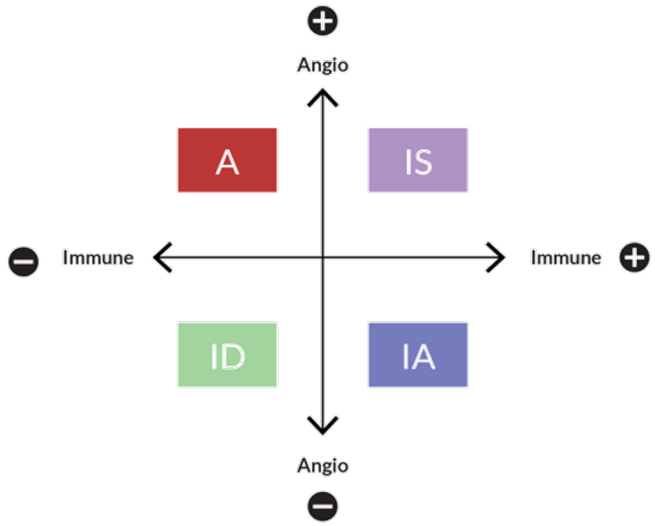
Xerna TME Panel Outputs Per-Patient Probability of Subtype

Lack of biomarkers to identify patients most likely to benefit from targeted therapies remains a **significant unmet need** to improve outcomes for patients, **Xerna TME panel** is a novel solution for therapies that target the tumor microenvironment

- **Machine-learning based, artificial neural net model** using RNAseq technology for RNA derived from FFPE tumor tissue.
- Identifies the **dominant biology** of the tumor microenvironment and assigns into **therapeutically actionable tumor subtypes** defined by angiogenesis and immune gene expression.
- Model was **trained on biology**, **validated on multiple clinical cohorts**, and **tested for prediction to drug response** across hundreds of samples from **multiple different tumor types**.
- ANN algorithm outputs have **robust and binary-like distributions**, allowing for **high confidence biomarker calls**.
- TME subtypes have **varying prevalence** across tumor types, have **prognostic value** for determining survival and disease recurrence risk, and are **predictive for response** to anti-angiogenic and immune targeting therapies.
- Xerna TME panel has shown **predictive potential** in:
  - Navicixizumab + paclitaxel in Ovarian Cancer for ORR, PFS (high angiogenesis subtypes, A + IS)
  - Bavituximab + Pembrolizumab in Gastric Cancer ORR (high immune subtypes, IA + IS)
  - Nivolumab or Pembrolizumab monotherapy in Gastric Cancer ORR (immune active IA subtype has highest ORR)
  - Ramucirumab + paclitaxel in Gastric Cancer ORR (high angiogenesis subtypes, A + IS)
  - CPI + novel immune therapy in Keytruda refractory Melanoma ORR, PFS (immune suppressed subtype, IS)
  - CPI as maintenance in randomized Gastric cancer trial for PFS, OS (high immune subtypes, IA + IS)



A = Angiogenic:

high angiogenesis + low immune signature score

IS = Immune Suppressed:

high angiogenesis + high immune signature

IA = Immune Active:

low angiogenesis + high immune signature

ID = Immune Desert:

low angiogenesis + low immune signature

Overcoming Current Limitations in Bringing Precision Medicine to More Cancer Patients – Xerna TME Panel

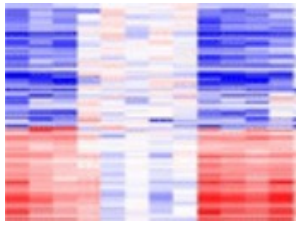
Current Challenges in Oncology Precision Medicine

Most oncology biomarkers that guide therapy are primarily **DNA-based** testing to identify driver mutations and inform treatment

- Only **~20% of cancer patients** benefit from genomics-based precision medicine

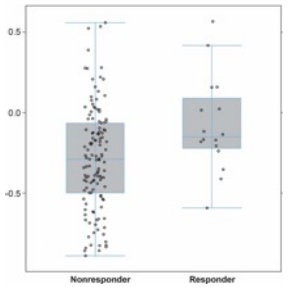
Lack of biomarkers to identify patients most likely to benefit from targeted therapies

- Remains a **significant unmet need** to improve outcomes for patients



RNA-based signatures have **yet to be validated** as predictive biomarkers of clinical response

- Datasets are rich, but **limitations in analytical approaches** often fail to capture the complexity of gene interactions and biological processes



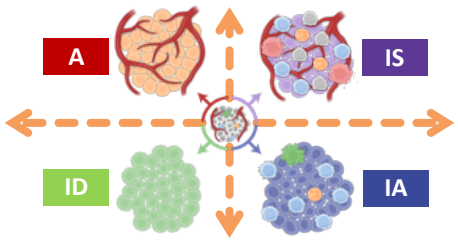
Methodological and technology limitations: **reliance on small populations, lack of robust separation of data points** and use of **standard statistical tests to define thresholds**

- **Limited applicability** to larger populations
- **Poor replication** of findings
- **Low confidence** in biomarker calls

The Xerna™ TME Panel Solution

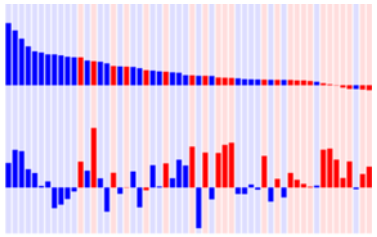
Our biomarker platform is **RNA-based** and focuses on cancer biologies that are relevant to large numbers of patients

- Xerna TME panel is focused on angiogenesis and immune biology and relevant to **as many as ~80% of patients**



Xerna TME panel is **trained on biology that is commonly shared by all solid tumors**

- Defined TME subsets **align to specific therapeutic modalities** that are currently available and in development



Using a **machine-learning algorithm**, we interrogate multiple gene interactions (~100)

- **Captures the complexity** of these inter-related biologic processes and define a tumor's dominant biology.

Advanced analytics are used to compute scores that define biological subtypes overcoming challenges of using linear measurements around a population

- **Robust** and **binary-like biomarker designations**

Complex Interrelationships Exist Between Angiogenesis and Immune Biologies Within the Tumor Microenvironment

VEGF has many pleiotropic effects resulting in induction of angiogenesis and suppression of anti-tumor immunity.

① Induction of pathological angiogenesis

② Blocking T cell extravasation

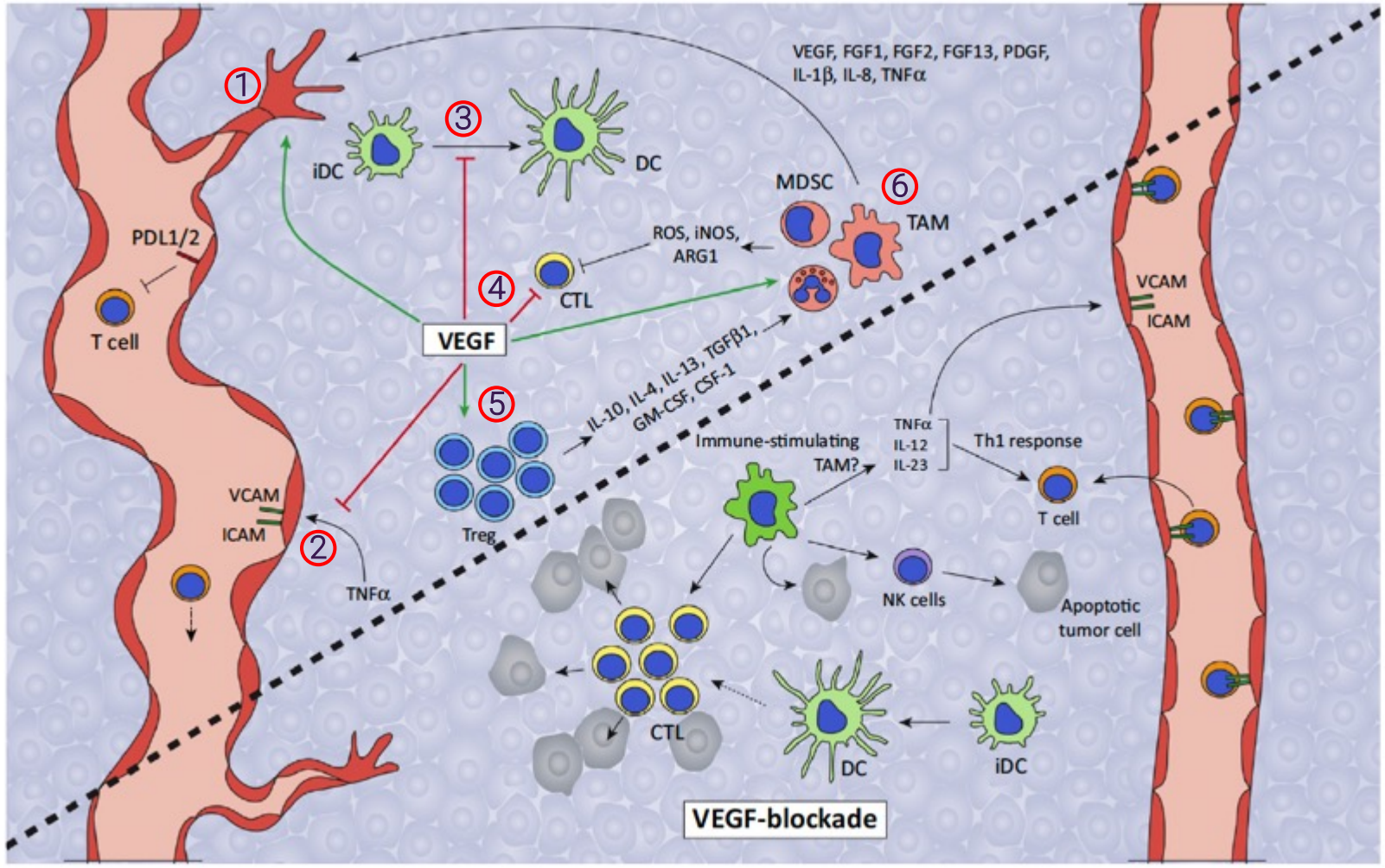
③ Inhibition of dendritic cell maturation

④ Inhibition of T cell proliferation

⑤ Induction of Treg proliferation

⑥ Recruitment of Immune-suppressive cells

MDSCs and TAMs produce factors to further inhibit T cell activation and activity as well as to promote angiogenesis.



Adapted from Rivera, L.B. and Bergers, G. Trends in Immunology. April 2015, 36(4): 240-249

Xerna TME Panel Designed to Identify the Dominant Biology of the Tumor Microenvironment

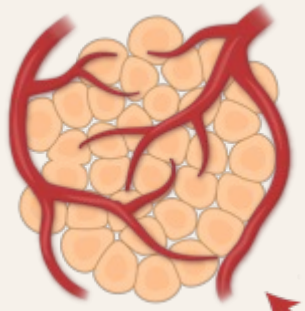
Tumor Agnostic Subtypes

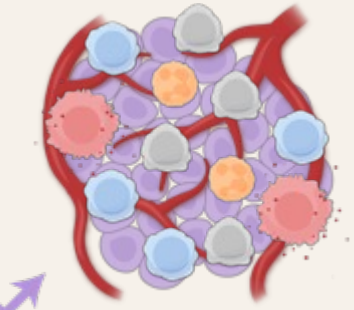
High Abnormal/Pathological Blood Vessel Score-- Subtypes: A + IS

A

Angiogenesis Group (A)

High angiogenesis +
low immune signature score





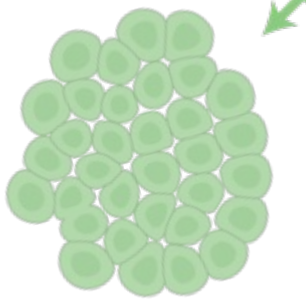
IS

Immune Suppressed (IS)

- High angiogenesis + high immune signature score
- Dysfunctional blood vessels inhibit function of many types of immune cells, and block infiltration of T cells

Low Immune Score
Subtypes: A+ID

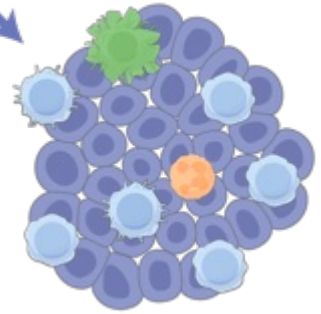
High Immune Score
Subtypes: IS + IA



ID

Immune Desert (ID)

Low angiogenesis +
low immune signature score



IA

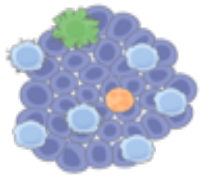
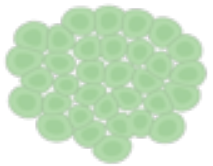
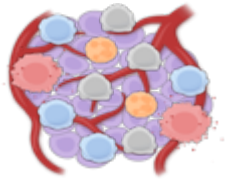
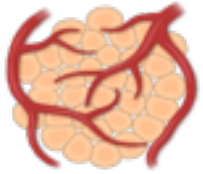
Immune Active (IA)

- Low angiogenesis + high immune signature score
- Immune cell trafficking not impaired but still immune cells are not fully active

Suppressed T cell
Inactive T cell
Active T cell
M1 macrophage
M2 macrophage

Low Abnormal/Pathological Blood Vessel Score-- Subtypes: ID + IA

Xerna TME Panel Subtypes Define Distinct Aspects of the Tumor Microenvironment

Xerna TME Subtype	Correlations that Support Biology[1]	Prognosis[2]	Therapeutic Hypothesis
Immune Active (IA) 	• Expression of genes for inflammatory response and immune activation (i.e., PD-L1, IFNg, TNFa) • Histology showing tumor infiltration by myeloid/lymphoid cells • Correlates with MSI-High Subtypes	Best	Immune Checkpoint Inhibitors
Immune Desert (ID) 	• Lack of immune or angiogenesis gene signatures • Histology marked by low vessel density and low immune cell infiltration	Mod.-Good	Tumor Vaccines
Immune Suppressed (IS) 	• Angiogenesis gene and protein expression profile (i.e. VEGFR2, ACVRL1, Tie2, PDGFRb) • Gene expression inflammation, M2 macrophage biology and Treg signatures (i.e., TIM3, IL-10, and TGFb) • Histology marked by dense, pathological vessels as well as infiltration of myeloid and lymphoid cells	Mod.-Poor	Combination Immune Therapies
Angiogenesis (A) 	• Angiogenesis gene and protein expression profile (i.e., VEGFR2, ACVRL1, Tie2, PDGFRb) • Histology marked by dense, dysfunctional vessels	Worst	Anti-Angiogenic Agents

[1]Uhlik et al, Cancer Research, 2016, 76(9) and AACR Poster Presentation, March 2021, and Data on File
[2]Based upon CRC recurrence-free survival (AACR Poster Presentation, March 2021) and gastric cancer overall survival (Uhlik et al, Cancer Research, 2016, 76(9))
[3]Rivera and Bergers, Trends in Immunol, 2015, 36(4)

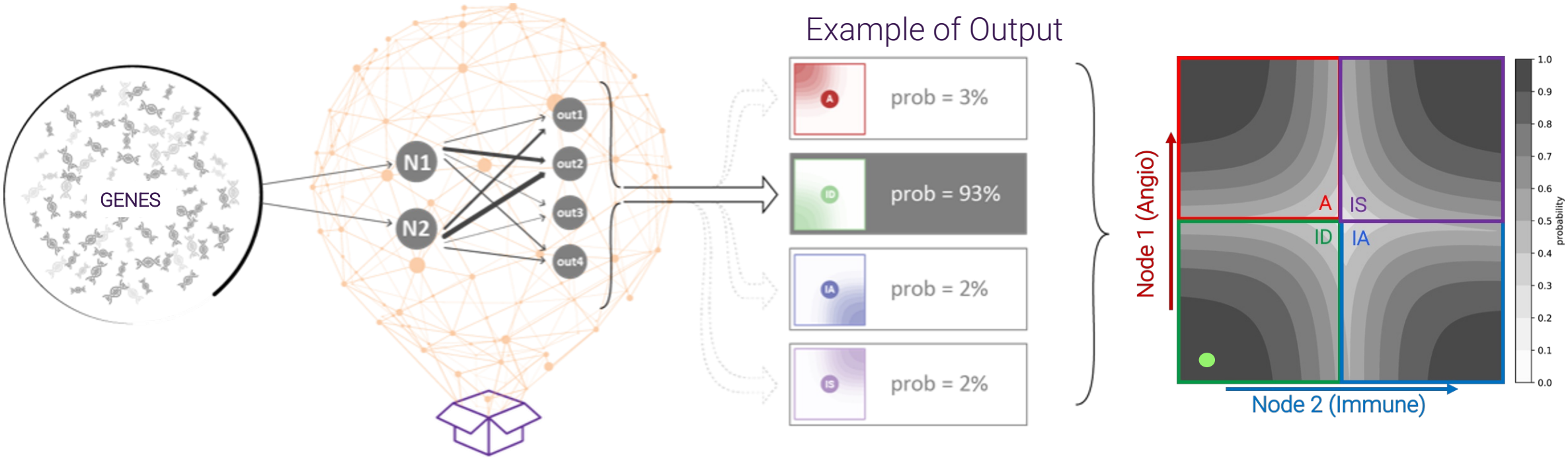
Patient Sample Cohorts Used for Development and Testing

	Tumor Type	Independent Cohorts		Xerna TME Panel Successfully Predicted Outcomes
Training:	Gastric	ACRG, no targeted therapy, comparable clinical history[1]	N=298	N/A
	Multiple Solid Tumors	Misc. Biobanked Samples[2]	N= ~1,100	N/A
Gene List and Algorithm Locked				
Testing:	Gastric/GEJ:	Immune checkpoint inhibitor (ICI)[3] Anti-angiogenic + Chemo[4] Combo Immune Therapy[5] Maintenance ICI[6]	N=73 N=49 N=57 N=82	
	Ovarian	Anti-angiogenic + Chemo[7]	N=33	
	Colorectal	CIT Stage 0-2[8]	N=557	
	Melanoma	Innate Immune Modulator + ICI[6]	N=38	
	Multiple Solid Tumors	Other clinical collections and public sources, multiple indications[9]	N > 3100	Ongoing

[1] *Asian Cancer Research Group (ACRG); publicly available data from Cristescu et al, Nature Medicine 2015*
[2] *HTG Molecular Diagnostic Inc.; samples purchased - Gastric (N=337), colorectal (N=370), and ovarian (N=392)*
[3] *Samsung Medical Center; samples from clinical practice*
[4] *Samsung Medical Center; samples from clinical practice*
[5] *ONCG100 clinical trial (NCT04099641); samples from OncXerna sponsored trial*
[6] *Analyses not yet publicly disclosed*
[7] *Navi1b clinical trial (NCT03030287); samples from OncXerna sponsored trial; Fu et al, JCO 2022 doi: 10.1200/JCO.21.01801*
[8] *Cartes d'Identite des Tumeurs (CIT); publicly available from Marisa et al, PLOS Medicine 2013*
[9] *Includes samples from The Cancer Genome Atlas TCGA) collections, among others*

Unboxing the Machine Learning “Black Box” Enabled Optimization & Interpretation of the Biomarker

Machine learning algorithm based on neural network with two nodes to read out four subtypes based on a probability score



Representation of Xerna TME Panel Process

Predictive Potential of the Xerna TME Panel Tested in a Gastric Patient Cohort Treated with Immune Checkpoint Inhibitor (ICI) Monotherapy

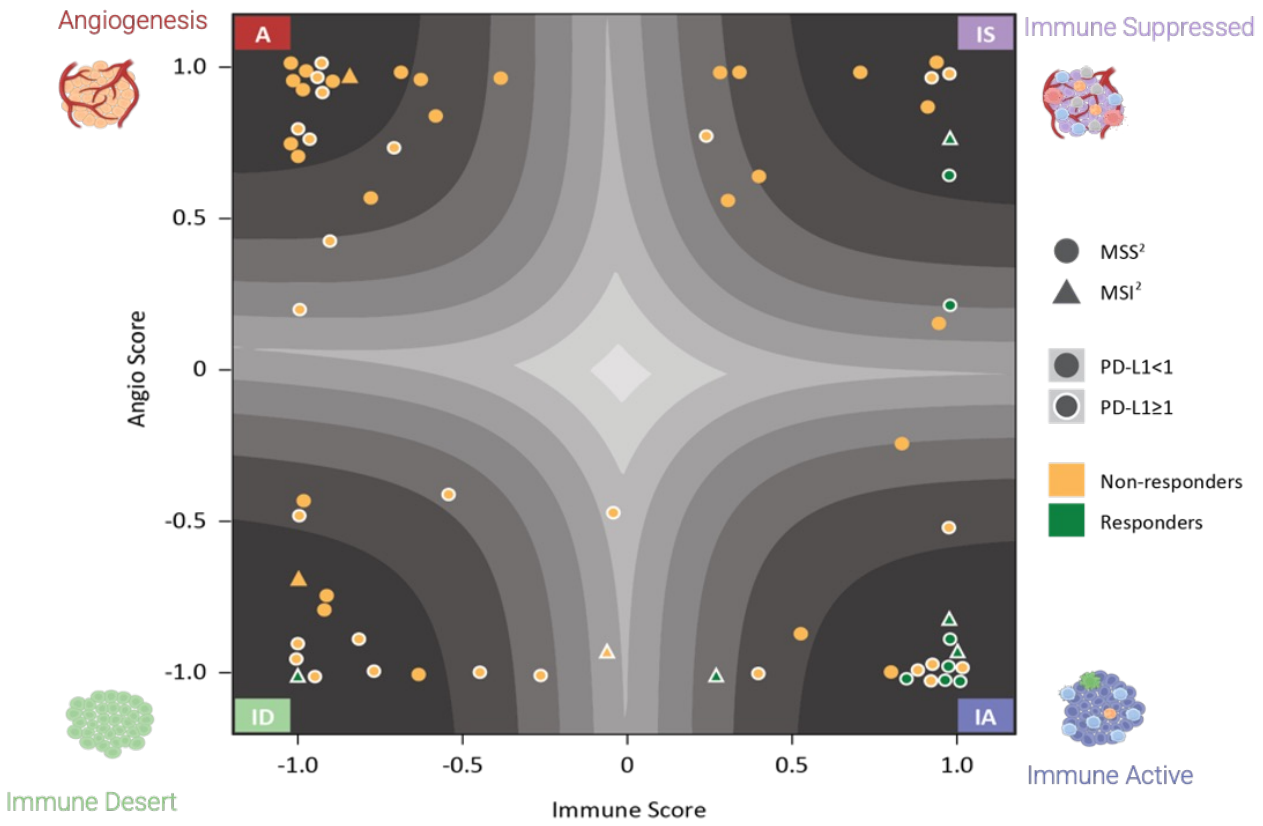
OPDIVO® (nivolumab)

KEYTRUDA® (pembrolizumab)

- 2nd and 3rd line gastric cancer patients treated at Samsung Medical Center with monotherapy pembrolizumab or nivolumab (N=73)
- ORR and PFS data was available for assessment of biomarker predictive potential
- MSI/MSS status and PD-L1 IHC CPS score determined for almost all patients
- Tumor biopsies were collected just prior to initiating ICI therapy
  - Samples were formalin-fixed paraffin-embedded (FFPE)
  - RNA was extracted and RNAseq run
  - Analyzed in the Xerna TME panel

TME Immune subgroups (IA and IS) were hypothesized to derive the most clinical benefit.

Predictive Capability of the Xerna TME Panel for Immune Checkpoint Therapy



Latent space plot of Xerna TME calls for samples from the Samsung gastric ICI cohort. Glyphs are shaped according to their MSS/MSI status, outlined according to their PD-L1 CPS score status, and color-coded according to their best response. Contours represent different levels of probabilities for the Xerna TME calls.

Gastric cancer patient cohort (N=73) treated with immune checkpoint inhibitor (ICI) monotherapy[2]

Best overall response rates[3] comparison (%)

High probability IA subtype	PD-L1 positive
58%	30%
MSS + IA subtype	MSS all-comers
33%	12%
MSS + PD-L1 + Immune High subtypes	MSS + PD-L1 + Immune Low subtypes
44%	0%
MSI-H Immune High subtypes	MSI-H Immune Low subtypes
100%	25%

Table of best clinical response for select subtypes in the Samsung gastric cohort treated with ICI monotherapy. Overall response rate in the entire cohort is 17.8%. "High probability" IA subtype samples include those samples with IA score probabilities of 0.9 or higher.

Biomarker Performance Characteristics - Immune Checkpoint Inhibitor Gastric Cohort

Data from Samsung Gastric Checkpoint Inhibitor (CPI) Cohort: Performance is *on par* with MSI-H

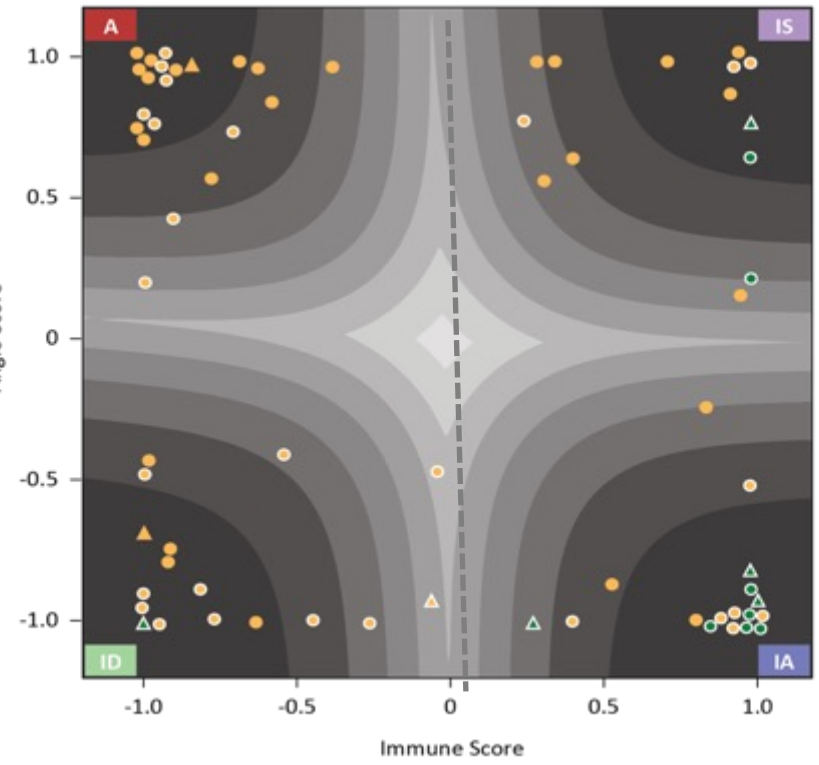
Biomarker Positive	ACC	Sensitivity	Specificity	PPV	NPV
Xerna TME Panel: IA ≥90% Probability	0.85 (62/73)	0.54 (7/13)	0.92 (55/60)	0.58 (7/12)	0.90 (55/61)
Xerna TME Panel: IA+IS	0.68 (50/73)	0.85 (11/13)	0.65 (39/60)	0.34 (11/32)	0.95 (39/41)
PD-L1 CPS ≥1	0.59 (41/69)	1.00 (12/12)	0.51 (29/57)	0.30 (12/40)	1.00 (29/29)
MSI-H	0.85 (62/73)	0.38 (5/13)	0.95 (57/60)	0.63 (5/8)	0.88 (57/65)

Biomarker Performance Characteristics
ACC (accuracy): number of correct predictions /total number of predictions
Sensitivity: true biomarker responses / total actual responses
Specificity: true biomarker non-responses / total actual non-responses
PPV (positive predictive value): true biomarker responses / total predicted biomarker responses
NPV (negative predictive value): true biomarker non-responses/ total predicted biomarker non-responses

CPS, combined positive score; MSI-H, microstatellite instability – high; NA, not applicable; PD-L1, programed death ligand-1

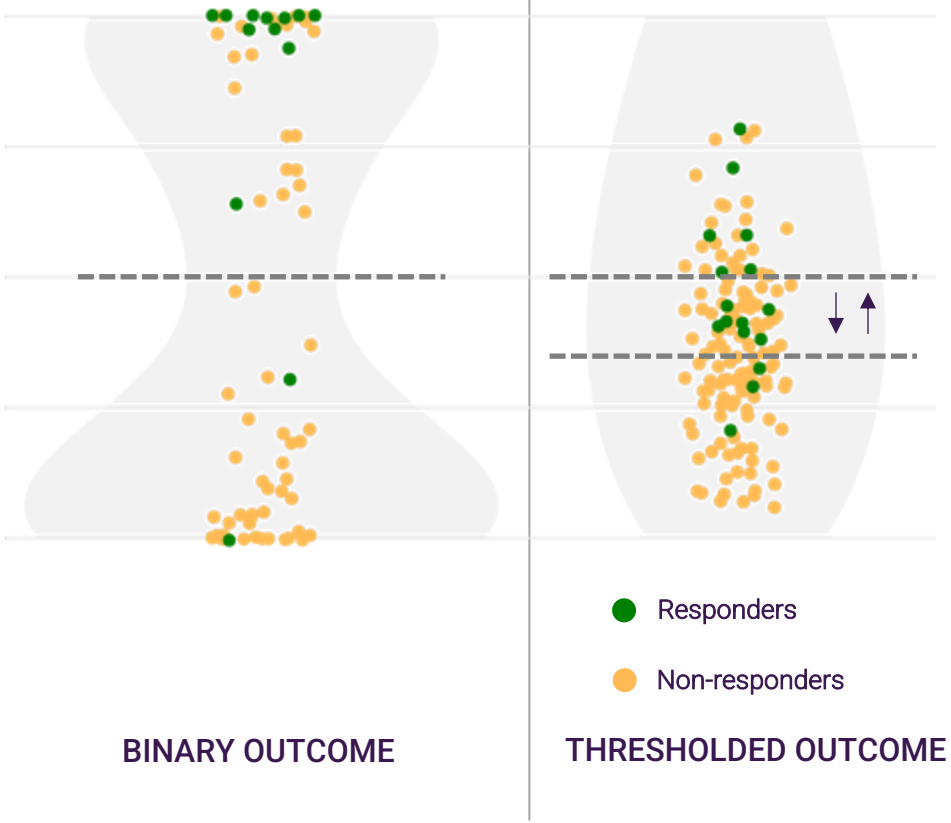
Xerna TME Algorithm Provides Clear Cut-points in Contrast to Historical Non-machine Learning Based Approaches and Results in Strong Analytical Performance

- The Xerna TME Panel generates binary-like biomarker outputs → thus assigning biomarker status is clear cut.
- Most current biomarker assays result in near-normal output distributions → thus many samples reside near the separation threshold.



A. Representation of Gastric ICI Xerna TME Panel Data

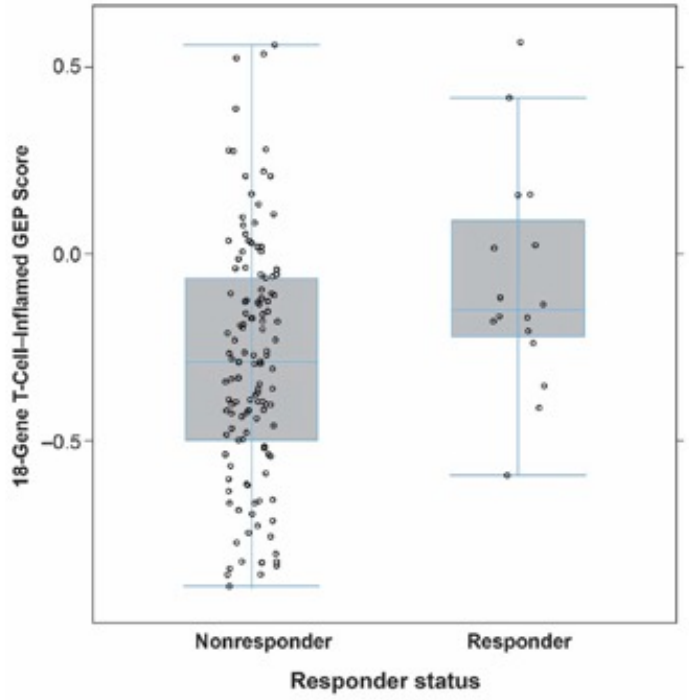
B. Representation of KEYNOTE-059 Nanostring GEP Score Data



BINARY OUTCOME

THRESHOLDED OUTCOME

Nanostring Data From KEYNOTE-059

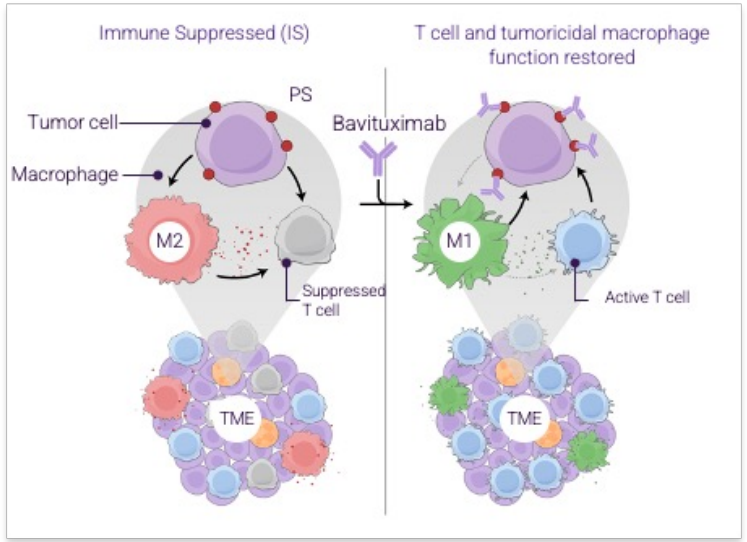


Fuchs et al, JAMA Oncol. 2018;4(5):e180013. doi:10.1001/jamaoncol.2018.0013

Xerna TME Profiling: Accurately Predicted Responses to Immune Checkpoint Therapy Even in IA + IS *(combining all Immune subgroups)*

Predictive Potential of the Xerna TME Panel Tested in a Gastric Cancer Patient Cohort Treated with a Combination of Immune Modulator and Immune Checkpoint Inhibitor

Bavituximab



Mechanism of Action

PS exposed in tumors by stress, including radiation, chemo, hypoxia

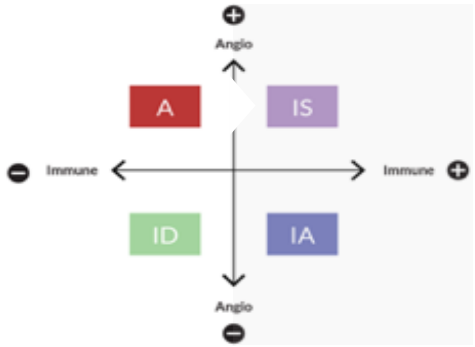
Designed to reverse immune suppression by inhibiting PS (TIM/TAM) signaling, activating immune cells

- Ph2 study of advanced adenocarcinoma gastric or gastroesophageal junction (GEJ) cancer with no prior immunotherapy (N=57 for biomarker analysis)
- Treatment with Bavituximab + Pembrolizumab
- ORR data was available for assessment of biomarker predictive potential - pre-specified per clinical study protocol (Prospective)
- Tumor samples were biopsies collected just prior to initiating trial therapy
  - Samples were formalin-fixed paraffin-embedded (FFPE)
  - RNA was extracted and RNAseq run
  - Analyzed in the Xerna TME panel
- *TME Immune subgroups (IA and IS) were hypothesized to derive the most clinical benefit.*

Prospective Testing Validates the Xerna TME Panel: Clear Bavi Activity in PD-L1 Negative Patients, More Responses in MSS with Pembro

The Immune Axis is Xerna TME Panel Positive for Bavi + Pembro

Immune and Angio Axes



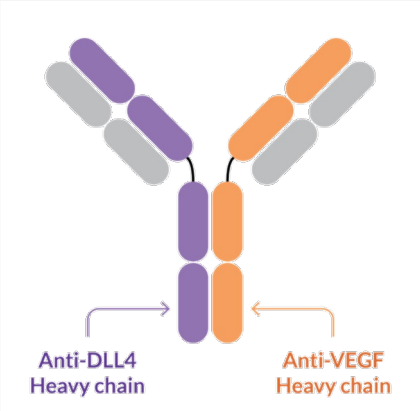
- Bavituximab treatment led to responses in advanced gastric patients with historical low response to Keytruda monotherapy (e.g., PD-L1 negative, CPS<1)
- Xerna TME Panel was able to identify responders on the Immune Axis (IS + IA)

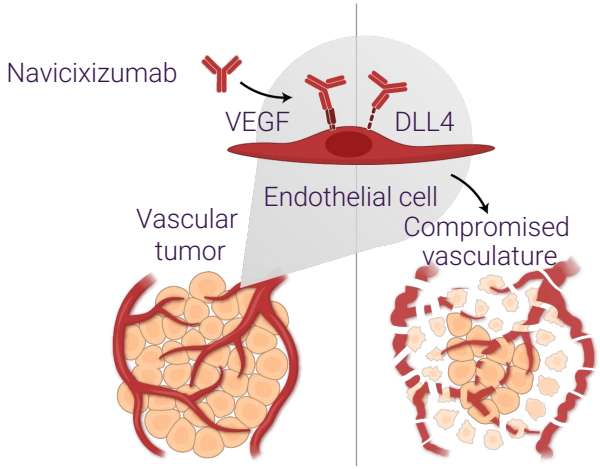
Patient Population	Clinical Benefit (%)	Bavituximab + Keytruda	Bavituximab + Keytruda (Xerna positive vs. negative)[2]
PDL-1 negative	ORR (PR+CR)	3/17 (18%)	2/5 (40%) vs 1/11 (9%)[3]
MSS[4]	ORR (PR+CR)	8/61[4] (13%)	7/32 (22%) vs 1/25 (4%)[5]

- Interim Data as of July 15, 2021
- [1] Keynote-059 and Samsung Medical (data on file)
- [2] IA+IS Xerna TME Biomarker Positive (IA+IS) ;Biomarker Negative (A+ID) Profile
- [3] 1 patient did not have biomarker result
- [4] known MSI high excluded from trial; MSI-H (Microsatellite Instability); MSS (Microsatellite Stable); confirmed MSS n=43 (14% ORR)
- [5] 4 patients did not have biomarker result; confirmed MSS ORR 25% vs 5%

Predictive Potential of the Xerna TME Panel Tested in an Ovarian Patient Cohort Treated with Anti-angiogenic + Chemotherapy

Navicixizumab





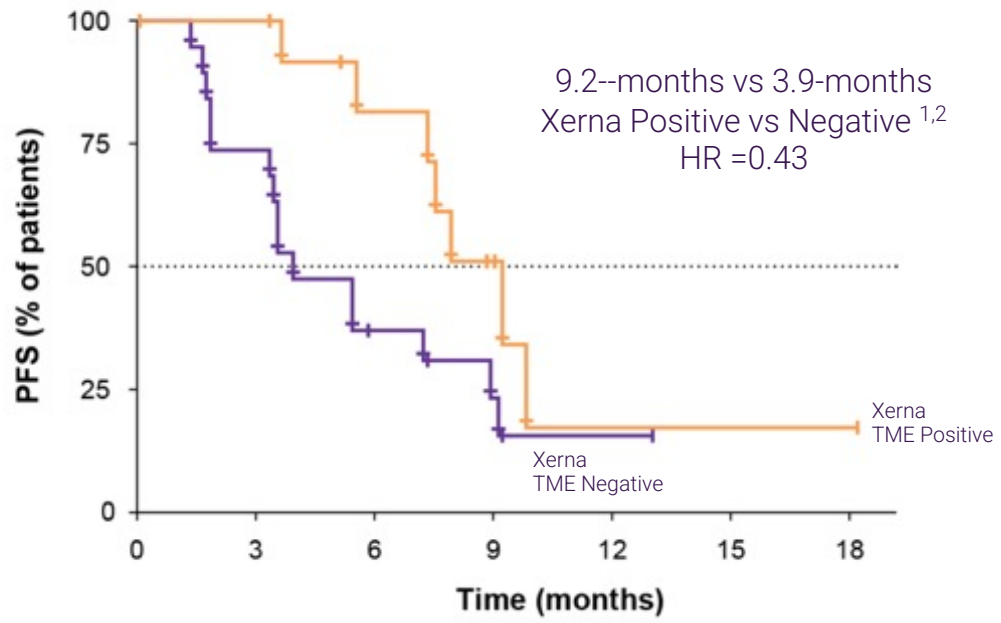
- Ph1b study[1] of 3rd line and beyond high grade ovarian, primary peritoneal or fallopian tube cancer most having received prior bevacizumab (N=33 for biomarker analysis)
- Treatment with Navicixizumab + Paclitaxel
- ORR and PFS data was available for assessment of biomarker predictive potential
- Most tumor samples were archival; few biopsies collected just prior to initiating trial therapy
  - Samples were formalin-fixed paraffin-embedded (FFPE)
  - RNA was extracted and RNAseq run
  - Analyzed in the Xerna TME panel
- *TME Angio subgroups (A and IS) were hypothesized to derive the most clinical benefit.*

[1] Fu et al, JCO 2022 doi: 10.1200/JCO.21.01801

Xerna TME Panel Identifies Patients Most Likely To Benefit from Navi

Navicixizumab + Paclitaxel in Phase 1B Trial[1] in Patients with Platinum Resistant Ovarian Cancer

PFS



5.3-months improvement in median PFS for Xerna biomarker positive patients

Overall Response Rate (ORR)

Navi + Pac (all patients) (n=44)	Navi + Pac Xerna TME Positive[2,3] (n=13)	Navi + Pac Xerna TME Negative[2,3] (n=20)[4]
43%	62%	25%

Xerna identified patients that were more likely to respond

Post-Avastin Subgroup

56% ORR in Xerna Positive Avastin-treated patients

1 Fu et al, JCO 2022 doi: 10.1200/JCO.21.01801
2 Angiogenesis subtypes (A+IS) is Xerna TME biomarker positive for Navi / Biomarker negative is (IA+ID)
3 33 patients with tumor tissue available were used for Xerna TME Panel testing
4 One patient did not have response data