IL PERCORSO ASSISTENZIALE E LE PROSPETTIVE TERAPEUTICHE PER IL MESOTELIOMA PLEURICO NELLA REGIONE EMILIA ROMAGNA

AtezoMeso Study

Phase III Study With Atezolizumab Versus Placebo In Malignant Pleural Mesothelioma Patients After Pleurectomy/ Decortication

EUDRACT Number 2020-003762-39

GOIRC–03-2019

Maria Pagano
AUSL-IRCCS
Reggio Emilia

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

OECI COMPREHENSIVE Cancer Centre

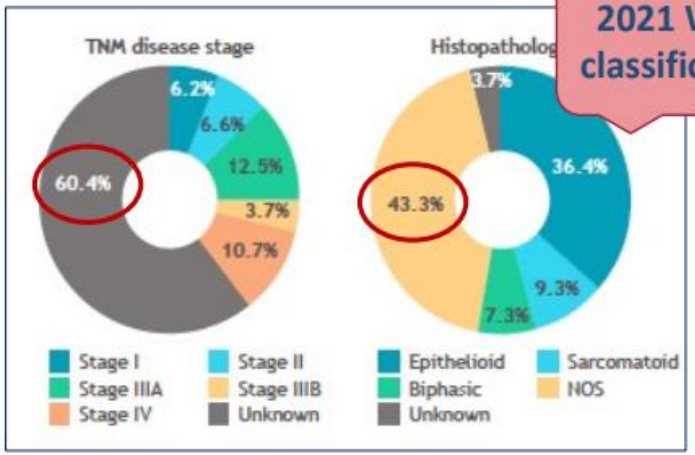
Background

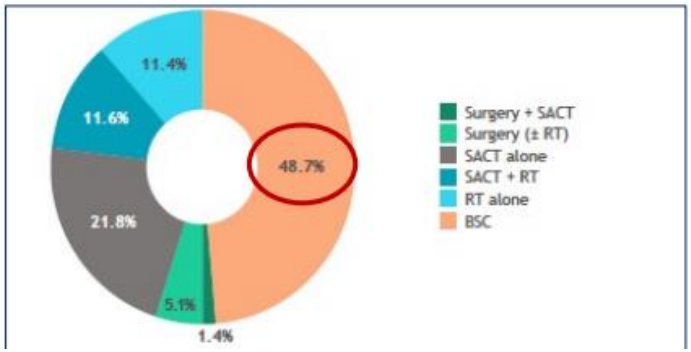
- Pleurectomy/Decortication in MPM

- Immunotherapy in MPM

Malignant Pleural Mesothelioma

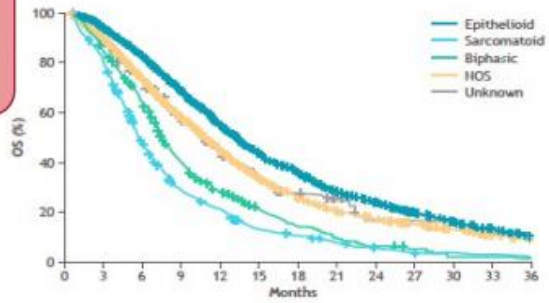
Complesso processo stadiativo e diagnostico



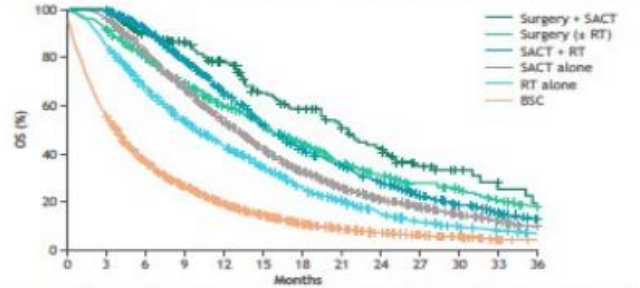


2021 WHO classification

Prognosi infausta, condizionata da istologia e eleggibilità ad approccio multimodale



	N	Median OS months (Q1-Q3)	1-year OS		3-year OS	
			n	% (95% CI)	n	% (95% CI)
Epithelioid	1402	13.4 (7.9-23.6)	631	56 (53-59)	58	11 (9-13)
Sarcomatoid	262	5.8 (3.4-10.5)	47	21 (17-27)	< 6	2 (0-6)
Biphasic	271	7.4 (4.5-13.6)	58	27 (22-34)	< 6	1 (0-5)
NOS	1083	10.9 (5.7-18.9)	419	46 (43-49)	50	9 (7-11)
Unknown	96	10.5 (5.8-21.6)	28	45 (35-58)	< 6	11 (4-31)



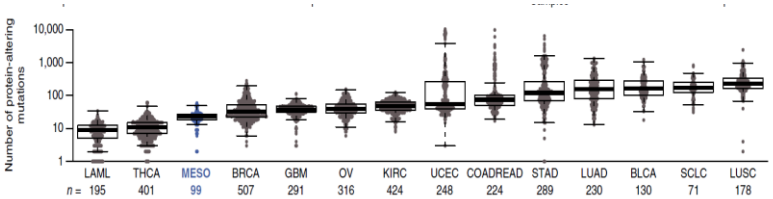
	N	Median OS months (Q1-Q3)	1-year OS		3-year OS	
			n	% (95% CI)	n	% (95% CI)
Surgery + SACT	135	21.5 (13.1-35.1)	84	79 (72-86)	7	20 (11-34)
Surgery (± RT)	478	15.4 (7.4-30.3)	250	60 (55-64)	42	19 (15-23)
SACT + RT	1099	15.7 (10.0-25.9)	663	65 (62-68)	84	13 (11-16)
SACT alone	2059	12.9 (7.3-21.4)	918	53 (51-56)	85	10 (9-12)
RT alone	1077	10.0 (4.8-18.3)	425	44 (41-47)	43	7 (6-9)
BSC	4604	3.8 (1.4-9.6)	742	20 (18-21)	76	5 (4-5)

Baas P ESMO 2020

Is MPM immunogenic?

CON

- Moderate mutational load (*Bueno, Nat Genet 2016)*



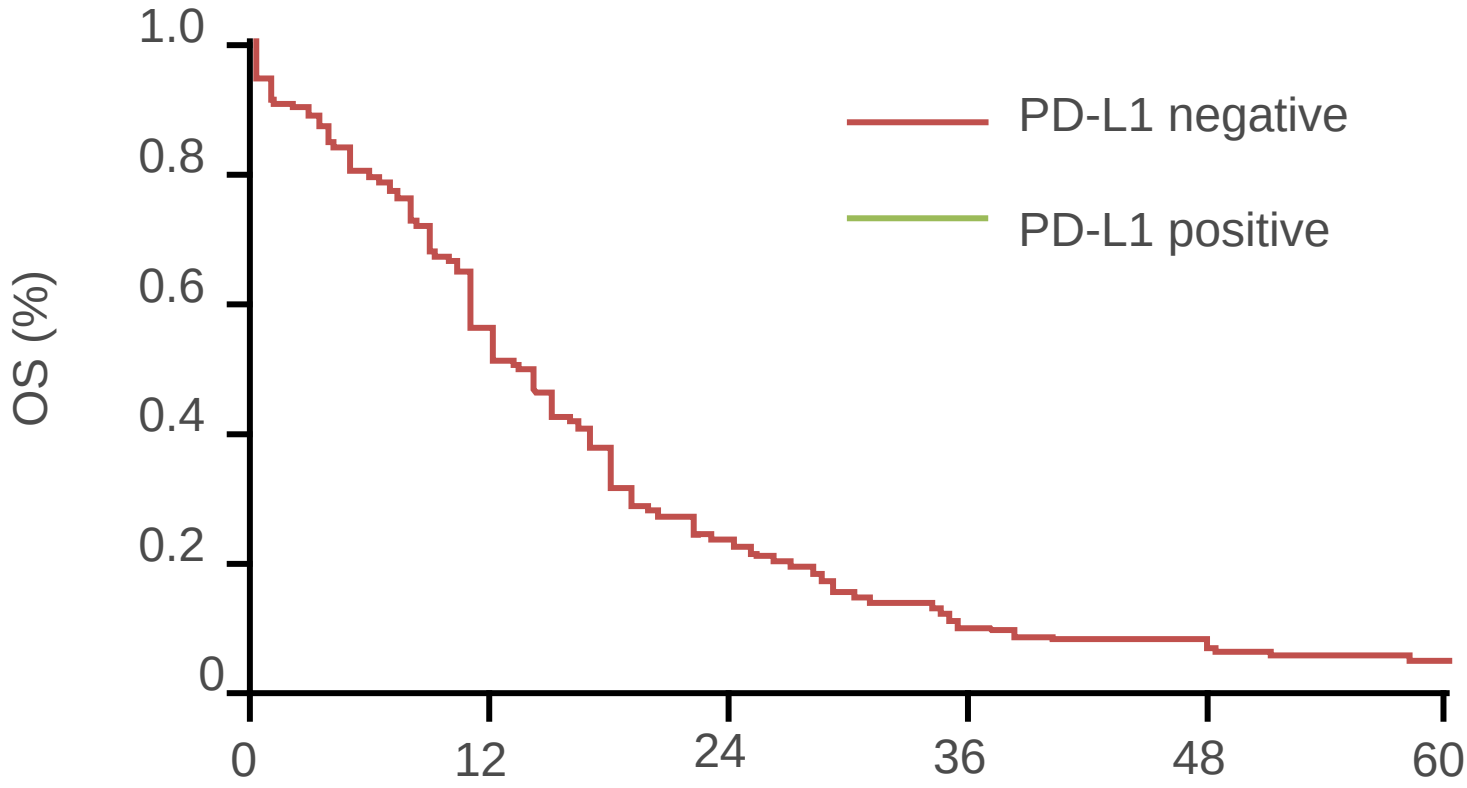
- Limited neo-epitope
- High PDL-1 expression uncommon

PRO

- *WT1* overexpression in epithelioid MPM (*Kumar Singh, 1994*)
- Silencing of the antigen presenting function of DC's by tumor-derived soluble factors, leading to a defective induction of CTL response
- PDL-1 expression in ~40%
  - Non-epithelioid subtype
  - Increased immunological infiltrates

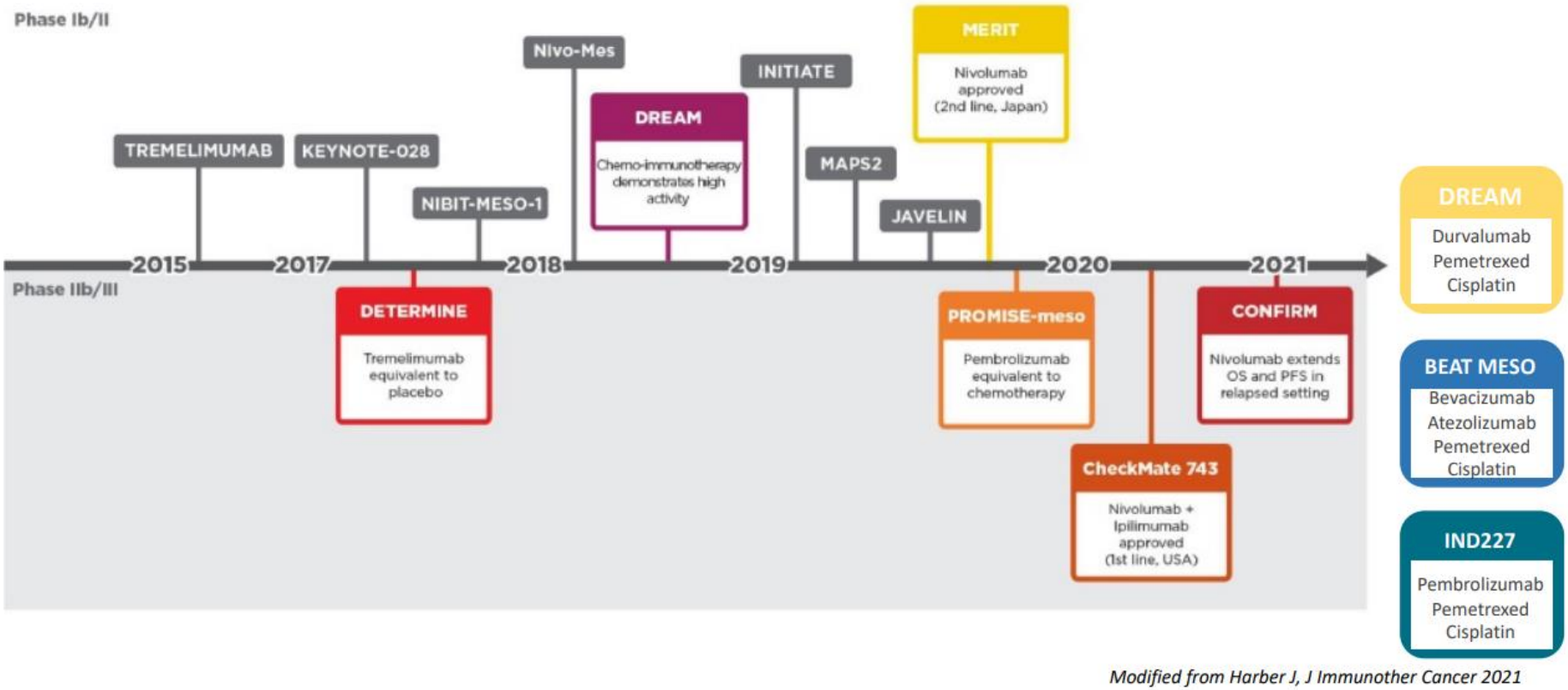
PD-L1 in Mesothelioma

PD-L1 identified in mesothelioma tumor cells and associated with poor prognosis



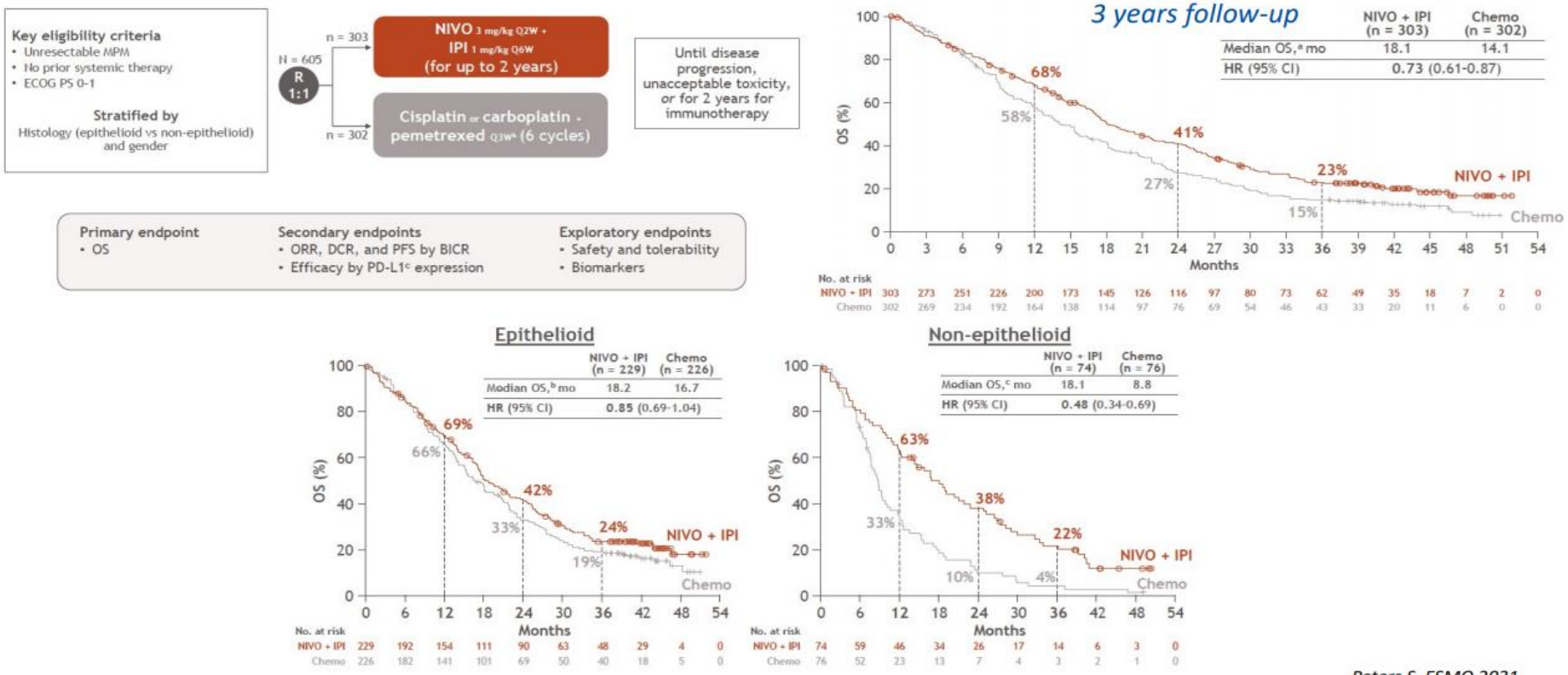
Mansfield AS, et al. J Thorac Oncol. 2014;9:1036-1040;

Malignant Pleural Mesothelioma
inibitor checkpoint



Modified from Harber J, J Immunother Cancer 2021

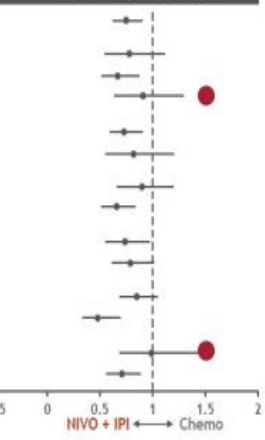
Malignant Pleural Mesothelioma
inibitor checkpoint



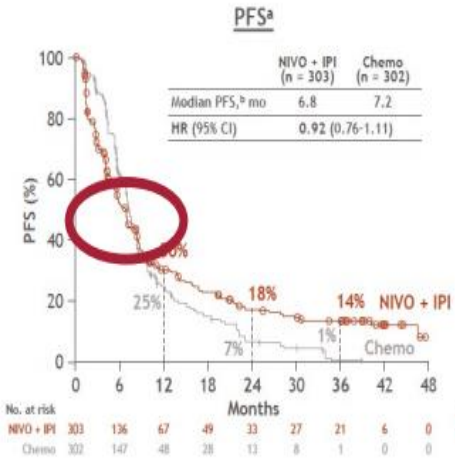
Peters S, ESMO 2021

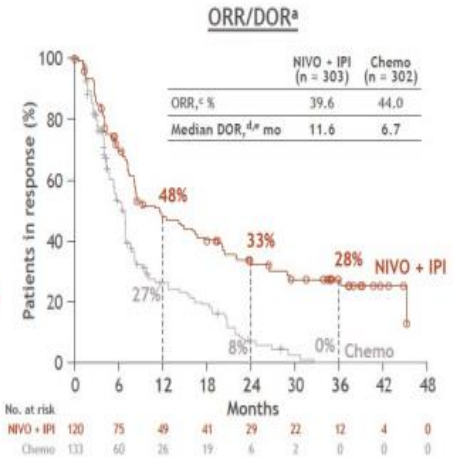
Malignant Pleural Mesothelioma inibitor checkpoint

Subgroup	Median OS, mo: NIVO + IPI (n = 303)	Median OS, mo: Chemo (n = 302)	Unstratified HR
All randomized (N = 605)	18.1	14.1	0.75[a]
< 65 years (n = 167)	17.2	13.3	0.78
≥ 65 to < 75 years (n = 281)	20.3	14.5	0.67
≥ 75 years (n = 157)	16.9	15.5	0.91
Male (n = 467)	**17.5**	**13.7**	**0.73**
Female (n = 138)	**21.1**	**18.0**	**0.82**
ECOG PS 0 (n = 242)	20.7	19.5	0.90
ECOG PS ≥ 1[b] (n = 363)	17.0	11.6	0.66
Never smoker (n = 249)	17.9	14.1	0.74
Former smoker[c] (n = 318)	17.6	14.9	0.79
Epithelioid (n = 455)	**18.2**	**16.7**	**0.85**
Non-epithelioid[d,e] (n = 150)	**18.1**	**8.8**	**0.48**
PD-L1 < 1% (n = 135)	17.3	16.6	0.99
PD-L1 ≥ 1%[f] (n = 451)	18.0	13.3	0.71



Minimum follow-up: 35.5 months.





Comment

THELANCET-D-20-19423

S0140-6736(21)00147-1

Embargo: January 21, 2021—23:30 (GMT)

Immune checkpoint inhibitors in mesothelioma: a turning point

«Necessaria una migliore conoscenza del microambiente tumorale e della eterogeneità intrinseca a ciascun sottotipo istologico, così come una attenta selezione dei pazienti in base al rapporto rischio/beneficio»

Peters S, ESMO 2021; Ceresoli GL, Lancet 2021

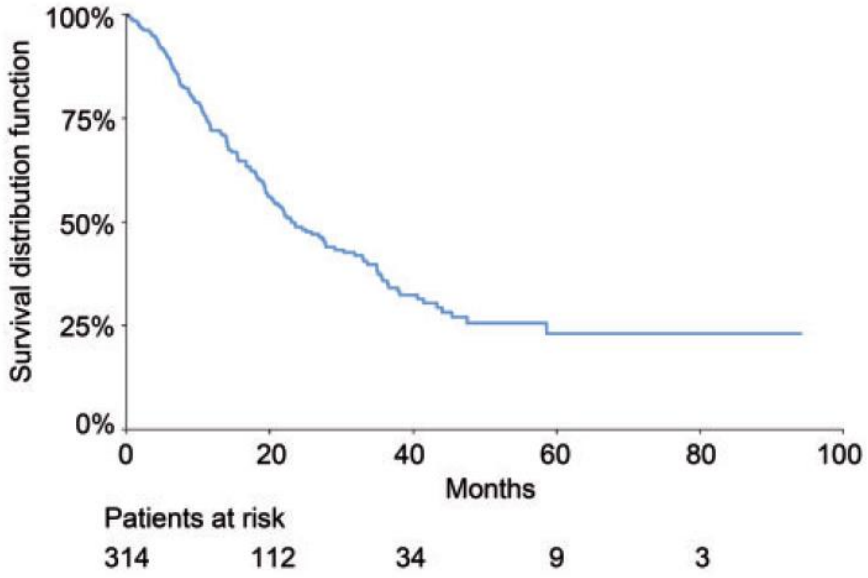
European Journal of Cardio-Thoracic Surgery 52 (2017) 63–69
doi:10.1093/ejcts/ezx079 Advance Access publication 12 April 2017

ORIGINAL ARTICLE

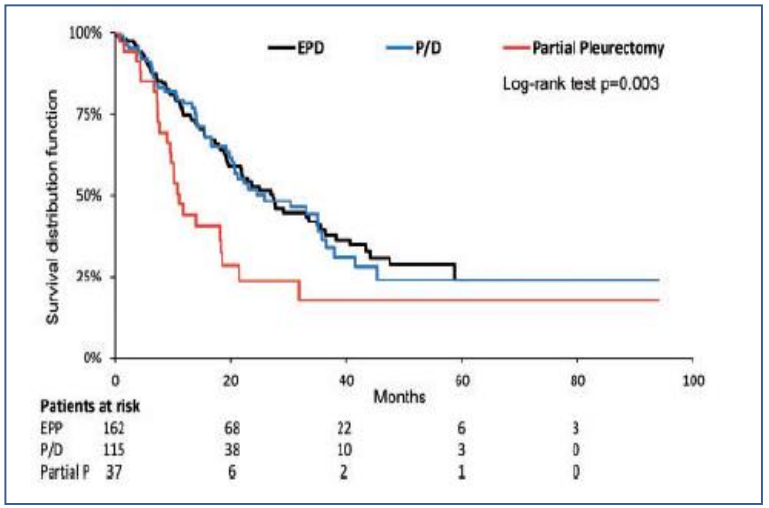
Cite this article as: Marulli G, Breda C, Fontana P, Ratto GB, Leoncini G, Alloisio M *et al*. Pleurectomy–decortication in malignant pleural mesothelioma: are different surgical techniques associated with different outcomes? Results from a multicentre study. Eur J Cardiothorac Surg 2017;52:63–9.

Pleurectomy–decortication in malignant pleural mesothelioma: are different surgical techniques associated with different outcomes? Results from a multicentre study†

Giuseppe Marulli[a,*], Cristiano Breda[b], Paolo Fontana[b], Giovanni Battista Ratto[c], Giacomo Leoncini[c], Marco Alloisio[d], Maurizio Infante[d], Luca Luzzi[e], Piero Paladini[e], Alberto Oliaro[f], Enrico Ruffini[f], Mauro Roberto Benvenuti[g], Gianluca Pariscenti[g], Lorenzo Spaggiari[h], Monica Casiraghi[h], Michele Rusca[i], Paolo Carbognani[i], Luca Ampollini[i], Francesco Facciolo[j], Giovanni Leuzzi[j], Felice Mucilli[k], Pierpaolo Camplese[k], Paola Romanello[a], Egle Perissinotto[a] and Federico Rea[a]



- 314 patients
- 162 (51.6%) patients EP/D
- 115 (36.6%) patients P/D
- 37 (11.8%) patients partial P
- Median OS 23.0 months



Journal of SURGICAL ONCOLOGY

Volume 118, Issue 7
December 1, 2018
Pages 1178-1187

RESEARCH ARTICLE | Full Access

Short-term outcomes of pleurectomy decortication and extrapleural pneumonectomy in mesothelioma

Through the initial keyword search, 431 eligible papers included 30-day mortality and 373 included postoperative complication rate (Figure 1). After title and abstract screening, 401 (30-day mortality) and 343 (postoperative complications) papers were excluded because the articles were irrelevant to the research question. Full-text analysis yielded 20 distinct datasets covering 30-day mortality and 19 distinct datasets covering postoperative complications in EPP and P/D (Table 1).[15-40]

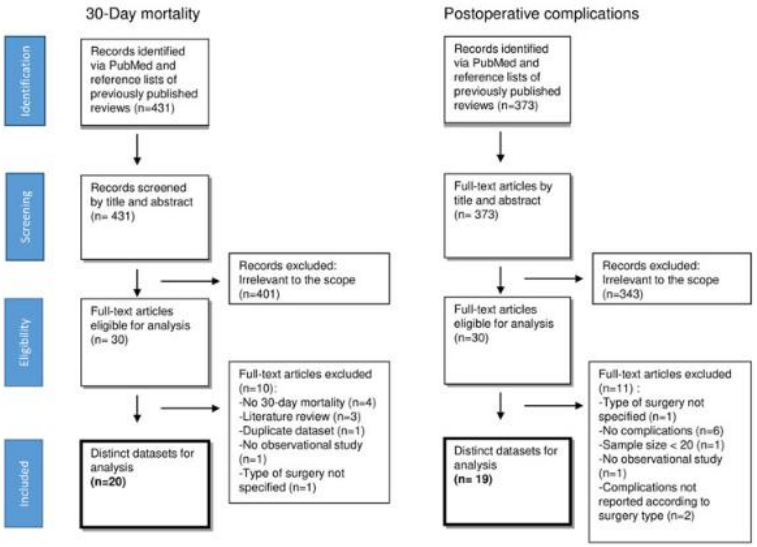


TABLE 2 Description of the study population according to type of surgery

Variable	P/D[a] (*n* = 267)	EPP[b] (*n* = 233)	*P*-value
Mean (± SD) age (y)	68.5 (± 10.1)	60.8 (± 11.6)	< 0.0001
Mean (± SD) hospital length of stay (d)	11.8 (± 11.6)	10.9 (± 13.9)	0.36
Gender (male)	80.1%	76.0%	0.26
Race			
White	86.5%	94.0%	0.02
Black	3.8%	1.3%	
Other	9.7%	4.7%	
Ethnicity			
Spanish/Hispanic	6.0%	3.4%	0.11
Not of Spanish/Hispanic origin	89.9%	94.9%	
Unknown	4.1%	1.7%	
Insurance			< 0.0001
No insurance	4.9%	3.4%	
Medicare	59.2%	37.4%	
Private	30.3%	56.2%	
Other (including Medicaid)	5.6%	3.0%	
Type of admission			< 0.0001
Emergency/ urgent	31.8%	1.7%	
Elective	68.2%	98.3%	
Discharge status			
Died	5.6%	6.4%	0.08
Home	62.2%	70.4%	
In-patient care	32.2%	23.2%	
Comorbidities			
Cardiovascular	46.8%	37.3%	0.03
Pulmonary	17.6%	11.2%	0.04
Neurologic	1.5%	0.9%	0.51
Diabetes	16.9%	6.9%	0.0007
Anemia	12.7%	9.9%	0.32
Substance use/psychiatric disorders	4.9%	2.6%	0.18
Hypothyroidism	7.5%	4.7%	0.20
Metastatic cancer	34.5%	79.8%	< 0.0001
Solid tumor w/out metastasis	10.9%	3.4%	0.0015
Weight loss	6.0%	3.0%	0.11
Fluid and electrolyte disorders	14.6%	17.2%	0.43
Other	7.1%	7.7%	0.80
Number of comorbidities			
0	13.9%	4.3%	0.0003
≥ 1	86.1%	95.7%	
Intraoperative blood transfusion	33.7%	47.6%	0.0015

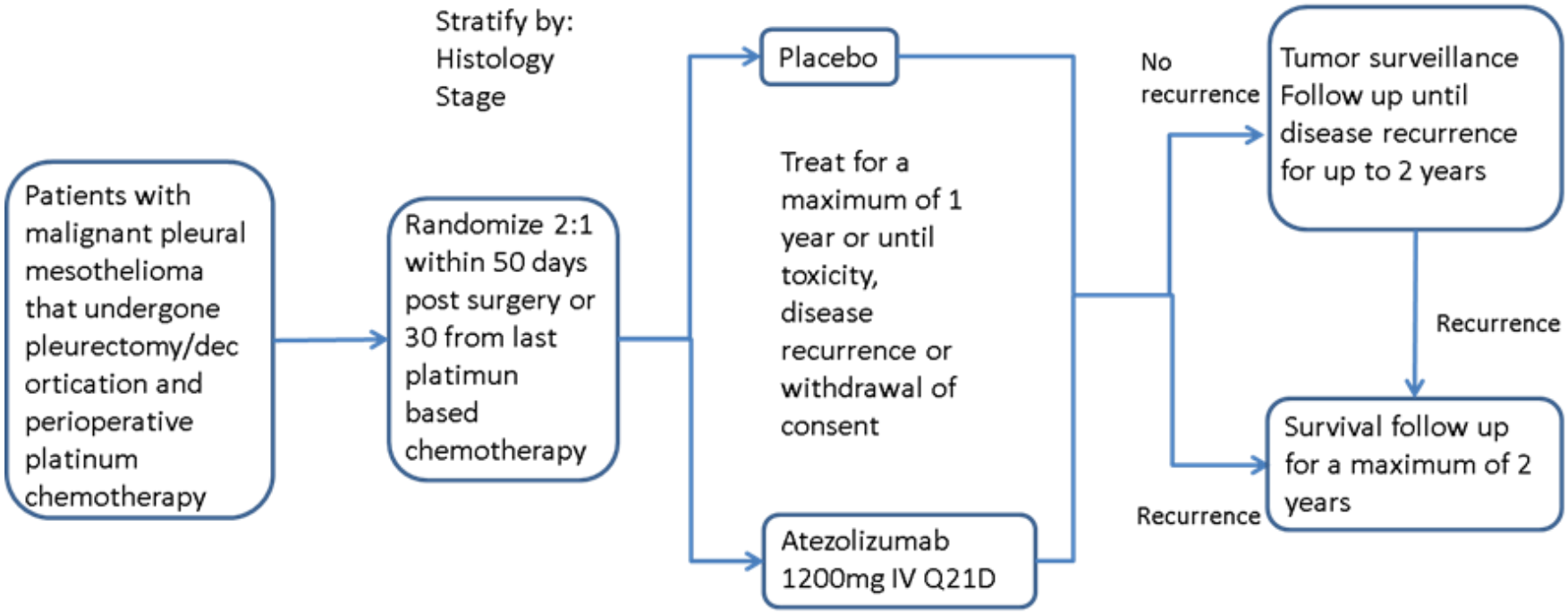
[a]P/D = pleurectomy/decortication.
[b]EPP = extrapleural pneumonectomy.

Background
P/D and Immunotherapy

Surgical tumor reduction may create a host environment more amenable to immunotherapy by

- reducing the ratio of tumor cells versus antitumor effector T lymphocytes
- reducing the quantities of intratumor and/or systemic immunosuppressive cells
- ablating tumor-derived paracrine factors that promote local recruitment of immunosuppressive cells

AtezoMeso Study design



3 pts; 21 Italian Oncology Center

Primary Objective

Primary Objective	Corresponding Endpoint
To evaluate the efficacy of atezolizumab in patients with MPM	DFS, defined as the time from initiation of study treatment to first recurrence of disease or death for any cause, whichever occurs first. DFS will be calculated based on disease status evaluated by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).

Secondary Objectives

Secondary Objectives	Corresponding Endpoint
To evaluate the safety of atezolizumab in patients with MPM	Incidence, nature and severity of serious adverse events (SAEs) and non-serious adverse events (AEs) related to atezolizumab treatment graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 5.
To evaluate the efficacy of atezolizumab in patients with MPM	OS, defined as the time from start of study drug to the date of death from any cause.
To evaluate health status utility and HR QoL of atezolizumab in patients with MPM	EQ-5D-3L questionnaire

Explorative Objectives

Exploratory Objective	Corresponding Endpoint
To assess the role of biomarkers in the progression and fundamental biology of MPM **To evaluate biomarkers (e.g., cancer-related genes) as prognostic biomarkers**	Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Expression of PD-L1 protein in tumor tissue Presence/absence of other biomarkers in tumor tissue Correlations between PD-L1 expression and other biomarkers

Inclusion Criteria

•Histologically confirmed malignant pleural mesothelioma.

•Surgical resection (P/D), without macroscopic residual. In stage I patients without visceral involvement a total pleurectomy is allowed.

•Patients must have received at least 4 cycles of perioperative platinum/pemetrexed chemotherapy as per local practice. Less than 4 cycles of chemotherapy are allowed for clinical decisions

•In patients previously treated with neoadjuvant chemotherapy, randomization should occur within 50 days from surgical resection.

•In patients treated with adjuvant chemotherapy, randomization should occur within 30 ± 7 days from last dose of adjuvant treatment.

• ECOG/PS 0-1.

•Adequate organ function.

•Availability of 1 tumor block at baseline.

Exclusion criteria

- Patient with macroscopic residual disease after surgery.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Additional malignancy in the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- Active infection requiring systemic therapy.
- History of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- Active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.

Treatment Plan

- This is a randomized, placebo-controlled, double-blind study. The investigator, patient, and Sponsor will be blinded to treatment assignment.

- Patients will be randomized to one of the following treatment arms in a 2:1 ratio (experimental to control arm):
  - Arm A (experimental arm): atezolizumab iv 1,200mg every 21 days
  - Arm B (control arm): placebo iv every 21 days

- Randomization will be stratified by the following factors:
  - Histology
  - Stage

Determination of Sample Size

- The primary objective of this study is to explore the efficacy of the atezolizumab treatment after macroscopic radical surgery of patients with malignant pleural mesothelioma in terms of DFS

- Only prior data on the placebo group are available in literature from the MARS trial (median PFS on the control arm= 9 months) since immunotherapy is a new investigational approach for MPM.

- Assuming an accrual time of 24 months and a follow-up time of 24 months, a sample size of approximately 162 patients (randomized in a 2:1 ratio to arm A - atezolizumab treatment and arm B - placebo treatment) will allow to detect true hazard ratios of 0.62 with power 0.8 at a confidence level of 95%

Collateral studies

- During the study baseline tumor blocks will be centrally analyzed to determinate biological characteristics and gene expression. DNA sequencing will be performed using an extensively validated, Clinical Laboratory Improvement Amendments–certified, hybrid capture– based NGS platform (Foundation Medicine).

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[A]		End of treatment[A]	Tumor surveillance[A]	Survival Follow-up[A]
		Cycle 1 Day 1 (C1D1)	Subsequent cycles (cycle = 21 days)[A]			
Laboratory assessments[D]	X		X	X		
Thyroid function testing, urinalysis	X		X[E]	X		
12-lead ECG / ECHO	X		X[F]	X[F]		
Vital Signs[G]	X	X	X	X		
Randomization		X				
Tumor tissue sample	X					
EQ-5D-3L questionnaire	X		X[H]	X		
Tumor assessment	X		X[I]	X[I]	X[J]	
AE review	X	X	X	X		
Concomitant medication review	X	X	X	X		

IL PERCORSO ASSISTENZIALE E LE PROSPETTIVE TERAPEUTICHE PER IL MESOTELIOMA PLEURICO NELLA REGIONE EMILIA ROMAGNA

AtezoMeso Study

Phase III Study With Atezolizumab Versus Placebo In Malignant Pleural Mesothelioma Patients After Pleurectomy/ Decortication

EUDRACT Number 2020-003762-39

GOIRC–03-2019

Maria Pagano
AUSL-IRCCS
Reggio Emilia

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

OECI COMPREHENSIVE Cancer Centre