Immune Report Card & Precision Immunotherapy

Carl Morrison, DMV, MD
CSO, President, & Founder

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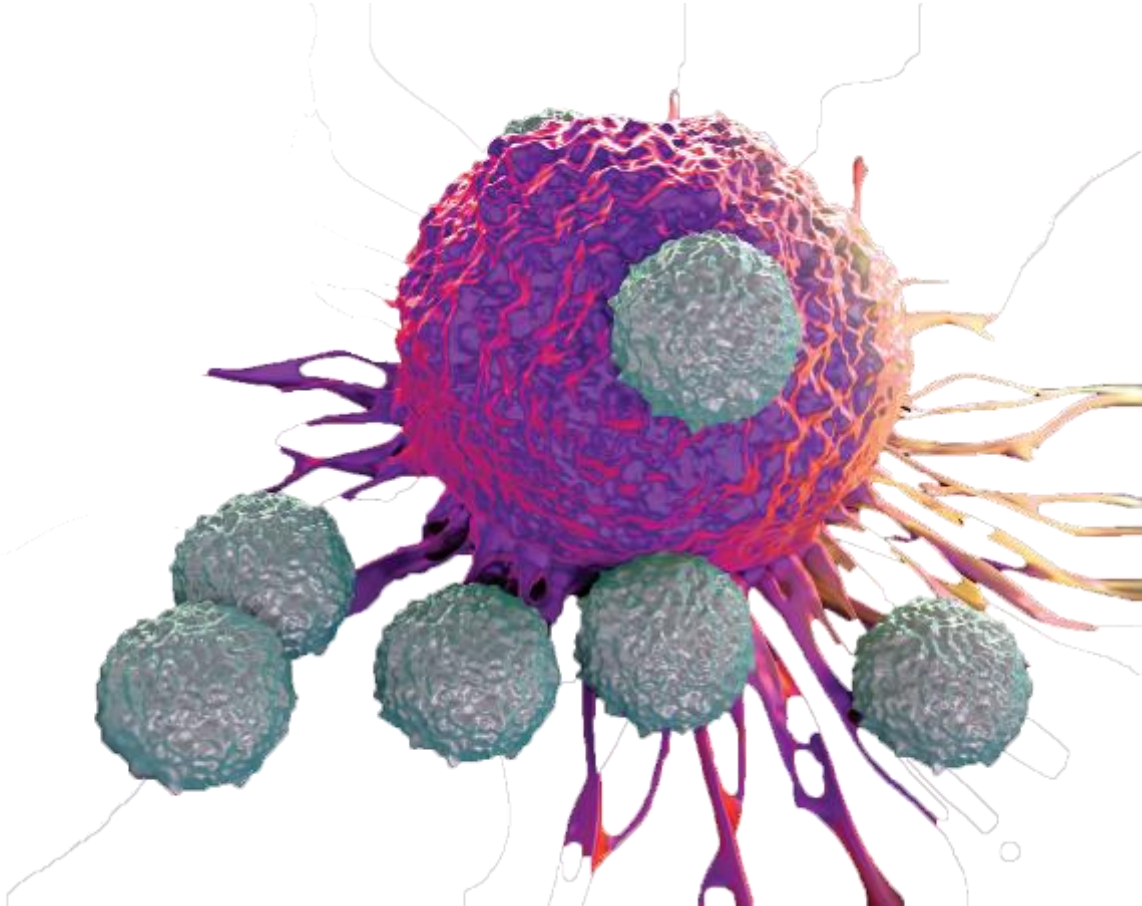
The Right Drug or the Right Trial...
for Every Patient.



Disclosures

- Faculty member of Roswell Park Cancer Institute
- President and Chief Scientific Officer of OmniSeq Inc.
- Work presented here was funded by OmniSeq

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OmniSeq® is a subsidiary of the Roswell Park Cancer Institute in Buffalo, New York.

Buffalo Niagara Medical Campus

Buffalo General Medical Center
A Kaleida Health Facility

JOHN R. OISHEI Children's Hospital

ROSWELL PARK CANCER INSTITUTE

OmniSeq®

University at Buffalo
The State University of New York
School of Public Health and Health Professions

We are a CLIA approved molecular diagnostics laboratory specializing in next generation sequencing

We utilize molecular diagnostics to help clinicians find the right drug or the right trial, for every patient

Two Separate, But Related Tests

How do we choose the best immunotherapy?

How do we predict immunotherapy response?

Same RNA-seq and DNA-seq

Same wet lab SOP

Same baseline bioinformatics

- CLIA/CAP
- NYS CLEP approved

Foundational Tools to Guide Treatment Decisions for I/O

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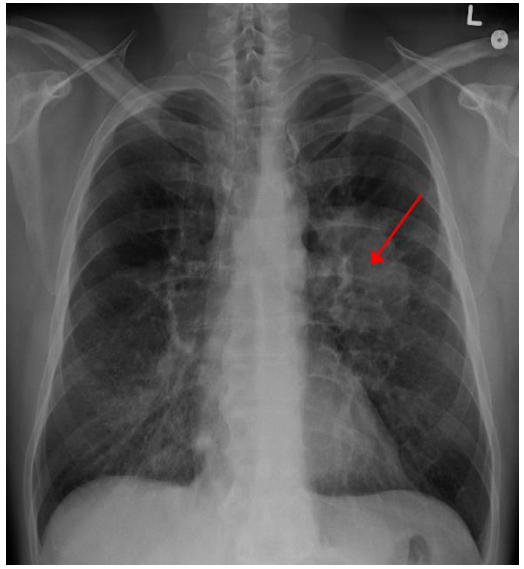
Tumor



FFPE Tissue

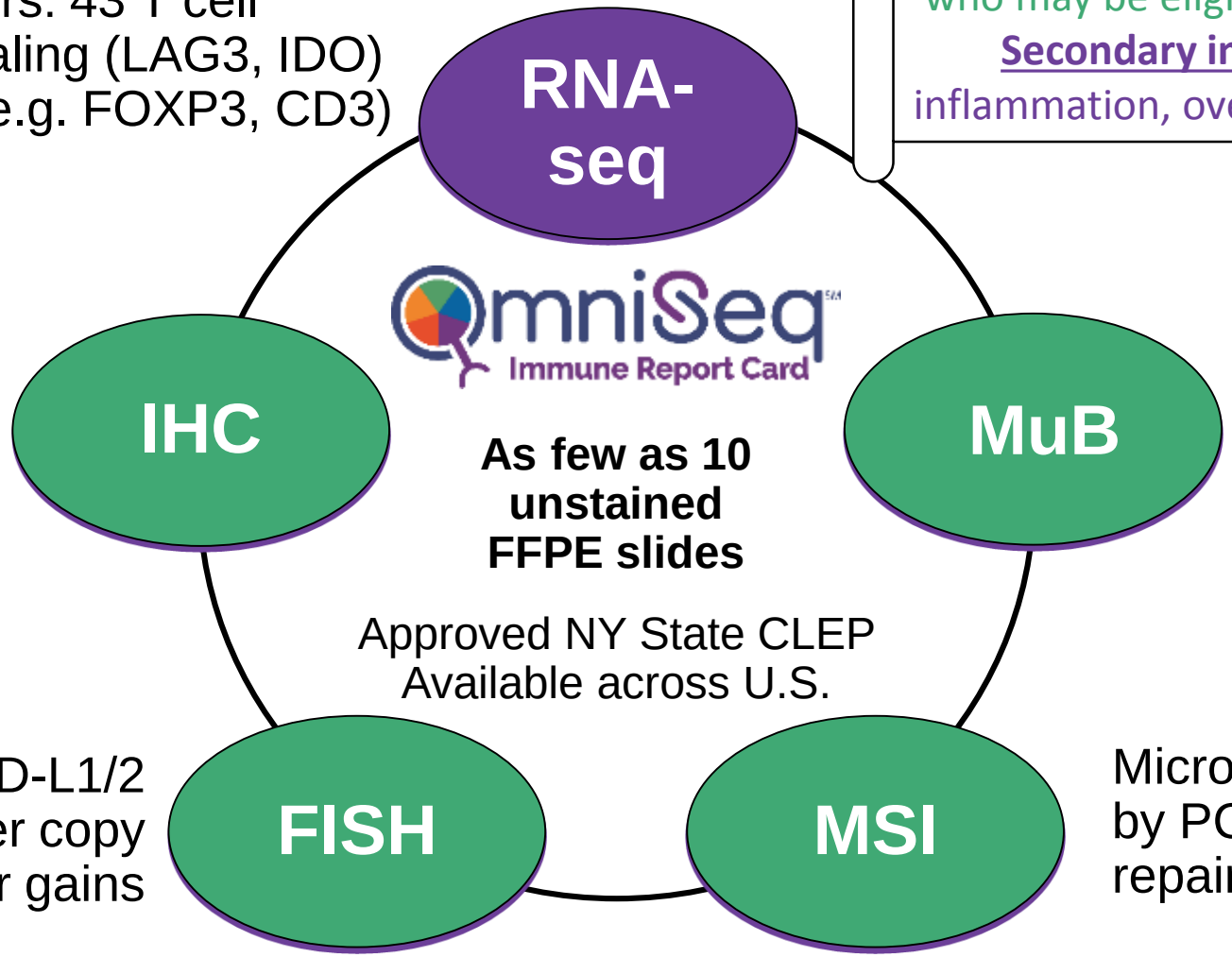
Sample Requirements

- Pan cancer solid tumor
- FFPE tissue
  - resection specimens
  - needle core biopsy specimens
  - cell blocks from fine needle aspirations
- >10% neoplastic tumor nuclei
- <50% necrosis
- 10ng DNA per assay
- 10 ng RNA per assay
- Unstained sections for FISH & IHC

Overview of Immune Report Card

Gene expression of 54 immune related markers: 43 T cell receptor signaling (LAG3, IDO) and 11 TILs (e.g. FOXP3, CD3)

Primary immune markers identify patients who may be eligible for checkpoint inhibitors
Secondary immune markers identify inflammation, overexpression, and phenotype



CD3, CD8, FDA assays PD-L1: 28-8 melanoma, SP142 urothelial carcinoma, 22c3 lung

Full exon sequencing >400 genes for mutational burden

Presence of PD-L1/2 gene cluster copy number gains

Microsatellite instability (MSI) by PCR for DNA mismatch repair deficiency

First-of-its-Kind Comprehensive Immune Profiling

This Just In! – Journal of Molecular Diagnostics

OmniSeq Immune Report Card

ELSEVIER

The Journal of Molecular Diagnostics

Available online 20 October 2017

In Press, Accepted Manuscript

Regular Article

Analytical Validation of a Next-Generation Sequencing Assay to Monitor Immune Responses in Solid Tumors

Jeffrey M. Conroy *, †, Sarabjot Pabla *, Sean T. Glenn *, ‡, Blake Burgher *, Mary Nesline *, Antonios Papanicolau-Sengos *, Jonathan Andreas *, Vincent Giamo *, Felicia L. Lenzo *, Fiona C.L. Hyland §, Angela Omilian ¶, Wiam Bshara ¶, Moachun Qin *, Ji He *, Igor Puzanov ‖, Marc S. Ernstoff ‖, Mark Gardner *, Lorenzo Galluzzi **, ††, ‡‡, Carl Morrison †

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https://doi.org/10.1016/j.jmoldx.2017.10.001

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https://doi.org/10.1016/j.jmoldx.2017.10.001

For more detailed questions, see publication

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How is IRC used in clinical practice?

1st immunotherapy line

1) On-label: Provides all companion and complementary diagnostics.
    1) PD-L1 IHC (22C3, 28-8, SP142)
    2) Mutational burden
    3) MSI

2) Off label: Provides multiple levels of evidence for checkpoint blockade response

3) On-Off label: Provides additional information as to inflamed versus immune desert

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How is IRC used in clinical practice?

2nd immunotherapy line

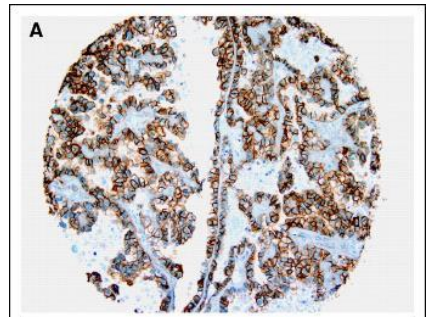
1) On-Off label: Provides information as to highly expressed immune-related therapeutic targets, i.e. optimal selection of combination immunotherapy

Assumptions of Precision Immunotherapy

Expression & Response

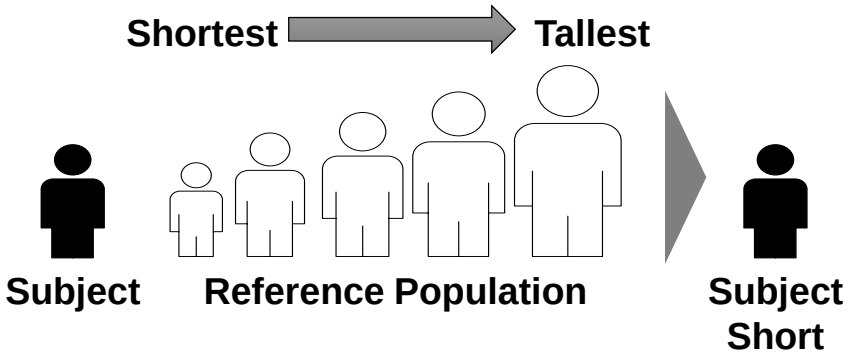
Overexpression of a drug target is associated with response to that agent

HER2 and Herceptin



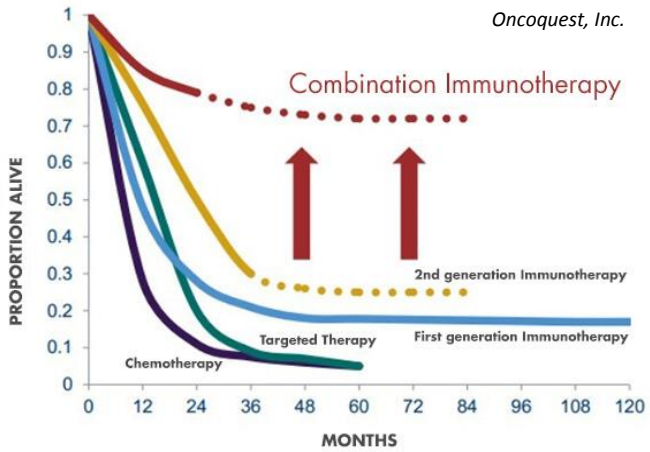
Determining Over-Expression

There is a reasonable, objective method to determine overexpression of immune targets



Combination Efficacy

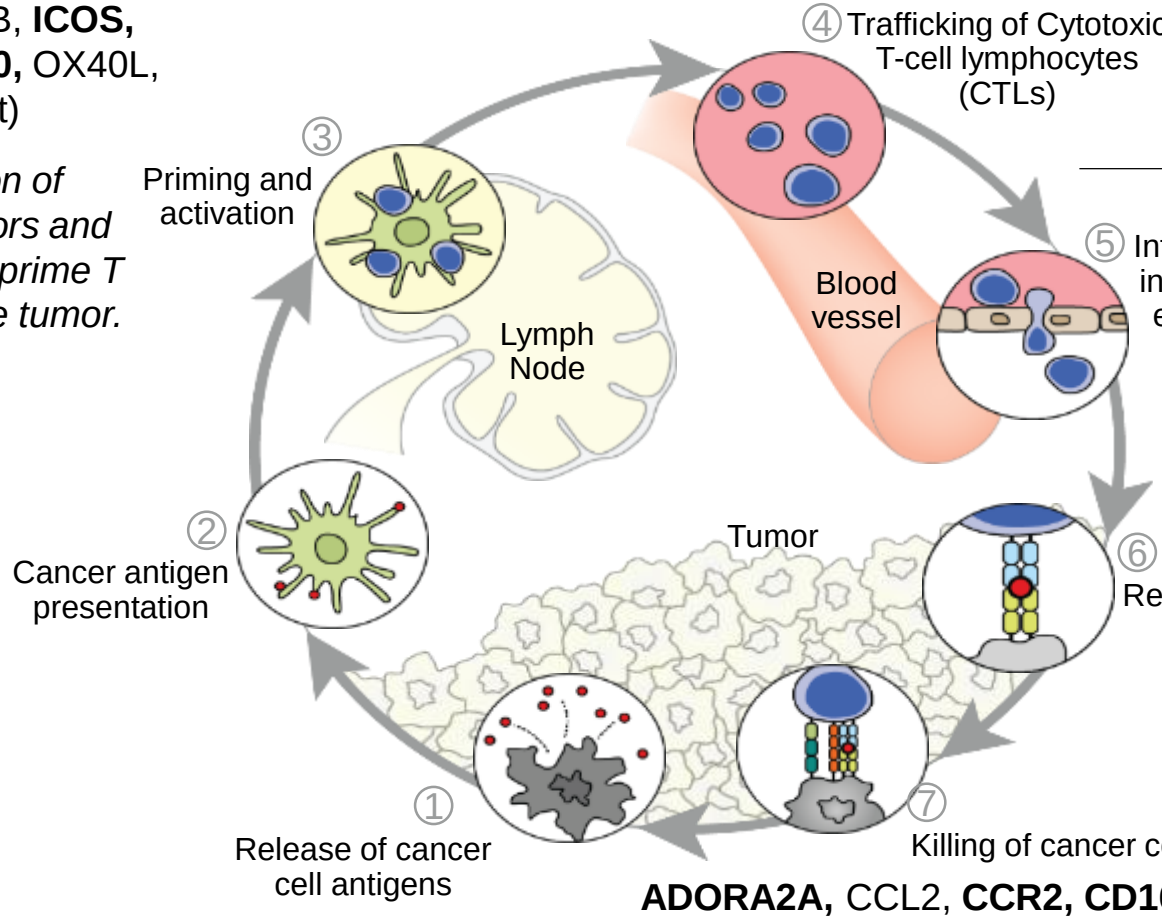
Combination immunotherapy may improve response and survival compared to targeted therapy and mono-immunotherapy



IRC Enables Interrogation of Specific Immune Markers

CD137, CD27, CD28, **CD40,** CD40LG, CD80 (B7-1), CD86 (B7-2), **GITR,** GZMB, **ICOS,** ICOSLG, IFNG, **OX40,** OX40L, TBX21 (T-bet)

Direct interaction of stimulatory receptors and ligands required to prime T Cells to infiltrate the tumor.



CXCL10, CXCR6, DDX58, GATA3, **IL10,** IL1B, MX1, STAT1, **TGFB1, TNF**

Pro and Anti inflammatory cytokines and chemokines released in the stroma and vessels drive the movement of T cells to the tumors.

CD2, CD20, CD3, CD4, CD8, FOXP3, KLRD1, SLAMF4

Markers that identify and control the function of Tumor Infiltrating Lymphocytes: Cytotoxic, T Reg, T Helper

BTLA, **CTLA4, LAG3, PD-1, PD-L1,** PD-L2, **TIM3,** TNFRSF14 (HVEM), **VISTA (B7-H5)**

Direct interaction of immune checkpoint receptors and ligands required to inhibit T Cells to initiate cancer cell death.

ADORA2A, CCL2, **CCR2, CD163, CD38,** CD39, CD68, **CSF1R, IDO1**

Metabolic Immune Escape and Myeloid Suppression genes inhibit activated T Cells from killing cancer cells.

Bold indicates directly druggable target

Source: Reprinted from *Immunity*, Volume 39, Chen, Daniel S. et al., Oncology Meets Immunology: The Cancer-Immunity Cycle, 1-10, Copyright 2013, with permission from Elsevier. http://dx.doi.org/10.1016/j.immuni.2013.07.012

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How is IRC used in clinical practice? AN EXAMPLE

2nd immunotherapy line

LBA18 - Efficacy of BMS-986016, a Monoclonal Antibody That Targets Lymphocyte Activation Gene-3 (LAG-3), in Combination With Nivolumab in Pts With Melanoma…

Date	10 September 2017
Event	ESMO 2017 Congress
Session	Developmental therapeutics
Topics	**Cancer Immunology and Immunotherapy** **Melanoma and other Skin Tumours**
Presenter	Paolo Ascierto
Citation	Annals of Oncology (2017) 28 (suppl_5): v605-v649. 10.1093/annonc/mdx440
Authors	P.A. Ascierto[1], P. Bono[2], S. Bhatia[3], I. Melero[4], M.S. Nyakas[5], I. Svane[6], J. Larkin[7], C. Gomez-Roca[8], D. Schadendorf[9], R. Dummer[10], A. Marabelle[11], C. Hoeller[12], M. Maurer[13], C.T. Harbison[14], P. Mitra[13], S. Suryawanshi[13], K. Thudium[13], E. Muñoz Couselo[15] **Author Affiliations**

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phase 1/2a study (NCT01968109), BMS-986016 (anti–LAG-3) + nivolumab (anti–PD-1) showed promising antitumor activity in the mel prior IO cohort

68 pts were treated; 57% had prior anti–CTLA-4 and 46% had ≥ 3 lines of prior therapy. In 61 efficacy-evaluable pts, ORR was 11.5% (1 complete, 6 partial [1 unconfirmed] responses); DCR was 49%. Median DOR was not reached (min [0.1+], max [39.3+]).

- ORR 3.5-fold higher in pts with LAG-3 expression ≥ 1%
- Enhanced responses correlated with LAG-3 expression, irrespective of PD-L1 expression

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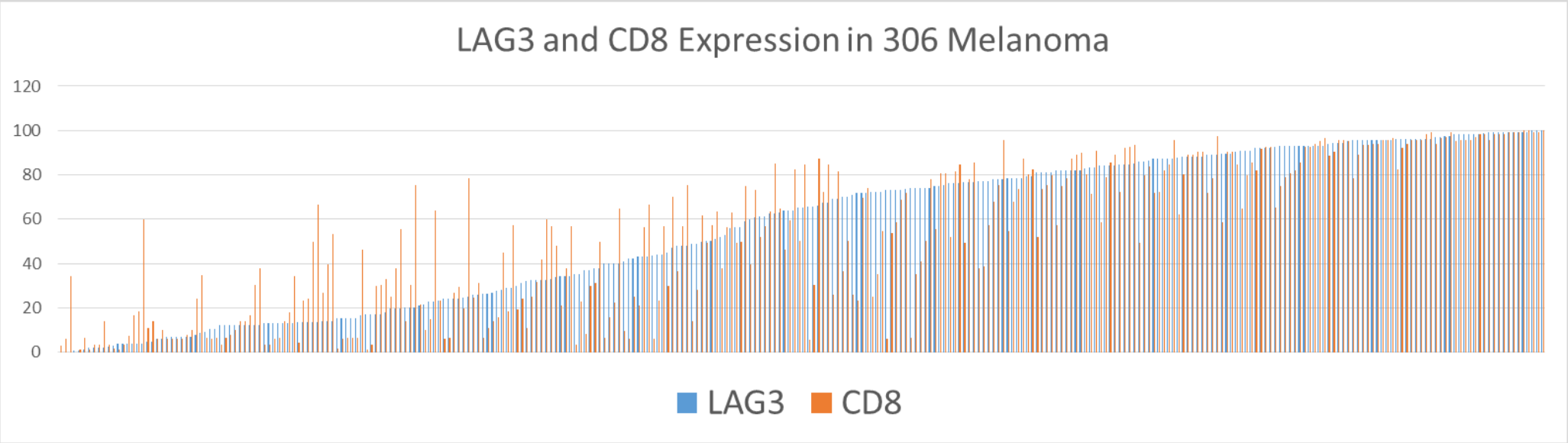
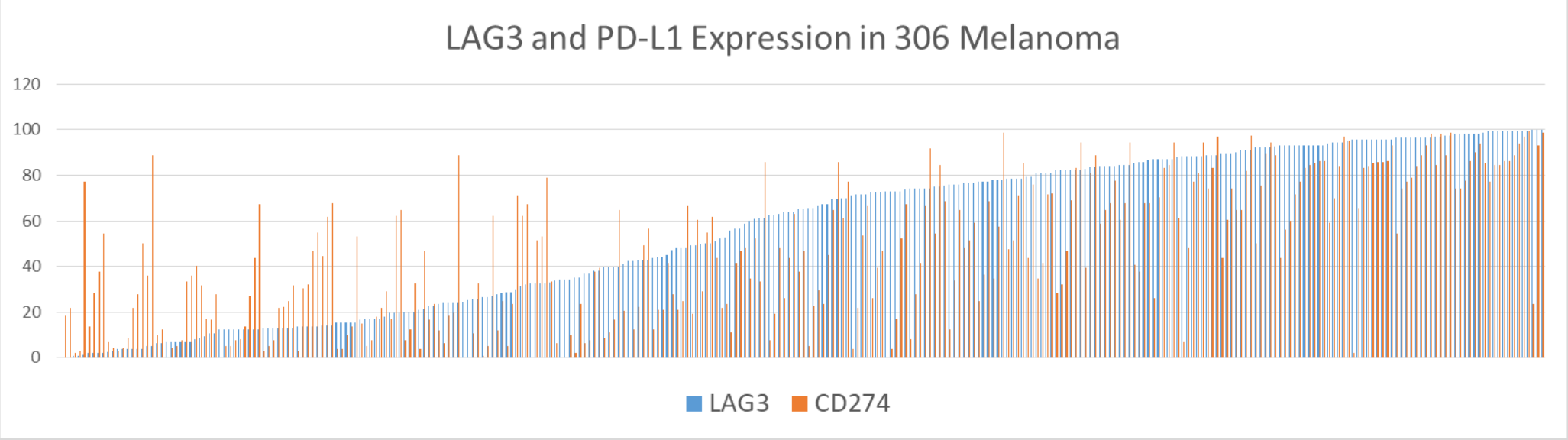
How is IRC used in clinical practice? AN EXAMPLE





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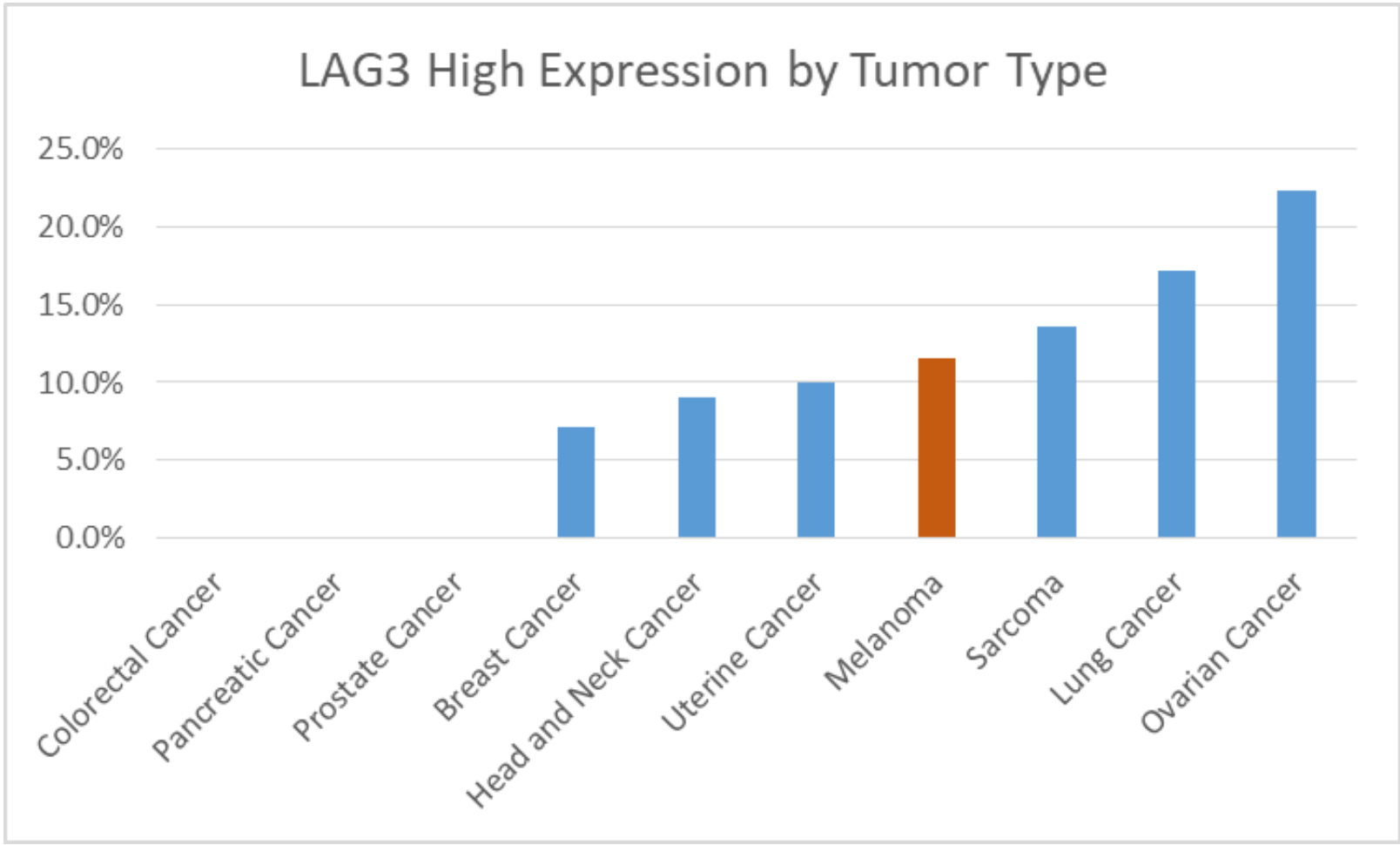

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1-800-781-1259

PATIENT

Name	[redacted]	MRN	[redacted]	DOB	[redacted] Gender [redacted]

ORDER INFORMATION

Order ID	[redacted]	Provider	[redacted]
Practice	[redacted]		
Indication	C43.9, Malignant melanoma of skin, unspecified, Stage IV	Report Date	[redacted]

TEST SPECIMEN

Specimen ID	[redacted]	Specimen Source	Lung, Left Upper Lobe, Wedge Resection	Collected	[redacted]
Specimen Facility	[redacted]			Received	[redacted]

PRIORITY IMMUNE MARKER RESULTS FOR MELANOMA

Marker	Test	Result	Therapeutic Association	Key References
PD-L1	IHC	0% Neoplastic Cells Positive	Increased progression free survival for first line combination nivolumab+ipilimumab compared to ipilimumab alone in patients with unresectable/metastatic melanoma (CheckMate 067).	PMID: 26027431
TILS	RNA-Seq	High (Highly inflamed)	Increased likelihood of response to anti-PD-L1-PD1 therapy (Mellman et al.).	PMID: 28102259
CD3/CD8	IHC	Infiltrating	Increased overall survival in solid tumor types (Ascierto et al.).	PMID: 23452415
Mutational Burden	DNA-Seq	2.644/Mb (Low)	Decreased clinical benefit from ipilimumab in melanoma (Van Allen et al.).	PMID: 26359337
Microsatellite Instability	PCR	Stable	Lack of objective response to pembrolizumab in microsatellite stable colorectal cancer (NCT01876511).	PMID: 26028255
PD-L1/L2 Copy Number	FISH	Not Amplified	Unknown objective response for nivolumab in Hodgkin's Lymphoma (NCT01592370).	PMID: 25482239

SUMMARY INTERPRETATION

This melanoma with a low mutational burden is considered very immunogenic and is highly inflamed with a high number of CD8+ T-cells in an infiltrating pattern and negative expression of PD-L1 by IHC (0% neoplastic staining; 28-8 clone). RNA-seq analysis showed a discordant result for PD-L1 with a moderately high level of expression that is explained by positive staining in immune cells by IHC that is not captured by the TPS method of evaluation. The negative result for PD-L1 by IHC would support first line combination nivolumab+ipilimumab compared to nivolumab or pembrolizumab alone as a better choice for the patient (CheckMate 067). If toxic side effects for nivolumab+ipilimumab are a consideration for this patient then the highly inflamed nature of this tumor would support nivolumab or pembrolizumab alone. If this patient has previously failed checkpoint blockade, which is not uncommon in melanoma, an additional consideration should be combination immunotherapy in a clinical trial setting. Moderately high to highly expressed immune-related genes in this tumor that are the target of immunomodulatory immunotherapeutics include ADORA2A, CCR2, CD137, CD27, ICOS, and LAG3. Other moderately expressed markers in this tumor that are therapeutic targets include CD38, CSF1R, CTLA4, IDO1, IL10, PD-1, PD-L1, and TNF. This patient may be eligible for multiple clinical trials that focus on the different highly expressed markers, often in combination with a PD-1 axis inhibitor (see clinical trials).

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IMMUNE PHENOTYPE DETAILS

Marker	Rank	Interpretation	Function	Therapies
Checkpoint Blockade (PD-1/CTLA4)				
PD-1	80	Moderate	Co-inhibitory	Nivolumab; Pembrolizumab; ABBV-181; AGEN2034; BGB-A317; BI 754091; JNJ-63723283; MEDI0680; MGD013; PDR001; PF-06801591; REGN2810; TSR-042
CTLA4	81	Moderate	Co-inhibitory	Ipilimumab; Tremelimumab; AGEN1884; BMS-986218; MK-1308
PD-L1	75	Moderate	Co-inhibitory	Atezolizumab; Avelumab; Durvalumab; CA-170; CX-072; FAZ053; KN035; LY3300054
PD-L2	83	Moderate	Unknown	
Checkpoint Blockade (Other)				
BTLA	83	Moderate	Co-inhibitory	
LAG3	88	High	Co-inhibitory	BI 754111; BMS-986016; LAG525; MGD013; MK-4280; REGN3767; TSR-033
TIM3	69	Moderate	Co-inhibitory	LY3321367; MBG453; TSR-022
VISTA (B7-H5)	51	Moderate	Co-inhibitory	CA-170
TNFRSF14 (HVEM)	56	Moderate	Unknown	
T-cell Primed				
CD137	89	High	Co-stimulatory	Urelumab; Utomilumab
CD27	92	High	Co-stimulatory	Varlilumab
CD28	80	Moderate	Co-stimulatory	
CD40	64	Moderate	Co-stimulatory	ADC-1013; APX005M; CP-870,893; RO7009789; SEA-CD40
CD40LG	83	Moderate	Co-stimulatory	
GITR	55	Moderate	Co-stimulatory	BMS-986156; GWN 323; INCAGN01876; MEDI1873; MK-4166; TRX518
ICOS	95	Very High	Co-stimulatory	GSK3359609; JTX-2011
ICOSLG	27	Low	Co-stimulatory	
OX40	68	Moderate	Co-stimulatory	BMS-986178; GSK3174998; INCAGN01949; MEDI0562; MEDI6383; MEDI6469; MOXR0916; PF-04518600
OX-40L	93	High	Co-stimulatory	
GZMB	95	Very High	Anti-tumor effector	
IFNG	89	High	Anti-tumor effector	
CD80 (B7-1)	59	Moderate	Unknown	
CD86 (B7-2)	84	Moderate	Unknown	
TBX21 (T-bet)	81	Moderate	Unknown	
Myeloid Suppression				
CCL2	34	Low	Immunosuppressive	

Expression Interpretation Key:

Very High: 95-100	High: 85-94	Moderate: 50-84	Low: 20-49	Very Low: 0-19

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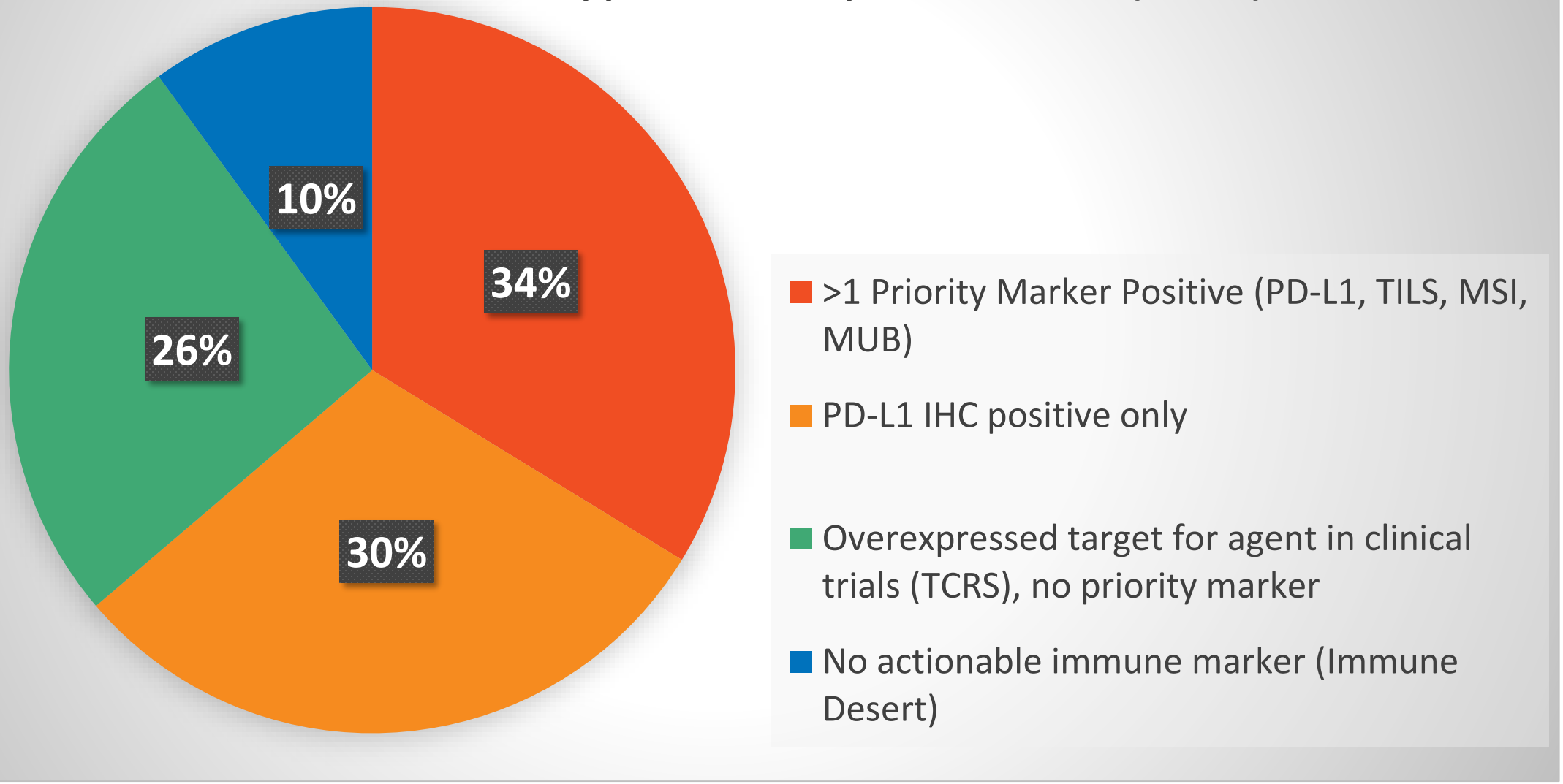
IMMUNE PHENOTYPE CLINICAL TRIALS

Trial Name	Phase	NCT ID	Location*
Marker: LAG3	**Immune Phenotype: Checkpoint Blockade (Other)**		
An Investigational Immuno-therapy Study to Assess the Safety, Tolerability and Effectiveness of Anti-LAG-3 With and Without Anti-PD-1 in the Treatment of Solid Tumors	1/ 2	NCT01968109	1-24 miles Seattle, WA
Study of TSR-033 With an Anti-PD-1	1	NCT03250832	Over 200 miles Oklahoma City, OK
A Study of MGD013 in Patients With Unresectable or Metastatic Neoplasms	1	NCT03219268	Over 200 miles Nashville, TN
This Study Tests the New Medicine BI 754111 Alone or in Combination With Another New Substance BI 754091 in Patients With Advanced Cancer. The Study Tests Different Doses to Find the Best Dose for Continuous Treatment.	1	NCT03156114	Over 200 miles Oklahoma City, OK
Study of REGN3767 (Anti-LAG-3) With or Without REGN2810 (Anti-PD1) in Advanced Cancers	1	NCT03005782	Over 200 miles San Antonio, TX
Study of MK-4280 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Adults With Advanced Solid Tumors (MK-4280-001)	1	NCT02720068	Over 200 miles San Antonio, TX

Immune Report Card Actionability



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TITLE: Prospective Multi-center Comprehensive Immune Profiling to Predict Treatment Response for FDA-approved Checkpoint Inhibitors in Melanoma

HYPOTHESIS: Comprehensive immune profiling (CIP) can be used to predict treatment responses for checkpoint blockade inhibition.

STUDY DESIGN: Blinded single-arm study.

SITE(S): Will open at RPCI in January 2018, additional sites will be added

OmniSeq Immune Report Card℠

Booth 635

SITC Posters

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Friday, November 10, 12:30-2pm, 6:30-8pm

- **P15:** Overexpression Of Immunotherapeutic Targets In The Immune Desert Phenotype.

- **P17:** The Immune-excluded Phenotype Beyond Colorectal Cancer.

Saturday, November 11, 12:30-2pm, 6:30-8pm

- **P14:** Comprehensive Characterization Of Solid Tumor Immune Profiles For Precision Immunotherapy Using Immune Report Card.

- **P16:** Secondary Immunotherapeutic Targets In Inflamed Tumors

Acknowledgements

OmniSeq®

Jeffrey Conroy
Sean Glenn
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LabCorp Laboratory Corporation of America

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Steve Anderson
Keith Hanigan

ROSWELL PARK CANCER INSTITUTE

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Elizabeth Brese
Angela Omilian
Wiam Bshara