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IRANIAN SOCIETY OF MEDICAL ONCOLOGY AND HEMATOLOGY
ISMOH

Systemic treatment of malignant pleural mesothelioma

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Malignant pleural mesotheliom(MPM)

Introduction

-The most common type of mesothelioma(81%)

-median age at presentation :72 year

-Most patients have advanced disease at presentation

-Median os is approximately 1 year

-5 year os is about 10%

Type of MPM

-Epitheliod
-Sarcomatoid
-biphasic(mixed)

Staging

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis present

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1	N0	M0
Stage IB	T2-T3	N0	M0
Stage II	T1-T2	N1	M0
Stage IIIA	T3	N1	M0
Stage IIIB	T1-T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Staging

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura with or without involvement of: -visceral pleura -mediastinal pleura -diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: -Involvement of diaphragmatic muscle -Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but **potentially resectable** tumor. Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least one of the following features: -Involvement of the endothoracic fascia -Extension into the mediastinal fat -Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall -Nontransmural involvement of the pericardium
T4	Locally advanced **technically unresectable** tumor. Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: -Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction -Direct transdiaphragmatic extension of the tumor to the peritoneum -Direct extension of tumor to the contralateral pleura -Direct extension of tumor to mediastinal organs -Direct extension of tumor into the spine -Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

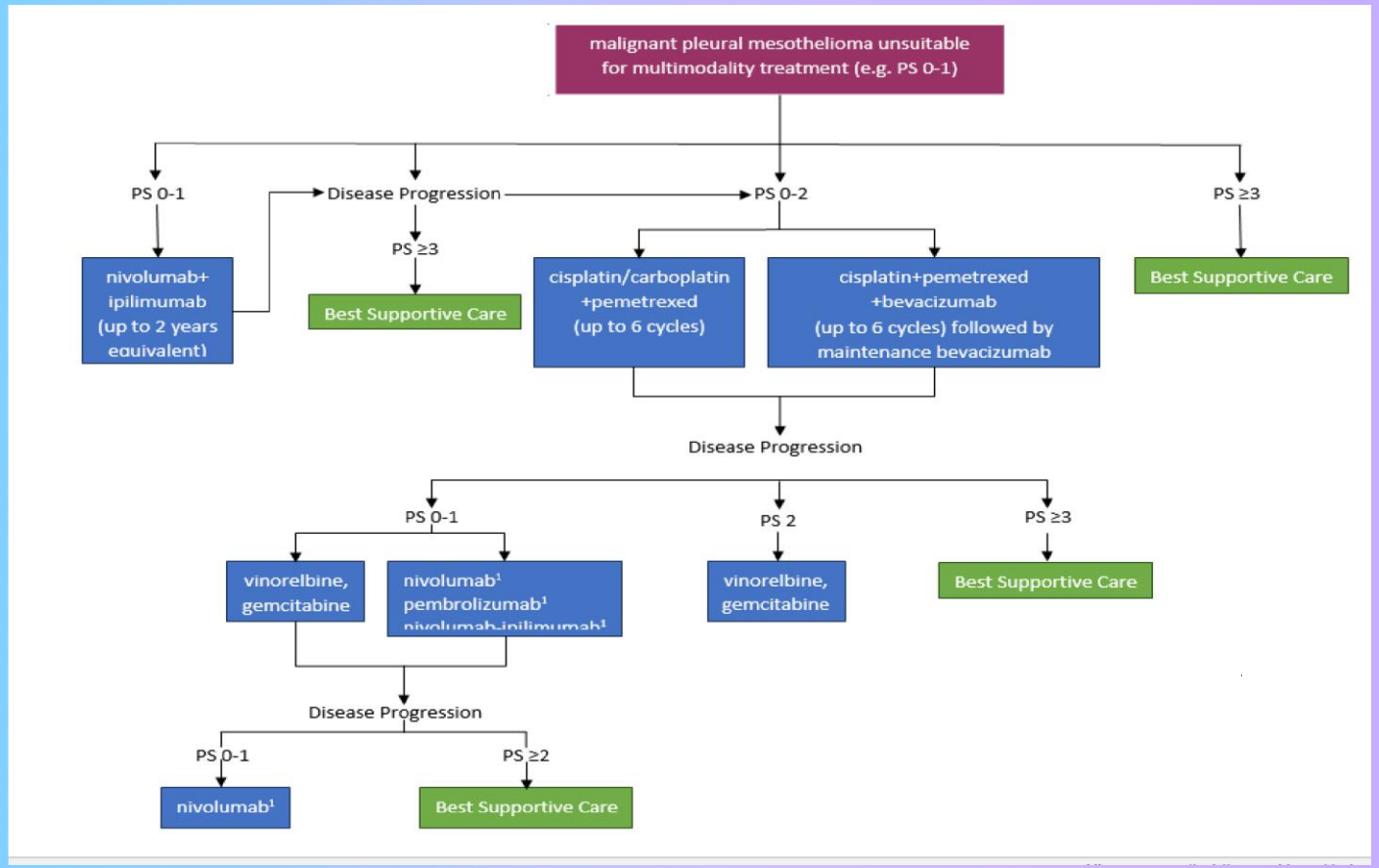
Treatment

1-surgical candidate(EPP-lung sparing P/D-Extended P/D) + adjuvant treatment
2-nonsurgical candidate

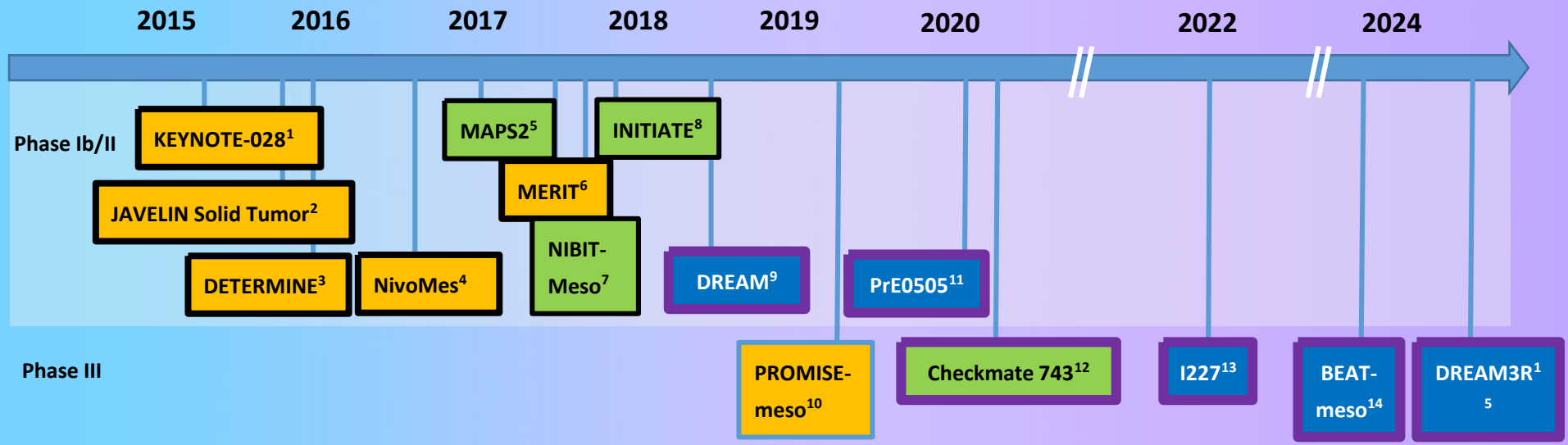
Options in nonsurgical candidates

-Chemotherapy

-Immunotherapy


malignant pleural mesothelioma unsuitable for multimodality treatment (e.g. PS 0-1)
PS 0-1
Disease Progression
PS 0-2
PS ≥3
nivolumab+ ipilimumab (up to 2 years equivalent)
PS ≥3
Best Supportive Care
cisplatin/carboplatin +pemetrexed (up to 6 cycles)
cisplatin+pemetrexed +bevacizumab (up to 6 cycles) followed by maintenance bevacizumab
Best Supportive Care
Disease Progression
PS 0-1
PS 2
PS ≥3
vinorelbine, gemcitabine
nivolumab[1] pembrolizumab[1]
vinorelbine, gemcitabine
Best Supportive Care
Disease Progression
PS 0-1
PS ≥2
nivolumab[1]
Best Supportive Care

History of IO trials in MPM



THE LANCET

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First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

Prof Paul Baas, MD • Prof Arnaud Scherpereel, MD • Prof Anna K Nowak, PhD • Prof Nobukazu Fujimoto, MD • Prof Solange Peters, MD • Prof Anne S Tsao, MD • et al. Show all authors

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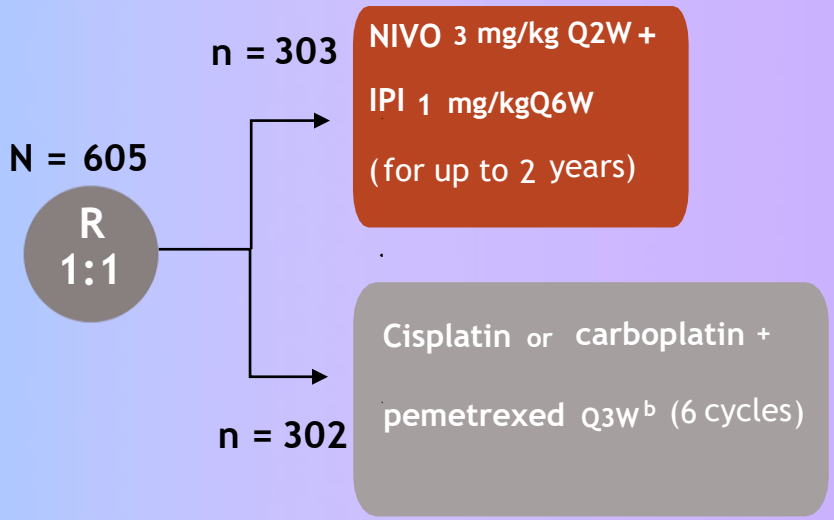
Key Eligibility Criteria

- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0 - 1

Stratified by:

histology (epithelioid vs non-epithelioid) and gender



Until disease progression, unacceptable toxicity *or* for 2 years for immunotherapy arm

Primary Endpoint

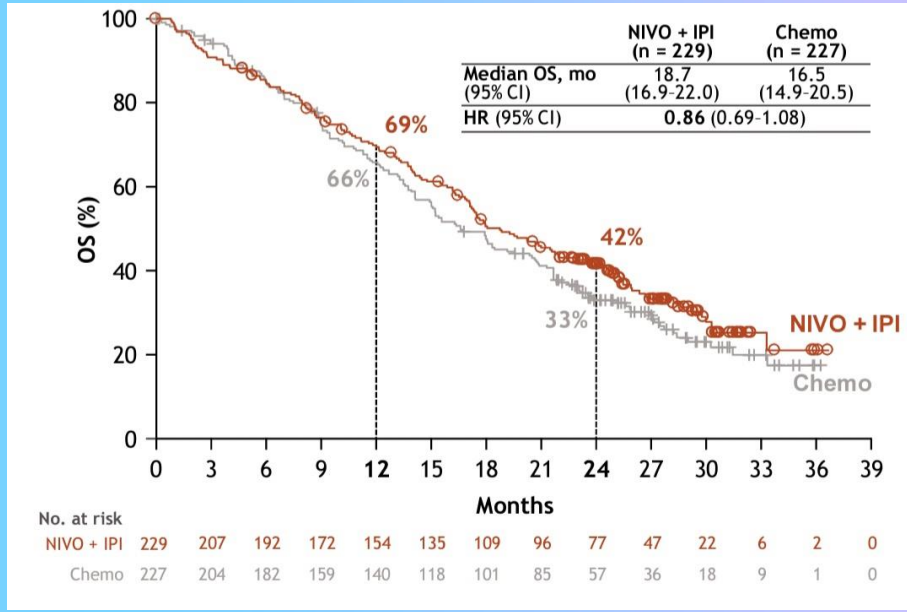
- OS

Secondary Endpoints

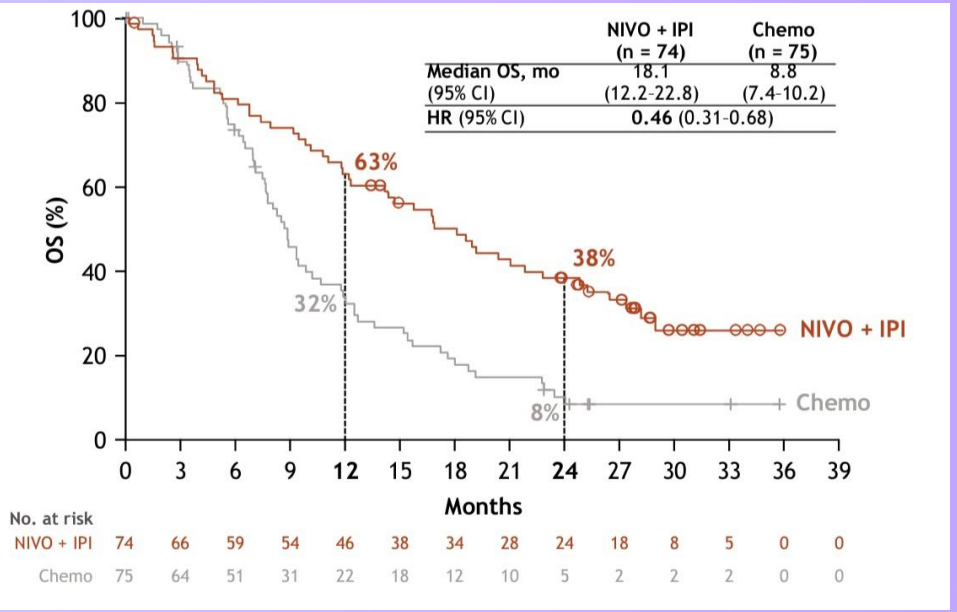
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker

	NIVO + IPI (n = 303)	Chemo (n = 302)
Age, median (range), years	69 (65-75)	69 (62-75)
Male, %	77	77
ECOG performance status		
0, %	38	42
1, %	62	57
Smoking status		
Never, %	42	40
Current / former, %	57	57
Histology,[a] %		
Epithelioid	76	75
Non-epithelioid[b]	24	25
Prior radiotherapy, %	10	9
PD-L1 quantifiable at baseline,[c] n	289	297
< 1%,[d] %	20	26
≥ 1%,[d] %	80	74

Epithelioid



Non-epithelioid



- Primary endpoint is met! (HR 0.74, P = 0.002);
- 2-year OS rates were 41% vs27%
- Survival benefit with NIVO + IPI vs chemo was observed regardless of histology;
- PD-L1 data was descriptive in nature, precluding firm conclusions
- The safety profile of NIVO + IPI was consistent with that previously seen at this dose and schedule
- This is the first positive randomized trial of dual immunotherapy in first line treatment of patients with unresectable MPM and therefore NIVO+ IPI should be considered as a new standard of care

Maintenance therapy

• Maintenance pemetrexed is not recommended in patients after first-line platinum-pemetrexed chemotherapy [II, E]. (Dudnik et al. Clin Lung Cancer 2020)

• NVALT19: switch maintanance gemcitabine vs BSC (PFS significant better) (de Gooijer et al, Lancet Resp Med 2021)

Second line therapy?

- Pembrolizumab (s.a.) has similar outcomes to single agent chemotherapy and is a treatment option (II, C)
- Nivolumab (s.a) is superior to best supportive care in immunotherapy naïve patients and is a treatment option (I, A) (Fennell et al, WCLC 2020/21)
- Combination nivolumab-ipilimumab can be considered as a second-line treatment option (III, C)
- Reintroduction of platinum-pemetrexed or pemetrexed chemotherapy has second-line activity in selected circumstances (III,C)
- Single agent gemcitabine or vinorelbine have limited second line activity, as suggested by objective response rates, or OS in MPM (II,C) • RAMES studie: gem-ramucirumab versus gem-placebo. (Superior OS outcome)

What is up and coming?

- DREAM3R study chemo vs chemo + durvalumab 1st line
- BEAT Meso carbo/pem/bev vs. carbo/pem/bev/atezo
- Lots of phase II studies in second line (BAP1 targeted; Mesothelin targeted; IO combo's)

Questions

- Should ipi/nivo become 1st line therapy?
  - For all types?
  - For non epitheliod only?
- How to deal with PD-L1 expression?
  - Use it for selection?
- For second line:
  - Nivolumab, pembrolizumab, combo or chemotherapy and ramucirumab?

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