



Comment on “EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach”

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The authors ought to be congratulated on standardizing pathological classification detailed analysis of currently available evidence of the pleural mesothelioma (1). They have reviewed the importance of adequate tissue sampling, and pathology reporting of features that include architecture, nuclear grading and histological characteristics that are important prognostic markers. These are important in the diagnosis and management considerations in mesothelioma. At present, it is not uncommon for patients to be referred to specialized centers where the pathology reporting of sampled tissue is suboptimal and the basic details are lacking which makes arriving at management decisions more challenging. This proposal hopefully will help and set some expectations of detailed pathological reporting to provide the clinicians with adequate information that are necessary for management decisions. This proposal further emphasizes why it is important that the patients with mesothelioma should be managed in specialized mesothelioma centers to allow proper diagnostic evaluation, pathologic classification and treatment decisions. The authors had attempted to identify histologic and molecular biomarkers that are prognostic in nature so that we identify patients with more aggressive disease. Establishing predictive pathologic information that inform treatment decisions is still a subject of research. There are ongoing efforts in searching for actionable biomarkers in mesothelioma but there has been no level 1 evidence or FDA approved therapies for this fatal disease yet (*Table 1*).

BAP1 germline mutations that result in loss of function of *BAP1* protein seem to inform a better overall prognosis and response to platinum-based chemotherapy in mesothelioma patients. A study published by Hassan *et al.* suggested that patients with pleural mesothelioma with loss-of-function mutations in *BAP1* and other DNA repair genes appeared to benefit from platinum chemotherapy compared with patients without inherited mutations (2).

The Mesothelioma Stratified Therapy Trial (MiST) is a multi-drug Phase II Trial in Malignant Mesothelioma that is exploring the benefit of Rucaparib in *BRCA1/BAP1* mutant mesothelioma, Abemaciclib in p16INK4A negative mesothelioma, Atezolizumab & Bevacizumab in PD-L1 positive mesothelioma patient and pembrolizumab & bemcentinib in patients with No specific biomarker (NCT03654833). More collaborative efforts among the mesothelioma experts are required to expedite enrollment in global trials that could bring some guidance.

Biomarker driven clinical trials are strongly needed because the traditional histologic classification has not made significant change to the current standards in treating mesothelioma for the last 2 decades (*Figure 1*). We agree that a multidisciplinary approach with more specific histopathologic and biomarker identification is essential for better understanding of the disease but a more collaborative approach to identify these patients and enroll them in global clinical trials will help patients, physicians and scientist to answer these questions more rapidly. We

also believe that access to real world data that incorporates relevant biomarker information in all patients and treatment outcomes could expedite reclassification of mesothelioma not only on the basis of histologic features but also on

the basis of current trends in cancer care using molecular biomarkers. We congratulate the multi institutional contributor to this valuable and practical standardization of histological classification of pleural mesothelioma.

Table 1 Current list of BAP1 loss and NF2 mutant biomarker driven clinical trials in mesothelioma

Sponsor	Product	MOA	Phase	Biomarker	Country	NCT#
NCI	Olaparib	PARB inhibitor	II	BAP1 loss	US	NCT03531840
Univ of Florida	Niraparib	PARB inhibitor	II	BAP1 loss	US	NCT03207347
Epizyme Inc.	Tazemetostat	EZH2 inhibitor	II	BAP1 loss	US	NCT02860286
MSK/Takeda	Pevonedistat (MLN4924)	NEDD8 inhibitor	I/II	NF2 mutant	US	NCT03319537
Verastem Oncology	VS-6063 (Defactinib)	FAK inhibitor	I/II	NF2 mutant	US	NCT02004028
NHS/Verastem/Merck & Co.	VS-6063 (Defactinib)/Pembrolizumab	FAK inhibitor + PD1	I/II	NF2 mutant	UK	NCT02758587

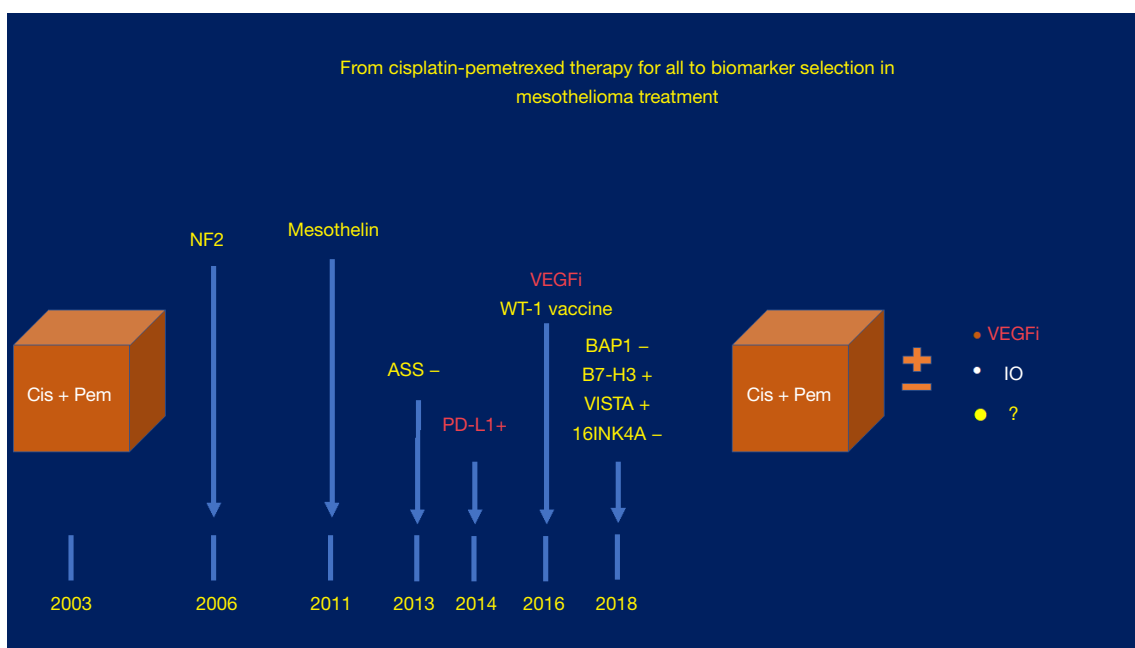


Figure 1 Historical timeline in search of actionable targets in mesothelioma. Cis, cisplatin; Pem, pemetrexed; NF, neurofibromatosis; ASS, arginosuccinate synthetase; PD-L1, programmed death receptor ligand 1; WT-1, Wilms tumor; VEGF, vascular endothelial growth factor; VISTA, set immunoregulatory receptor antibody; p16^{Ink4a}, the principal member of the Ink4 family of CDK inhibitors; IO, immunotherapy.

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Footnote

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