A091 · Clinico-genomic features predict distinct metastatic phenotypes in cutaneous melanoma

Presenter: Tyler Aprati — Dana-Farber Cancer Institute

Authors: Tyler J. Aprati, Chi-Ping Day, Daniel Lee, Alexander Pan, Justin Jee, Giuseppe Tarantino, Micheal P. Manos, Hannah Faulkner, Marta M. Holovatska, Karam Khaddour, Catherine H. Feng, Kelly P. Burke, Marc Glettig, Zoe Weaver Ohler, Rajaa El Meskini, Christine G. Lian, Jiajia Chen, Tolulope Adeyelu, Andrew Elliott, Genevieve M. Boland, F. Stephen Hodi, Rizwan Haq, Alexander N. Shoushtari, Nikolaus Schultz, Jeffrey Ishizuka, Alexander Gusev, Maryclare Griffin, Kenneth L. Kehl, David Liu

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Metastasis drives mortality and morbidity in cancer. While some patients develop broad metastatic disease across multiple organs, others exhibit organ-specific spread. To identify mechanisms underlying metastatic organotropism, we analyzed clinico-genomic data from over 7,000 patients with metastatic cutaneous melanoma in three independent cohorts (one primary discovery and two validation cohorts including a nationwide electronic health record-derived deidentified database), leveraging machine learning approaches to clinical data. We found that female sex and increased tumor mutational burden associate with decreased metastatic potential, while older age associates with increased lung and adrenal metastases. Using unsupervised analyses, patients clustered into four metastatic patterns: a “highly metastatic” cluster characterized by involvement of many organs, a “low metastatic” cluster characterized by few metastatic sites (mostly lymph node metastases), and two additional clusters each characterized by metastasis to specific sites (brain and lung). Mutations in B2M and PTEN associated with increased overall metastatic potential. PTEN mutations were also associated with brain metastases but were enriched only in the “highly metastatic” cluster and not the brain-specific cluster. Mutations in GNAQ or GNA11 (GNA) associated with increased liver metastasis, and this association was validated in two independent cohorts. To functionally validate this association, we tested and demonstrated liver tropism in two GNA-mutant genetically engineered cutaneous melanoma mouse models of metastasis. Overall, our study elucidates distinct phenotypes of metastasis in patients with melanoma and identifies novel clinical and genomic associations that illuminate the drivers of clinical metastatic organotropism.

Clinico-genomic features predict distinct metastatic phenotypes in cutaneous melanoma

Tyler J. Aprati[*1,2,3], Chi-Ping Day[4], Daniel Lee[5], Alexander Pan[5], Justin Jee[6], Giuseppe Tarantino[1,2,3], Michael P. Manos[1], Hannah Faulkner[1], Marta M. Holovatska[1], Karam Khaddour[1,3], Catherine H. Feng[1], Kelly P. Burke[1,2,3,14], Marc Glettig[1,2,9], Zoe Weaver Ohler[8], Rajaa El Meskini[8], Christine Lian[17], Jiajia Chen[1,2,3], Tolulope Adeyelu[16], Andrew Elliott[16], Genevieve M. Boland[15], F. Stephen Hodi[1,3], Rizwan Haq[1,3], Alexander N. Shoushtari[6,10], Nikolaus Schultz[6], Jeffrey J. Ishizuka[5,11,12,13], Alexander Gusev[1,2,3], Maryclare Griffin[7], Kenneth L. Kehl[1,3], and David Liu[1,2,3]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA; [3]Harvard Medical School, Boston, MA, USA; [4]Cancer Data Science Laboratory, Center for Cancer Research, National Cancer Institute, NIH, MD, USA; [5]Yale Cancer Center, CT, USA; [6]Memorial Sloan Kettering Cancer Center, NY, USA; [7]University of Massachusetts Amherst, MA, USA; [8]Center for Advanced Preclinical Research, Frederick National Laboratory for Cancer Research, National Cancer Institute, Frederick, MD, USA; [9]ETH Zürich, Zürich, Switzerland; [10]Weill Cornell Medical College; [11]Department of Internal Medicine (Oncology), Yale School of Medicine, New Haven, CT, USA; [12]Department of Immunobiology, Yale School of Medicine, New Haven, CT, USA; [13]Department of Pathology, Yale School of Medicine, New Haven, CT, USA; [14]Department of Immunology, Blavatnik Institute, Harvard Medical School, MA, USA; [15]Massachusetts General Hospital, Boston, MA, USA; [16]Caris Life Sciences, Irving, TX; [17]Department of Pathology, Mass General Brigham, Boston, MA

Abstract

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