Use of the 40-gene expression profile (40-GEP) test to identify immune suppressed patients with Brigham and Women's Hospital (BWH) T1-T2a cutaneous squamous cell carcinoma (cSCC) at higher risk of metastasis: Implications for adjuvant radiation

Karina Brito, BS[1], Brian Martin, PhD[2], Jennifer Siegel, PhD[2], Shauna Campbell, MD[1], Melissa McEnery-Stonelake MD[3], Jon Meine MD[3], Jessica L. Geiger MD[4], Christine Poblete-Lopez MD[3], Alok Vij MD[3], Allison Vidimos MD[3], and Shlomo A. Koyfman, MD[1]

[1]Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, [2]Castle Biosciences, Inc., Friendswood, TX,
[3]Department of Dermatology, Cleveland Clinic, Cleveland, OH
[4]Department of Solid Tumor Oncology, Cleveland Clinic, Cleveland, OH

ASTRO Annual Meeting
Washington, DC
Oct 1, 2024

Abstract #1065

Financial Conflict of Interest Disclosures

- K Brito, M McEnery-Stonelake, J Meine, JL Geiger, C Poblete-Lopez: nothing to disclose

- B Martin and J Siegel: Employees and stock/stock options holders, **Castle Biosciences, Inc.**
- S Campbell: Presenter, **Accuray.**
- A Vij: Speaker for **Regeneron**; Speaker and Researcher (PI) for **Mimedx.**
- A Vidimos: Principal Investigator, **Castle Biosciences, Inc.** Author, **UptoDate**. Principal Investigator, **Pellepharm**. Advisory Board, **Inhibitor Therapeutics.**
- S Koyfman: Principal Investigator and consultant, **Castle Biosciences, Inc.** Consultant/research funding, **Merck**. Principal Investigator, **BMS**. Principal Investigator, **Regeneron**. Ad board, **Galera Therapeutics**. Author, **UptoDate.**

Immunosuppression as high-risk factor for cutaneous squamous cell carcinoma (cSCC)

- Patients with high-risk cSCC have good outcomes after Mohs surgery
  - 95.7% disease-specific 5-year survival[1]

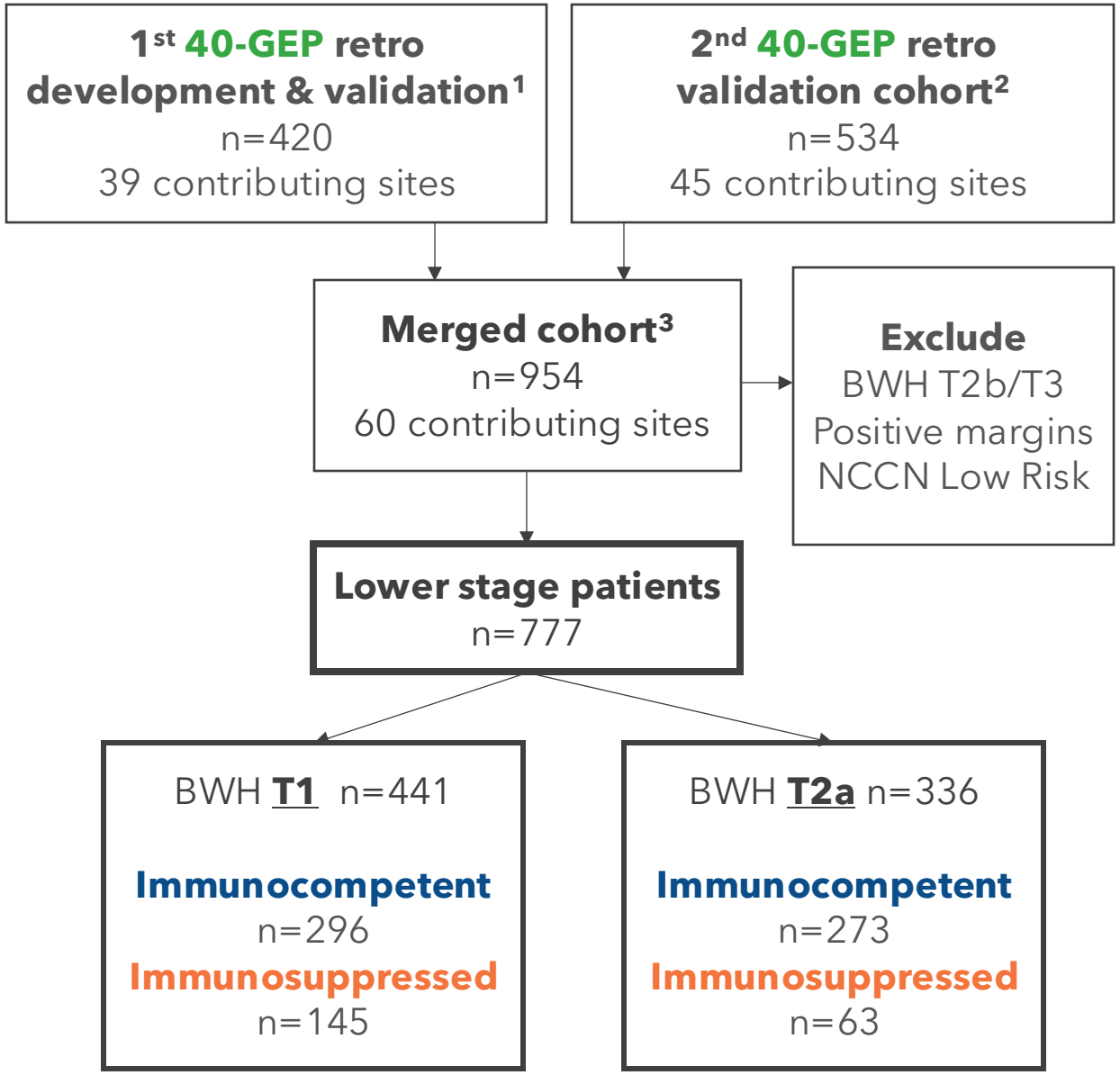
- Immune suppressed (IS) patients tend to present with higher stage cSCC and have inferior outcomes in some studies[2]
  - **Which lower stage patients (eg, BWH T1-T2a[3]) may be at higher risk due to immune status and therefore may potentially benefit from intensified management and treatment?**

- The 40-gene expression profile (40-GEP) test can independently predict likelihood of metastasis for patients with high-risk cSCC beyond staging and clinicopathologic risk factors alone[4-6]
  - **Class 1: Low Risk**
  - **Class 2A: Higher Risk**
  - **Class 2B: Highest Risk**
- **Hypothesis**
  - The 40-GEP can further refine risk stratification in immunosuppressed patients, who may already have a higher risk of metastasis (vs immunocompetent)

1. Soleymani T et al. *J Am Acad Dermatol*. 2023; 88(1):109–17. **2.** Wackel M et al. *JID Innovations*. 2024; 100294. **3.** Jambusaria-Pahlajani A et al. *JAMA Dermatol*. 2013; 149(4):402.
4. Wysong A et al. *J Am Acad Dermatol*. 2021; 84(2):361–9. **5.** Ibrahim SF et al. *Future Oncol*. 2022; 18(7):833–47. **6.** Wysong A et al. *Dermatol Ther (Heidelb)*. 2024; 14(3):593–612.

Patients & study design

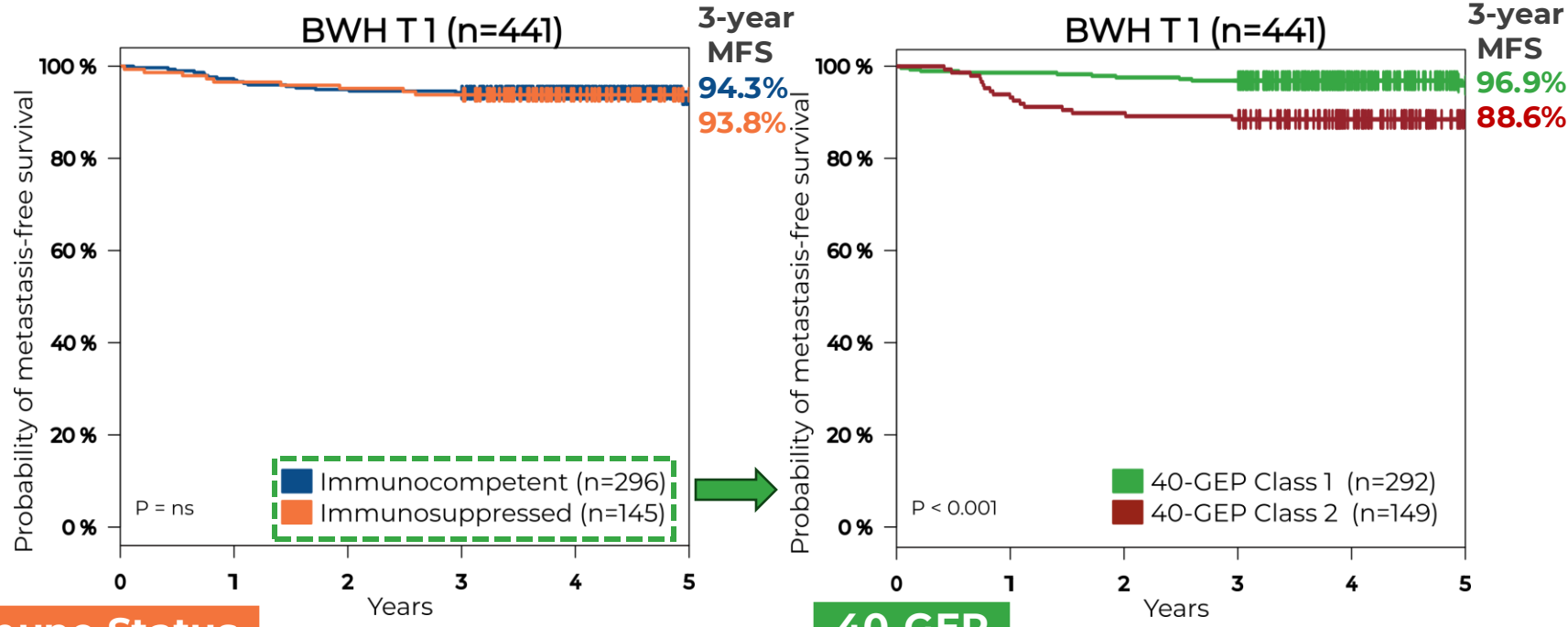
- Analysis from 954 cSCC patients from study of two retrospective cohorts merged[3]
  - ✓ **1+** NCCN high-risk factors[4]
  - ✓ BWH **T1/T2a** tumors (lower risk stages)
- cSCC-associated event or 3-year **minimum** follow-up required
  - Median, 4.36 years (IQR: 3.6, 5.5)
- History of **immunosuppression** (n=208):
  - Organ transplant (68.8%)
  - Therapy for hematologic malignancy (23.1%)
  - Other inflammatory condition, immunotherapy, HIV, etc. (8.2%)
- Analyze risk stratification by immune status and then by **40-GEP test results**



1. Wysong A et al. *J Am Acad Dermatol*. 2021; 84(2):361–9. **2.** Ibrahim SF et al. *Future Oncol*. 2022; 18(7):833–47. **3.** Wysong A et al. *Dermatol Ther (Heidelb)*. 2024; 14(3):593–612.
4. NCCN Guidelines®, Squamous Cell Skin Cancer V.1.2024.

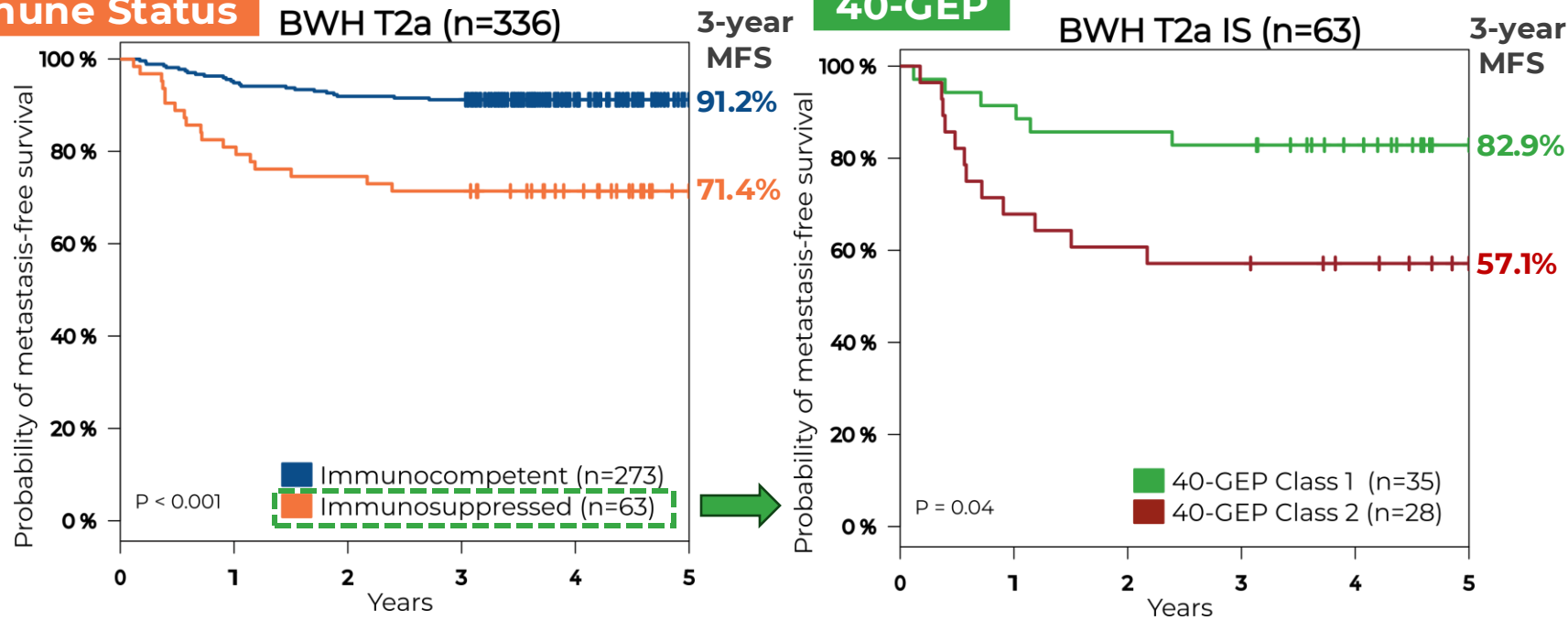
3-year metastasis-free survival and 40-GEP risk stratification

- BWH T1 patients had the same metastatic risk, independent of immune status
- **40-GEP** significantly stratified metastatic risk in T1 patients overall
- BWH T2a patients under chronic immunosuppression show significantly decreased MFS relative to immunocompetent patients
- **40-GEP** stratifies risk for IS patients to guide further management considerations



Immune Status

40-GEP



Multivariable analysis: 40-GEP and clinicopathologic risk factors

- Several risk factors were statistically significant, independent predictors of metastasis
  - **40-GEP Class 2 test result**
  - **NCCN Very High Risk**
  - **Immunosuppression**
- Not statistically significant
  - ***BWH T2a stage***

Multivariable Cox Regression		
Risk Factor	**Hazard Ratio (95% CI)**	***P* value**
40-GEP Result		
Class 2 (2A+2B) *(vs Class 1)*	**3.01** (1.52-4.02)	**<0.001**
Clinicopathologic Risk Factors		
NCCN Very High Risk (*vs High Risk*)	2.33 (1.35-4.00)	**0.002**
Immunosuppression (*vs Immunocompetent*)	2.47 (1.52-4.02)	**<0.001**
BWH T2a (*vs T1*)	1.53 (0.88-2.65)	ns

Conclusions: Patients with immunosuppression and 40-GEP Class 2 results

- Immunosuppressed (IS) patients in this cohort have inferior outcomes in BWH T2a stage
- The 40-GEP further stratifies IS patients into groups with more favorable (Class 1) and less favorable (Class 2A/B) MFS in T2a patients
- Regardless of immune status, patients with Class 2B results have been predicted to be significantly more likely to benefit from adjuvant radiation therapy, which would be cost-saving[1-4]
- **Immunosuppressed, BWH T2a, 40-GEP Class 2B:** Treatment intensification, such as adjuvant radiation therapy, should be strongly considered in this higher-risk population

THANK YOU

1. Arron ST et al. *Int J Radiat Oncol Biol Phys*. 2024; S0360-3016(24)00685-0. **2.** Moody BR et al. *Dermatol Ther (Heidelb)*. 2024; 14(4):861–73. **3.** Somani AK et al. *J Clin Aesthet Dermatol*. 2024; 17(1):41–4. **4.** Ruiz ES et al. *Future Oncology*. 2024; Article in press, e-published 4 Sept.