BIOMARKERS in Advanced and Metastatic Melanoma

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In the United States, melanoma is the **5th most common cancer**[1,2]

While most melanomas are highly curable when diagnosed early, the 15% of patients diagnosed with **regional or metastatic disease have a poor prognosis**[1,3]

Regional disease[1,3]

1 in 4 will *not* survive 5 years after diagnosis

Prognosis for regional disease varies widely by stage and stage subgroup[4]

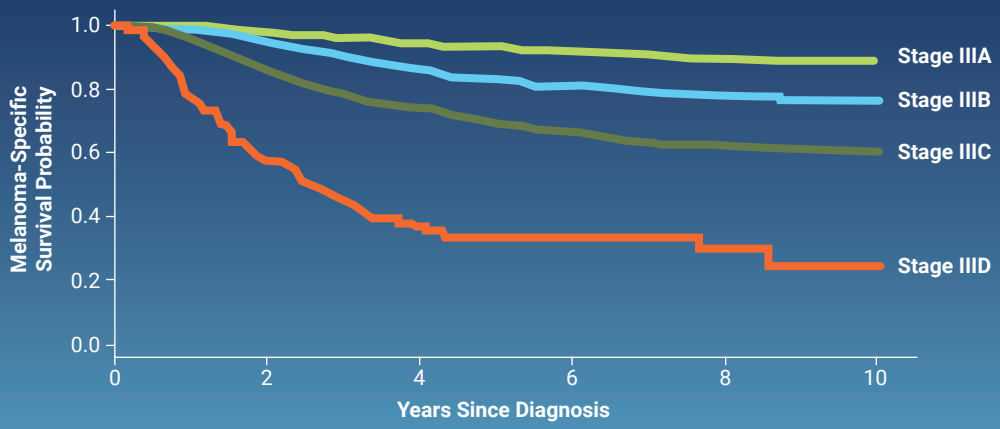

Image adapted from Gershenwald JE et al.[4]

Metastatic disease[1,3]

- **2 in 3** will not survive 5 years after diagnosis

Similar to stage IIID, **only 50%** of patients with metastatic disease will **survive 1 year after diagnosis**[3]

Unlike other common cancers that have seen an explosion of new biomarkers, there are relatively **few molecular or cellular biomarkers for advanced melanoma**[5-7,a]

- Prognosis is based primarily on histopathologic and clinical features[4,8,9]

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[a]Common cancers with multiple predictive and/or prognostic biomarkers include NSCLC, BC, PCa, and CRC.
BC, breast cancer; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PCa, prostate cancer.

Prognostic Markers Required for **Complete Pathologic Staging by AJCC**

Breslow depth	**Greater depth associated with worse outcomes**[4] Prone to interobserver variability[10]
Ulceration[4]	**Presence of ulceration associated with poor prognosis** Host reaction required to distinguish ulceration from processing artifact
Sentinel lymph node disease burden[4]	**Greater disease burden is associated with shorter OS** Disease burden is defined as either the number of positive lymph nodes or the size of the largest melanoma deposit
Microsatellites[4]	**The presence of microsatellites and/or intransitive metastases is associated with a worse prognosis**
LDH serum[4]	**LDH serum greater than the upper level of normal is connected with poor prognosis for stage IV disease**

More Factors Associated With Worse Prognosis

Higher mitotic rate[4]

Older age[9]

Male sex[9]

Liver, brain, or bone metastases[11]

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AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase; OS, overall survival.

Additional Prognostic Biomarkers

BRAF V600 mutations

Occur in 45% of patients. Before the approval of targeted agents and immunotherapies, these mutations were associated with worse melanoma-specific survival in patients with T≥2b disease[12,13]

- Can be assessed with NGS, allele-specific PCR, pyrosequencing, high-resolution melting analysis, ddPCR, and IHC (VE1 clone)[14,15]

NRAS mutations

Occur in 28% of patients. Prior to therapeutic advances, these mutations were associated with worse melanoma-specific survival in patients with T≥2b disease[12,13]

- Can be assessed with NGS and ddPCR

ctDNA

Detectable ctDNA before surgical resection in patients with stage III disease, associated with significantly shorter OS[16]

- Can be assessed with ddPCR[15,16]

TILs

Brisk TILs (TILs that fully infiltrate the tumor) are linked with a 14.2% gain in OS relative to patients with absent TILs or nonbrisk TILs[17,18]

- Can be assessed with histologic analysis[18]

INF-γ signature

Increased gene expression of INF-γ and other immune-related disease is associated with a better prognosis[13,19]

- Can be assessed with RNA-seq[19]

Gene expression profiling assays

Available assays like the DecisionDx®-Melanoma test may have prognostic value but are not superior to prognosis determined by clinicopathologic features[20]

- Can be assessed with RT-PCR[21,22]
- Currently **not recommended** by professional societies[5,9]

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DecisionDx-Melanoma is a registered trademark of Castle Biosciences.

ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; IHC, immunohistochemistry; INF, interferon; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; T, tumor; TIL, tumor-infiltrating lymphocyte.

National Comprehensive Cancer Network® (NCCN®) Recommended Predictive Biomarkers[5]

BRAF V600 mutations

- Occur in 45% of patients and were associated with a poor prognosis before the development of targeted and immunotherapies[12,13,23,24]
  - *BRAF* V600E mutations are associated with younger age[12,13,23,24]
  - *BRAF* V600K mutations differ from *BRAF* V600E mutations; these are associated with older patients[12,13,23,24]

Can be assessed with Sanger sequencing, allele-specific PCR, ddPCR pyrosequencing, high-resolution melting analysis, NGS, and IHC[14,15]

- Allele-specific PCR and IHC (VE1 clone) can only detect *BRAF* V600E mutations[14,15]
- NCCN recommends confirmatory testing if IHC is negative[5]

NCCN recommends testing for *BRAF* V600 mutations in all patients with stage III at high risk for recurrence and stage IV disease[5]

KIT mutations

- Occur in 2% to 5% of cutaneous melanomas, 10% to 15% of mucosal melanomas, and 10% to 15% of acral melanomas[5,9,13,24]

Can be assessed with IHC, PCR with sequencing, and NGS[5,24,25]

NCCN recommends testing for *KIT* mutations in appropriate patients with stage IV disease[5]

NCCN recommends broad molecular profiling, if feasible, for patients with stage IV disease[5]

NCCN does not recommend testing for PD-L1 or TMB at this time[5]

Emerging Predictive Biomarkers for Immunotherapy

TMB[5]
Assessed by WES or large NGS panel

INF-γ signature[26]
Assessed by RT-PCR

FOXP3 expression[27]
Assessed by IHC

TILs invasion in the TME[28]
Assessed by IHC

PD-L1, programmed cell death ligand 1; TMB, tumor mutation burden; TME, total mesothelial excision; WES, whole-exome sequencing.

Summary

Patients with advanced or metastatic melanoma face a poor prognosis[1,3]

Although there are relatively few actionable biomarkers, identification of predictive and prognostic biomarkers is an area of active research[5-7]

NCCN recommends testing[5]:
- All patients with stage III and stage IV melanoma for *BRAF* V600 mutations
- Appropriate patients with stage IV melanoma for *KIT* mutations

NCCN does not recommend using GEP assays to assess prognosis or using PD-L1 or TMB to guide clinical decisions[5]

GEP, gene expression profiling.

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