LUNG IMMUNE PROGNOSTIC INDEX (LIPI) CAN IDENTIFY THE FAST-PROGRESSOR TO IMMUNE CHECKPOINT INHIBITORS (ICI) IN MICROSATELLITE INSTABILITY (MSI) OR MISMATCH REPAIR DEFICIENT (dMMR) TUMOURS

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INTRODUCTION

- **Microsatellite instability (MSI)** is a well described carcinogenesis pathway.
- MSI is associated with a deficiency of DNA repair system: **Mismatch Repair (dMMR).** This phenotype is observed in 1 to 30% of patients according to tumour type, and can be related to Lynch syndrome.
- MSI-H/dMMR is considered the first predictive marker of efficacy for ICIs with tissue/site-**agnostic** approval. However, around 39% of cases are refractory and no additional biomarker has been identified.

OBJECTIVE

- **We explored the prognostic value of pretreatment LIPI in MSI-H/dMMR patients (pts) treated with ICI, particularly to identify the fast-progressors (FP).**

METHODS

- **Design**: International retrospective multicenter study (7 centers)
- **Study population**: Patients, aged > 18 years, treated with immune checkpoints inhibitors (ICI) for a MSI-H tumour between April 2014 and May 2019.
- **Data collection**: Clinical, biological data were collected at baseline
- **Primary endpoints**: OS and fast progressor rate (fast-PD),
- **Secondary endpoints:** PFS and objective response rate (ORR)
- We defined fast-PD as the occurrence of death in the 12 weeks following ICI start.
- **LIPI calculation**: LIPI was calculated based on dNLR [neutrophils/leucocytes-neutrophils]>3 + LDH>Upper Limit of Normality (ULN). LIPI groups were: good (0 factor), intermediate (interm.; one factor) and poor (2 factors), Table 1.
- **Statistical analysis:** The association of demographic, clinical, and biological factors with survival was assessed with multivariate Cox-proportional-hazards model. The association between LIPI and fast-PD ORR and DCR was evaluated with a logistic regression. Median OS and PFS were calculated with the Kaplan Meier method, and rates were calculated at 1 year.

LIPI	
Good	dNLR < 3 **AND** LDH < ULN
Intermediate	dNLR > 3 **OR** LDH > ULN
Poor	dNLR > 3 **AND** LDH > ULN

Table 1 : LIPI score calculation, as reported by Mezquita et al, JAMA Oncol 2018.

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RESULTS

STUDY POPULATION

- We included a total of 151 patients between April 2014 and May 2019
- The median follow-up of 32.1 months (95%CI:24.8-36.3)
- Main baseline characteristics are summarized in table 1
- Immune checkpoint inhibitors were administered in monotherapy in 87% of the patients

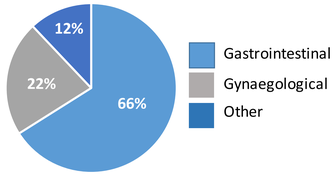
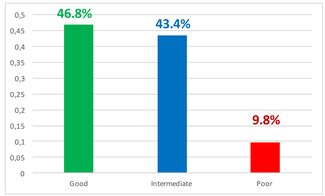


Figure 1: tumour locations in our study

LIPI groups

- **LIPI groups were distributed as follows**:
  - ✓ good (n=67, 46.8%)
  - ✓ intermediate (n=62, 43.4%)
  - ✓ poor (n=14, 9.8%)



Characteristics		LIPI Good (N=67)	LIPI Intermediate (N=62)	LIPI Poor (N=14)	p
Age	> 65	30 (46.15%)	23 (37.1%)	8 (57.14%)	0.32
Gender	Female	35 (52.24%)	39 (62.9%)	8 (57.14%)	0.47
Lynch syndrome	yes	20 (38.46%)	16 (29.63%)	3 (27.27%)	0.63
Synchronous metastasis	yes	23 (34.85%)	26 (41.94%)	5 (35.71%)	0.70
Line of ICI start	> 2	31 (46.27%)	25 (40.32%)	4 (30.77%)	0.55
N# mets at ICI start	> 2	11 (17.46%)	16 (26.67%)	6 (42.86%)	0.11
Bone metastasis	yes	2 (2.99%)	6 (9.68%)	4 (28.57%)	0.01
Brain metastasis	yes	0 (0%)	5 (8.06%)	2 (14.29%)	0.01
ECOG-PS	0-1	56 (94.9%)	57 (95.0%)	7 (58.3%)	0.002
	2-3	3 (5.1%)	3 (5.0%)	5 (41.7%)	

ICI: Immune Checkpoint Inhibtors, ECOG-PS: performance status

Table 2: patients' characteristics according to LIPI group

LIPI, independent prognostic factor

PROGNOSTIC FACTORS

In multivariate analysis, after adjustment on tumour site, number of metastatic sites, ECOG-PS, platelet count and albumin, LIPI score was an independent prognostic factor for OS.

		Overall survival			Progression free survival		
		HR	95%CI	p	HR	95%CI	p
Tumour site (vs Gastrointestinal)	Gynaecological	1.52	0.75-3.07	0.02	1.53	0.84-2.81	0.0002
	Other	2.83	1.35-5.95		4.08	2.08-8.01	
Number of metastatic site	> 2	1.97	1.05-3.69	0.03	1.06	0.61-1.85	0.84
ECOG PS	≥ 1	2.00	0.98-4.09	0.06	1.91	1.10-3.31	0.02
Platelets count (G/L)	Continuouss	1.00	1.00-1.01	0.06	-	-	-
Albumin (g/L)	> 35	0.96	0.50-1.82	0.89	0.96	0.58-1.59	0.87
LIPI (vs Good)	**Intermediate**	**1.36**	**0.70-2.61**	**0.03**	**1.09**	**0.65-1.82**	**0.07**
	Poor	**3.25**	**1.33-7.95**		**2.41**	**1.12-5.19**	

Table 4: Cox multivariate HR for OS and PFS, after adjustment on tumour site, number of metastatic sites, ECOG-PS, platelet count and albumin

CLINICAL OUTCOMES by LIPI groups

FAST-Progressors

- Overall, the 12-weeks death rate (Fast-PD) was significantly higher in the LIPI poor group (36%) (**p = 0.02**)

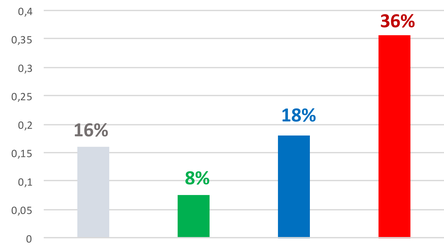
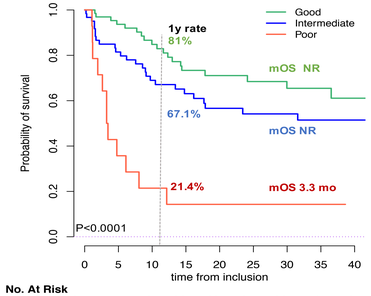


Figure 2: Fast progressor rate according to LIPI group

Overall SURVIVAL

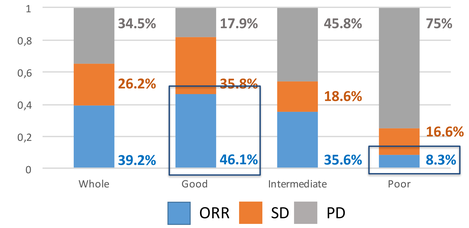
Overall, median OS Not reached (95%CI, 23.4 to NR)



No. At Risk									
Good	65	57	46	36	29	24	22	19	12
Intermediate	61	47	37	30	25	21	20	13	10
Poor	14	5	3	2	2	2	2	1	0

Best RESPONSE

- The ORR was significantly lower in the LIPI poor group (8%) (**p = 0.03**)

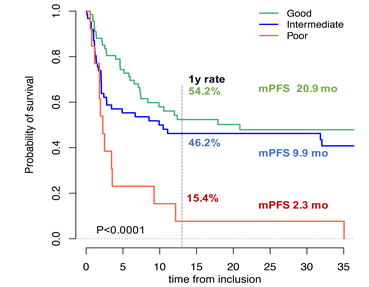


ORR: objective response rate, SD: stable disease, PD: progression disease

Figure 3: Best esponse according to LIPI group

Progression-Free SURVIVAL

Overall, median PFS was 10.5 months (95%CI, 7.1 to 35.1)



No. At Risk								
Good	67	48	32	27	22	17	16	14
Intermediate	62	32	27	22	20	18	17	12
Poor	13	3	2	1	1	1	1	1

CONCLUSION

- **LIPI was associated with immunotherapy outcomes in patients with MSI-H or dMMR tumours**
- **LIPI score can identify a subgroup of patients that will not benefit from ICI for a MSI high tumour**
- **It is a simple and accessible worldwide biomarker related to the host that should be prospectively investigated**