ESMO PRECEPTORSHIP ON
Malignant Pleural Mesothelioma

Steven Kao BHB MBChB PhD FRACP
November 2019
**DISCLOSURES**

**Served on Advisory Boards:** AstraZeneca; Pfizer; Boeringher

**Honorarium to my institution:** MSD, BMS, Roche, AstraZeneca, Pfizer, Boeringher

**Travel Support:** BMS, Roche, AstraZeneca
OUTLINE

Treatment strategies in unresectable/inoperable disease
- Standard of care
- Evolving landscape of immunotherapy
- Potential targets/treatments

Treatment strategies in resectable disease

Practice points in 2019
Not accounting for projections in Asia
Estimated future cases for Japan alone is 66,000 in the upcoming decades;
In China, the numbers will be substantially more*

CLINICAL FEATURES – HIGH SYMPTOM BURDEN

- Insidious onset before chest pain (60%) or breathlessness (60%)
- Other symptoms: cough, weight loss, fever/sweats (<30%)
- Pleural effusion in up to 95%
- Mean time from symptoms to diagnosis: 2-3 months

Robinson et al. Lancet 2005;366:397
GENERAL TREATMENT ALGORITHM

Staging and Medical Work-Up

Stage I-III
- Multimodality Therapy
- Medically Inoperable

Stage IV
- Systemic Therapy
  - First line:
    - Cisplatin + pemetrexed
    - Cisplatin + pemetrexed + bevacizumab
  - Second line:
    - Vinorelbine

Observation
- Non-bulky disease
- Minimal/no symptoms
- Epithelioid histology

Therapeutic clinical trials are optimal at all branches
UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III

Stage IV

Medically Inoperable

Systemic Therapy

First line:
• Cisplatin + pemetrexed
• Cisplatin + pemetrexed + bevacizumab

Second line:
• Vinorelbine

Three Trials Worth Remembering
UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III

Medically Inoperable

Stage IV

Systemic Therapy

EMPHASIS Trial

First line:
- Cisplatin + pemetrexed
- Cisplatin + pemetrexed + bevacizumab

Second line:
- Vinorelbine
THE TRIAL THAT CHANGED OUR OUTLOOK ON CHEMOTHERAPY

**Primary objective:** OS (HR = .67)

- **Pemetrexed** 500 mg/m² q 21D
- **Cisplatin** 75 mg/m² q 21D

- **Placebo** q 21D
  - Cisplatin 75 mg/m² q 21D

**456 patients**

**Stratification:** Performance status, histology, gender, WBC, disease measurability, baseline homocysteine

Vogelzang et al. JCO 2003
CISPLATIN + PEMETREXED IMPROVES OVERALL SURVIVAL

Median cycles of cisplatin/pemetrexed received was 6
CISPLATIN/PEMETREXED IMPROVES QOL

UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III

Medically Inoperable

Stage IV

Systemic Therapy

First line:
- Cisplatin + pemetrexed
- Cisplatin + pemetrexed + bevacizumab

Second line:
- Vinorelbine

MAPS Study
MAPS (THE MESOTHELIOMA AVASTIN CISPLATIN PEMETREXED STUDY)

Open-label, multi-centre randomized phase II-III trial

A

- Malignant Pleural Mesothelioma (MPM)
- Histologically proven
- PS= 0-2
- No cardiovascular comorbidity
- Chemo naive

B

Pemetrexed 500 mg/m² D1
Cisplatin 75mg/m² D1
6 cycles, Q21D

Surveillance

No cross-over allowed

Maintenance Bevacizumab
15 mg/kg D1, Q21D until progression

Stratification: center, histology (epithelioid vs. sarcomatoid/mixed), PS (0-1 vs. 2), smoking status (active vs. never-smoker)

Zalcman et al. Lancet 2016;387:1405
ADDITION OF BEVACIZUMAB IMPROVES OVERALL SURVIVAL (1° ENDPOINT)

Median 18.8 v 16.1 mo
UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III

Medically Inoperable

Stage IV

Systemic Therapy

First line:
- Cisplatin + pemetrexed
- Cisplatin + pemetrexed + bevacizumab

Second line:
- Vinorelbine

MS01 Trial
(extrapolation)
MS01 TRIAL (TOTAL OF 840 PTS PLANNED)

MVP = mitomycin, vinblastine, cisplatin
V = vinorelbine 30mg/m² weekly for 12 weeks

Muers et al. Lancet 2008
OVERALL SURVIVAL

Muers et al. Lancet 2008
UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III
- Medically Inoperable
  - Systemic Therapy
    - First line:
      - Cisplatin + pemetrexed
      - Cisplatin + pemetrexed + bevacizumab
    - Second line:
      - Vinorelbine

Therapeutic clinical trials are optimal at all branches
UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III
- Medically Inoperable

Stage IV
- Systemic Therapy
  - First line:
    - Cisplatin (carboplatin) + pemetrexed
    - Cisplatin + pemetrexed + bevacizumab
  - Second line:
    - Vinorelbine

?Carboplatin Equivalence
### EXPANDED ACCESS PROGRAMME RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>843</td>
<td>861</td>
</tr>
<tr>
<td>RR</td>
<td>26%</td>
<td>21.7%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td>TTP</td>
<td>7 months</td>
<td>6.9 months</td>
</tr>
<tr>
<td>Grade III/IV neutropaenia</td>
<td>24%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Carboplatin is a reasonable choice of platinum partner, particularly where cisplatin is contraindicated

UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III

Medically Inoperable

Stage IV

Systemic Therapy

First line:
• Cisplatin (carboplatin) + pemetrexed
• Cisplatin + pemetrexed + bevacizumab

Second line:
• Vinorelbine

Maintenance

Pemetrexed
ALLIANCE STUDY: CALGB 30901

- Patients received 4-6 cycles of platinum and pemetrexed
- If at least SD – randomised 1:1 to pemetrexed vs observation
- 49 patients analysed for efficacy (early closure due to slow accrual)

Dudek AZ et al. ASCO 2019 (Abst 8517)
UNRESECTABLE AND/OR INOPERABLE DISEASE

Staging and Medical Work-Up

Stage I-III
- Medically Inoperable

Stage IV
- Systemic Therapy
  First line:
  - Cisplatin (carboplatin) + pemetrexed x 6C
  - Cisplatin + pemetrexed + bevacizumab
  Second line:
  - Vinorelbine
RETROSPECTIVE EXPERIENCE IN 2\textsuperscript{ND} LINE SETTING FROM MEMORIAL SLOAN KETTERING CANCER CENTRE

URGENT NEED TO IMPROVE TREATMENT OPTIONS in MPM

Zauderer et al. Lung Cancer 2014
### SINGLE AGENT PD1/PD-L1 BLOCKADE IN MESOTHELIOMA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Keynote-028¹</th>
<th>Uni of Chicago²</th>
<th>NivoMes³</th>
<th>MERIT (Japan)⁴</th>
<th>JAVELIN meso⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td>PD-L1 selection</td>
<td>≥ 1%</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>no of patients</td>
<td>25</td>
<td>64</td>
<td>34</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>92%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Responses</td>
<td>CR</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>20%</td>
<td>22%</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>52%</td>
<td>41%</td>
<td>23%</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>16%</td>
<td>?</td>
<td>53%</td>
<td>32%</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>5.4</td>
<td>4.1</td>
<td>2.6</td>
<td>6.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>18</td>
<td>11.5</td>
<td>11.8</td>
<td>17.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Predictive value of PD-L1</td>
<td>Not Reported</td>
<td>-ve</td>
<td>-ve</td>
<td>1%: Trend for PFS &amp; OS</td>
<td>5%: trend for ORR, PFS &amp; OS</td>
</tr>
</tbody>
</table>

¹ Alley et al. Lancet Oncol 2017; ² Desai et al. World Lung 2018 (NCT02399371); ³ Quispel-Janssen et al. JTO 2018; ⁴ Okada et al. CCR 2019; ⁵ Hassan et al. JAMA Oncol 2019
## COMBINATION IMMUNOTHERAPY IN MESOTHELIOMA

<table>
<thead>
<tr>
<th>Trial</th>
<th>MAPS-2¹</th>
<th>NIBIT-Meso²</th>
<th>INITIATE³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Nivolumab + ipilimumab</td>
<td>nivolumab</td>
<td>Tremelimumab + durvalumab</td>
</tr>
<tr>
<td>PD-L1 selection</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No of patients</td>
<td>62</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>100%</td>
<td>70%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Responses**

<table>
<thead>
<tr>
<th></th>
<th>MAPS-2¹</th>
<th>NIBIT-Meso²</th>
<th>INITIATE³</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>28%</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>SD</td>
<td>22%</td>
<td>25%</td>
<td>37%</td>
</tr>
<tr>
<td>PD</td>
<td>50%</td>
<td>56%</td>
<td>35%</td>
</tr>
</tbody>
</table>

| Median PFS (mo) | 5.6 | 4  | 5.7 | 6.2 |
| Median OS (mo)  | 15.9| 11.9| 16.6| Not Reached |

**Predictive value of PD-L1**

- 1%: + for ORR
- 25%: + for ORR & DCR

ETOP 9-15 PROMISE-MESO TRIAL

Key eligibility criteria:
- Malignant pleural mesothelioma (all histologies)
- Progression after previous platinum-based chemotherapy
- ECOG PS 0-1
- Measurable or evaluable disease according to RECIST 1.1 criteria
- Adequate haematological, renal, and liver function
- Availability of tumour tissue for translational research

*Stratification factor:
Histological subtype: Epithelioid vs. Non-epithelioid

R* 1:1

Pembrolizumab
200 mg fixed dose i.v. day1 of each 3 week cycle (q3w)

Institutional choice Chemotherapy
- Gemcitabine 1000 mg/m² d1/8 q3w i.v. or
- Vinorelbine 30 mg/m² d1/8 q3w i.v. or
- Vinorelbine 60/80 mg/m² d1/8 q3w p.o.

Treatment until progression by RECIST 1.1, max 2 years*
* beyond PD allowed in case of clinical benefit

RECIST 1.1 Assessment:
Every 9 weeks for the first 6 months and 12 weeks thereafter

Cross-over to pembrolizumab allowed at progression

Primary endpoint:
Progression-free survival (PFS) assessed by blinded independent central review (BICR)

Secondary endpoints:
- Objective response rate (ORR)
- Time to treatment failure (TTF)
- Overall survival (OS)
- Investigator assessed (IA) PFS
- Adverse events

Correlative endpoints:
- Outcome by PD-L1 status

Popat et al. ESMO 2019
PROMISE-MESO: EFFICACY

### Progression-Free Survival by BICR

<table>
<thead>
<tr>
<th>Group</th>
<th>Events/N</th>
<th>Median PFS (95%CI)</th>
<th>6m PFS% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>56/71</td>
<td>3.4 m (2.2, 4.3)</td>
<td>27.4% (17.1, 38.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>62/73</td>
<td>2.5 m (2.1, 4.2)</td>
<td>25.0% (15.5, 35.6)</td>
</tr>
</tbody>
</table>

HR* (95% CI): 1.06 (0.73, 1.53)  
p= 0.76

*Stratified by histological subtype

92% (91/99) BICR PDs were identified also by IA

### Overall Survival: ITT analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths/N</th>
<th>Median OS (95% CI)</th>
<th>6m OS% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>34/71</td>
<td>11.7 m (7.4, NE)</td>
<td>72.9% (60.8, 81.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>37/73</td>
<td>10.7 m (7.6, NE)</td>
<td>68.5% (56.5, 77.8)</td>
</tr>
</tbody>
</table>

HR* (95% CI): 1.04 (0.66, 1.67)  
p= 0.85

*Stratified by histological subtype

Adjusting for Cross-over

<table>
<thead>
<tr>
<th>Analysis</th>
<th>HR* (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censored</td>
<td>1.44 (0.77, 2.67)</td>
<td>0.25</td>
</tr>
<tr>
<td>IPW</td>
<td>1.07 (0.67, 1.71)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

**NE:** Not estimable
**BEST OVERALL RESPONSE + DURATION OF RESPONSE (DOR) BY BICR**

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab N (%)</th>
<th>Chemotherapy N (%)</th>
<th>Stratified p=0.004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>22% (13%, 33%)</td>
<td>6% (2%, 14%)</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>16 (21.9)</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>17 (23.3)</td>
<td>23 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Progression of Disease (PD)</td>
<td>33 (45.2)</td>
<td>35 (49.3)</td>
<td></td>
</tr>
<tr>
<td>Not Evaluable (NE)</td>
<td>7 (9.6)</td>
<td>9 (12.7)</td>
<td></td>
</tr>
<tr>
<td><em><em>Median DOR</em> (95% CI)</em>*</td>
<td>4.6 months (2.2, 10.3)</td>
<td>11.2 months (6.2, 15.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Updated as of August 2019

16 responders
→ 7 PD and 4 deaths

4 responders
→ 3 PD
### ADVERSE EVENTS (N=142)

<table>
<thead>
<tr>
<th>Safety cohort</th>
<th>Pembrolizumab (N of patients (%))</th>
<th>Chemotherapy (N of patients (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event (AE)</td>
<td>70 (97.2)</td>
<td>65 (92.9)</td>
</tr>
<tr>
<td>Any Treatment-related AE (TrAE)</td>
<td>50 (69.4)</td>
<td>51 (72.9)</td>
</tr>
<tr>
<td>TrAEs of grade 3-5</td>
<td>14 (19.4)</td>
<td>17 (24.3)</td>
</tr>
<tr>
<td>TrAEs leading to treatment discontinuation</td>
<td>6 (8.3)</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>TrAEs leading to death</td>
<td>1* (1.4)</td>
<td>1** (1.4)</td>
</tr>
</tbody>
</table>

* Confusion

**Dyspnea, with disease progression being the primary cause of death

#### Most frequent treatment-related AEs (≥10%)

- Fatigue
- Diarrhea
- Nausea
- Anorexia
- Constipation
- Pruritus
- Mucositis oral
- Dry skin
- Vomiting
- Rash maculo-papular
- Neutrophil count decreased

![Graph showing most frequent treatment-related AEs](image)

* p<5%
**PD-L1 STATUS**

<table>
<thead>
<tr>
<th>Deaths/N</th>
<th>Median OS (95%CI)</th>
<th>6m OS (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo.</strong></td>
<td>9/17</td>
<td>9.9 m (4.0, NE)</td>
</tr>
<tr>
<td><strong>Pembro.</strong></td>
<td>7/19</td>
<td>11.7 m (7.6, NE)</td>
</tr>
</tbody>
</table>

Graph showing overall survival with **TPS <1%**.

HR* (95%CI): 0.72 (0.26, 2.00)  
p* = 0.53

Graph showing overall survival with **TPS ≥1%**.

HR* (95%CI): 1.47 (0.69, 3.11)  
p* = 0.32
CHEMO-IMMUNOTHERAPY COMBINATION 1ST LINE: DREAM

Sample Size: 54 patients
Primary endpoint: PFS (mRECIST for MPM) at 6 months
Secondary endpoints: Objective tumour response rate, PFS (iRECIST), OS, safety

Nowak et al. World Lung 2018
# Chemo-immunotherapy Combination 1st Line: DREAM

<table>
<thead>
<tr>
<th></th>
<th>Confirmed response mRECIST (%)</th>
<th>Confirmed response iRECIST (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (48)</td>
<td>27 (50)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (37)</td>
<td>20 (37)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (15)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

Median PFS, mo (95% CI)
- Chemotherapy + Durvalumab: 6.2 (5.5-9.0)
- PFS6: 31/54 (57%)

Nowak et al. World Lung 2018
1ST LINE IMMUNOTHERAPY TRIALS IN PROGRESS

- CheckMate-743\textsuperscript{1} (Phase III)
  - Nivolumab + ipilimumab vs. pemetrexed and cisplatin or carboplatin

- CCTG Trial\textsuperscript{2} (Phase II/III)
  - Cisplatin/pemetrexed vs. cisplatin/pemetrexed + pembrolizumab vs. pembrolizumab (phase II only)

- BEAT-Meso\textsuperscript{3} (Phase III)
  - Chemo + atezolizumab + bevacizumab vs. chemo + bevacizumab

- DREAM3R (Phase III)
  - Chemo + durvalumab vs. chemo + placebo

1. NCT02899299; 2. NCT02784171; 3. NCT03762018
POTENTIAL TARGETS/THERAPY

- Argininosuccinate synthetase 1-deficient (common in sarcomatoid histology) – ADI-PEG20 (Arginine deprivation with pegylated arginine deiminase – ADAM trial)

- BAP1 – inactivation exposes a vulnerability to EZH2 inhibition – Tazemetostat trial (NCT02860286)

- Intracavitary CAR-T cell + pembrolizumab (NCT02414269)

- Gene therapy: AdIFN with celecoxib + gemcitabine (NCT03710876)
RESECTABLE DISEASE

Staging and Medical Work-Up

Stage I-III

Multimodality Therapy

Therapeutic clinical trials are optimal at all branches
# International Prospective Studies in Extrapleural Pneumonectomy (EPP)

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage</th>
<th>Number of patients</th>
<th>ITT Median survival (months)</th>
<th>EPP operative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Induction Chemo</td>
<td>EPP</td>
<td>RT</td>
</tr>
<tr>
<td>Weder, 2004</td>
<td>T1-3 N0-2</td>
<td>19 (cis/gem x3)</td>
<td>16 (84%)</td>
<td>13 (68%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weder, 2007</td>
<td>T1-3 N0-2</td>
<td>61 (cis/gem x4)</td>
<td>45 (74%)</td>
<td>36 (59%)</td>
</tr>
<tr>
<td>Rea, 2007</td>
<td>T1-3 N0-2</td>
<td>21 (carbo/gem x4)</td>
<td>17 (81%)</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>Flores, 2006</td>
<td>T-43 N0-2</td>
<td>19 (cis/gem x4)</td>
<td>9 (47%)</td>
<td>8 (42%)</td>
</tr>
<tr>
<td>Krug 2009</td>
<td>T1-3 N0-2</td>
<td>77 (cis/pem x4)</td>
<td>57 (74%)</td>
<td>44 (57%)</td>
</tr>
<tr>
<td>Van Schil, 2010</td>
<td>T1-3 N0-1</td>
<td>59 (cis/pem x3)</td>
<td>42 (73%)</td>
<td>38 (64%)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td>256</td>
<td>186 (73%)</td>
<td>154 (60%)</td>
</tr>
</tbody>
</table>

RANDOMISED EPP TRIAL

Median survival:
14.4 months (EPP arm) vs. 19.5 months (no EPP arm)
HR between EPP and no EPP groups = 1.9, p=0.082
EXTENDED PLEURECTOMY/DECORTICATION (P/D)

MARS2 (ClinicalTrials.gov NCT02040272)
- Feasibility study comparing extended PD vs no extended PD following cisplatin/pemetrexed chemotherapy
  - Ability to randomise 50 patients within the first 24 months or to recruit 25 patients within any 6 month period

EORTC 1205 (ClinicalTrials.gov NCT02436733)

Primary endpoint:
Rate of success to complete the full treatment at 20 weeks
- Full protocol treatment
- Alive and no PD No persisting G3/4 toxicities (CTCAE V 4.0)
PRACTICE POINTS IN MPM IN 2019

- Resectable disease
  - No high level evidence – EPP vs. extended P/D
  - Multimodal therapy incorporating chemotherapy, radiotherapy and surgery - a possible option in highly selected patients
  - Ideally in the setting of clinical trial; otherwise highly specialist surgical centres

- Unresectable disease
  - First line setting:
    - 6 cycles of cisplatin (carboplatin) + pemetrexed without maintenance
    - 6 cycles of concurrent cisplatin/pemetrexed + bevacizumab followed by maintenance bevacizumab
  - Second line setting: No optimal regimen
    - Vinorelbine the default option
    - Pembrolizumab not superior to chemotherapy
    - Predictive biomarkers for immunotherapy efficacy desperately needed

- Watch the space:
  - Immunotherapy combo or chemotherapy/immunotherapy combo
THANK YOU