

Analysis of expression of PD-L1 in malignant pleural mesothelioma

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Disclosure slide

- No relevant relationship to disclosure

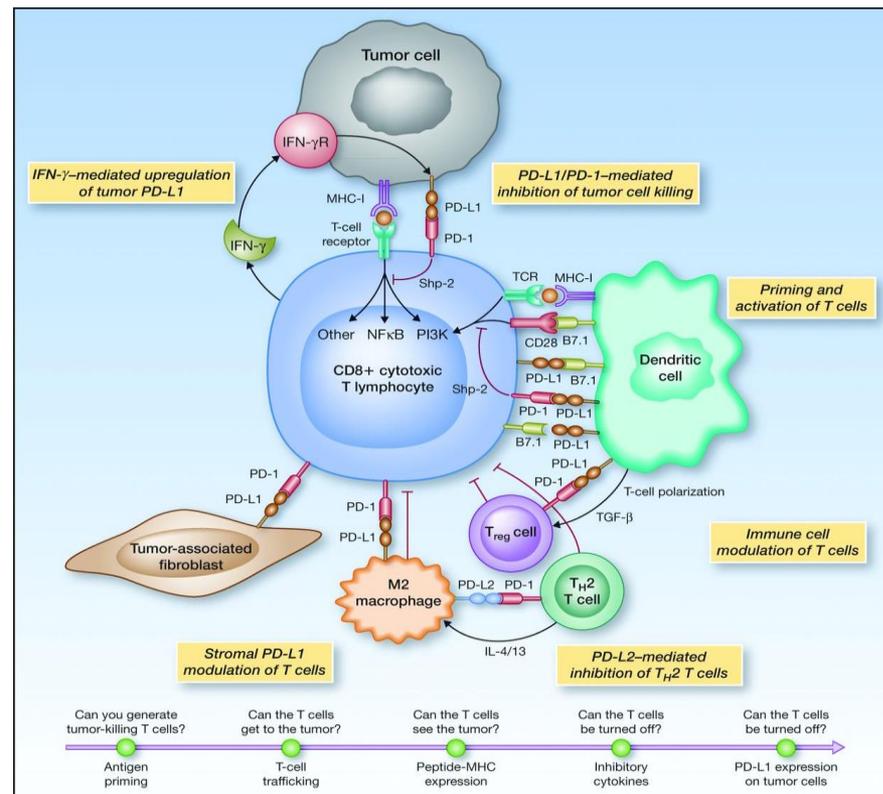
Introduction

- MPM immunogenic tumor
- Investigate immunotherapy novel therapeutic approach.
 - Monoclonal antibodies and tumor vaccines are in development to treat patients with tumor expressing mesothelina¹⁻³ and WT-1⁴
 - CTLA4 inhibitor (tremelimumab) encouraging clinical activity⁵

¹Insmi 2010, ²Kreitman 2009, ³Hassan 2010, ⁴Krug 2010, ⁵Calabro 2013

PD-1/PD-L1

- Limits activity T cells and plays a role in the tumor immune escape
- PD-L1 (B7-H1) expression prevalent human tumors and associated with prognosis
- PD-L1/PD-1 inhibitors promising results



Chen D, Clin Cancer Res 2012

PD-L1 IHC positivity

Antibody	Host	Cutoff
5H1	Rabbit/EC	5% membranous staining tumor cells
22C3	Mouse/EC	≥1% tumor cells (weak 1-49%; strong 50-100%) membranous tumor cell staining or inflammatory infiltrate
SP142	Rabbit/EC	≥1% tumor immune cells
E1L3N	Rabbit/IC	No background

EC: extracellular IC: intracellular

PD-1/PD-L1 MPM

- Tumor model PD-L1 highly expressed on tumor cells and within stroma and PD-L1 blockade results in T cell activation¹
- Series 106 p FFPE 40% positivity (5H1)²
 - Median percent PD-L1 + tumor cells 35%
 - Expression cytoplasmic (43%) and cytoplasmic and membranous (33%)
 - All sarcomatoid PD-L1+
 - OS 5 m PD-L1+ and 14.5 m PD-L1-

Objectives

- The primary objective for this study is to evaluate the expression of PD-L1 in MPM
- Secondary objectives:
 - Prognostic role
 - Association clinical variables

Methods

- 119 consecutives p from 2000-2014 Vall d'Hebron University Hospital and 12 de Octubre University Hospital
- PD-L1 rabbit monoclonal antibody E1L3N XP[®] Cell Signaling
- Staining PD-L1 two independent pathologists
- Positive $\geq 1\%$ tumor cells (membrane, cytoplasm)
 - Intensity staining: weak, moderate and strong

Patient characteristics

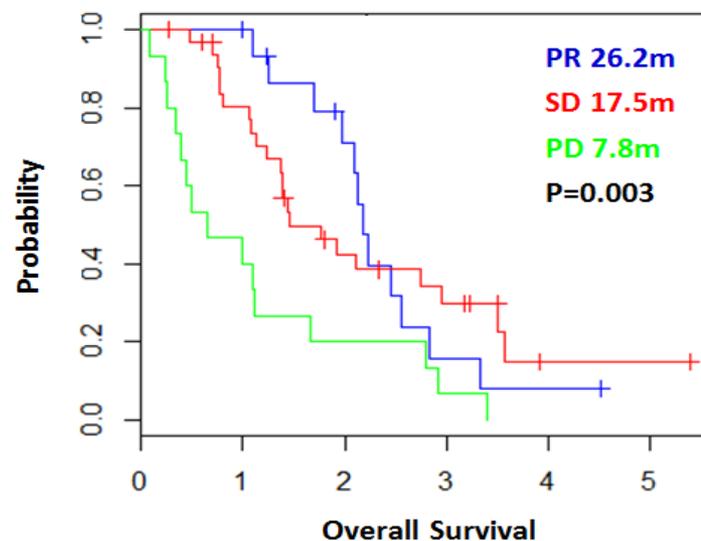
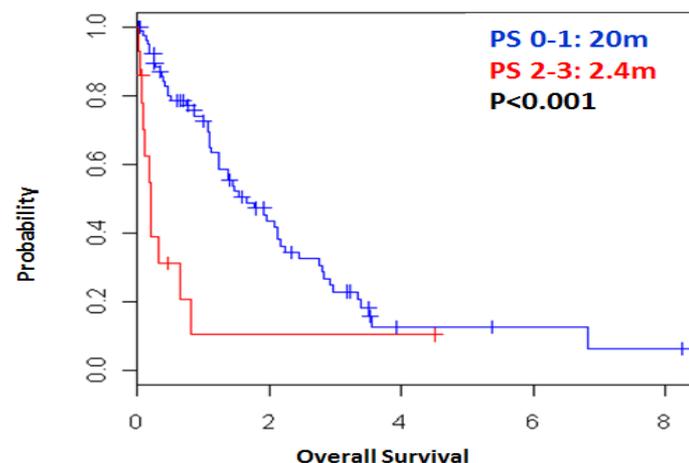
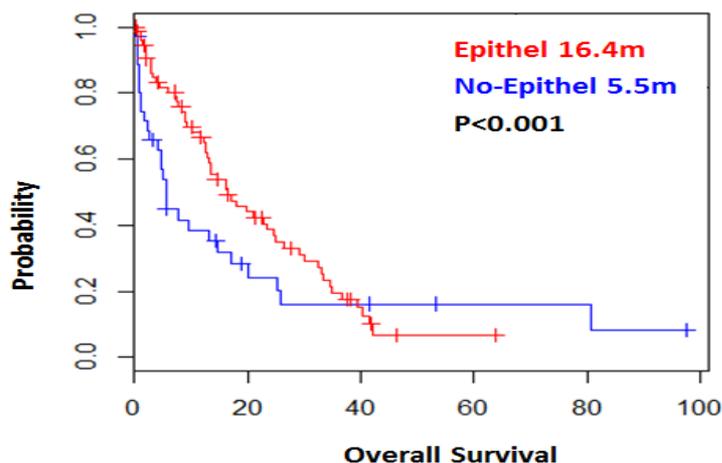
Clinical characteristic		N=119	%
Gender	Male	85	71.4
	Female	34	28.6
Smoke	Current	33	27.7
	Former	28	23.5
	No smoker	41	34.4
	Unknown	17	14.3
Asbestos exposure	Yes	53	44.5
	No	38	31.9
	NA	28	23.5
PS	0	19	20.2
	1	61	64.9
	2	10	10.6
	3	4	4.3
	NA	25	26.6
	Localization	Right	64
Left		45	37.8
NA		10	7.4

Clinical characteristics		N=119	%
Pleural effusion	Yes	92	77.3
	No	14	11.8
	NA	13	10.9
Stage	I-II	27	22.6
	III-IV	77	64.7
	NA	15	12.6
Histology	Epithelioid	78	65.5
	Sarcomatoid	12	10.1
	Biphasic	5	4.2
	NOS	24	20.2
Systemic treatment	Yes	78	65.6
	No	31	26.1
	NA	10	8.4

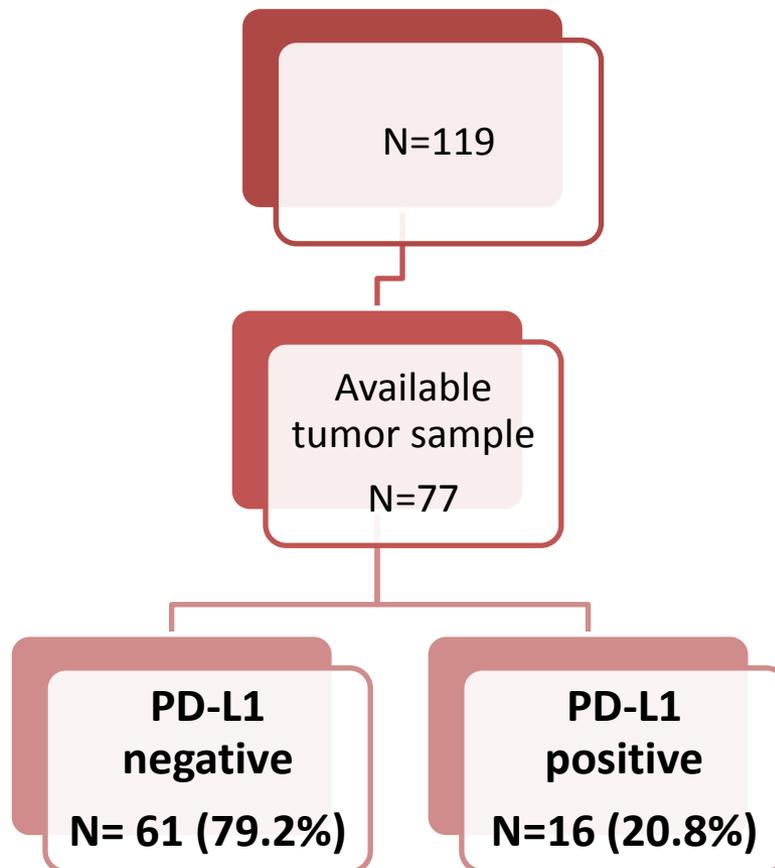
NA: no available, NOS: not otherwise specified

Survival results

- OS 13.8 months
- Improve survival PS, epithelioid histology, response to chemotherapy



IHC results

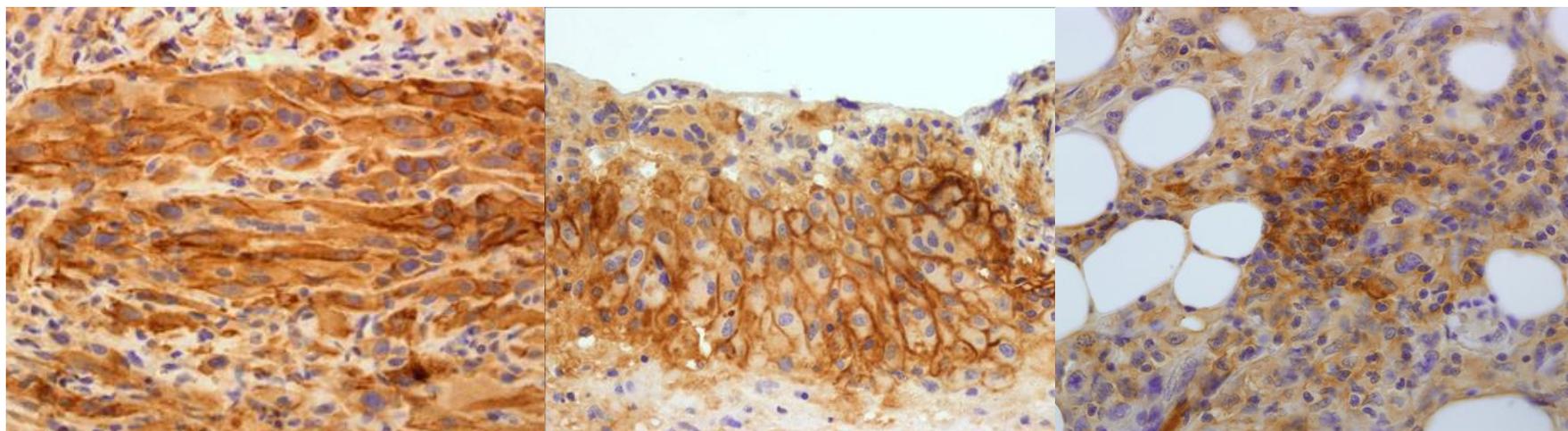


Localization of staining

PD-L1+cytoplasm

PD-L1+ membrane

PD-L1+ immune infiltrate



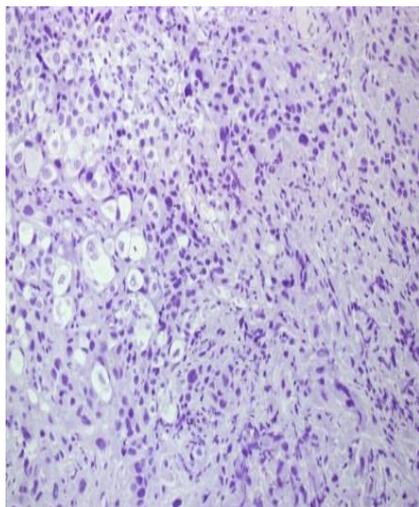
Localization	N=16
Cytoplasm	16
Membrane	14
Immune infiltrate	4

All p with I. Infiltrate
PD-L1 + also
stained in
membrane and
cytoplasm

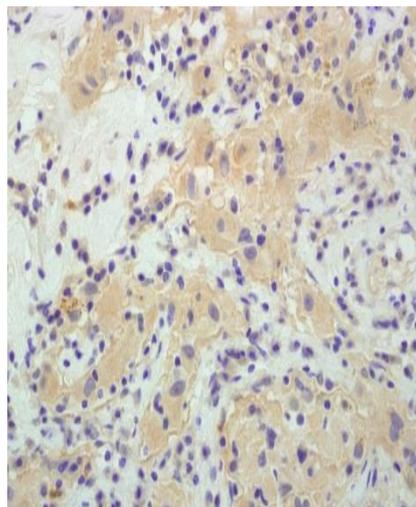
Percentage tumor cell

Percentage tumor cell	N=16	%
1-5%	10	62.5
≥5-10%	3	18.7
≥10%	3	18.7

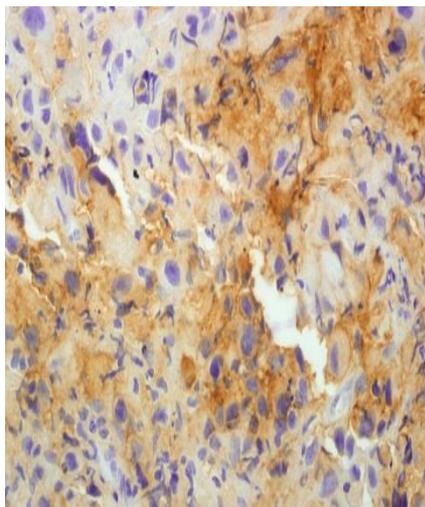
Intensity of staining



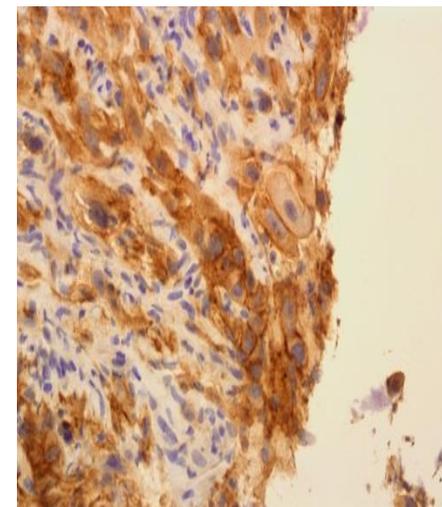
Negative: 61p



Weak: 9p



Moderate: 4p



Strong: 3p

Association PD-L1 expression clinical variables

Characteristic	PD-L1 + (n,%)	PD-L1 - (n,%)	p
Median age	69	66	0.6
Sex: Male/Female	11 (68)/5(32)	43 (70)/18 (30)	0.38
Histology			0.003
Epithelioid	7 (43.7)	46 (77.7)	
No epithelioid	9 (56.2)	15 (28.3)	
Smoking status	10 (63)	33 (54)	0.61
Asbestos exposure	5 (32)	31 (51)	0.14
Stage III-IV	13 (81)	48 (79)	0.26
Chemotherapy	10 (62)	45 (73)	0.3

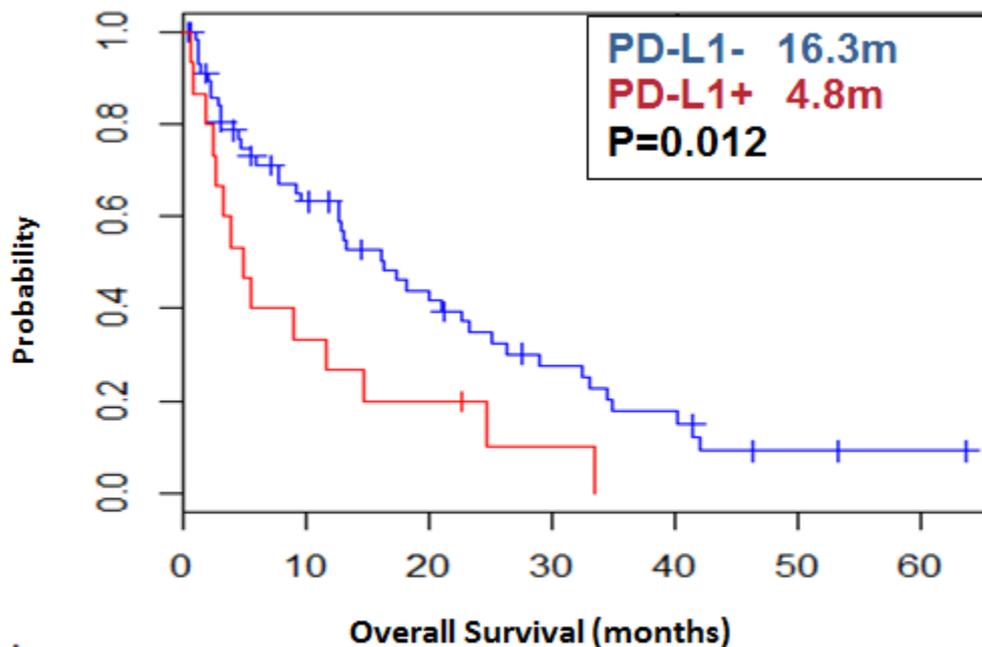
PD-L1 in no-epithelioid

- PD-L1 positive n=16: Epithelioid: 7p/No epithelioid n=9p

Histology	N	PD-L1 +	%
Sarcomatoid	4	2	50
Biphasic	5	5	100
NOS	11	2	18

NOS: no otherwise specification

PD-L1 expression and survival

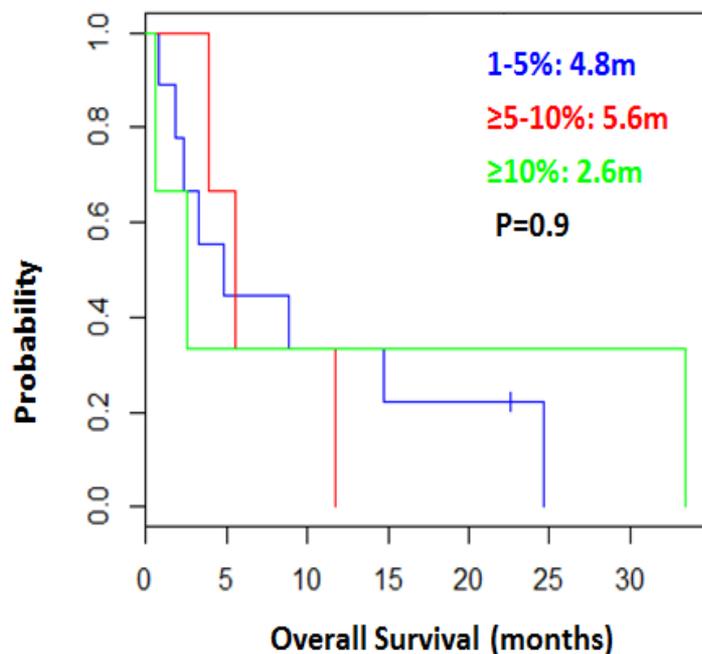


No. at Risk

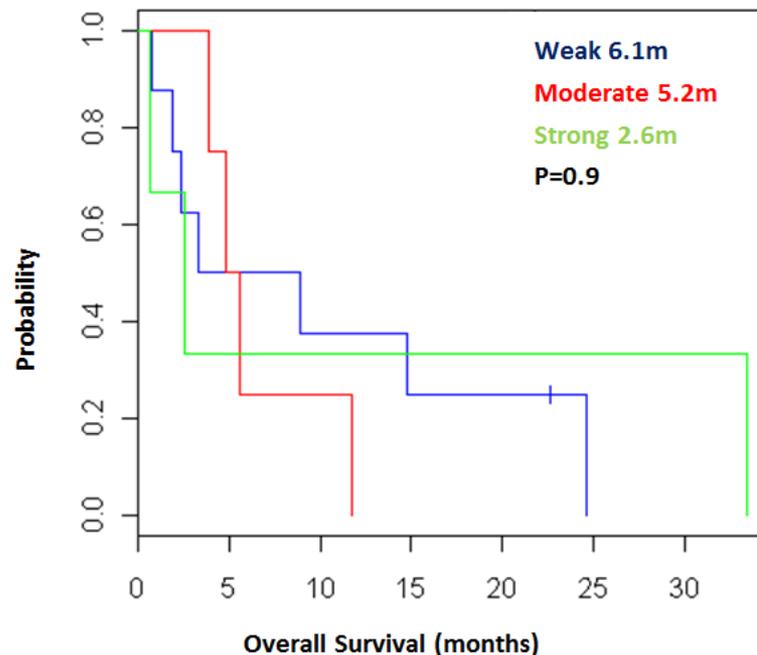
	0	10	20	30	40	50	60
Negative	59	32	20	11	7	2	1
Positive	15	5	3	1	0	0	0

Survival PD-L1 positive

OS percentage tumor cells



OS intensity staining



Multivariate analysis

- Cox multivariate:
- After adjusting for performance status, histology and response to chemotherapy
- PD-L1 significant prognostic factor
- HR 2.08, 95% CI 1.12-3.88; $p=0.021$

Summary/Conclusions

- 20% of MPM express PD-L1+ (E1L3N™)
- More frequent in non epithelioid
- PD-L1 negative prognostic factor in MPM
- Measurement of PD-L1 and prognostic value prospective validation
- PD-L1 potential target for mesothelioma treatment