Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

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GRAND ROUNDS CLINICI DEL MERCOLEDÌ

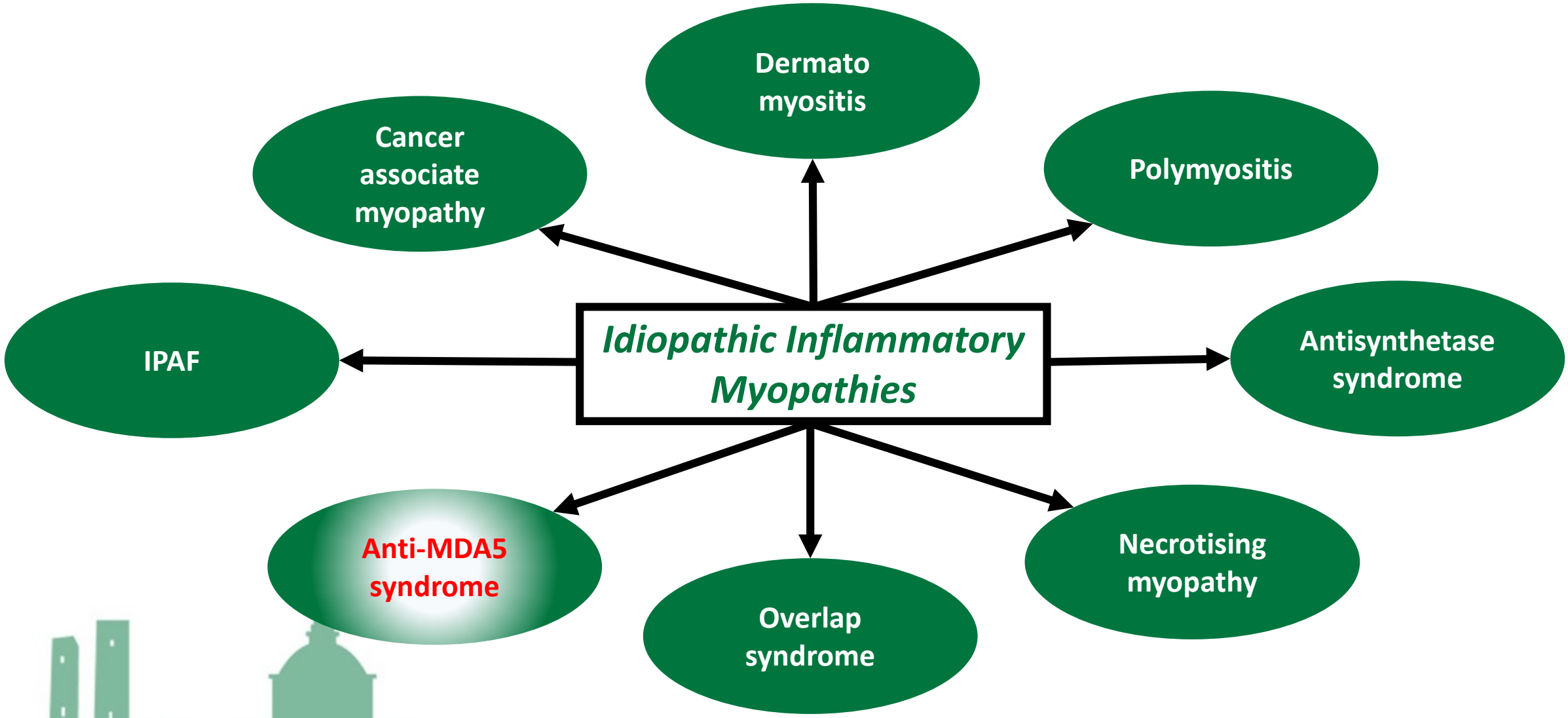
con il Policlinico San Matteo

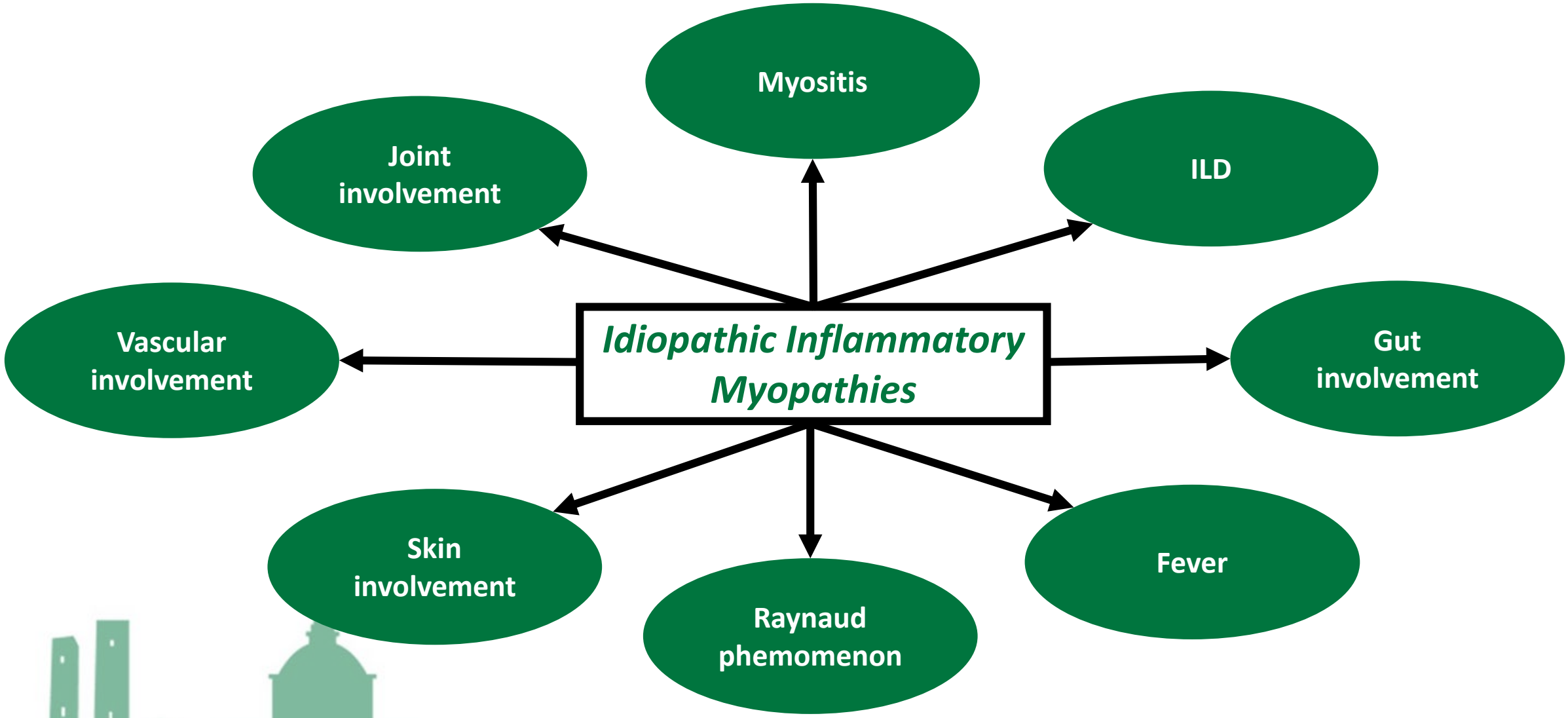
Aula Magna "C. Golgi" & WEBINAR

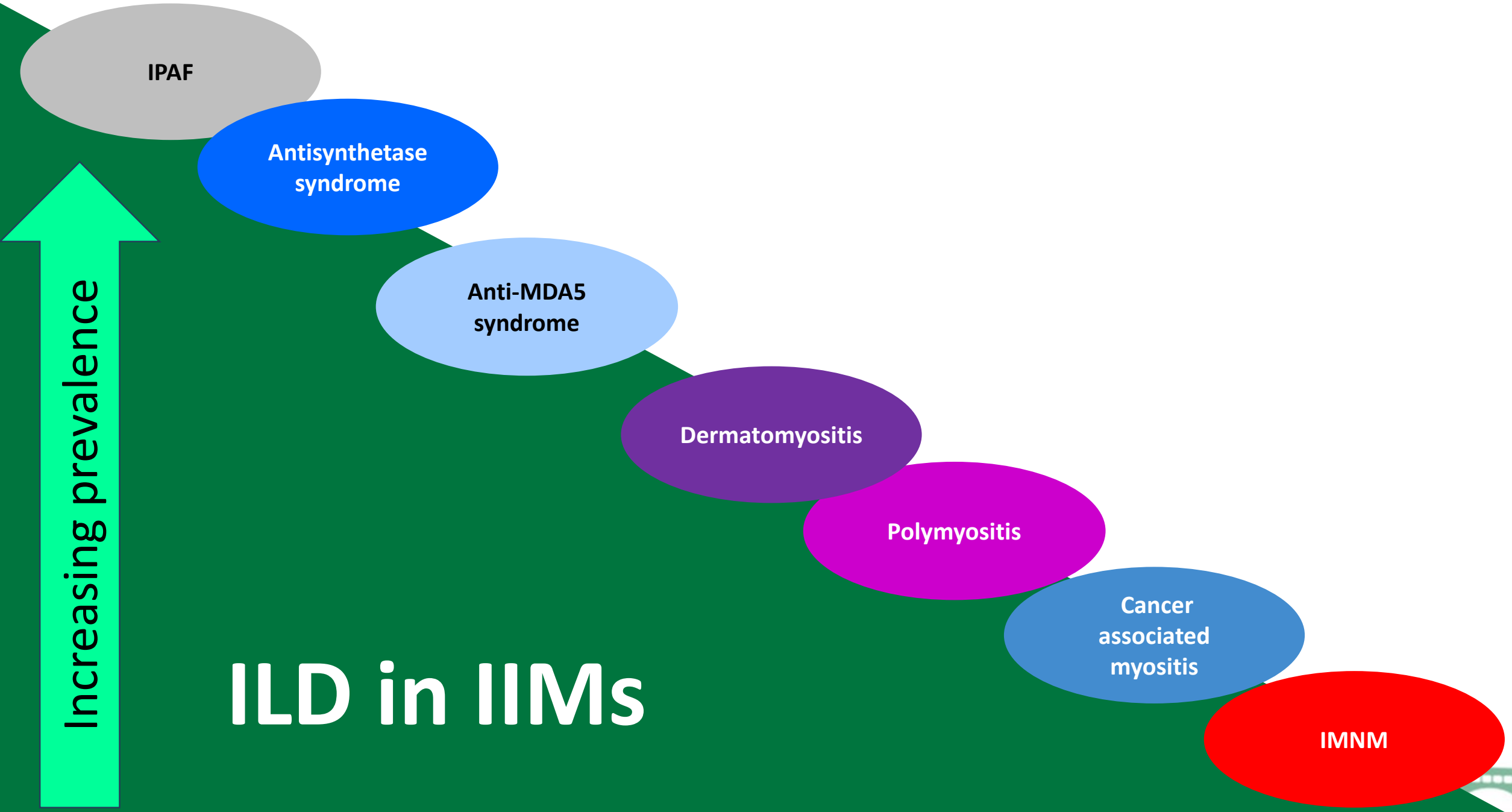
17 OCT 2024

Lorenzo Cavagna, Rheumatology Unit

An emergency to consider: the anti-MDA5 syndrome


Dermato myositis
Cancer associate myopathy
Polymyositis
IPAF
Idiopathic Inflammatory Myopathies
Antisynthetase syndrome
Anti-MDA5 syndrome
Overlap syndrome
Necrotising myopathy


Myositis
Joint involvement
ILD
Vascular involvement
Idiopathic Inflammatory Myopathies
Gut involvement
Skin involvement
Raynaud phemomenon
Fever


IPAF
Antisynthetase syndrome
Anti-MDA5 syndrome
Dermatomyositis
Polymyositis
Cancer associated myositis
IMNM
Increasing prevalence
ILD in IIMs

Myositis Specific and associated autoantibodies

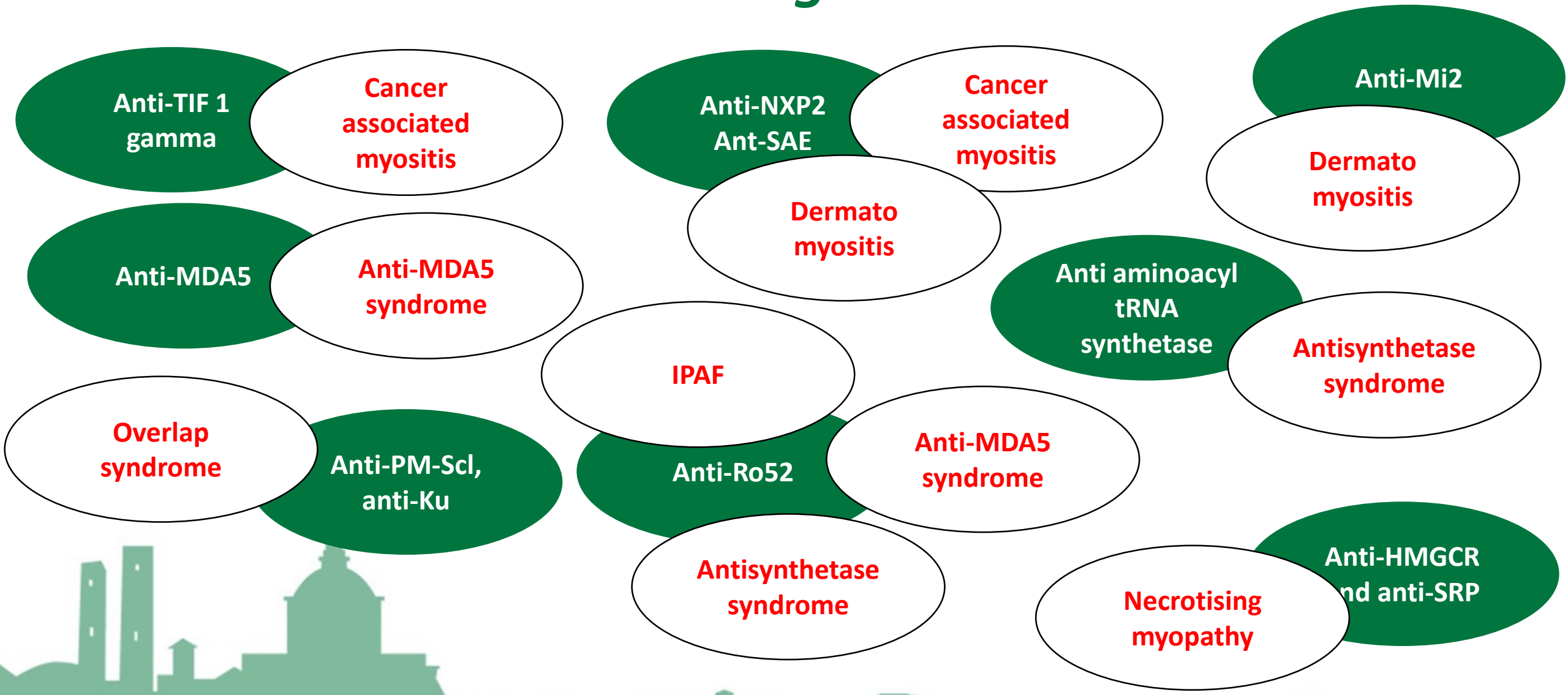
Auto-antibodies*	Autoantigen target
Anti-aminoacyl tRNA synthetase - **Jo-1** - **PL7** - **PL12** - **OJ** - **EJ** - **Zo, KS, Ha, etc**	*Aminoacyl-tRNA synthetase* - Histidyl – tRNA synthetase - Threonyl – tRNA synthetase - Alanyl – tRNA synthetase - Isoleucyl – tRNA synthetase - Glycyl – tRNA synthetase - Other t-RNA synthetase
Anti-Mi-2	Nucleosome remodelling deacetylase complex
Anti-TIF-1γ	Transcriptional intermediary factor 1 gamma
Anti-NXP2	Nuclear matrix protein 2
Anti-SAE	Small ubiquitin-like modifier activating enzyme (SAE)
Anti-MDA5	Melanoma Differentiation Associated gene5 (MDA5)
Anti-SRP	Signal recognition particle (SRP)
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase (HMGCR)

PM-Scl

RNP

Anti-Ro52

The clinical-serological correlations



2017 EULAR/ACR IIMs Classification Criteria

Muscle involvement

Variable	Score points: No biopsy	Score points: Biopsy
Age of onset of first related symptoms		
18–40	1.3	1.5
≥40	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo-1 (anti-histidyl-tRNA synthetase) autoantibody positivity	3.9	3.8
Elevated serum levels of creatine kinase (CK)* *or* lactate dehydrogenase (LDH)* *or* aspartate aminotransferase (ASAT/AST/SGOT)* *or* alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4
Muscle biopsy features		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

Skin involvement

Lundberg I, et al. ARD 2017 PMID: 29079590

Issues in the classification of myositis patients: an ongoing process

NO ILD

NO JOINT INVOLVEMENT

ONLY ANTI-Jo1 Ab (is this an antisynthetase syndrome?)

NO RAYNAUD PHENOMENON

NO FEVER

NO SHORT TERM DISEASE (only > 6 months)

DEFINE DYSPHAGIA

NO HIKER'S FEET

NO MECHANIC'S HANDS

NO ALDOLASE

Zanframundo G, et al. Clin Exp Rheum 2024; PMID 38372711

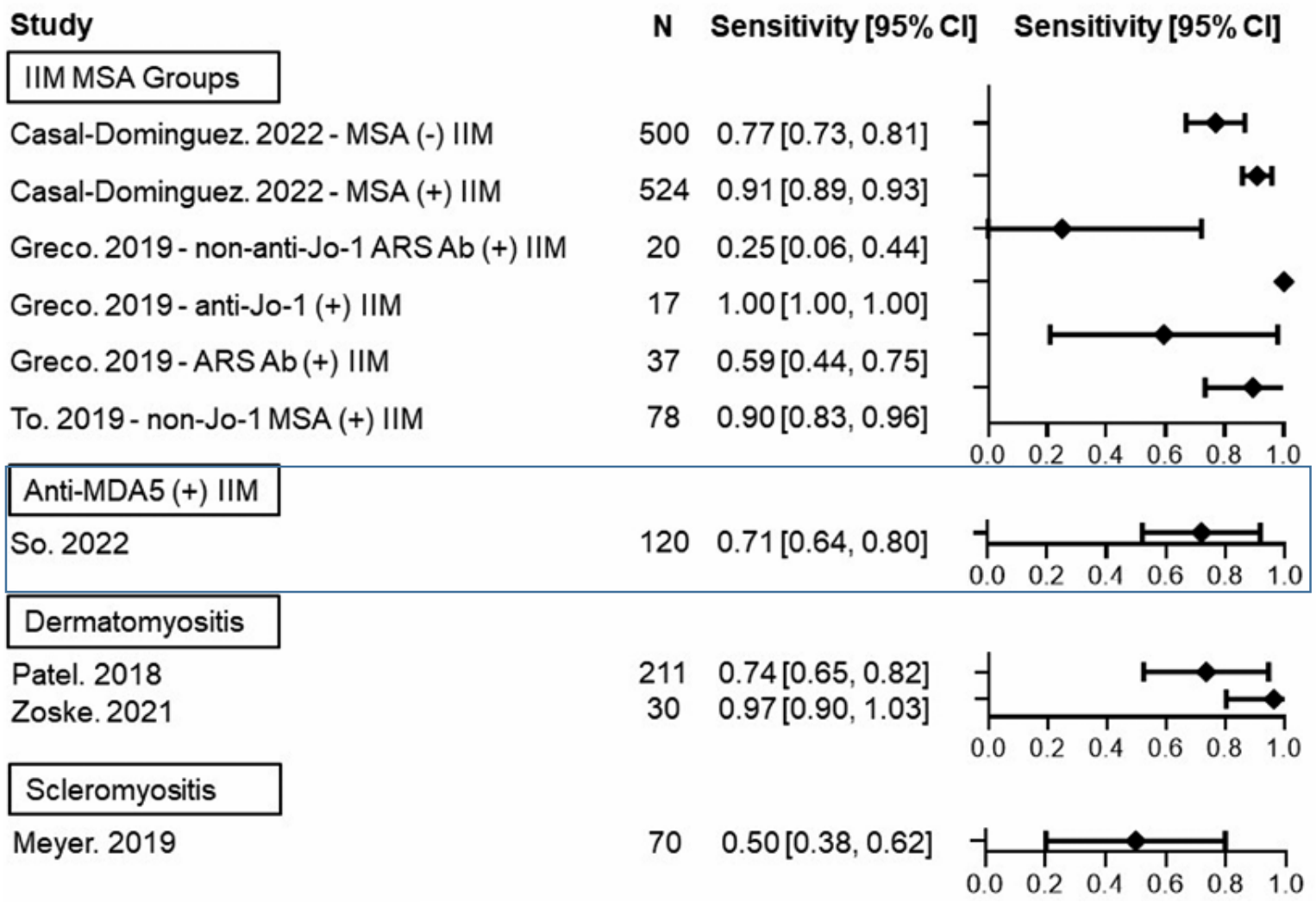
Performance of 2017 EULAR/ACR IIMS Classification Criteria

ORIGINAL PERFORMANCE

OVERALL
Sensitivity 87.7%
Specificity 98%

DM
Sensitivity 90%
Specificity 100%

PM
Sensitivity 73%
Specificity 99%



Saygim D, et al. Clin Exp Rheumatol 2024
PMID: 38436279

Patient: K.G., 55 years old female, biologically male (no gender transition), never smoker, nurse.
Previous clinical history apparently unremarkable

CLINICAL HISTORY ONSET (other Hospitals)

May 2021	Jul 2021	Jan 2022	Jul 2022	Aug 2022
NSIP/OP	**1st ILD flare**		**2nd ILD flare** Spontaneous Pneumodediastinum	ILD improvement Pneumodistinum resolution
6MP 80 mg x 3 D (I.V.) → PDN 5 mg/D	PDN 50 mg/D	STOP PDN	6MP 1 g x 3 D (I.V.)	Azathioprine 100 mg/D PDN 50 mg/D
No O2 therapy	No O2 therapy		HFNC	2 L/min (at rest/overnight) 5 L/min (on exertion)

ANA and ENA always negative; improvement with corticosteroids;
NO COVID19

✓ **September 2022: pre-FLARE status**

- 09/09 pulmonology outpatient clinic assessment
  - **O2 therapy: 1 L/min at rest/overnight, and 3 L/min on exertion**
  - Prednisone: tapering from 50 to 40 mg/day
  - Azathioprine maintained

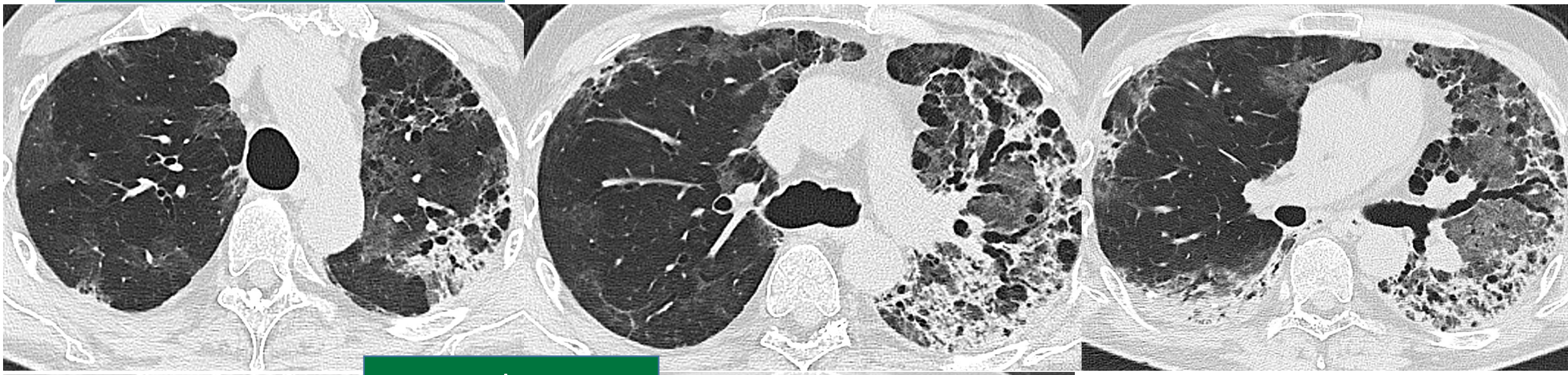
✓ **September 2022:**

- **17/09: 3rd FLARE, with dyspnea and cough worsening; fever (38° C)**
- 23/09: further clinical worsening and Emergency Department referral (ASST Lodi)
  - CRP 24.3 mg/dl, PCT 0.16 (N), Sars-CoV2 nasal swab negative
  - Blood gas analysis (O2 15 L/min reservoir): PaO2 62.9, PaCO2 37.6, SaO2 92.5%
  - Blood gas analysis (Venturi mask FiO2 60%): PaO2 91.8, PaCO2 42.3, SaO2 97.4%

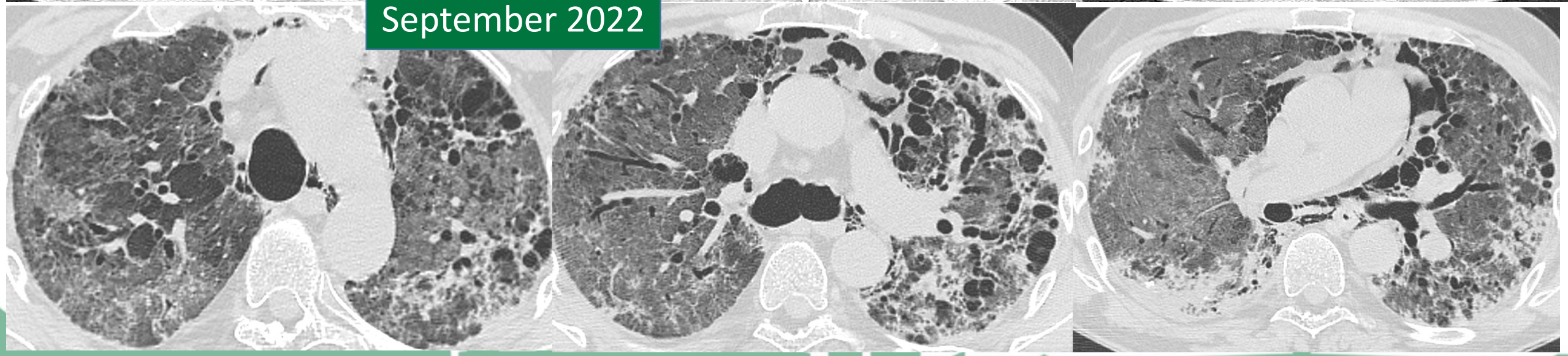
✓ **September 2022:**

- 23/09: ASST Lodi Pulmonology Unit admission
  - HFNC (then NIV)
  - Lab. tests: normal CPK; **ferritinemia (869 ng/ml), lymphopenia (960/mmc)**, ESR 84 mm/1h, CRP 24.3 mg/dl
  - Levofloxacin and piperacilline/tazobactam (but no INFECTIONS were identified)
  - New chest HRCT: worsening of lung involvement with **NSIP and OP aspects; pneumomediastinum (on HFNC)**

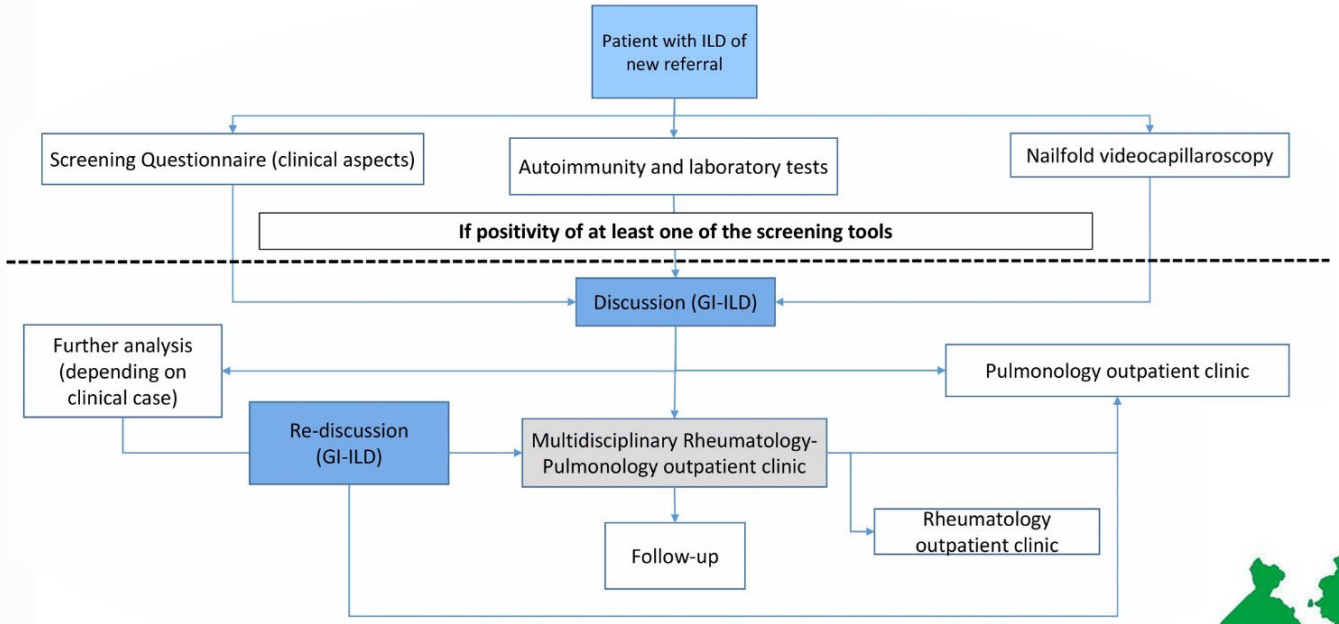
August 2022



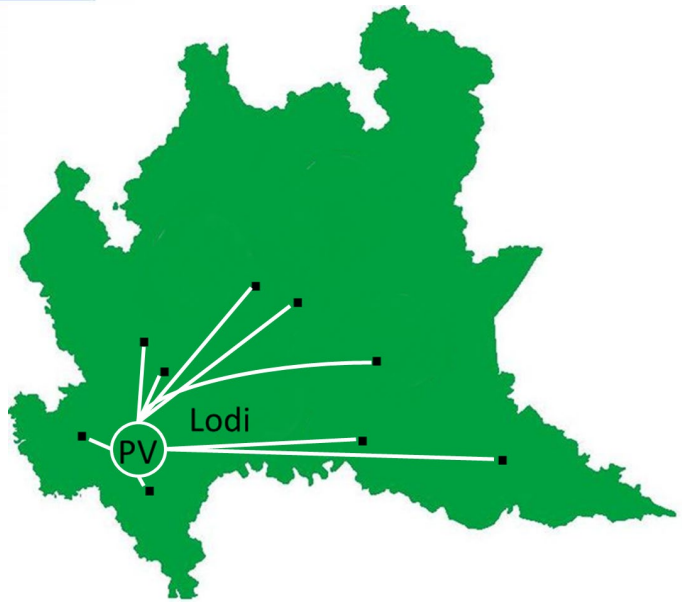
September 2022



IRCCS Policlinico S.Matteo National and Regional Hub for CTD-ILD: ILD platform for patients screening



Tirelli C, et al. Front Med (Lausanne) 2020, PMID: 32133362.



✓ **September 2022:**

- 27/09: search for myositis specific/associated antibodies; Rheumatology consultation: ……**mild dysphagia and mechanic's hands** at disease onset (2021) disappeared after corticosteroids therapy…»
- 28/29/30-09: 6MP 1 g I.V.
- 29/09: AUTOIMMUNITY: **anti-MDA5** antibodies positivity (ANA and ENA negative)

Diagnosis of anti-MDA5 syndrome

The anti-MDA5 syndrome characteristics

Anti-MDA5 antibodies 100% of case

- *Anti-Ro52 antibodies: 32% of cases*
- *ANA cytoplasmic positivity: 19% of cases*
  - *ANA negative: 32% of case*

Serological markers

Other common lab findings: hyperferritinemia and lymphopenia

Skin involvement *: 74% of cases

Arthritis §: 51% of cases

Myositis: 51% of cases

Interstitial lung disease: 72% of cases

Main clinical findings

* Skin ulcers, mechanic's hands, and dermatomyositis rashes

§ Not rarely close to RA

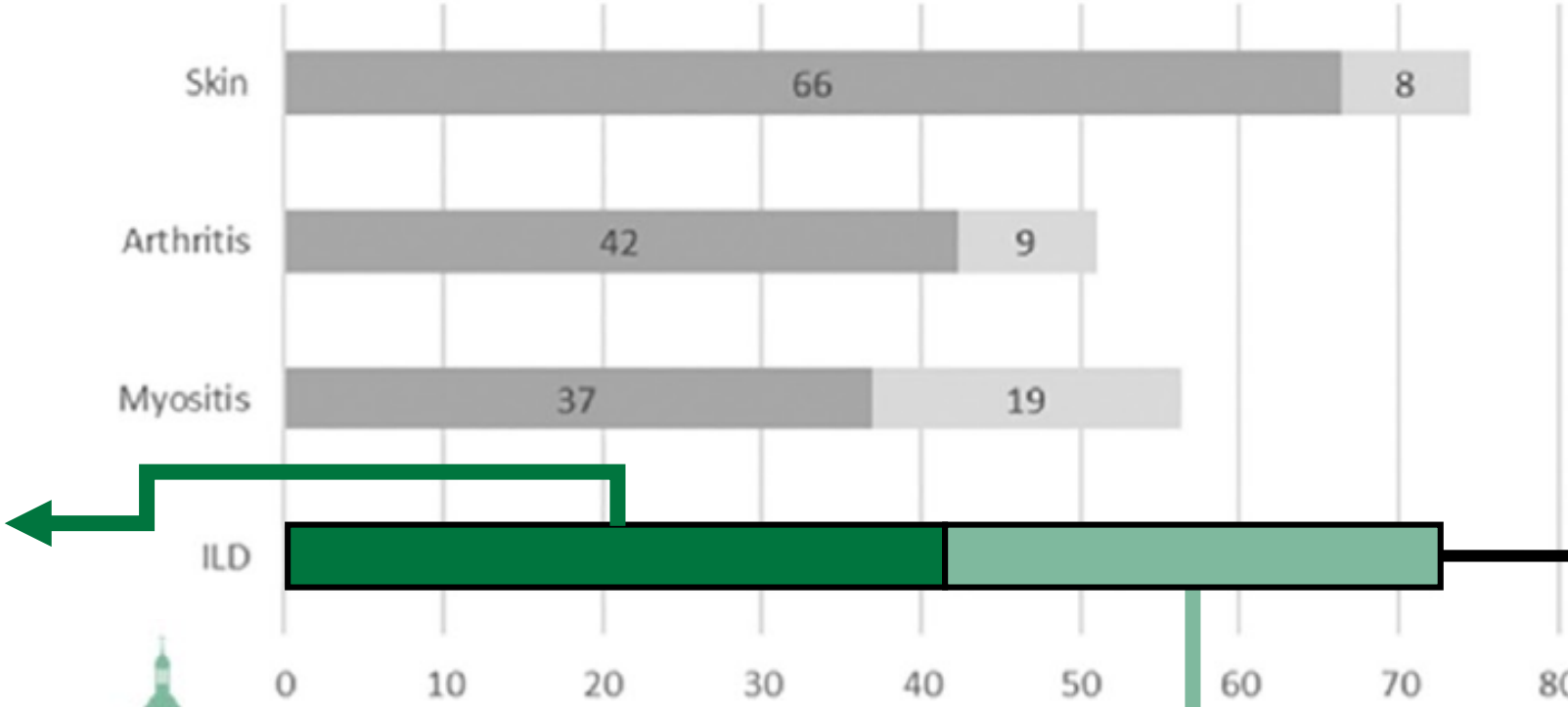
Raynaud's phenomenon 30% of cases

Fever: 29% of cases

Other findings

Cavagna L, et al. Clin Exp Rheum 2022 PMID: 35200123

Clinical spectrum time course in non-Asian patients positive for anti-MDA5 antibodies



Total: 149 patients

42% of patients had ILD from disease onset

72% of patients had ILD

30% of patients had ILD after disease onset

Cavagna L, et al. Clin Exp Rheum 2022 PMID: 35200123

Pneumomediastinum

Spontaneous pneumomediastinum in anti-MDA5 positive dermatomyositis: prevalence, risk factors, and prognosis

- Prevalence 9.4%
- Median time to onset: 5.5 months
- High rate of fever, and infections (CMV and fungal)
- No impact in the prognosis

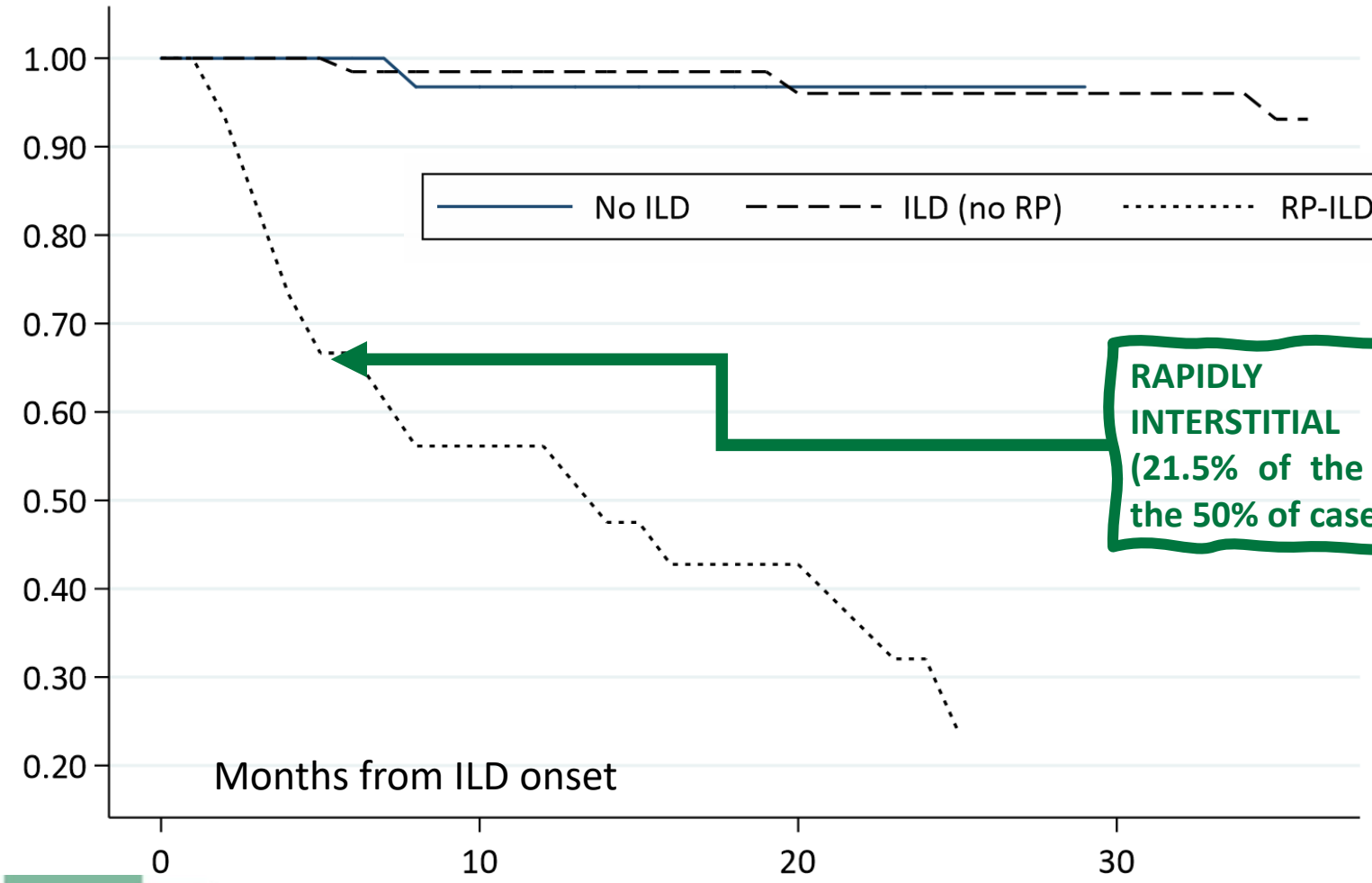
Qiwen J, et al Semin Arthritis Rheum 2024 PMID: 38185078

Prognosis of spontaneous pneumomediastinum occurring in DM or PM patients with ILD according to antimelanoma differentiation-associated gene 5 antibody status: a retrospective cohort study

- In anti-MDA5 antibody spontaneous pneumodiastinum occurrence is associated with higher mortality

Kazuya A, et al. RMD open 2023 PMID 36759007

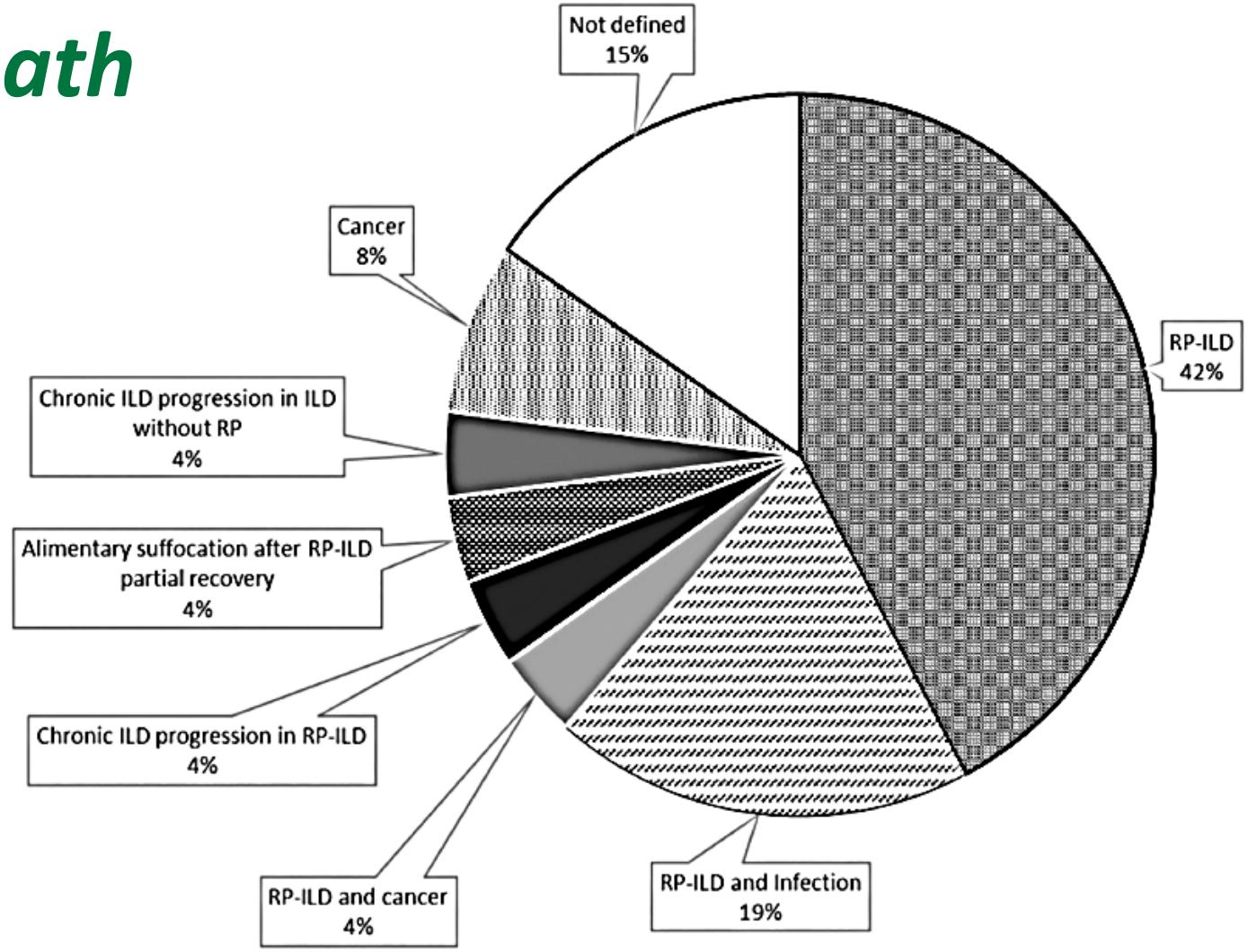
Kaplan-Meier survival curve



RAPIDLY PROGRESSIVE INTERSTITIAL LUNG DISEASE (21.5% of the cohort) in about the 50% of cases anti-Ro52 +

Cavagna L, et al. Clin Exp Rheum 2022 PMID: 35200123

Overal causes of death



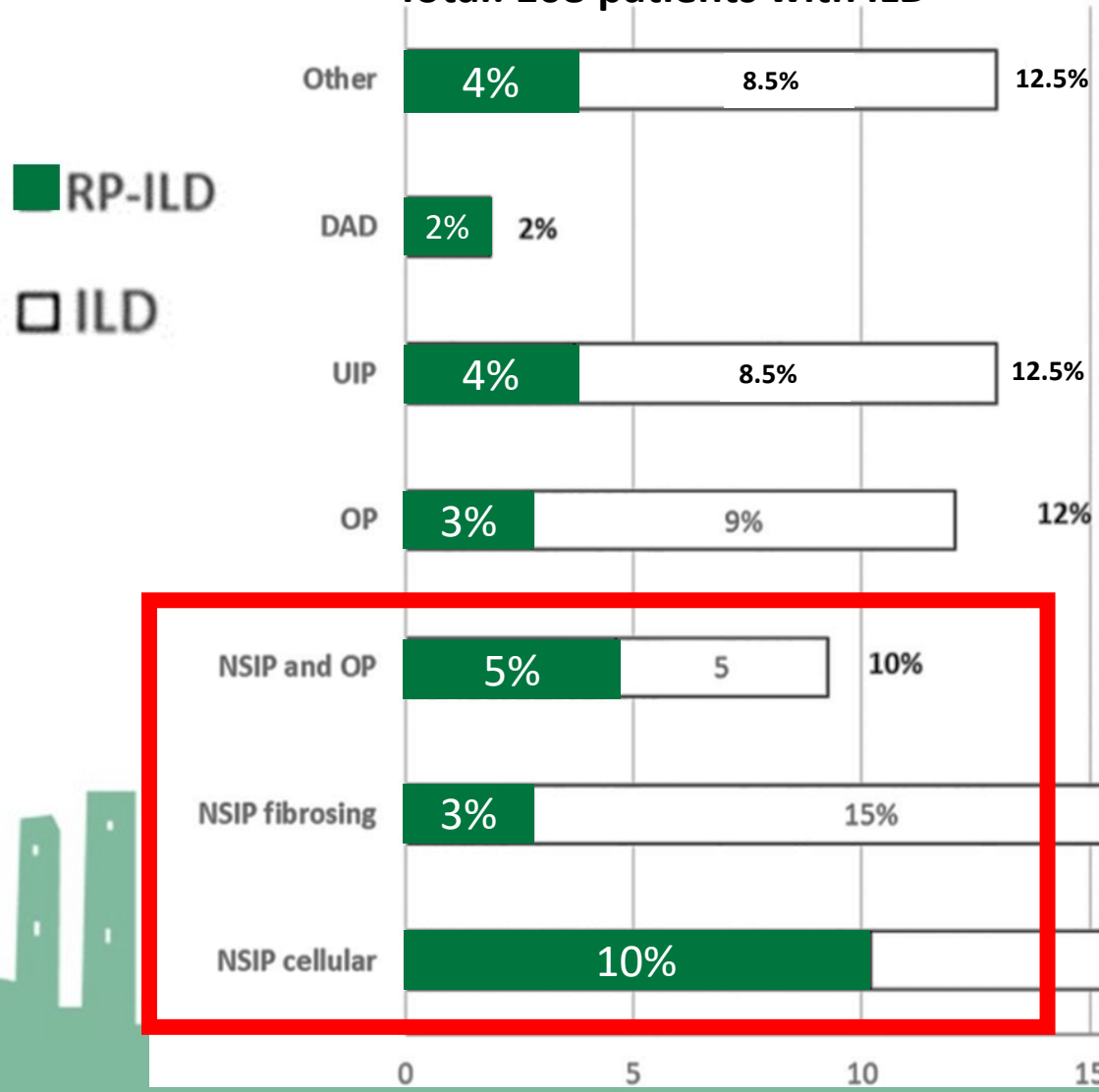
Cavagna L, et al. Clin Exp Rheum 2022 PMID: 35200123

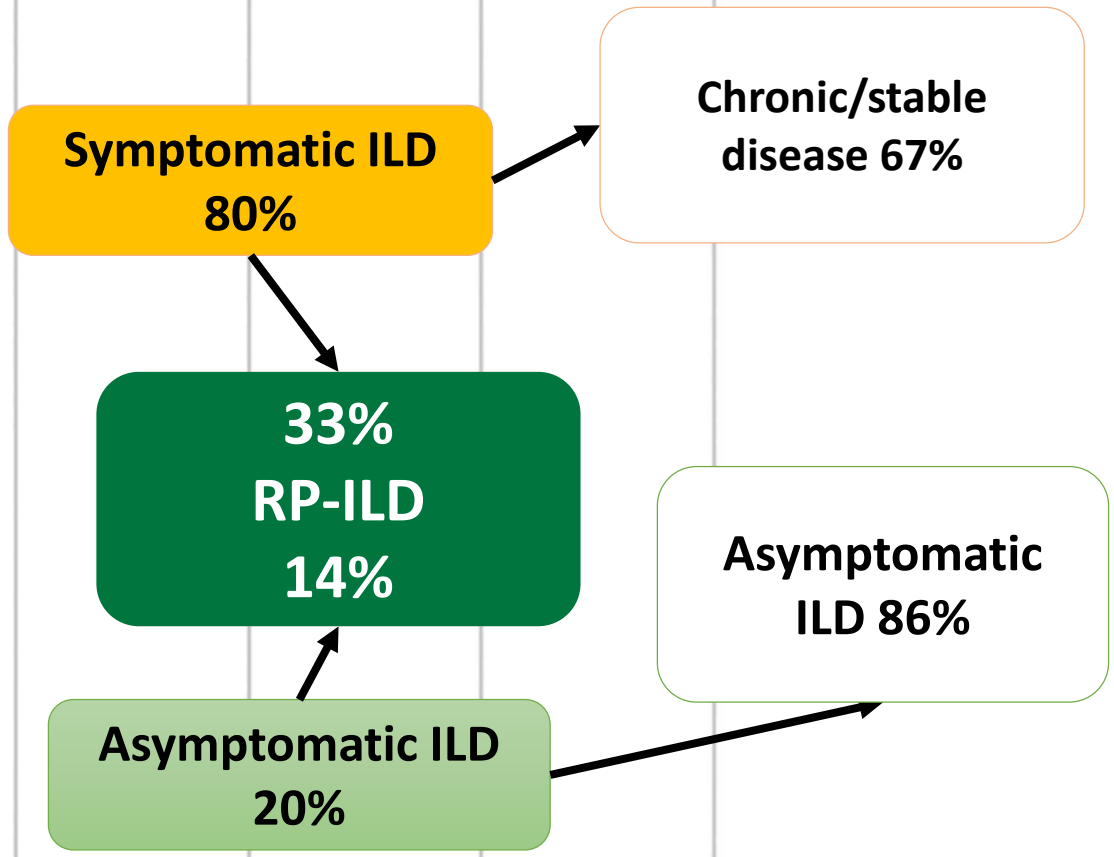
Clin Exp Rheum; 2022; 40: 274-283.

Pattern of ILD involvement (even in RP-ILD)

Total: 108 patients with ILD

Cavagna L, et al. Clin Exp Rheum 2022 PMID: 35200123





RP-ILD treatment approach

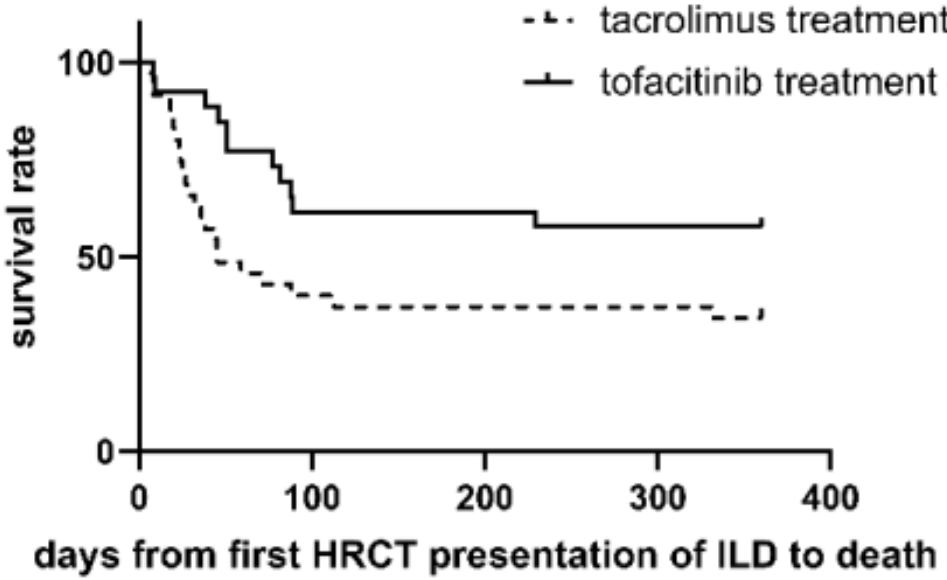
RP-ILD	Number (%)	Steroid pulses (1 g/day for 3-5 days, IV)	Steroid (PO)	Cyclosporine (PO)	Micophenolate mofetil (PO)	Cyclophos-phamide (IV)	Rituximab (IV)	IVIG	ECMO	No immuno-suppressive treatment
In ICU (alive)	13 (41)	5 (16)	1 (3)	1 (3)	5 (16)	5 (16)	5 (16)	1 (3)	2 (6)	0 (0)
In ICU (**death**)*	19 (59)	13 (41)	0 (0)	7 (22)	1 (3)	9 (28)	5 (16)	7 (22)	4 (13)	1 (3)
In the 6 months before ICU admission	28 (87%)	4 (13)	6 (19)	6 (19)	6 (19)	6 (19)	6 (19)	6 (19)	0 (0)	3 (9.5%)

ICU: intensive care unit; MMF: mycophenolate mofetil; RTX: rituximab; IVIG: intravenous immunoglobulins; ECMO: extracorporeal membrane oxygenation; PDN: prednisone; IV: intravenous; PO: per os.

TREATMENT PERFORMED BEFORE THE ADMISSION IN ICU

Cavagna L, et al. Clin Exp Rheum 2022 PMID: 35200123

A Retrospective Analysis of Outcome in MDA5-Related Interstitial Lung Disease Treated with Tofacitinib or Tacrolimus



35 pts

26 pts

Overall

6 month mortality: tofa=38.5% tac = 62.9% (P=0.028)

12 mont mortality: tofa=44% tac = 65.7% (P=0.031)

RP-ILD

6-month mortality RP-ILD: tofa=76.9% tac=95.5% (p=0.021)

12-month mortality RP-ILD: tofa=84.6% tac=100% (p=0.017)

The adjusted model showed that tofacitinib exposure was associated with a 1-year mortality lower risk HR=0.438, 95% CI 0.200-0.960 (p=0.039).

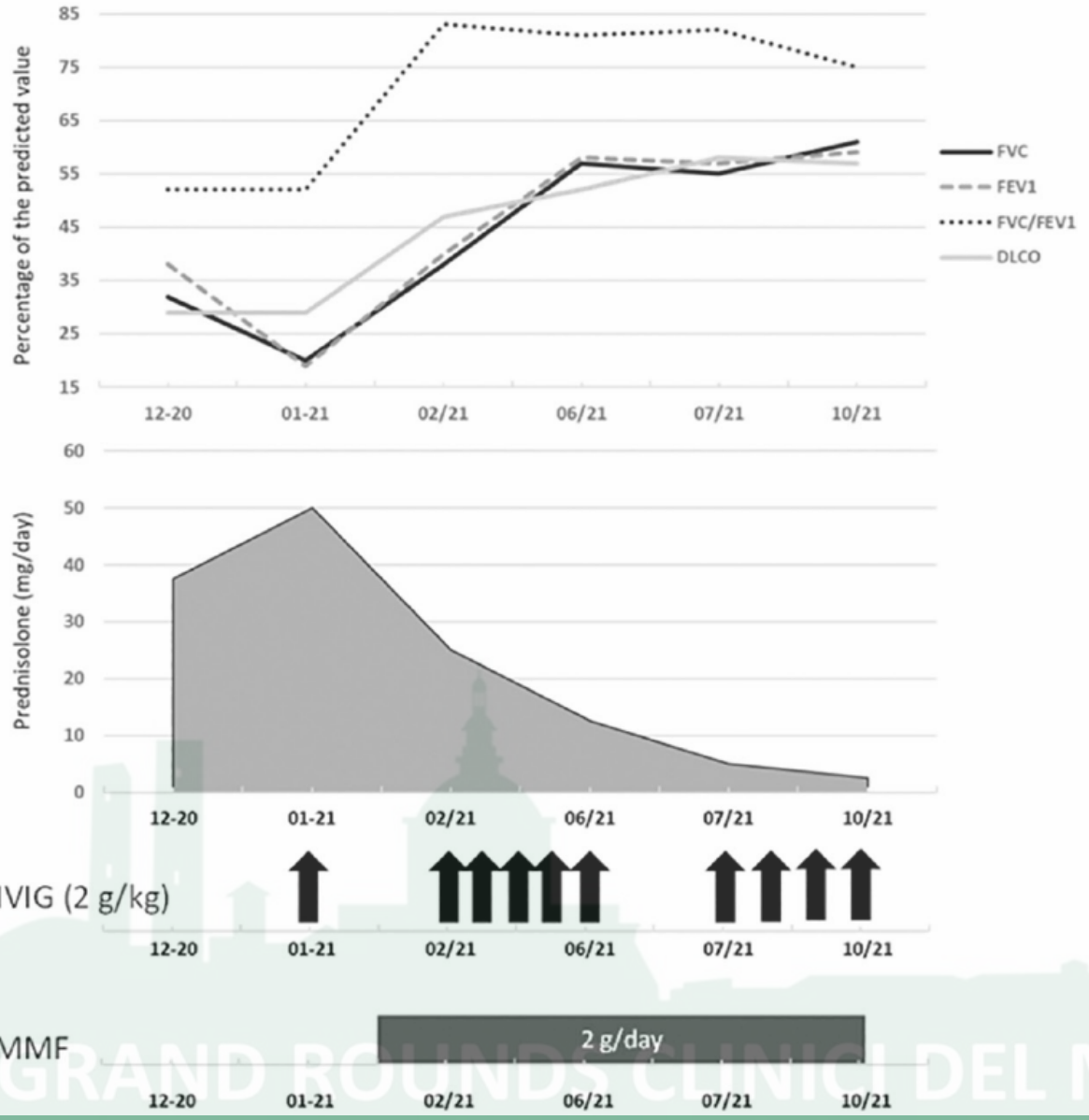
Fan L et al. J Rheumatol. 2024 PMID: 38185078

Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis

The IVIG group (n = 31) showed significantly lower 6-month mortality rate than the non-IVIG group (n = 17) (22.6% vs 52.9%; P =0.033). The IVIG group patients had a higher remission rate at 3 months (71.0% vs 41.2%; P =0.044). Gradual reduction was observed in the first 3 months with regard to the titre of anti-MDA5 autoantibody, the serum level of ferritin and the ground glass opacification GGO scores.

Wang LM, et al. Rheumatology (Oxford) 2022 PMID: 34940809

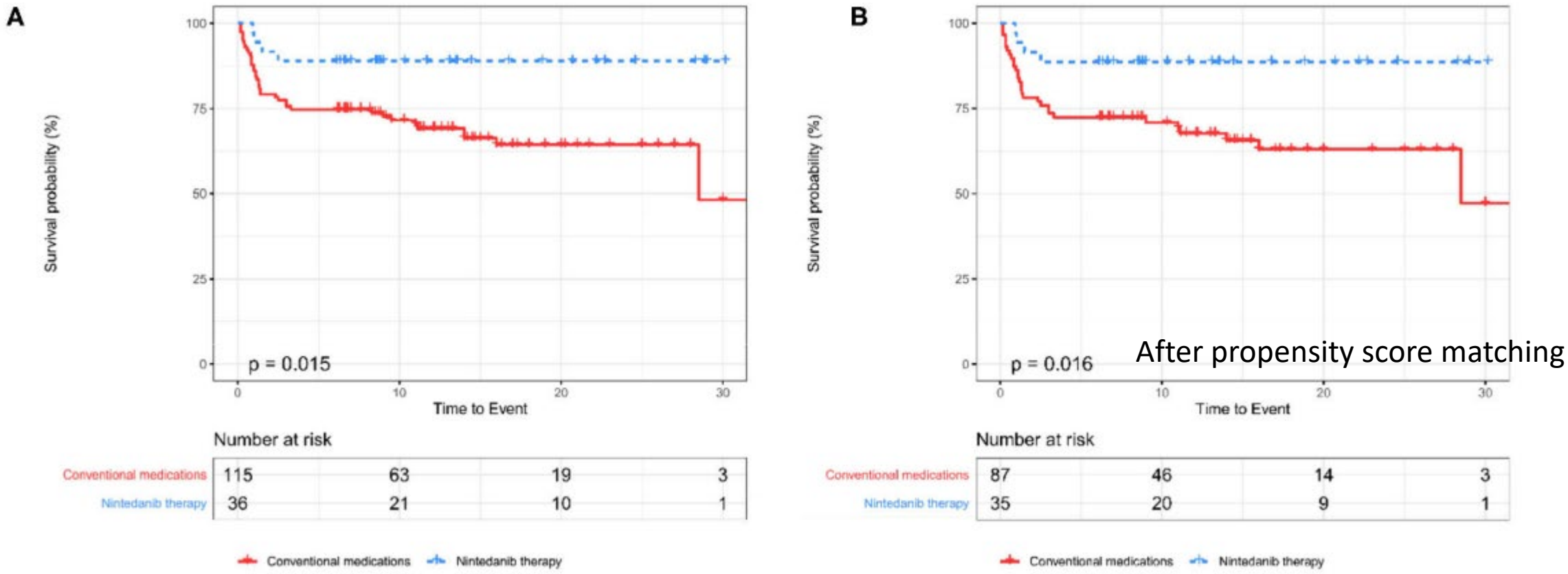
Respiratory failure due to concomitant interstitial lung disease and diaphragmatic involvement in a patient with anti-MDA5 dermatomyositis: a case report



	Jan. 2021	Feb. 2021	June 2021
Diaphragm ultrasound			
Right			
Expiratory thickness (cm)*	0.18	0.18	0.18
Inspiratory thickness (cm)*	0.21	0.21	0.30
Thickening fraction (%)*	15.09	18.52	25.45
Excursion – normal inspiration (cm)*	1.10	1.07	1.47
Excursion – forced inspiration (cm)*	2.00	2.10	3.40
Left			
Expiratory thickness (cm)*	0.20	0.20	0.19
Inspiratory thickness (cm)*	0.24	0.24	0.26
Thickening fraction (%)*	20.00	21.67	36.84
Excursion – normal inspiration (cm)*	2.17	2.07	2.00
Excursion – forced inspiration (cm)*	3.70	3.90	4.10

Grignaschi S, et al. Clin Exp Rheum 2022 PMID: 35200123

Efficacy and Tolerability of Nintedanib in Idiopathic-Inflammatory-Myopathy-Related Interstitial Lung Disease: A Pilot Study



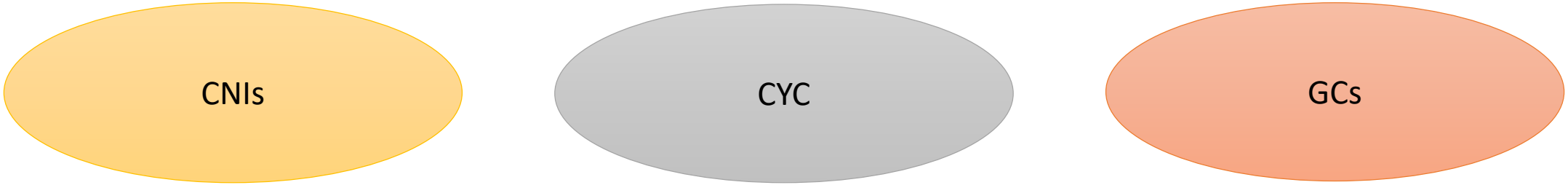
After propensity score matching

"Lower incidence of RP-ILD (P = 0.017, P = 0.014, respectively) in patients with nintedanib therapy" (anti-MDA5 + patients: 25 in conventional treatment and 9 in nintedanib + conventional treatment---MTX, Cys, CYC, etc, etc)

Liang J, et al. Front Med (Lausanne) 2021 PMID: 33614683

Treatment

- No clinical trials or high-level evidence
- **Glucocorticoids** in combination with immunosuppresant is the most widely uses approach
- Some evidence on TRIPLE COMBINATION THERAPY:



- Triple combination therapy provides better outcomes but higher incidence of opportunistic infections Other treatments to be taken into account

IVIG

PEX

RTX
(high doses)

TOFA
(better than TAC?)

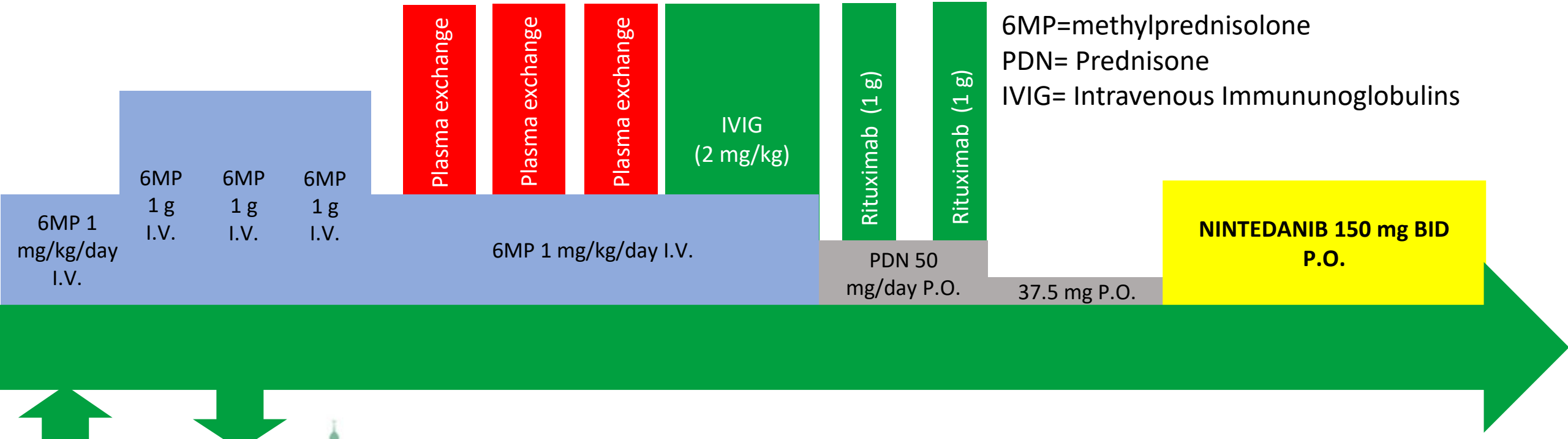
NINTEDANIB

J Rheumatol. 2022 Dec;49(12):1356-1364
Nat Rev Rheumatol. 2024 Jan;20(1):48-62.

Semin. Arthritis Rheum. 50, 776–790 (2020).
Arthritis Rheumatol. 72, 488–498 (2020).

Clin. Rheumatol. 37, 1983–1989 (2018).
Wang LM, et al. Rheumatology (Oxford) 2022

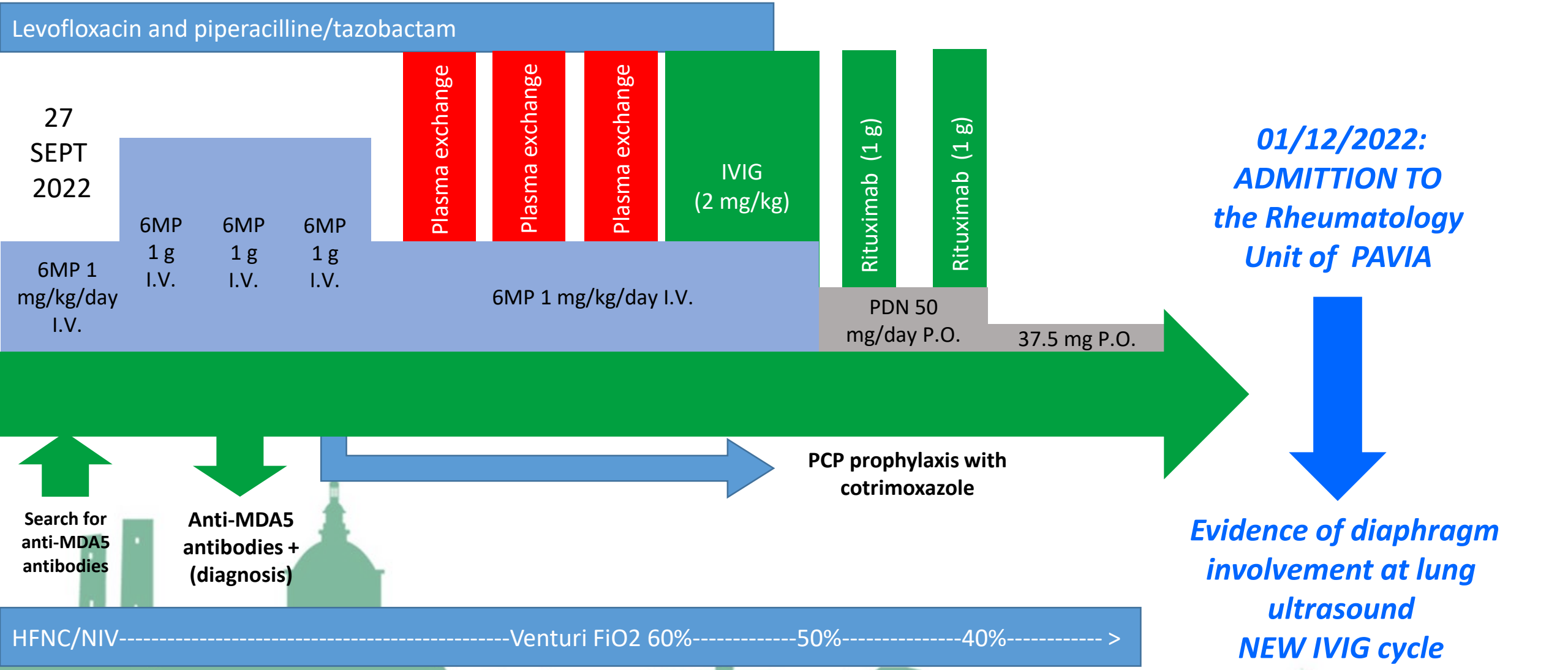
The Pavia's anti-MDA5 syndrome RP-ILD therapeutic approach



Search for anti-MDA5 antibodies

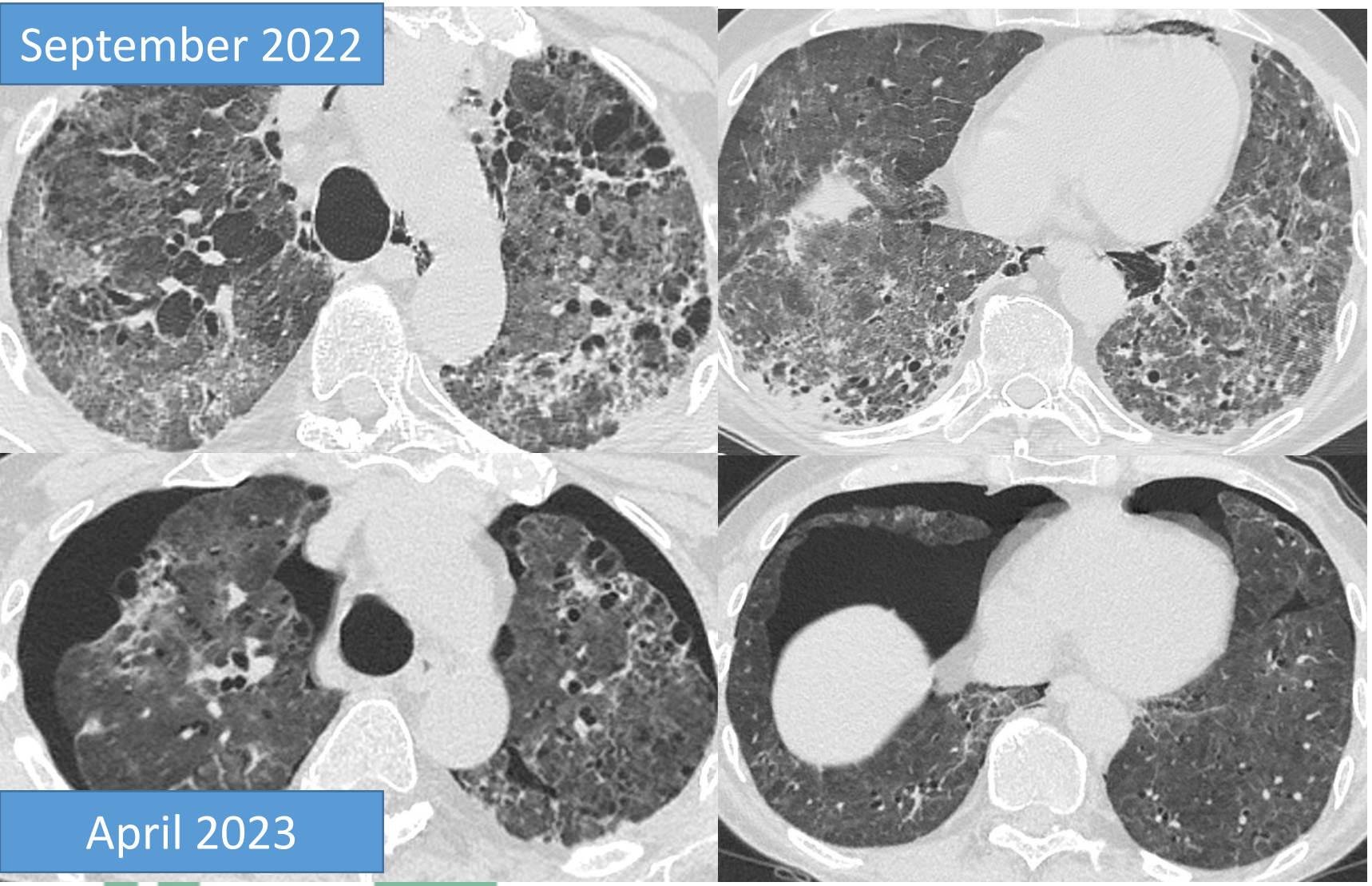
Anti-MDA5 antibodies + (diagnosis)

Evolution of the clinical case



After this approach the patient improved from the respiratory standpoint and diaphragm motility increased; corticosteroids were tapered to 12.5 mg/day and O2 therapy to 2 L/min; montly IVIg were mantained

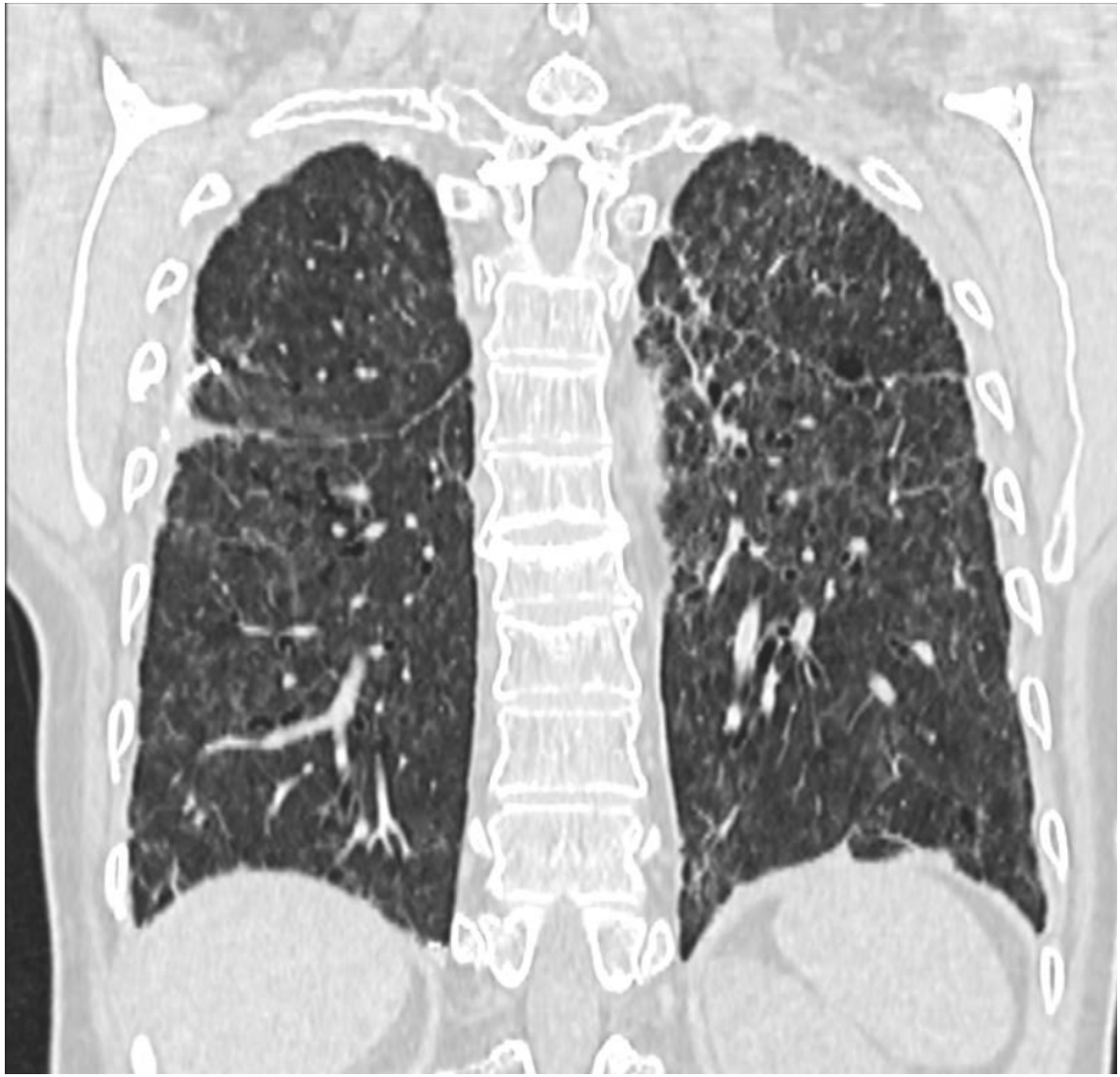
In April 2023, during the combined pneumo-rheumatology assesment preliminary to the second infusion of RTX, evidence of pneumo-thorax and further admission in our hospital (no dysphnea, SaO2 95% at rest)



Marked improvement of inflammatory pulmonary lesions related to anti-MDA5 syndrome, despite the marked pneumothorax. Our Thoracic surgeons performed bullectomy and pleurodesis

- Nintedanib (150 mg BID) - started in July 2023 (marked fibrosis at May 2023 lung biopsy)
- IVIg stopped in Jan 2024
- Prednisone stopped in June 2024
- RITUXIMAB maintained until September 2024, then planned switch to mycophenolate mofetil (2 g/day)
- O2 therapy: 2 L/min (on exertion)

	Oct 2023	May 2024
VC	2.40 (76%)	2.41 (77%)
FVC	2.40 (76%)	2.41 (77%)
FEV1	2.08 (83%)	2.28 (91%)
Tiffeneau Index	86,58	94.57
MMEF 25-75	2.28 (96%)	3.86 (125%)
TLC	3.04 (64%)	3.14 (66%)
RV	0.80 (45%)	0.77 (43%)
DLCO	2.93 (38%)	3.01 (40%)
weight /height/BMI	60/1.6/23	60/1.6/23



May 2024

Flow – chart for anti-MDA5 syndrome suspect in ICU

Acute respiratory
Respiratory failure

NSIP with or
withou t OP

C-PAP

ECMO

Raynaud's
phenomenon

Pneumo
mediastinum

Fever

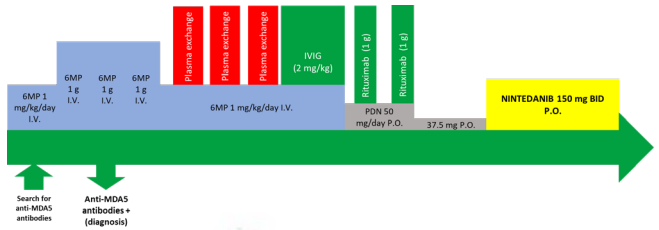
Skin ulcers

Anti-Ro52

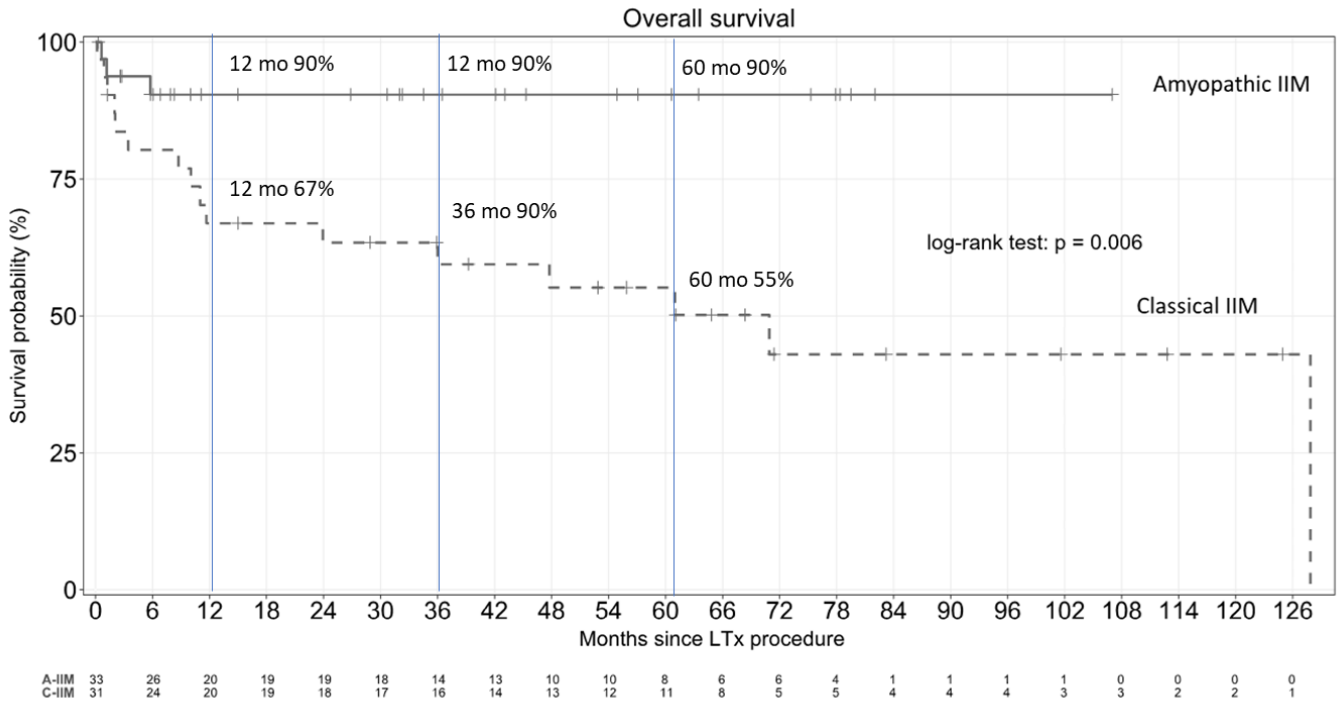
Hyperferritinemia

Lymphopenia

ANA and ENA negativity cannot rule out an anti-MDA5 syndrome



Lung transplantation for interstitial lung disease in idiopathic inflammatory myositis: A cohort study



- 110 ILD-IIM in EU were submitted to lung Tx in 19 Eu centers→ 64 evaluated
- 8/64 single lung Tx 56 DLT
- 33 (52%) amyopathic IIM → shorter disease duration at Tx
- Classic IIM had more frequent cancer diagnosis, more frequent swallowing impairment , more frequent PH

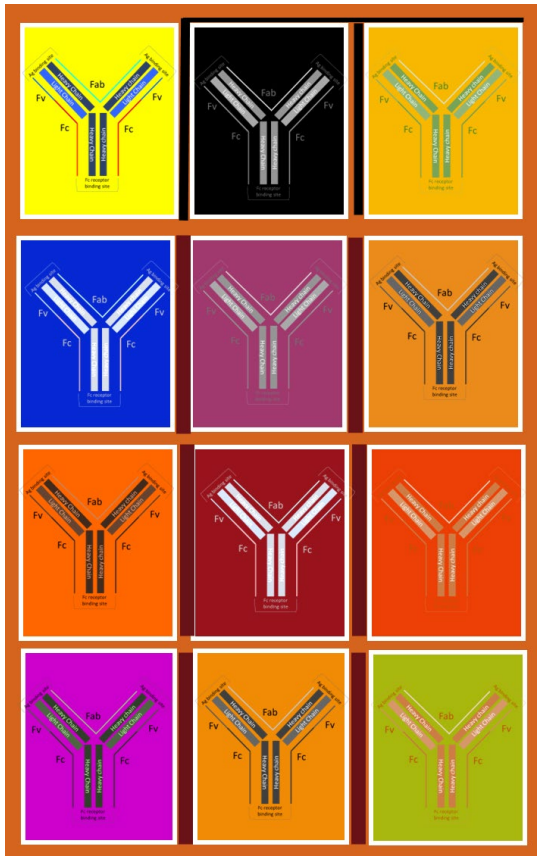
Variables significantly associated with poorer survival:

……

- c-IIM (as opposed to a-IIM),
- Skin involvement,
- The number of immunosuppressive lines before LTx

Riviere A, et al. Am J Transplant 2022 PMID: 35988032

Why not all anti-MDA5 positive patients develop RP-ILD?



Different isotypes and isoforms of anti-MDA5 antibodies may exist and lead to different effects on the clinical pattern of the disease

THE PIANO PROJECT (PRIN 2022 funded):

Pathways Involved in the action of ANti-MDA5 antibodies: impact On the innate immunity

- Full-length recombinant MDA5 production
- Identification and isolation of individual B-cells producing anti-MDA5 Abs
- Single B cell sequencing
- In vitro mAb production and characterization (single antibody specificities)
- Structural studies (with and without MDA5)
- Effect of anti-MDA5 antibodies alone or with **ferritin** on the interferon type I and NF-KB pathway on different cell-lines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