APSR RESPIRATORY UPDATES

Volume 10 Issue 11 Newsletter Date: November 2018

APSR EDUCATION PUBLICATION

Inside this issue: Mesothelioma

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Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial.

Authors: Maio M et al.
Reference: Lancet Oncol. 2017 Sep;18(9):1261-1273.
URL: https://doi.org/10.1016/S1470-2045(17)30446-1

No therapies have shown a survival benefit as second-line treatment for relapsed or refractory malignant mesothelioma, and consequently no agents have been approved for use following progression on first-line therapy. However, an immunotherapy-masked immune checkpoint inhibitor has shown promising antitumor activity across various types of cancer. Tremelimumab is a selective human immunoglobulin G2 monoclonal antibody against CTLA-4 that promotes T-cell activity but does not deplete regulatory T cells. Two previous investigator-initiated phase 2 trials have shown the clinical activity of Tremelimumab. In the present article, the authors compared Tremelimumab with a placebo in patients with unresectable pleural or peritoneal malignant mesothelioma after progression on one or two previous systemic treatments for advanced disease. A double-blind, placebo-controlled, phase 2b trial was performed at 105 study centers across 19 countries. The primary endpoint was the overall survival (OS). A total of 571 patients were randomly assigned to receive Tremelimumab or a placebo. The median OS in the intention-to-treat population did not differ markedly between the 2 groups (7.7 months [95% confidence interval {CI} 0.76-1.12], P=0.41 in the Tremelimumab group; and 7.3 months [95% CI 5.9-8.7] in the placebo group [hazard ratio 0.92 {95% CI 0.76-1.12} p=0.41]). Adverse events of grade 3 or worse occurred in 65% patients in the Tremelimumab group, and the most common events were dyspnea (9%), diarrhea (15%), and colitis (7%). This trial showed that Tremelimumab monotherapy did not improve the patient survival.

Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomized, open-label, phase 1b trial.

Authors : Alley EW et al.
Reference : Lancet Oncol. 2017 May;18(5):623-630
URL : https://doi.org/10.1016/S1470-2045(17)30169-9

A total of 20%-40% of malignant mesotheliomas express PD-L1, which appears to be associated with a worse prognosis than PD-L1-negative disease. KETNOTE-028 is a phase 1b, multi-center, non-randomized, open-label, multi-cohort trial. The inclusion criterion is histologically confirmed locally advanced or metastatic malignant pleural mesothelioma. Twenty-five patients were eligible for inclusion in the study. Eighteen patients had historically confirmed epithelioid mesothelioma, and two had biphasic histology. Patients received 10 mg/kg pembrolizumab (Merck, Kenilworth, NJ, USA) intravenously every 2 weeks on day 1 of each cycle until documented disease progression, intolerable toxicity, physician's decision to terminate, withdrawal of consent, or they reached the maximum 24 months of pembrolizumab treatment. The primary endpoints were safety and tolerability. Sixteen (64%) patients reported a treatment-related adverse event, the most common of which were fatigue (6 [24%]), nausea (6 [24%]), and arthralgia (5 [20%]). Five (20%) patients reported Grade 3 adverse events. Three patients required dose interruption because of immune-related adverse events. No treatment-related deaths or discontinuations occurred. Five (20%) patients had a partial response, for an objective response of 20% (95% confidence interval 6.8%–40.7%), and 13 (52%) of 25 had stable disease. The authors concluded that Pembrolizumab is well tolerated and may confer anti-tumor activity in patients with PD-L1-positive malignant pleural mesothelioma, although further investigation is needed.

Assessment of potential predictors of calretinin and mesothelin to improve the diagnostic performance to detect malignant mesothelioma: results from a population-based cohort study.

Authors: Casjens S et al.
Reference: BMJ Open 2017 Oct 11;7(10):e017104
URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652464/

The most prominent blood-based marker for mesothelioma is mesothelin, showing a specificity of 89% (95% confidence interval [CI] 86%-91%) and a sensitivity of 58% (95% CI 54%-62%) for the discrimination of patients with mesothelioma from asbestos-exposed subjects, according to a recent study. Calretinin is another individual blood-based marker that has shown up to 71% sensitivity at a fixed specificity of 95%. The authors conducted a prospective population-based cohort study (HNRS) to analyze mesothelin and calretinin in plasma samples from a large group of cancer-free men with a comprehensive set of auxiliary data in order to identify predictors of positive tests to improve the specificity of the markers for the early detection of malignant mesothelioma. The cut-off values of positivity for mesothelin and calretinin were ≥1.5 ng/ml and ≥1.0 ng/ml, respectively. A total 569 men without malignant disease at the time of blood sampling were selected for the analysis. Mesothelin concentrations ≥1.5 nM (specificity 95.8%, 95% CI 93.8%-97.2%) and calretinin concentrations ≥1.0 ng/mL (specificity 94.0%, 95% CI 91.7%-95.7%) were observed in 24 and 34 subjects, respectively. Only five men had both markers above these cut-offs. Renal dysfunction was a major predictor of elevated levels of both biomarkers. The authors concluded that mesothelin and calretinin showed high specificities in this cohort of cancer-free elderly men. Calretinin might be a useful adjunct to mesothelin for the early detection of mesothelioma, increasing the specificity to 99.1% (95% CI 97.9%-99.7%) for this marker panel.

National Cancer Database Report on Pneumonectomy Versus Lung-Sparing Surgery for Malignant Pleural Mesothelioma.

Authors: Verma V et al.
Reference : J Thorac Oncol. 2017 Nov;12(11):1704-1714.
URL: https://doi.org/10.1016/j.jtho.2017.08.012

Controversy exists regarding the optimum surgical technique for malignant pleural mesothelioma (MPM). In this article, the authors evaluated American national practice patterns and outcomes of MPM treated with extrapleural pneumonectomy (EPP) versus lung-sparing extended pleurectomy/decortication (P/D) using the National Cancer Database (NCDB). Multivariable logistic regression ascertained clinical factors independently associated with P/D receipt. A Kaplan-Meier analysis was used to evaluate the overall survival (OS) between cohorts; multi-

variable Cox proportional hazards modeling was used to evaluate the factors associated with the OS. Among the 1307 patients extracted from the NCDB, 271 (21%) underwent EPP, and 1036 (79%) underwent P/D. Patients receiving P/D were older (p = 0.028), whereas those undergoing EPP were more likely to live in a rural area (p = 0.044), live farther from the treating facility (p = 0.039), and receive treatment at an academic center (p = 0.050).There were no marked differences between the cohorts in 30-day readmission or mortality rates (all p > 0.05). The procedure type was influenced by sociodemographic and geographical factors, without marked differences in the survival or postoperative mortality and readmission rates between techniques.

External validation of prognostic indices for overall survival of malignant pleural mesothelioma.

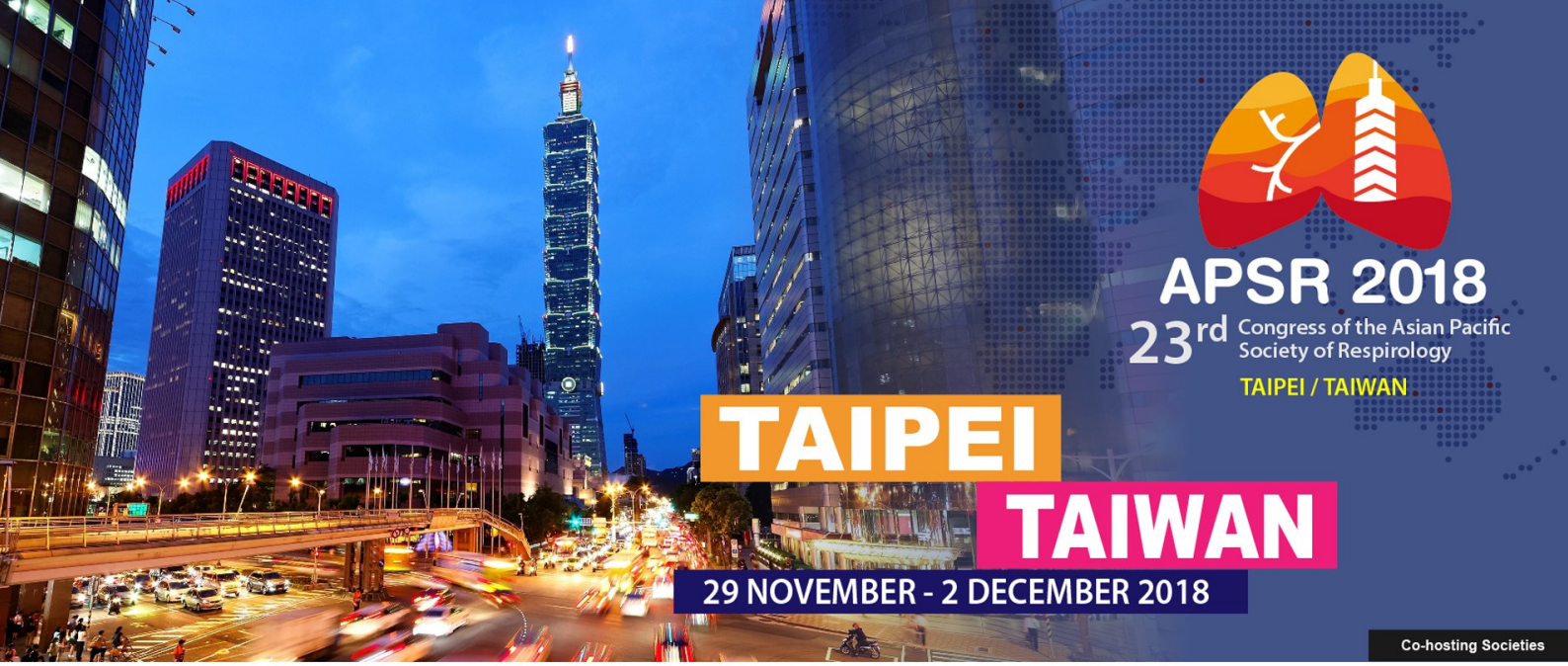
Authors: Kataoka Y et al.
Reference : Lung Cancer. 2017 Nov;113:88-92.
URL: https://doi.org/10.1016/j.lungcan.2017.09.012

There are several prognostic indices (PIs) for predicting the overall survival (OS) in malignant pleural mesothelioma (MPM) patients. Before using a clinical prediction model in the actual clinical setting, an empiric evaluation of its performance based on datasets that were not used to develop the model (i.e. external validation) is essential. In this article, the authors conducted an external validation of the PIs for MPM (the Eastern Cooperative Oncology Group Performance Status, the European Organization for Research and Treatment of Cancer index, regimen, PS, histology or stage [rPHS] index, and Tagawa index). A retrospective cohort study was performed on MPM patients treated at two tertiary hospitals in Japan between 2007 and 2015. The primary outcome was the OS. The participants comprised 183 patients who underwent surgical treatment (n =61), chemotherapy (n =101), and best supportive care (BSC, n=21). The median OS rates were 1014 days for surgery, 690 days for chemotherapy, and 545 days for BSC. Consequently, each PI showed poor discrimination for MPM patients who underwent surgical treatment. The rPHS index showed moderate discrimination for patients given chemotherapy and BSC. In conclusion, further updating is necessary for individual prediction.

Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study.

Authors: Calabrò L et al.
Reference: Lancet Respir Med. 2018 Jun;6(6):451-460.
URL: https://www.clinicalkey.com.au/#!/content/journal/1-s2.0-S2213260018301516

Tremelimumab, an anti-CTLA4 monoclonal antibody, initially showed good activity when used alone in patients with mesothelioma but did not improve the overall survival of patients who failed on first- or second-line chemotherapy compared with placebo in the DETERMINE study. The authors aimed to investigate the efficacy and safety of first- or second-line tremelimumab combined with durvalumab, an anti-PD-L1 monoclonal antibody, in patients with malignant mesothelioma. In this open-label, non-randomized, phase 2 trial, patients with unresectable pleural or peritoneal mesothelioma received intravenous tremelimumab (1 mg/kg body weight) and durvalumab (20 mg/kg body weight) every 4 weeks for 4 sessions, followed by maintenance intravenous durvalumab at the same dose and schedule for 9 sessions. The primary endpoint was the proportion of patients with an immune-related objective response. A total of 40 patients with mesothelioma were enrolled. Eleven (28%) patients had an immune-related objective response (all partial responses; confirmed in 10 patients), with a median response duration of 16.1 months (interquartile range [IQR] 11.5–20.5). Twenty-six (65%) patients had immune-related disease control, and 25 (63%) had disease control. The median immune-related progression-free survival was 8.0 months (95% confidence interval [CI] 6.7–9.3), the median progression-free survival was 5.7 months (95% CI 1.7–9.7), and the median overall survival was 16.6 months (95% CI 13.1–20.1). The baseline tumor PD-L1 expression was not correlated with the proportion of patients who had an immune-related objective response or immune-related disease control, with the immune-related progression-free survival, or with the overall survival. The combination of tremelimumab and durvalumab appeared to be effective, with a good safety profile in patients with mesothelioma, warranting further exploration.



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Thursday 29 November 2018 - APSR Congress 2018, Taipei, Taiwan

Time (morning)	*Session*	*Invited Speakers*	*What to expect?*
9.00 - 9.30	**Welcome & Introduction to Transparency** **Modern-day multilevel transparency in science publishing**	**Prof Paul Reynolds** Co-Editor in Chief RESPIROLOGY	**Introducing the program**: Research publishing becomes increasingly more difficult and transparency is key to success. Openness and clarity in line with international consensus is nowadays expected from authors, journals and publishers. We will provide an overview of what transparency requires from each of them, followed by an illustration of the important role played by journal transparency online in the **journal selection** process by authors
9.30 -9.55	**Masterclass** *Perspective:* **Journal transparency in peer review**	**Prof Philip Bardin** Co-Editor in Chief RESPIROLOGY	**Insight by the expert**: Insight into a journal's peer review process helps an author's understanding of how to meet a journal's standard of a successful research publication.
9.55-10.45	**Workshop** *Training:* **Openness in Manuscript writing**	**Dr Anke van Eekelen** **&** **Dr Lieve Bultynck** Editorial Office RESPIROLOGY	**Insight by the experts**: Research transparency in new submissions is an essential requisite for journals to select the best new studies for publication. We will give advice to authors how to enhance comprehensiveness, clarity and quality of a new manuscript, focussing on: (i) Clinical study design and available international reporting guidelines for transparency, (ii) Best practice statements covering research ethics approval, clinical trial registration, data sharing and author contribution, (iii) Manuscript layout, writing style & plagiarism.
10.45 - 11.00	*Morning Tea*		
11.00 - 11.25	**Masterclass** *Perspective:* **Sharing research facilitates collaboration**	**Prof Martin Kolb** Chief Editor European Respiratory Journal (ERJ)	**Insight by the expert**: The added value for researchers of sharing specialized expertise, knowledge and data (inter)nationally is to broaden opportunities for collaborative research, helping to improve quality outcomes of relevance for publication with impact.
11.25 - 11.50	**Masterclass** *Training:* **Track record transparency: Open Researcher and Contributor ID (ORCID)**	**Chieh-Chih Estelle Cheng** Engagement Lead, Asia-Pacific Region, ORCID	**Insight by the expert**: Individual contributions to research don't have to go unnoticed any longer with an official ORCID identifier and author –controlled publication and track record information freely accessible online. Unambiguity of *who is who* opens up discoverability and opportunities to connect with peers in research around the world.
11.50 - 12.15	**Masterclass** *Training:* **Clarity on Open Access publishing**	**Alison Bell** Journal Publishing Manager Research, WILEY	**Insight by the expert:** The ins & outs of publication models supporting openness: Green and Gold Open Access. How they enhance transparency and regulate use and re-use of publications
12.20 - 12.30	**Panel discussion** **The reality of achieving transparency in the wider Asia Pacific region**	**Panel of all speakers** **Moderator**: Prof Paul Reynolds	**Q&A session** on the practical implications of transparency requirements for researchers with different cultural backgrounds

Nintedanib Plus Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Phase II Results From the Randomized, Placebo-Controlled LUME-Meso Trial.

Authors: Grosso F et al.
Reference: J Clin Oncol. 2017 Nov 1;35(31):3591-3600.
URL: http://ascopubs.org/doi/10.1200/JCO.2017.72.9012

For malignant pleural mesothelioma (MPM) patients with unresectable disease, systemic first-line treatment with pemetrexed and cisplatin is the standard of care, but the overall survival is poor. There is a clear need for more effective treatments. The RUME-Meso study was initially designed as a phase II, double-blind trial designed to assess the efficacy and safety of nintedanib plus chemotherapy as first-line treatment of MPM. Chemotherapy-naïve patients with unresectable, nonsarcomatoid MPM and stratified by histology (epithelioid or biphasic) were randomly assigned in a 1:1 ratio to receive up to 6 cycles of pemetrexed and cisplatin plus nintedanib (200 mg twice daily) or placebo followed by nintedanib plus placebo monotherapy until progression. The primary endpoint was the progression-free survival (PFS). Eighty-seven patients were randomly assigned. The primary PFS favored nintedanib (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.34-0.91; p=0.017). A trend toward an improved overall survival (OS) also favored nintedanib (HR, 0.77; 95% CI, 0.46-1.29; p=0.319). A benefit was evident in the epithelioid histology. Neutropenia was the most frequent grade ≥3 adverse event (AE; nintedanib 43.2% vs. placebo 12.2%), but the rates of febrile neutropenia were relatively low (4.5% in the nintedanib group vs. 0% in the placebo group). The addition of nintedanib to pemetrexed plus cisplatin resulted in an improvement in the PFS. The confirmatory phase III part of this study is ongoing.

NGR-hTNF in combination with best investigator choice in previously treated malignant pleural mesothelioma (NGR015): a randomised, double -blind, placebo-controlled phase 3 trial.

Authors: Gregorc V et al.
Reference: Lancet Oncol. 2018 Jun;19(6):799-811.
URL: https://doi.org/10.1016/S1470-2045(18)30193-1

Malignant pleural mesothelioma has a poor prognosis, and few treatment options remain after failure of first-line chemotherapy. NGR-hTNF is a vascular-targeting drug that increases the penetration of intratumoral chemotherapy and T-cell infiltration by modifying the tumor microenvironment. This phase III trial was aimed at assessing the efficacy and safety of NGR-hTNF in patients with advanced malignant pleural mesothelioma who failed a first-line pemetrexed-containing regimen. Eligible patients had pathologically proven disease of any histological subtype (epithelial, sarcomatoid, or mixed). Patients were randomly assigned to receive weekly NGR-hTNF 0.8 μg/m^2 intravenously plus the best investigator choice (gemcitabine, vinorelbine, doxorubicin, or best supportive care only; n=200), or placebo plus best investigator choice (n=200). The primary endpoint was the overall survival (OS). The OS did not differ markedly between the two treatment groups (median 8.5 months [95% confidence interval {CI}, 7.2-9.9] in the NGR-hTNF vs. 8.0 months [95% CI, 6.6-8.9] in the placebo group; hazard ratio [HR], 0.94; 95% CI, 0.75 to 1.18; p=0.58). Grade ≥3 study-emergent adverse events occurred in 136 (70%) patients receiving NGR-hTNF versus 118 (61%) patients receiving placebo, with the most common event being neutropenia (18% vs. 19%). Although there were no significant differences in the OS (primary endpoint) among the predefined patient subgroups, the results suggest a benefit from treatment with NGR-hTNF in the subgroup of patients with a short treatment-free interval (duration between the end of first-line therapy and the start of second-line therapy; HR, 0.68; 95% CI, 0.49-0.95; p=0.020). The hypothesis-generating findings from the subgroup analyses deserve a confirmatory randomized trial, as patients who rapidly progress after first-line treatment have a poor prognosis.

Radiotherapy for the treatment of malignant pleural mesothelioma.

Authors: Perrot M et al.
Reference: Lancet Oncol 2017 Sep;18(9):e532-e542
URL: https://doi.org/10.1016/S1470-2045(17)30459-X

Malignant pleural mesothelioma is an aggressive disease that continues to be associated with poor outcomes. Although this disease is traditionally considered to be resistant to radiotherapy, recent evidence suggests that radiotherapy can produce positive outcomes. This review focuses on the role of radiotherapy in mesothelioma treatment over the past 42 years, with particular

emphasis on the results of clinical trials evaluating the role of high-dose hemithoracic radiotherapy. Three of the four randomized trials concerning prophylactic radiotherapy have produced negative findings. The benefit of this approach has not yet been demonstrated in clinical trials. Many studies on palliative radiation have been retrospective. Since the optimum palliative dose remains unclear, a prospective phase 2 study was performed to assess the effect of a predefined radiotherapy regimen of 20 Gy in 5 fractions over 5 weeks on pain control. Fourteen (35%) of the 40 patients reported improvement in their pain. These results led to multicenter phase 2 randomized dose-escalation study. Over the past 15 years, the development of new, highly conformal radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT), has enabled investigators to optimize the delivery of high-dose radiotherapy to the whole of the hemithorax. Prospective single-arm trials have shown that the median survival of patients who have completed high-dose hemithoracic radiotherapy after extrapleural pneumonectomy can reach 23.9-39.4 months, regardless of the chemotherapeutic response, suggesting that IMRT may exert an intrinsic benefit on this subset of patients. These observations have led to a change in practice, with the introduction of adjuvant pleural IMRT after pleurectomy-decortication and the development of induction accelerated hemithoracic IMRT followed by extrapleural pneumonectomy.

Geographic and socioeconomic factors in patients with malignant pleural mesothelioma in New South Wales and their impact upon clinical outcomes.

Authors: Linton A et al.
Reference: Respirology 2017 Jul;22(5):978-985.
URL: https://doi.org/10.1111/resp.12981

The impact of geographic and socioeconomic factors on the survival of patients with malignant pleural mesothelioma (MPM) is unclear. To clarify this, the authors analyzed the relationship between these factors and the treatment provision in patients with MPM. A total of 910 patients (67% residing in major cities; 92% <50 km from the multidisciplinary team [MDT]) awarded compensation between 2002 and 2009 with additional MPM incidence data from the New South Wales (NSW) Cancer Registry were enrolled in this study. The influence of the geographic remoteness, distance from the oncological MDT and the Index of Relative Socioeconomic Ad-

vantage and Disadvantage upon the survival (IRSAD), clinical features and treatment received was analyzed. In a multivariate analysis, age >70 years (hazard ratio [HR] = 1.39), male gender (HR =1.36), non-epithelioid histological subtype (HR = 2.18) and IRSAD status by decreasing quintile (HR = 1.06) were found to be independent prognostic factors, indicating that the socio-economic status significantly affects the health outcomes, despite the presence of 'universal' health care. This may be attributed to the fact that socioeconomically disadvantaged patients were significantly less likely to receive chemotherapy than more advantaged patients (37.4% vs. 54.8%; P = 0.001). In contrast, there was no significant advantage for patients residing in major cities (10.6 months vs. 8.8 months; P = 0.162) or within 50 km of the MDT (10.3 months vs. 7.8 months; P = 0.539) compared with those located more remotely. This finding suggests that patients residing further from oncology services suffer no significant impact on their survival. These conclusions are quite interesting, although further research is warranted to seek additional explanations for the differences observed on comparing the treatments and outcomes of compensated and non-compensated MPM patients in NSW.

APSR Respiratory Updates is an initiative of the APSR Education Committee

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