# Melanoma Research Review™

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Issue 35 - 2020


## In this issue:



### Abbreviations used in this issue:

**AE** = adverse event; **CNS** = central nervous system; **DSS** = disease-specific survival; **ECS** = extracapsular spread; **ESMO** = European Society of Medical Oncology; **GEP** = gene expression profile; **GI** = gastrointestinal; **ICI** = immune checkpoint inhibitor; **pCR** = complete pathological response; **RFS** = relapse-free survival; **SEER** = Surveillance, Epidemiology, and End Result; **SLN** = sentinel lymph node.



# Welcome to the 35th issue of Melanoma Research Review.

The lead articles in this issue summarise the recent ESMO Guidelines for the management of local regional melanoma and metastatic melanoma. The spectrum of clinical scenarios is extensive and there are very few controversial areas that are not covered. The guidelines are recommended resources. The long-term results of the COMBI-AD trial are also included in this issue. In the 5-year follow-up patients who had resected stage III melanoma with BRAF V600E or V600K mutations, adjuvant therapy with dabrafenib plus trametinib resulted in a longer duration of survival without relapse or distant metastasis than placebo. Updated results from the KEYNOTE-054 trial at 3-year median follow-up confirm the ongoing effectiveness of adjuvant pembrolizumab in high-risk stage III melanoma.

A systematic review and meta-analysis reports the prognostic ability of gene expression profile tests among patients with localised melanoma varied by AJCC stage and appeared to be poor at correctly identifying recurrence in patients with stage I disease. Another study investigating the prognostic implications of extracapsular spread in melanoma lymphadenopathy found that extracapsular spread was associated with poorer disease-free, melanoma specific and overall survival. Researchers developed and validated a prognostic nomogram for primary vulvar melanoma using the SEER database. They found the nomogram was a useful tool for predicting overall survival of vulvar melanoma with good discrimination and clinical applicability.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,


**Professor Michael Henderson**
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## ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee

**Authors:** Keilholz U, et al

**Highlights:**

- A melanoma consensus conference, organised by the ESMO Guidelines Committee, was attended by 32 experts from 14 countries
- The experts compiled recommendations (with supporting evidence) on controversial topics in melanoma management
- Recommendations for metastatic melanoma in this manuscript include the following:
  - targeted versus immunotherapy
  - treatment sequencing and duration
  - management of brain metastases

**Comment:** Commentary provided in the article below.

***Reference: Ann Oncol. 2020 Aug 4;S0923-7534(20)39939-7***
Abstract

## ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee

**Authors:** Michielin O, et al

**Highlights:**

- A melanoma consensus conference, organised by the ESMO Guidelines Committee, was attended by 32 experts from 14 countries
- The experts compiled recommendations (with supporting evidence) on controversial topics in melanoma management
- Recommendations for locoregional melanoma in this manuscript include:
  - indications for sentinel lymph node biopsy and radical lymph node dissection
  - adjuvant targeted versus immunotherapy
  - adjuvant therapy in specific situations (after node dissection, stage IIIA, resected stage IV, in-transit metastasis)
  - adjuvant therapy toxicity management

**Comment:** These two articles summarise the recent European Society of Medical Oncology (ESMO) Guidelines for the management of firstly local regional melanoma and secondly metastatic melanoma. A group of experts met in late 2019 to develop recommendations on controversial topics where the available evidence was limited or conflicting. Prior to the meeting literature reviews were prepared and individual panels developed guidelines, which were then debated by the whole conference. Each recommendation is classified by a formal level of evidence and the strength of the recommendation and a level of consensus among the 32 participants at the conference. The spectrum of clinical scenarios is extensive and there are very few controversial areas that are not covered. Even though these recommendations are now 12 months old the vast majority of the controversial topics are little further advanced making these documents highly relevant and valuable. They are strongly recommended.

***Reference: Ann Oncol. 2020 Aug 4;S0923-7534(20)39940-3***
Abstract

## Five-year analysis of adjuvant dabrafenib plus trametinib in stage III melanoma

**Authors:** Dummer R, et al

**Summary:** In the primary analysis of this phase 3 trial the authors reported 12 months of adjuvant dabrafenib plus trametinib resulted in significantly longer relapse-free survival (RFS) than placebo in patients with resected stage III melanoma with BRAF V600E or V600K mutations. This article reports 5-year results for RFS and survival without distant metastasis as the site of the first relapse. The authors note overall survival (OS) was not analysed, as the required number of events to trigger the final OS analysis had not been reached. At 5 years, the percentage of patients who were alive without relapse was 52% with dabrafenib plus trametinib and 36% with placebo (hazard ratio for relapse or death, 0.51). The percentage of patients who were alive without distant metastasis was 65% with dabrafenib plus trametinib and 54% with placebo (hazard ratio for distant metastasis or death, 0.55).

**Comment:** This article reports the long-term results at five years of the COMBI-AD trial which randomised patients with BRAF V600E or V600K mutated stage III melanoma to 12 months of dabrafenib with trametinib or placebo. The survival advantage for treatment persists (RFS, 52% vs 36% at 5 years) and no further information on toxicity has come to light (no patients remain on treatment). Most recurrences occur within three years and with this prolonged follow-up the survival curves appeared to be plateauing suggesting that the treatment is preventing rather than delaying disease recurrence. As with other studies reporting adjuvant therapy in stage III melanoma the long-term survival results are awaited however as nearly half the patients in the placebo arm received either targeted therapy or immune checkpoint inhibitor (ICI) for recurrence the final results may not be entirely reflective of the effectiveness of treatment.

***Reference: N Engl J Med. 2020 Sep 17;383(12):1139-1148***
Abstract

## Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: Updated results from the EORTC 1325-MG/KEYNOTE-054 trial

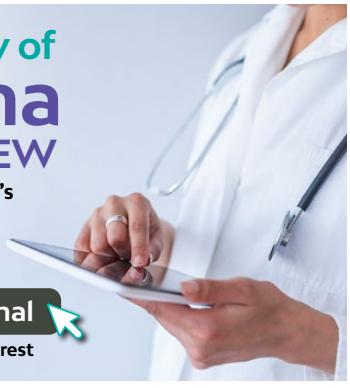
**Authors:** Eggermont AMM, et al

**Summary:** The phase III KEYNOTE-054 trial evaluated pembrolizumab at 200 mg (n = 514) or placebo (n = 505) every 3 weeks for 1 year in patients with resected high-risk stage III melanoma. On the basis of 351 RFS events at a 1.25-year median follow-up, pembrolizumab prolonged RFS (HR, 0.57; P < .0001) compared with placebo. This report is an updated RFS analysis at the 3.05-year median follow-up. The authors reported pembrolizumab (190 RFS events) compared with placebo (283 RFS events) resulted in prolonged RFS in the overall population (3-year RFS rate, 63.7% vs 44.1% for pembrolizumab vs placebo, respectively; HR, 0.56) and in the PD-L1-positive tumour subgroup (HR, 0.57). They also noted the impact of pembrolizumab on RFS was similar in subgroups, in particular according to staging, and BRAF mutation status (HR, 0.51 vs 0.66 for V600E/K v wild type).

**Comment:** This report is an important update of the KEYNOTE-054 study, which randomised patients with stage III melanoma (including stage IIIa with deposits >1 mm) to pembrolizumab or placebo. This analysis and immediate follow-up of three years confirms a sustained RFS benefit (HR = 0.56). The benefit was seen across multiple subgroups including BRAF status and PD-L1 status. The least benefit was seen in patients with stage IIIA, the best prognosis group. No difference by tumour ulceration was noted as has been reported for interferon nor was any difference in outcome noted by BRAF status. This study confirms the ongoing effectiveness of adjuvant pembrolizumab and indicates that long-term OS is likely to be improved in this practice changing study.

***Reference: J Clin Oncol. 2020 Sep 18; Online ahead of print***
Abstract





## Histopathological features of complete pathological response predict recurrence-free survival following neoadjuvant targeted therapy for metastatic melanoma

**Authors:** Tetzlaff MT, et al

**Summary:** The investigators reviewed surgical resection specimens from 59 dabrafenib and trametinib treated patients to identify whether histopathological features of the pathological response further delineated risk of relapse. They found patients achieving complete pathological response (pCR) (49%) had longer RFS compared with patients who did not (P = 0.005). Patients whose treated tumour showed any hyalinised fibrosis had longer RFS versus those without (P = 0.014). In contrast necrosis (P = 0.012) and/or immature/proliferative fibrosis (P = 0.026) correlated with shorter RFS. Furthermore, absence of pCR or presence of immature fibrosis independently predicted shorter RFS. Among pCR patients, mature/hyalinised-type fibrosis correlated with improved RFS (P = 0.035).

**Comment:** The increasing interest in neoadjuvant therapy for stage III melanoma has sparked great interest in response prediction. In general the depth of response to neoadjuvant therapy is associated with improved outcomes. This study of 59 patients who underwent lymphadenectomy after adjuvant BRAF MEK inhibition with dabrafenib and trametinib had a complete pathological response rate of 49%. Relapse free survival was significantly improved in this group. Other significant histological features identified in this study included hyaline fibrosis which was associated with improved RFS and the extent of necrosis and immature /proliferative fibrosis which were associated with poorer RFS. Given that approximately one third of patients after neoadjuvant therapy will relapse, reporting of these histological features is likely to become commonplace although clearly much work remains to be done before treatment decisions based on histological features of the response can be made.

***Reference: Ann Oncol. 2020 Jul 31;S0923-7534(20)39992-0***
Abstract

## Performance of gene expression profile tests for prognosis in patients with localized cutaneous melanoma: A systematic review and meta-analysis

**Authors:** Marchetti MA, et al

**Summary:** The team systematically assessed the performance of prognostic gene expression profile (GEP) tests in patients with stage I or stage II cutaneous melanoma. Seven studies were identified (5 assessing DecisionDx-Melanoma and 2 assessing MelaGenix) including a total of 1,450 study participants. They reported performance of both GEP tests varied by AJCC stage. Of patients tested with DecisionDx-Melanoma, 623 had stage I disease and 212 had stage II disease. Among patients with recurrence, DecisionDx-Melanoma correctly classified 29% with stage I disease and 82% with stage II disease. Among patients without recurrence, the test correctly classified 90% with stage I disease and 44% with stage II disease. Of patients tested with MelaGenix, 88 had stage I disease and 245 had stage II disease. Among patients with recurrence, MelaGenix correctly classified 32% with stage I disease and 76% with stage II disease. Among patients without recurrence, the test correctly classified 77% with stage I disease and 43% with stage II disease.

**Comment:** Although uncommonly used in Australia, commercially available gene expression profile tests for patients with early-stage melanoma are increasingly being used in planning treatment after definitive surgical excision. This study was a formal meta-analysis of the published results of the two main commercially available tests, DecisionDX-Melanoma and MelaGenix. Nearly 1,500 patients from seven studies form the basis of this report. The studies had a high risk of bias with other methodological issues which cloud the evaluation of these results. In summary performance of these tests varied by stage. Patients with stage I disease had a higher risk of a false positive GEP result than stage II patients where the issue was predominantly false-negative results. The future of these tests which are most likely to benefit patients with stage II disease (by identifying patients who may benefit from adjuvant therapy) will undoubtedly depend upon much larger and prospective evaluation and likely incorporation of other prognostic factors which are not included in the current tests.

***Reference: JAMA Dermatol. 2020 Jul 29;156(9):1-10***
Abstract

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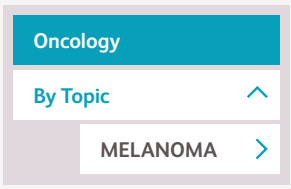


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MT = mutant; WT = wild-type.

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## Vitamin D intake is associated with decreased risk of immune checkpoint inhibitor-induced colitis

**Authors:** Grover S, et al

**Summary:** The objective of this study was to identify potential factors associated with development of ICI colitis. The retrospective analysis included a discovery cohort of melanoma patients from Dana-Farber Cancer Institute who received PD-1, CTLA-4, or combination ICIs. External confirmation was performed on an independent cohort from Massachusetts General Hospital. The discovery cohort included 213 patients of whom 37 developed ICI colitis (17%). Vitamin D use was recorded in 66/213 patients (31%) before starting ICIs. The investigators concluded vitamin D use conferred significantly reduced odds of developing ICI colitis (OR 0.35). They also demonstrated this in the confirmatory cohort (OR 0.46) of 169 patients of whom 49 developed ICI colitis (29%). It was noted pre-treatment neutrophil-to-lymphocyte ratio ≥5 predicted reduced odds of colitis (OR 0.34) only in the discovery cohort.

**Comment:** Based on previous data, which suggested a protective effect of vitamin D in patients with inflammatory bowel disease, this study set out to explore a possible role for vitamin D in patients receiving ICI therapy and a possible effect on gastrointestinal (GI) immune related adverse events (AEs). Although a retrospective review, data from two institutions was analysed separately. In the second group the diagnosis of immune colitis was confirmed by biopsy in 17% (70% of all patients had diarrhoea). Not surprisingly bowel symptoms and colitis were most common in patients receiving combined ICI therapy. Vitamin D use was obtained from the medical record at the time of commencement of ICI so there is no guarantee that patients continued to take it during treatment nor were vitamin D levels available in most patients. The risk of colitis was reduced significantly (OR = 0.46, 0.2-0.9) among the patients taking Vit D. Although intriguing this data requires further validation.

***Reference: Cancer. 2020 Aug 15;126(16):3758-3767***
Abstract

## Survival outcomes in an older US population with advanced melanoma and central nervous system metastases: SEER-Medicare analysis

**Authors:** Sadetsky N, et al

**Summary:** The retrospective review included 2,522 patients aged > 65 years with advanced melanoma diagnosed from 2004 to 2011 and followed until 2013 from a population-based linked database. Central nervous system (CNS) metastases were present in 24.8% of patients at initial metastatic diagnosis; 16.5% developed CNS metastases during follow-up. The researchers found OS was better for patients without CNS metastases (median, 9.5 months) versus patients with CNS metastases (3.63 months). Among patients with CNS metastases, median OS for targeted therapy, immunotherapy, and chemotherapy was 6, 5.5, and 4.5 months, respectively, versus 2.4 and 2.1 months for local radiotherapy and no treatment, respectively. In addition, stereotactic radiosurgery demonstrated higher OS versus whole-brain radiation therapy (median, 4.98 versus 2.4 months).

**Comment:** This study was a retrospective review of the management of disseminated melanoma in elderly patients defined as greater than 65 years. Unlike many of the landmark studies this report includes data on CNS metastases. In this elderly group brain metastases were a common site of first recurrence (25%) and a further 17% (within 12 months) without brain metastases at first presentation developed them subsequently. Survival was poor in this elderly group; the median survival of patients with metastases was 3.6 months versus 9.5 months for patients without brain metastases. There was only a slight improvement in survival among the patients who received ICI or targeted therapy (6 and 4.5 months respectively). Stereotactic rather than whole brain radiotherapy was also associated with a modest improvement in duration of survival. The significance of this study is that it presents a more realistic overview of management of metastatic disease including CNS metastases and despite major improvements in management of melanoma the outlook for elderly patients with CNS metastases remains an issue.

***Reference: Cancer Med. 2020 Jul 15;9(17):6216-6224***
Abstract



## Extracapsular spread in melanoma lymphadenopathy: Prognostic implications, classification, and management

**Authors:** Lo M, et al

**Summary:** This retrospective analysis included 515 patients admitted to two centres with micro/macrometastatic lymphadenopathy for nodal surgery. The authors reported there was an increased frequency of extracapsular spread (ECS) disease in macrometastatic (N+) nodal disease compared with sentinel lymph node positive (SLN+) disease (52.4% vs. 16.2%; $p < 0.0001$). The absolute disease-specific survival (DSS) difference for SLN+ patients was approximately 30% at 10 years (66.2% vs. 37.2%; $p < 0.0001$), and the prognosis of SLN+/ECS+ patients was identical to N+/ECS- patients. They also reported ECS status was an independent prognostic indicator for DSS (HR 2.47; $p < 0.0001$) in patients with SLN+ disease. It was noted there were significant differences in nodal burden according to ECS status between the SLN+ and N+ subgroups. The authors suggest this may be due to differing biology in ECS+ tumours.

**Comment:** The current eighth edition AJCC staging system highlights the heterogeneity of stage III disease (lymph node spread) with 45 combinations of T-stage and N stage. The aim of this retrospective study was to investigate the prognostic significance of ECS in patients with lymph node involvement. ECS was seen in 16% of sentinel node positive patients and 54% of patients with macroscopic node involvement. In both groups of patients ECS was associated with a larger number of lymph nodes involved and larger tumour deposits suggesting ECS represents a more aggressive phenotype. ECS was associated with poorer disease-free, melanoma specific and overall survival. Among patients with microscopic lymph node involvement (detected by sentinel node biopsy) and ECS, the outcomes were identical to patients with macroscopic or clinically apparent lymph node involvement without evidence of ECS. Patients with macroscopic node involvement and ECS fared the worst. The authors make a case for incorporating ECS into the staging system however the paper contains no information on the extent of ECS which has been shown previously to be related to the risk of both regional and distant recurrence.

***Reference: Ann Surg Oncol. 2020 Sep 17. Online ahead of print.***
Abstract

## Construction and validation of a prognostic nomogram for primary vulvar melanoma: A SEER population-based study

**Authors:** Zhou H, et al

**Summary:** The investigators developed a nomogram to predict overall survival of vulvar melanoma. The study cohort, of patients diagnosed with vulvar melanoma between year 2004 and 2015 from Surveillance, Epidemiology, and End Result (SEER) database, were randomised to a training cohort (n = 517) and validation cohort (n = 220). The nomogram included age, race, tumour site, depth of tumour invasion, lymph node status, distant metastasis, tumour size, surgery, chemotherapy and radiotherapy. The investigators reported c-indexes for SEER stage, AJCC stage and this model were 0.561, 0.635 and 0.826, respectively. Furthermore, decision curve analysis revealed this model was superior in predicting survival.

**Comment:** This study used the large US SEER database to explore prognostic factors in vulval melanoma. Unlike other studies the number of patients was large and represents contemporary management unlike most single institution studies of this rare condition. Age (<69 vs >69 years) and tumour site (labia majora vs minor vs clitoris) had no impact on survival but the depth of tumour involvement, lymph node spread and tumour size greater than 20 mm were all associated with poorer survival. Given the inadequacies of the current staging systems the authors created a nomogram predicting survival at three and five years and evaluated it on a separate dataset. The data suggests that patients with tumours with limited depth of invasion particularly without lymph node involvement may have a relatively good prognosis and could avoid adjuvant therapies. The nomogram was relatively efficient at predicting outcomes on the validation set and whilst of interest it is unlikely to be of great practical significance given the variety of treatments including radiotherapy and chemotherapy used in this database which limits the applicability to current practice.

***Reference: Jpn J Clin Oncol. 2020 Aug 8;hyaa137. Online ahead of print.***
Abstract





 