (5.3)	<0.0001
Mucocutaneous	1357 (90.5)	237 (96)	0.0047
Mucocutaneous	1296 (86.4)	235 (95.1)	0.0001
Haematological	147 (9.8)	4 (1.6)	<0.0001
Renal	135 (9)	11 (4.5)	0.0167
Vascular	121 (8.1)	6 (2.4)	0.0016
Cardiovascular/ respiratory	116 (7.7)	23 (9.3)	0.3957
Constitutional	29 (1.9)	2 (0.8)	0.2152

Baseline Therapy	SLE(+) (*n* = 1500)	SLE(-) (*n* = 247)	*P*-value
Corticosteroids	1166 (77.7)	121 (49)	<0.0001
Immunosuppressants	654 (43.6)	77 (31.2)	0.0002
AZA	305 (20.3)	26 (10.5)	0.0003
MTX	181 (12.1)	38 (15.4)	0.1445
Mycophenolate Mofetil	145 (9.7)	9 (3.6)	0.0020
Antimalarials	997 (66.5)	178 (72.1)	0.0823

Results: SLE (+) patients had more hematological, renal, and vascular involvement as well as higher use of corticosteroids and immunosuppressants, except for MTX compared to SLE (-) patients. SLE (+) patients had a 3 month shorter time to flare over 12 month period than SLE (-). US patients were 67.5% IFN-1 high vs >80% IFN-1 high for non-US patients. US patients had the highest prevalence of SLE (-) at 22% compared to Mexico/ Central America/South America (10%), Europe (7%) and the rest of the world (5%). Corticosteroid utilization was lower in IFN-1 low compared to IFN-1 high across all sub-categories.

Conclusion: Combinatorial analysis of the four biomarkers revealed subsets of SLE patients that discriminate by disease manifestations, concomitant medication use, geography, time to severe flare and SRI-4 response. **Corticosteroid utilization was correlated with both serology and IFN-1 status, and these observations suggest that IFN-1 status does impact disease severity.**

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Type-1 Interferon Status in Systemic Lupus Erythematosus: A Longitudinal Analysis

Northcott M et al., Type 1 Interferon Status in Systemic Lupus Erythematosus: A Longitudinal Analysis.
Lupus Science & Medicine 2022:9:e000625.

Background: Type 1 interferon (IFN-1) is key to the development and progression of SLE as supported by the increased expression of IFN-stimulated genes (ISGs) in most patients. However, the clinical utility of repeated ISG expression assessment is unknown. As IFN-blocking drugs are being introduced as SLE therapies, we aimed to determine if longitudinal assessment of ISG levels correlated to IFN status and clinical findings.

Methods: Clinical data and whole blood were collected from adult SLE patients, prospectively, at a single lupus care clinic. Whole blood RNA samples were collected and stabilized in PAXgene tubes. IFN status was measured with the Modular Immune Profile test (DxTerity Diagnostics), that includes a panel of 4 ISGs (HERC5, IFI27, IFIT1 and RSAD2) and 3 housekeeping genes (ACTB, GAPDH, and TFRC). ISG RNA expression levels were normalized to expression levels of the housekeeping genes. A DxTerity 4-gene IFN-1 signature score was calculated by averaging the normalized gene expression values of the 4 ISGs. After thresholding, an IFN-1 score was determined and categorized as IFN-1 High or IFN-1 Normal. A stable IFN status was determined for patients that showed the same IFN high or low status in all serial testing events. Multiple statistical analysis methods were used to determine significance.

Results: 729 samples were analyzed from 205 SLE patients. At baseline, 62.9% of patients were IFN high, 30.2% IFN low, and 6.8% borderline. 142 patients participated in the longitudinal analysis with 87.3% of these patients showing stable ISG status over time. Clinical assessment of IFN high patients over time showed that IFN high patients had higher disease activity affecting multiple organs and spent less time in Lupus Low Disease Activity State (LLDAS) (Table 4). However, IFN score did not correlate with SLE Disease Activity Index in individual patients. A small subset of patients showed large fluctuations in ISG expression over time, but most were treated with high-dose glucocorticoids that correlated with ISG suppression. Of note, low-to-moderate dose glucocorticoids did not suppress ISG activity.

Conclusions: IFN high status is associated with indicators of more severe SLE disease activity. However, in this study the majority of patients showed stable expression of ISGs over time and a lack of correlation of ISG expression with disease activity. ISG expression changes were observed in some patients receiving high-dose, but not routine dose, glucocorticoids. Study findings suggest that baseline ISG measurement, but not serial ISG measurement, may be of value in the management of SLE.

Table 4: Composite disease activity measurements

Baseline Therapy	Initial IFN HIGH	Initial IFN LOW	*P*-value (Initial HIGH vs Initial LOW)	Multivariate Analysis	Stable IFN HIGH	Stable IFN LOW	*P*-value (Stable HIGH vs Stable LOW)	Multivariate Analysis
Time adjusted mean SLEDAI (AMS) Median [range]	4.2 [0-14.3]	2.0 [0-10.0]	P=,0.0001	P=0.01	4.2 [0-13.0]	2.6 [0-8.0]	P=0.001	P=0.07
Percentage time spent in LLDAS Median [range]	55.5 [0.100]	84.0 [0-100]	P=0.0003	P=0.06	61.0 [0-100]	91.0 [0-100]	P=0.001	P=0.16
Mild/Moderate flare during study period (n(%) of pateints with at least one flare)	69 (53.5%)	15 (25.8%	OR 3.31 [1.72-6.58] P=0.0004	OR 2.87 [1.44-5.93] P=0.003	46 (54.1%)	12 (30.8%)	OR 2.65 [1.21-6.09] P=0.017	OR 2.10 [0.88-5.19] P=0.10
Severe flare during study period (% of patients with at least one flare)	34 (26.4%)	4 (6.5%)	OR 5.19 [1.94-18.04] P=0.003	OR 5.35 [1.90-19.41] P=0.003	27 (31.8%)	3 (7.7%)	OR 5.59 [1.80-24.58] P=0.008	OR 5.69 [1.66-27.19] P=0.012

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Additional information for Table 1

*Percentages of responders, the differences between groups, 95% CIs and nominal p values were calculated using a stratified Cochran- Mantel- Haenszel method with stratification factors SLEDAI- 2K score at screening (<10 vs ≥10), GC dosage at week 0 (<10 mg/day vs ≥10 mg/day of prednisone or equivalent) and study. In the overall analysis, IFNGS status at screening (high vs low) was also a stratification factor. Patients treated with restricted medication beyond protocol- allowed thresholds and those who discontinued investigational product were classified as non- responders; between- group differences were calculated in percentage points (the percentage in the anifrolumab group minus the percentage in the placebo group), except as indicated.

‡Defined as an oral GC taper to ≤7.5 mg/day from week 40 to week 52 in patients receiving ≥10 mg/day of oral GCs at baseline (prednisone or equivalent).

ǂAmong patients with baseline CLASI- A score ≥10.

§Among patients with ≥6 swollen and ≥6 tender joints at baseline.

¶Values are annualised flare rates; difference is a rate ratio (with 95% CIs) rather than a percentage point difference. A flare is defined as either ≥1 new BILAG- 2004 A or ≥2 new BILAG- 2004 B items compared with the previous visit.

**FACIT- F response defined as a >3- point improvement from baseline to week 52.

‡‡SF- 36 MCS response defined as a >4.6- point improvement from baseline to week 52.

‡‡SF- 36 PCS response defined as a >3.4- point improvement from baseline to week 52.

BICLA, BILAG- based Combined Lupus Assessment; BILAG- 2004, British Isles Lupus Assessment Group 2004; C, complement; CI, confidence interval; CLASI- A, Cutaneous Lupus Erythematosus Disease Area and Severity Index- Activity; FACIT- F, Functional Assessment of Chronic Illness Therapy- Fatigue; GC, glucocorticoid; IFNGS, interferon gene signature; MCS, mental component summary; N, number of patients in group; n, number of responders; NA, not available; PCS, physical component summary; SF- 36, Short Form 36 Health Survey; SLE, systemic lupus erythematosus; SLEDAI- 2K, SLE Disease Activity Index 2000; SRI(4), SLE Responder Index of ≥4.

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