
Roche
1
Ventana
Companion
Diagnostics
Building the future of pathology through partnership
Lisa M. Williams, Ph.D.
National Technical Manager, Roche Tissue Diagnostics


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Our mission and vision,
focused on cancer patients

3

Pathologist founded and patient focused

Improve cancer patient lives by providing solutions

Our mission

To improve the lives of all patients afflicted with cancer

Our vision

To empower our customers by providing the highest quality, most innovative cancer diagnostic solutions

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A key healthcare challenge

Better personalization of cancer care

> Healthcare today is in crisis, as it is expensive, reactive, inefficient and focused largely on one-size-fits-all treatments for events of late stage disease. An answer is personalized, predictive, preventive and participatory medicine.

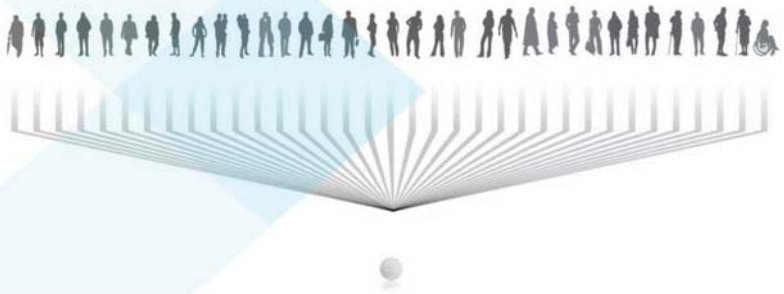
Ralph Snyderman, MD

Chancellor Emeritus, Duke University

Reference: The Case for Personalized Medicine, 3rd Edition
The Personalized Medicine Coalition (Oct 2011)

Why are predictive assays important?

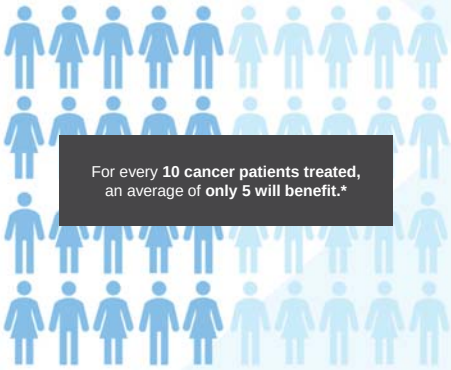
Traditional therapy: Same diagnosis, same treatment



One-size-fits-all approach

Why are predictive assays important?

Traditional therapy: Low treatment efficacy



For every **10 cancer patients treated,** an average of **only 5 will benefit.***

~1 in 2 respond

Reference: *Roche Personalized Healthcare brochure, 2011*

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Predictive assay and clinical utility

Is generated and proved in clinical trials

> "The *data generated from clinical trials validate both the efficacy of these drugs and the predictive performance of each allied biomarker assay* as it was performed during each of the trials. In this era of *evidence-based medical practice,* to what extent *can we afford to deviate from what was validated in the trials while there is no evidence to support doing so?*"

Kerr, K et al., *2016* . Programmed Death Ligand-1 Immunohistochemistry: Friend or Foe? *Arch Pathol Lab Med.* 140.

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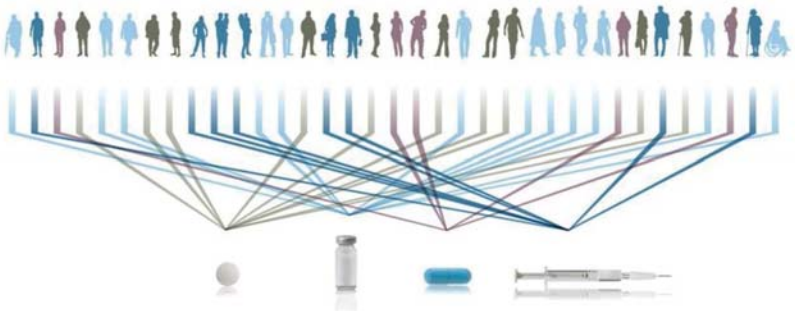
Why are predictive assays important?

Enable personalized care, facilitate better outcomes



Right therapy, for the right patient, at the right time

Value of personalized healthcare

Facilitated by predictive assays benefiting patients, physicians, and payers

$160B
of drug spend is ineffective[1]

$604M
annual savings if patients with metastatic colorectal cancer receive a genetic test prior to treatment[2]

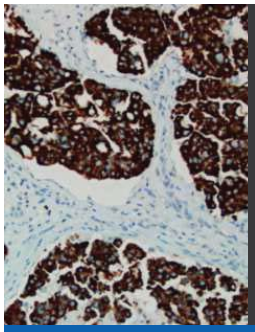
34%
decrease in chemo if women with breast cancer receive a genetic test prior to treatment[3]

$15B
savings CDx can deliver to health care[4]

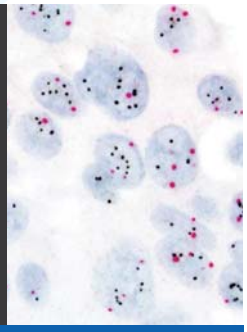
1. Personalized Medicine Coalition. The Case for Personalized Medicine. 4th ed.; 2014. http://personalizedmedicinecoalition.org/Resources/The_Case_for_Personalized_Medicine.
2. Shankaran V. Conference presentation at the Gastrointestinal Cancers Symposium. January 2009. Medscape web site. (Available at: http://www.medscape.com/viewarticle/586946)
3. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.
4. Genomic Health. Economic Validity. Genomic Health web site. (Available at: http://www.genomichealth.com/en-US/sitecore/content/Home/Breast/ManagedCareOrgs/EconomicValidity.aspx)

Why are predictive assays important?

The role of immunohistochemistry and in situ hybridization



IHC and ***ISH*** are powerful tools to identify patients who ***express specific biomarkers,*** and ***stratify those*** who are ***likely to benefit from*** specific treatments.



VENTANA ALK (D5F3) CDx Assay

INFORM HER-2 dual ISH Assay

Predictive assays, essential for personalized healthcare

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What is a companion diagnostic?

Provides predictive information; is required

A companion diagnostic is a ***test*** that ***accurately and reliably detects a biomarker*** and ***in clinical trials*** has demonstrated the ability to assist in ***differentiating patients who will or will not benefit from the associated drug.*** It is ***required*** for the ***safe*** and ***effective use*** of the ***drug.***

Reference: http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf

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What is a complementary diagnostic?

Provides important information; aids in the drug risk-benefit decision process

A complementary diagnostic aids in the ***risk-benefit decision*** process: it provides information about using a ***specific drug*** in the context of a clinically meaningful risk-benefit difference.

Reference: http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf

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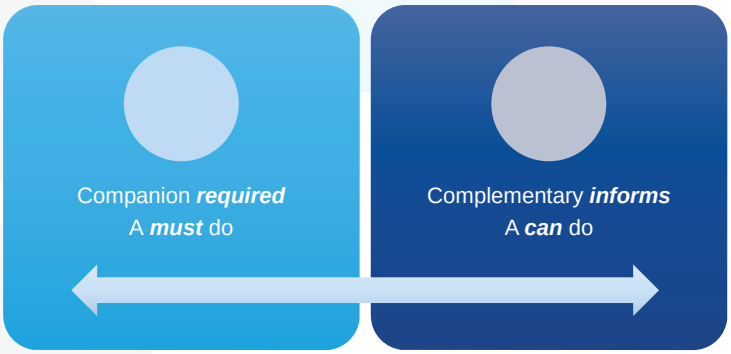
Companion is required, complementary informs

Both provide information about likely patient response



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Crizotinib, more effective in ALK positive NSCLC

More effective: Higher ORR and PFS

	ALK^{FISH+}/ALK^{IHC+} Concordant Cases [a]		ALK^{FISH+}/ALK^{IHC-} Discordant Cases [a]		All ALK^{FISH+} cases	
Therapy	Crizotinib N=60	Chemotherapy N=49	Crizotinib N=6	Chemotherapy N=8	Crizotinib N=66	Chemotherapy N=57
ORR [b] (%)	86.7%	44.9%	33.3 %	37.5 %	81.8%	43.9%
Median PFS (months) [c]	7.6	5.8	2.8	6.2	7.1	5.8

The **VENTANA ALK (D5F3) CDx Assay** is a **companion diagnostic** for **XALKORI® (crizotinib) and Zykadia® (ceritinib).**

[a]This table includes only those FISH+ cases that were tested with the Ventana ALK IHC assay under diagnostic protocol D032361 and yielded a valid, specimen-linked ALK IHC result. Patients with an indeterminate clinical response are excluded. [b]ORR = overall response rate. [c]PFS = progression-free survival.

Solomon, Benjamin J., et al. "First-line crizotinib versus chemotherapy in ALK-positive lung cancer." *New England Journal of Medicine* 371.23 (2014): 2167-2177.

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CDx/predictive assay development

Additional testing needed for a CDx assay

Product Classification	RUO	Analytical	Predictive
FDA Submission	No	No	PMA
CE Marked	No	Yes	Yes
Characterization Studies performed: Immunoreactivity (ToT ToB)	No	Yes	Yes
Robustness	No	Yes	Yes
Repeatability	No	Yes	Yes
Pre-analytical (fixatives, etc)	No	Yes	Yes
Stability Studies	No	Yes	Yes
Design Validation	No	Yes	Yes
Reader Precision	No	No	Yes
Inter-laboratory Reproducibility	No	No	Yes
Proof of utility in detecting a disease	No	No	Yes
Clinical utility proving device performance in relation to drug outcome or potential misdiagnosis	No	No	Yes
Possible claims	None	Detects biomarker	Companion diagnostic. Complementary diagnostic

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An assay is an entire system

Including antibody, detection, instrument and other components

Clinical trials use the ***entire system and… regulatory*** agencies approve the ***entire system.***

Using ***only parts of the system*** and not the entire system carries ***significant risk…*** and may lead to ***poor patient outcomes.***

- **Inappropriate** treatment decisions
- **Over-treatment** and side effects
- **Under-treatment** and missed opportunities

Vyberg et al. BMC Health Services Research (2015) 15:352

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VENTANA

A VENTANA predictive assay **is a complete system**

Changing a component can change results

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Our predictive assays, current and future

Biomarker	Technology	Therapy, indication	Roche Solution
HER2	IHC/ISH	Herceptin® BREAST	Roche VENTANA
EGFR	PCR (Tissue/Plasma)	Tarceva®, TAGRISSO™ NSCLC	Roche cobas®
ALK	IHC	Xalkori® Zykadia® NSCLC	Roche VENTANA
BRAF	PCR	Zelboraf® MELANOMA	Roche cobas®
C-KIT	IHC	GLEEVEC® GIST	Roche VENTANA
KRAS	PCR	Erbitux®, Vectibix® CRC	Roche cobas®
PD-L1 (SP142)	IHC	TECENTRIQ® Bladder/NSCLC	Roche VENTANA
PD-L1 (SP263)	IHC	IMFINZI™ Bladder	Roche VENTANA

*Based on 5 years of data from a leading external quality assessment scheme. Retrieved from http://www.nordiqc.org/eptitopes.htm.
†Data refers to PATHWAY and Ventana products.

RTU=ready to use.

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***HER2 (4B5), ER (SP1) and ALK (D5F3)** antibodies show*:*

- ***consistent performance***
- ***superior quality***

HER2 (4B5) antibody shows the most consistent performance and superior quality when compared to other on-market ER clones†

*Based on 5 years of data from a leading external quality assessment scheme. Retrieved from http://www.nordiqc.org/eptitopes.htm.

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***HER2 (4B5), ER (SP1) and ALK (D5F3)** antibodies show*:*

- ***consistent performance***
- ***superior quality***

ER (SP1) antibody shows the most consistent performance and superior quality when compared to other on-market ER clones*

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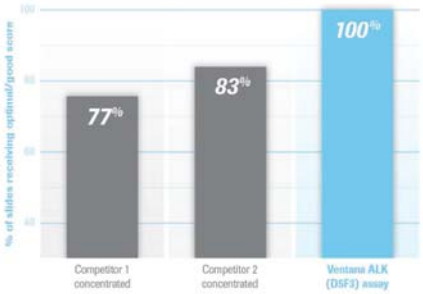
Roche demonstrates
consistently
high
performance

HER2 (4B5), ER (SP1) and ALK (D5F3) antibodies show*:

- consistent performance
- superior quality

Ventana ALK (D5F3) CDx assay IHC quality assessment



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Roche personalized healthcare portfolio

Consists of predictive assays across technologies

Molecular Diagnostics

Clinical Pathology

Anatomic Pathology

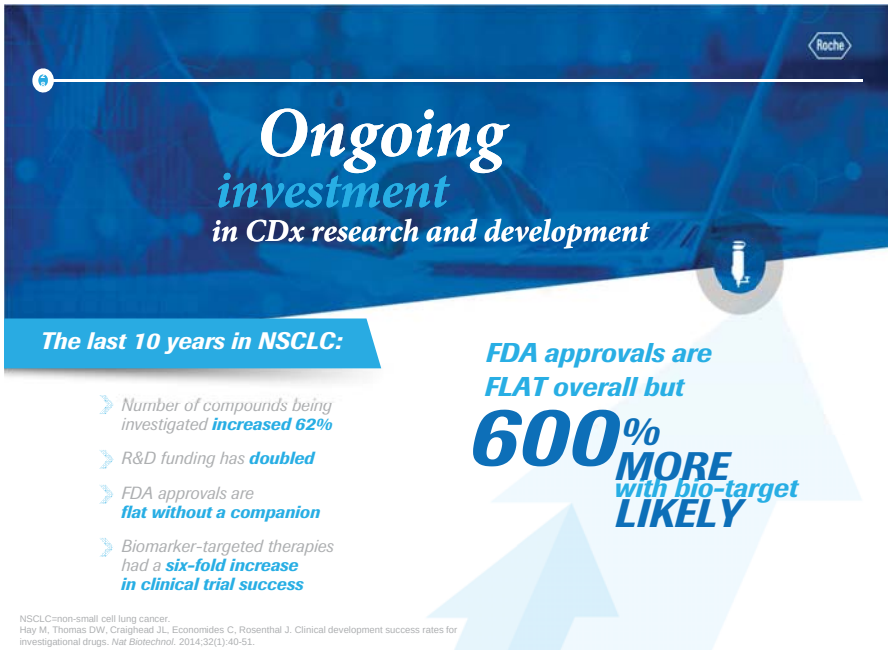
Sequencing Core

"Targeted diagnostic tests that ***help to improve medical decision-making*** not only offer clinical benefits for patients, but are also attractive through health economic benefits to regulatory authorities and payers."

Severin Schwan
CEO, Roche

"Change the practice of medicine by ***inventing tools that didn't exist before,*** rather than building a better microscope."

Tom Grogan
MD and Founder, Ventana Medical Systems, Inc.



NSCLC=non-small cell lung cancer.
Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014;32(1):40-51.

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What is our pharma strategy?

Offer pharma a premiere end to end solution

Biomarker Research	Pharma Services	IVD Development	Product Marketing and Commercialization
Antibody Development Rabbit Monoclonal Antibody manufacturer of first-in-class clones for RUO/IVD **DISCOVERY Portfolio** Instruments and reagents that empower pharma to conduct biomarker evaluation	**Assay Prototyping** Biomarker evaluation, efficient & robust LDT development **CAP/CLIA Lab** In-house lab for first in-human clinical trials and rapid "go/no-go" project determination	**Pathology Expertise** Dedicated to pharma clinical trials, assay algorithm development, CDx Assay training **Regulatory Experience** **Clinical Trial Support**	**Commercial Support** Education, pre-launch, training product marketing and commercialization ▪ Industry's #1 Commercial and Technical Support Network ▪ Largest global installed base ▪ #1 in IHC market share in all regions

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We work with the top global pharma companies

And have a solid pipeline of future predictive assays

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Our predictive assay future

Supported by a robust pipeline of innovative diagnostics

Early studies
(Phase I/II)

Outcomes studies
(Phase II/III)

FGF-19	FGFR2	HA	DLL3	PTEN	PD-L1	BCL-2	PD-L1	ALK
ATM	PTEN	HA	YES1	MSLN	HER2	cMYC	PD-L1	PD-L1
FGFR1	C4.4a	1D01	MUC16	TRK	PD-L1	HA	CD30	MSLN
ATM	MSLN	B7-H3	Napi2b	FOLR1	C4.4a			
PTEN	FGFR3	PSMA	ETBR	PTEN				
ATM	TF	CD37						
cMYC	HER3							
MSLN								

Bladder, Breast, CRC, Gastric, Lymphoma, Liver, Lung, Melanoma, Pancreatic, Prostrate, Ovarian, MPM, HNSCC, Esophageal, Renal

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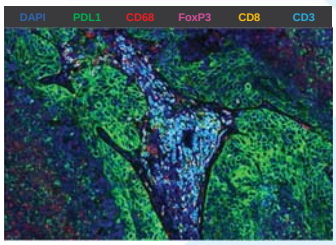
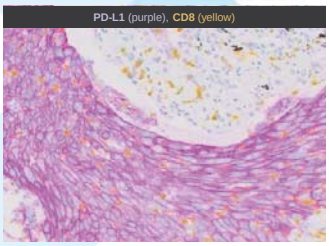
Limited tissue, many biomarkers

Future solution multiplexing: > 1 biomarker per slide





Some examples of biological questions:

- What is the ratio of key cell populations? *e.g. CD4 to CD8*
- In which distinct immune cell types is biomarker "X" expressed?
- Are biomarkers "A,B,C" co-expressed in the nucleus of a single cell?

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PD-L1 and the Tumor Microenvironment

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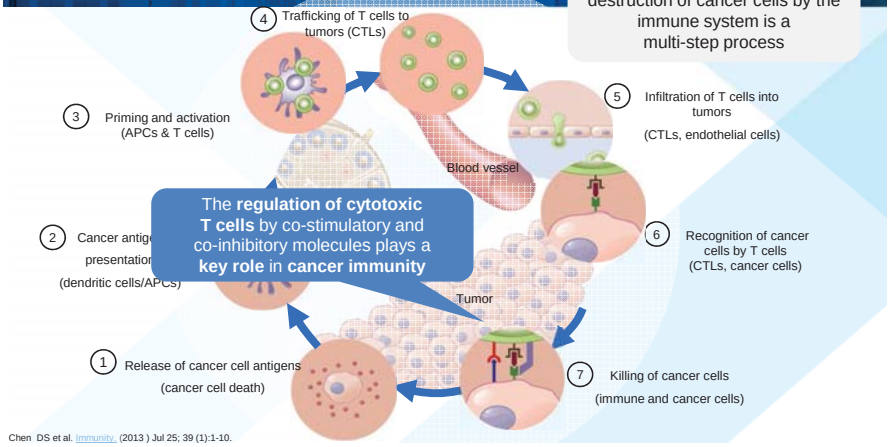
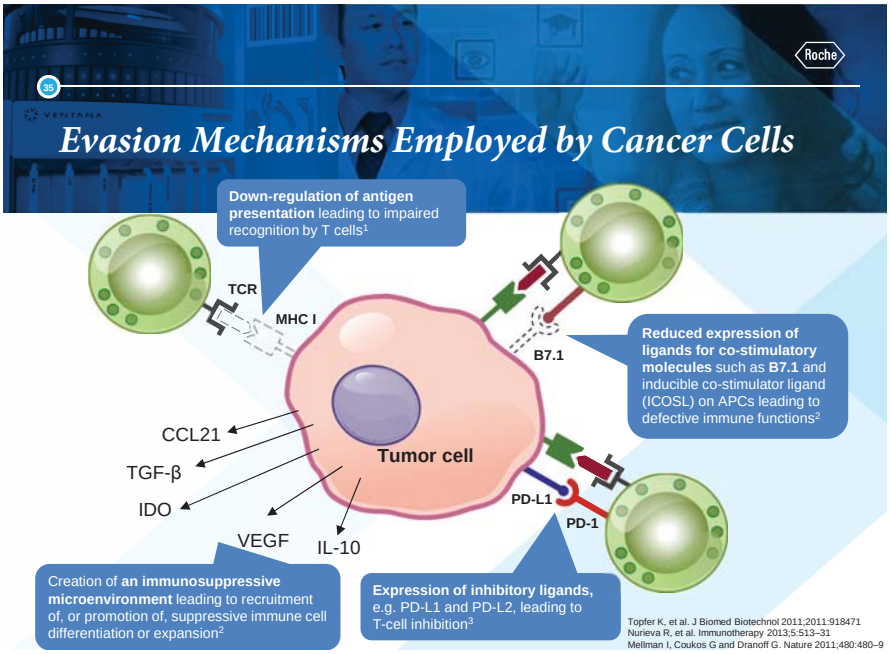
The Cancer Immunity Cycle

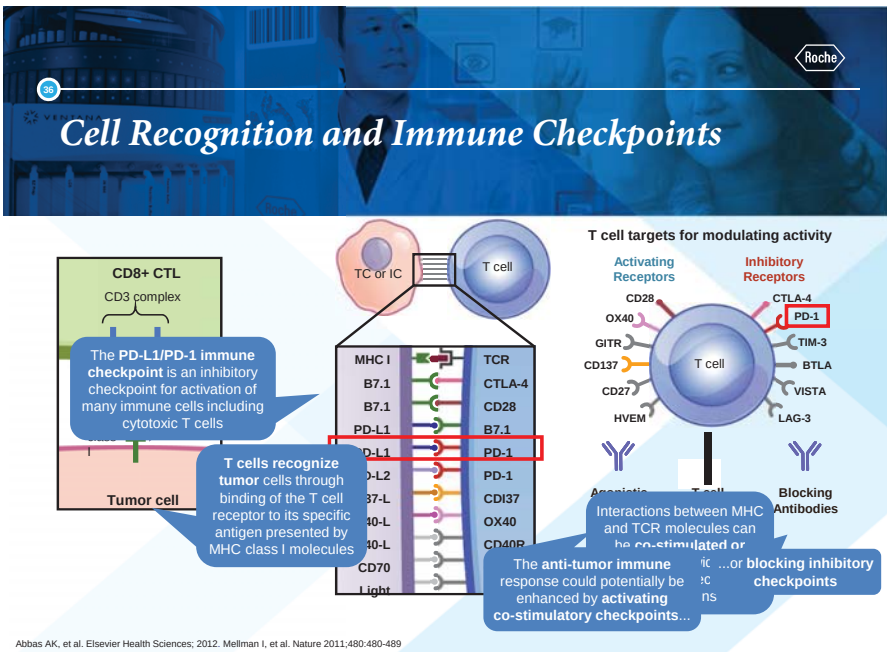
The detection, targeting and destruction of cancer cells by the immune system is a multi-step process



Chen DS et al. Immunity. (2013) Jul 25; 39 (1):1-10.



Topfer K, et al. J Biomed Biotechnol 2011;2011:918471
Nurieva R, et al. Immunotherapy 2013;5:513–31
Mellman I, Coukos G and Dranoff G. Nature 2011;480:480–9



Abbas AK, et al. Elsevier Health Sciences; 2012. Mellman I, et al. Nature 2011;480:480-489

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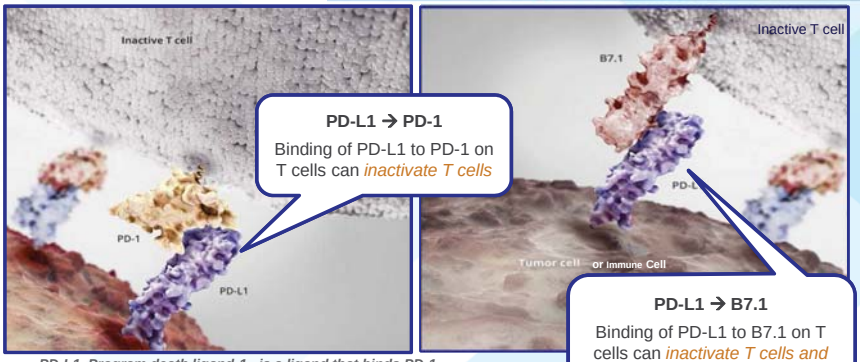
PD-1 and PD-L1

Part of the immune checkpoint pathway: inhibits T cell activity



- *PD-L1, Program death ligand-1, is a ligand that binds PD-1.*
- *PD-1, Program death receptor 1, is a receptor that binds PD-L1.*
- *PD-L1 and PD-1 are part the of the immune checkpoint pathway. This pathway limits T-cell proliferation and limits their ability to kill tumor cells.*

Lu J, et al. J Oncol Pharm Pract. 2014 Jun 9. pii: 1078155214538087

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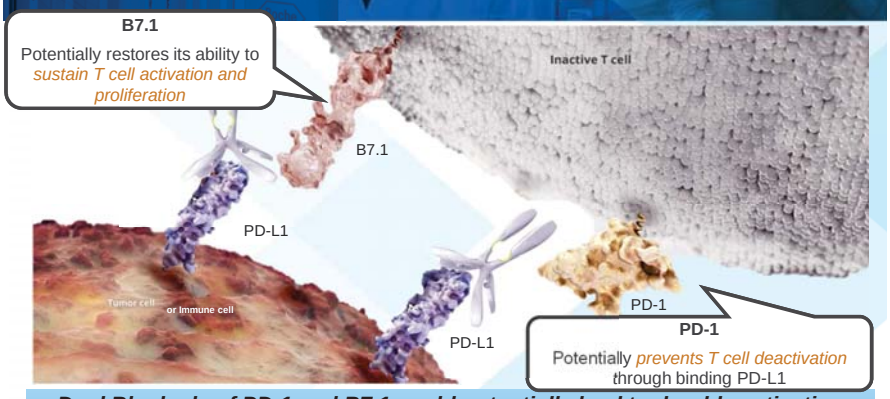
Blocking PD-L1

Restore T cell activation and proliferation



Dual Blockade of PD-1 and B7.1 could potentially lead to durable activation and proliferation of T Cells

Chen DS, Mellman I. *Immunity*. 2013

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PD-L1 Detection in Tumors

Detected in 11% to 100% in a variety of tumor types

Cancer	PD-L1 positive (%)	Cancer	PD-L1 positive (%)
Breast	31-34	Melanoma	40-100
Colon	53	Multiple myeloma	93
Esophageal	42	Ovarian	33-80
Gastric	42	Pancreatic	39
Glioblastoma/mixed glioma	100	Renal cell	15-24
Hepatocellular	45-93	Urothelial	28-100
Leukemias	11-42	Nasopharyngeal / HNC	46-100
Lymphomas	17-94	NSCLC	35-95

Chen, D et al, Clinical Cancer Res 18 (24): 6580-6587, 2012
Zandberg DP, et al. Oral Oncol. 2014 Jul;50(7):627-32

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PD-L1 Expression and Prevalence in Tumors

Phase I trial of atezolizumab (PCD4989g)

Tumor Type	Number (n)	PD-L1+ Immune Cells (IC)	PD-L1+ Tumor Cells (TC)
NSCLC	184	26%	24%
RCC	88	25%	10%
Melanoma	58	36%	5%
HNSCC	101	28%	19%
Gastric cancer	141	18%	5%
CRC	77	35%	1%
Pancreatic	83	12%	4%
Bladder	205	27%	11%

Herbst, RS, et al, Nature 515: 563-567, 2014
Powles, T et al, Nature 515: 558, 2014

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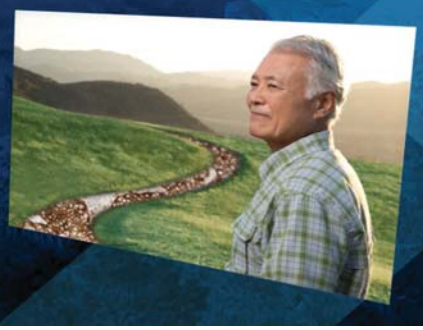
Personalized Medicine

VENTANA PD-L1 (SP263) Assay



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PD-L1 and Prognostic Relevance in Bladder Cancer

PD-L1

- Expressed in 28%-100% of human urothelial/bladder cancers[1] and
- 95% of lymphocytes that invade bladder tumors express PD-1[2]
- PD-L1 is associated with a more advanced stage and a higher tumor grade of bladder cancer, suggesting that PD-L1 may be a factor promoting disease progression[3-5]
  - A study looking at PD-L1 in 280 high-risk bladder cancer patients, found expression was associated with high-grade tumors[4]
  - Meta-analysis conducted in 352 bladder cancer patients, demonstrated that superficial bladder cancer had significantly lower PD-L1 expression than invasive bladder cancer[5]
- High-level of PD-L1 expression is associated with reduced survival[3,6]
  - In a study conducted in 65 surgically resected bladder cancer specimens, OS and RFS were significantly worse in patients with high-PD-L1 tumors than in those with low-PD-L1 tumors[6]

Blocking the PD-1/PD-L1 signaling may provide improved outcomes in the treatment of patients with bladder cancer[6]

OS = overall survival; RFS = recurrence-free survival.

1. Chen DS, et al. *Clin Cancer Res*. 2012;18:6580-6587. 2. Carneiro BA, et al. *Cancer Treat Rev*. 2015;41:170-178. 3. Huang Y, et al. *Oncol Rep*. 2015;33:3075-3084.
4. Inman BA, et al. *Cancer*. 2007;109:1499-1505. 5. Wang YU, et al. *Genet Mol Res*. 2015;14:1277-1286. -6. Nakanishi J, et al. *Cancer Immunol Immunother*. 2007;56:1173-1182.

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VENTANA PD-L1 (SP263) Assay

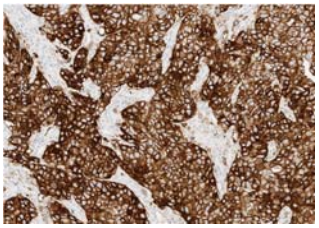
Intended Use for Urothelial Carcinoma

VENTANA PD-L1 (SP263) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP263 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue stained with OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument. PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background, or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered High if any of the following are met:

- **≥ 25% of tumor cells exhibit membrane staining; or**
- **ICP > 1% and IC+ ≥ 25% ; or**
- **ICP = 1% and IC+ = 100%**

PD-L1 High status as determined by VENTANA PD-L1 (SP263) Assay was associated with increased objective response rate (ORR) in a single arm study of IMFINZI™ (durvalumab).

This product is intended for in vitro diagnostic (IVD) use.



Positive UC tissue stained with PD-L1 (SP263) assay

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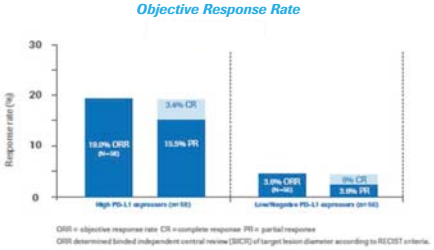
Durvalumab Bladder Outcome study

Patients with high PD-L1 expression VENTANA PD-L1 (SP263) assay:

- ***~5Xs the ORR compared to low or negative expression***
- ***Complementary Diagnostic for IMFINZI™ (durvalumab)***

Objective Response Rate



ORR = objective response rate; CR = complete response; PR = partial response.
ORR determined by blinded independent central review (BICR) of target lesion diameter according to RECIST criteria.

Massard C, et al. 2016. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol. 34(26):3119-25.

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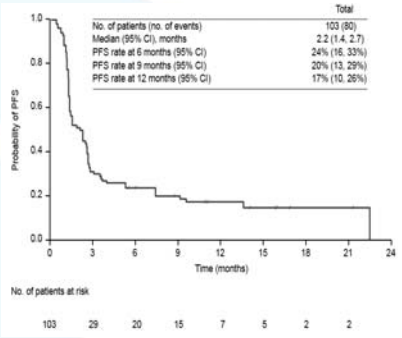
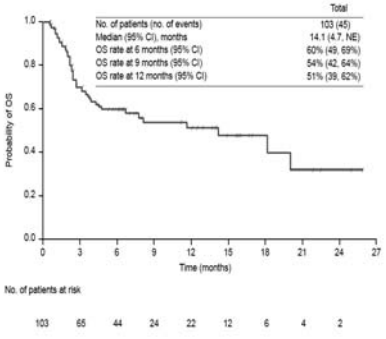
*Kaplan-Meier Survival Estimates in Primary Efficacy Population of UC Cohort**

Progression Free Survival



Overall Survival



*Given limited follow-up, OS data were considered immature at the time of data cutoff.
NE = not evaluable; No. = number; OS = overall survival; PFS = progression free survival.
Powles T et al. 2017. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma. *J Clin Onc.* 35(6_suppl).

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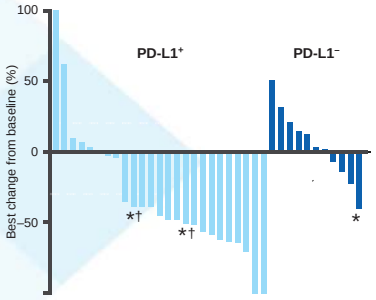
Best Change in Target Lesion Size by PD-L1 Status in Response to durvalumab in UBC Patients



PD-L1+ subgroup

76% (19/25) had a reduction in tumor size

PD-L1⁻ subgroup

36% (4/11) had a reduction in tumor size

Data cutoff on November 20, 2015
* Unconventional response.
† Unconfirmed response (all other patients with best tumor shrinkage ≥30% had confirmed responses).

Massard et al. 2016. Safety and efficacy of durvalumab (MEDI4736) , an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol.* 34(26).

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Confirmed ORR and DCR12 by PD-L1 Localization in UCB patients treated with Durvalumab

PD-L1 expression by location	PD-L1 status definition	ORR[a]		DCR12[b]	
		n/N (%)	95% CI	n/N (%)	95% CI
Unselected		13/42 (31.0)	17.6–47.1	20/42 (47.6)	32.0–63.6
TCs or ICs	PD-L1⁺ (≥25% TCs or ICs)	13/28 (46.4)	27.5–66.1	16/28 (57.1)	37.2–75.5
	PD-L1⁻ (<25% TCs and ICs)	0/14 (0.0)	0.0–23.2	4/14 (28.6)	8.4–58.1
TCs	PD-L1⁺ (≥25%)	7/15 (46.7)	21.3–73.4	8/15 (53.3)	26.6–78.7
	PD-L1⁻ (<25%)	6/27 (22.2)	8.6–42.3	12/27 (44.4)	25.5–64.7
ICs	PD-L1⁺ (≥25%)	10/18 (55.6)	30.8–78.5	12/18 (66.7)	41.0–86.7
	PD-L1⁻ (<25%)	3/24 (12.5)	2.7–32.4	8/24 (33.3)	15.6–55.3

IC = immune cells; TC = tumor cells

PD-L1 status determined from the most recently collected tissue sample (prior to first dose of study treatment) with a quantifiable result

aORR was defined as confirmed complete or partial response per RECIST v1.1 in response-evaluable; bDCR12 was defined as confirmed complete or partial response or stable disease for ≥12 weeks per RECIST v1.1. Data cutoff on November 20, 2015

Massard et al. 2016. Safety and efficacy of durvalumab (MEDI4736) , an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol*. 34(26).

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VENTANA PD-L1 (SP263) Assay

UC Interpretation

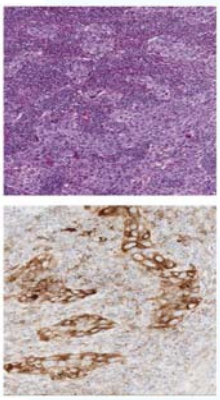

Table 4: VENTANA PD-L1 (SP263) Assay Scoring Algorithm for Urothelial Carcinoma

PD-L1 Interpretation	Staining Description
PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. Percent of tumor area occupied by any tumor-associated immune cells (ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining.	
High	PD-L1 Status is considered high if any of the following are met: • ≥ 25% of tumor cells exhibit membrane staining; or, • ICP > 1% and IC+ ≥ 25%; or, • ICP ■ 1% and IC+ ■ 100%.
Low/negative	PD-L1 Status is considered low/negative if: • none of the criteria for PD-L1 High Status are met.

Immune cells with 50% staining (IC+), Tumor cells with 100% staining. (Top row H&E 10X, PD-L1 20X.

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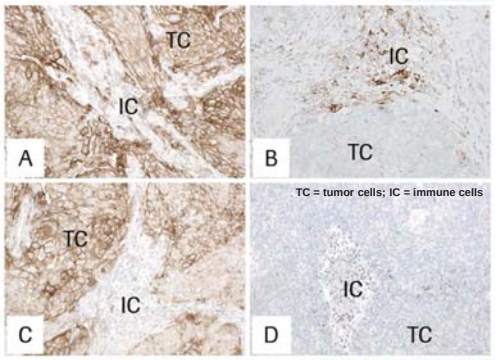
VENTANA PD-L1 (SP263) Assay

UC Interpretation

Tumor Biopsy with PD-L1 Immunostaining



TC+/IC+
≥25% TC and ≥25% IC

TC-/IC+
<25% TC and ≥25% IC

TC+/IC-
≥25% TC and <25% IC

TC-/IC-
<25% TC and ≥25% IC

Massard et al. *J Clin Oncol* 2016;June 6. pii: JCO679761. [Epub ahead of print].

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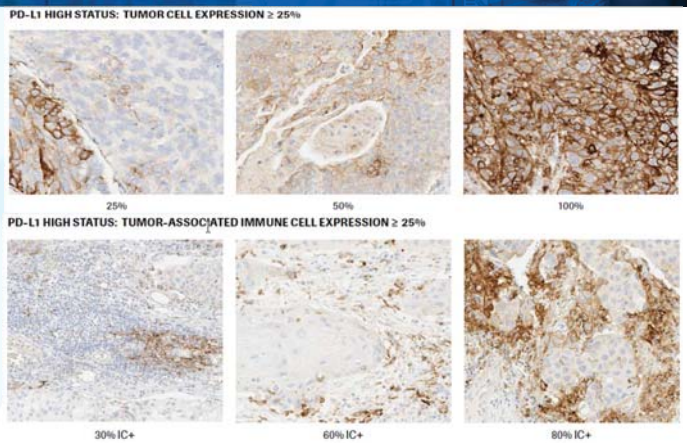
VENTANA PD-L1 (SP263) Assay

PD-L1 High Status: ≥ 25% TC / IC+ Expression



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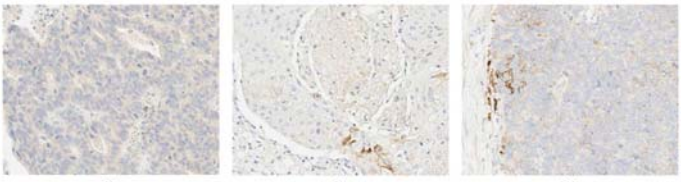
VENTANA PD-L1 (SP263) Assay PD-L1

Low/Negative Status: < 25% TC / IC+ Expression

PD-L1 LOW/NEGATIVE STATUS: TUMOR CELL EXPRESSION < 25%



0% 5% 10%

PD-L1 LOW/NEGATIVE STATUS: TUMOR-ASSOCIATED IMMUNE CELL EXPRESSION < 25%

0% IC+ 10% IC+ 20% IC+

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Roche demonstrates consistently high performance

VENTANA PD-L1 (SP263) Assay:

- Confident Diagnosis
- Reader Precision
- Lab Reproducibility

Reader precision	Overall percent agreement (95% CI)*
Inter-reader precision (average of all three reader pairwise comparisons for the first read) n =143	93.0%
Intra-reader precision (average of all three readers' agreement rates between first and second reads) n =145	92.4%

* CI- confidence interval

Inter-laboratory reproducibility	Overall percent agreement (95% CI)
Overall agreement (across sites, days and readers) n =778	92.3%
Inter-site agreement (average of site-to-site pairwise comparisons) n =7760	87.5%
Inter-reader agreement (average of reader-to-reader pairwise comparisons within each site) n =389	86.1%

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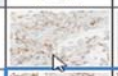
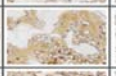
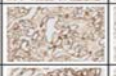
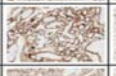
VENTANA PD-L1 (SP263) Assay

Fixative Recommendations for Optimal Staining

VENTANA PD-L1 (SP263) Assay Staining of Placenta Tissue Across Fixatives and Fixation Times

Time Point (Hrs)	Fixative					
	10% NBF	Zinc Formalin	PREFER fixative**	AFA**	Alcoholic Formalin**	95% Ethanol**
1*						
6						
12						
24						
48						
72						

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Personalized Medicine

VENTANA PD-L1 (SP142) Assay UC

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VENTANA PD-L1 (SP142) Assay

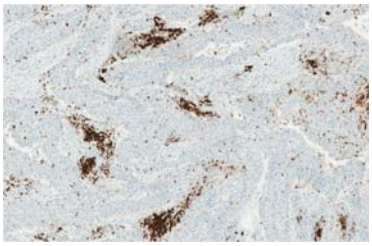
Intended Use for NSCLC and Urothelial Carcinoma

VENTANA PD-L1 (SP142) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) Urothelial carcinoma and non-small cell lung cancer (NSCLC) tissue stained with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a VENTANA BenchMark ULTRA instrument. Determination of PD-L1 status is indication-specific, and evaluation is based on either the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity or the percentage of PD-L1 expressing tumor cells (% TC) of any intensity.

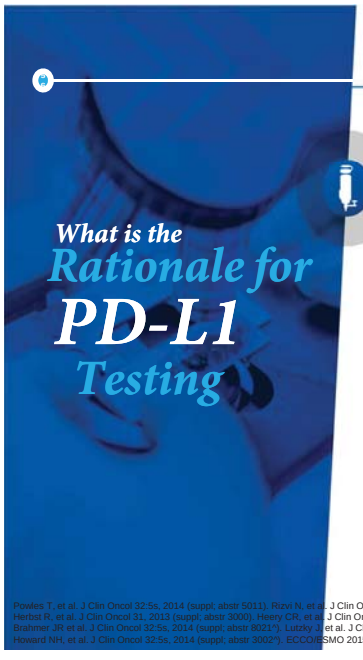
PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in **Urothelial carcinoma** tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ (atezolizumab).

PD-L1 expression in ≥ 50% TC or ≥ 10% IC determined by VENTANA PD-L1 (SP142) Assay in **NSCLC** tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab).

This product is intended for in vitro diagnostic (IVD) use.



Positive UC tissue stained with PD-L1 (SP142) assay, 10x

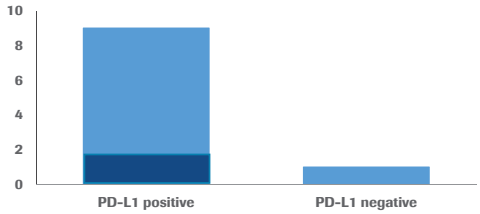


What is the Rationale for PD-L1 Testing

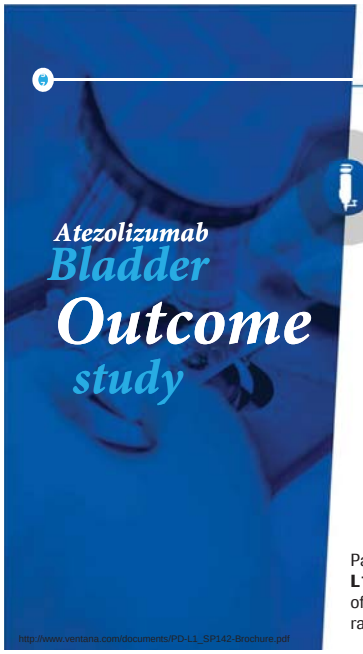
Patients with high PD-L1 expression VENTANA PD-L1 (SP142) assay:

- ***1.6-9Xs the ORR compared to low or negative expression***
- ***Complementary Diagnostic for TECENTRIQ™ (atezolizumab)***

Objective Response Rate



Powles T, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 5011). Rizvi N, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr TPS8123).
Herbst R, et al. J Clin Oncol 31, 2013 (suppl; abstr 3000). Heery CR, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 3064).
Brahmer JR et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8021^). Lutzky J, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 3001^).
Howard NH, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 3002^). ECCO/ESMO 2015 presentations, Vienna Austria. http://www.europeancancercongress.org/Scientific-Programme



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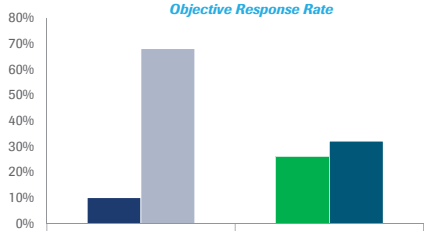
Patients with high PD-L1 expression VENTANA PD-L1 (SP142) assay:

- ***IC2 and IC3 PD-L1 expressors Atezo 3Xs more effective***
- ***Complementary Diagnostic for TECENTRIQ™ (atezolizumab)***

Objective Response Rate

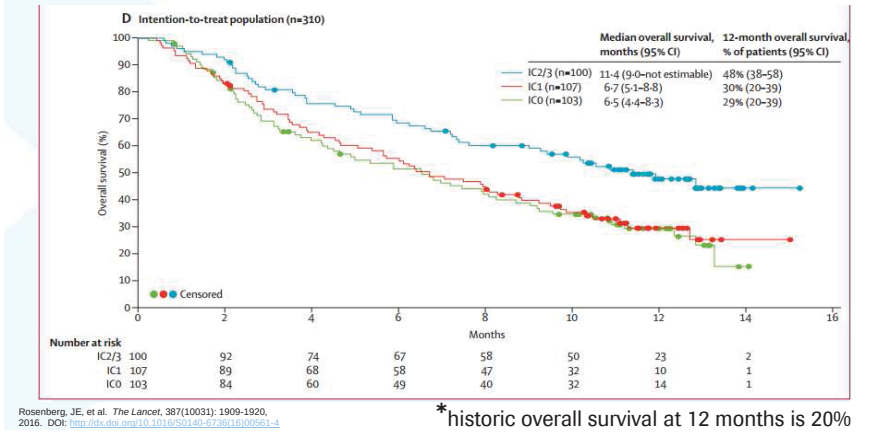


	<5%	≥5%
■ ORR	10%	26%
■ Prevalence	68%	32%

Patients with **high PD-L1 expression** identified by the **VENTANA PD-L1 (SP142) Assay** have **~3 times the objective response rate** (ORR) of patients with **low PD-L1 low expression**, who experience response rates equal to chemotherapy. (Data from IMvigor 210, a phase II trial.)

Roche

Overall Survival in PD-L1 Immune Cell groups in UC

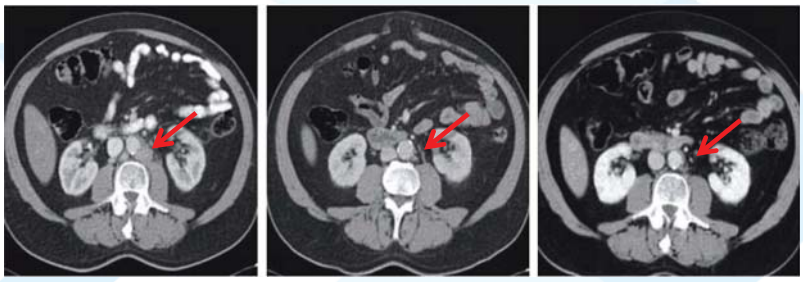


Rosenberg, JE, et al. *The Lancet*, 387(10031): 1909-1920, 2016. DOI: http://dx.doi.org/10.1016/S0140-6736(16)00561-4

*historic overall survival at 12 months is 20%

Response to atezolizumab in PD-L1+ UC Patient

Baseline	Post-cycle 2	Post-cycle 8

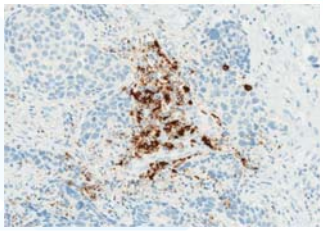


Powles, T et al, Nature 515: 558, 2014

VENTANA PD-L1 (SP142) Assay

UC Interpretation

Immune cell (IC) staining



Tumor –infiltrating immune cell staining assessment	PD-L1 expression
Absence of any discernible PD-L1 staining -or- Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering <5% of tumor area occupied by tumor cells, associated intratumoral and contiguous peritumoral stroma	<5%
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 5% of tumor area occupied by tumor cells, associated intratumoral and contiguous peritumoral stroma	≥5%

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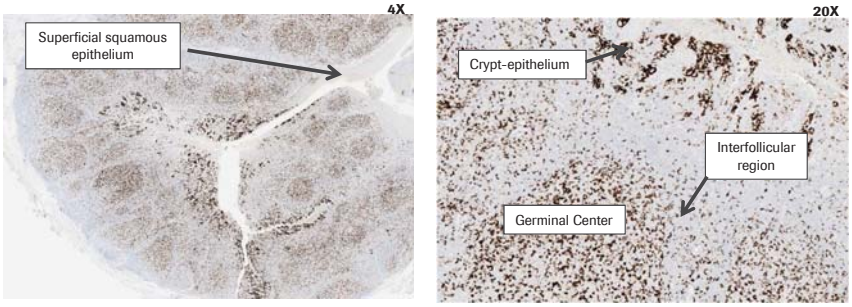
VENTANA PD-L1 (SP142) Assay

Tonsil control ***acceptable staining***



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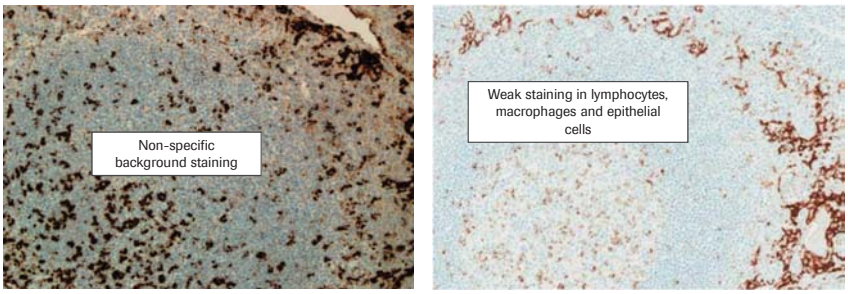
VENTANA PD-L1 (SP142) Assay

Tonsil control ***unacceptable staining***

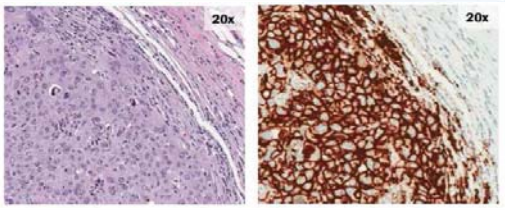


63

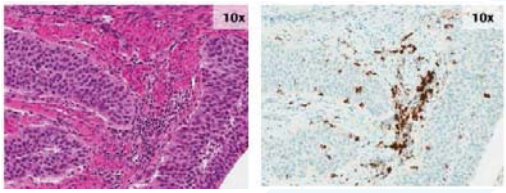
VENTANA PD-L1 (SP142) Assay

Examples of UC Staining

Tumor Biopsy with PD-L1 Immunostaining



Urothelial cancer tissue showing strong circumferential TC membrane staining



Urothelial cancer tissue showing dark brown punctate and linear IC staining

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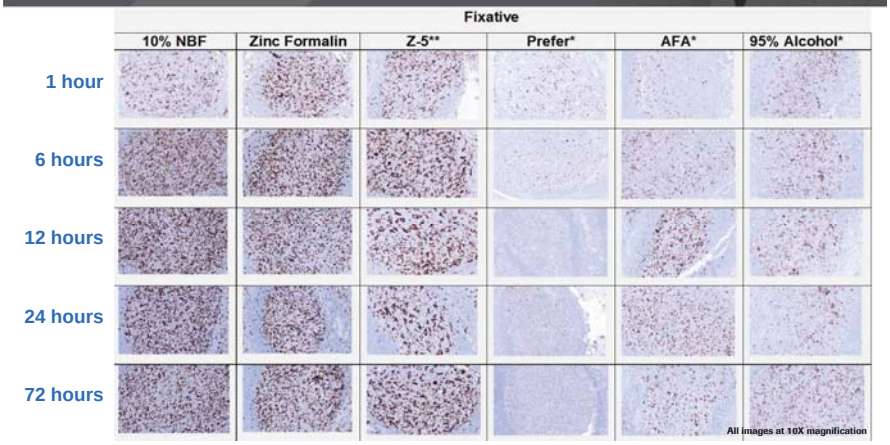
VENTANA PD-L1 (SP142) Assay

Fixative Recommendations for Optimal Staining



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VENTANA PD-L1 (SP142) Assay
UC Specimen and Assay Needs

SPECIMEN TYPES

- Acceptable UC tissue:
  - Resection, TURBT, Core needle biopsies
  - Primary or metastatic sites
- Adequacy: Contains at least 50 viable tumor cells with associated stroma
- Unacceptable tissues: cytology or decalcified bone

NUMBER OF SLIDES REQUIRED

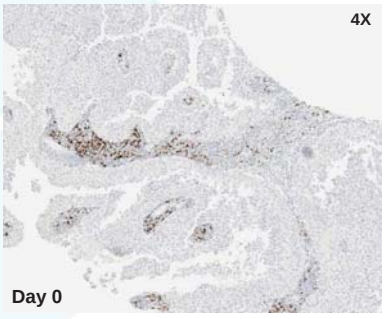
- Three serial sections from each case:
  - H&E, Negative control staining, PD-L1 (SP142) staining

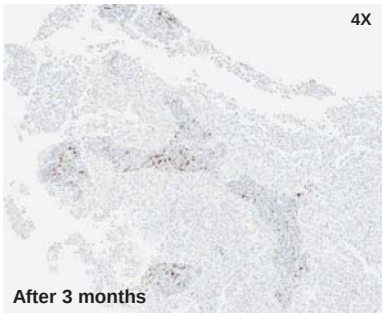
CONTROL TISSUE

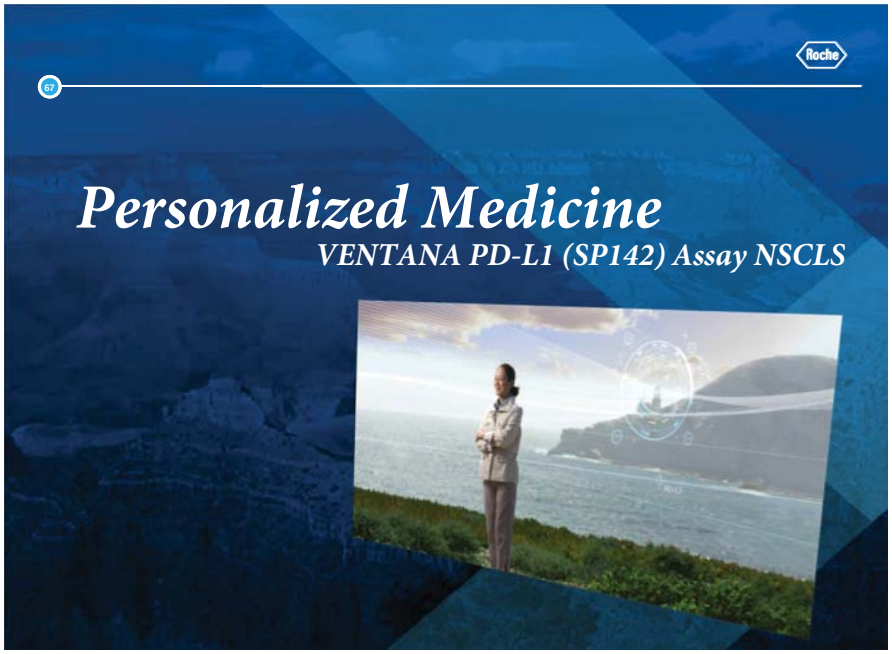
- Pre-qualified benign tonsil tissue

66

VENTANA PD-L1 (SP142) Assay
UC Specimen antigen stability





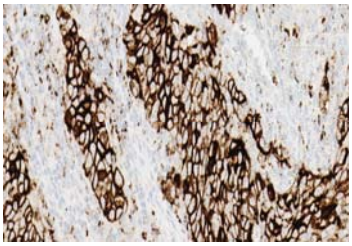


VENTANA PD-L1 (SP142) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) Urothelial carcinoma and non-small cell lung cancer (NSCLC) tissue stained with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a VENTANA BenchMark ULTRA instrument. Determination of PD-L1 status is indication-specific, and evaluation is based on either the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity or the percentage of PD-L1 expressing tumor cells (% TC) of any intensity.

PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in **Urothelial carcinoma** tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ (atezolizumab).

PD-L1 expression in ≥ 50% TC or ≥ 10% IC determined by VENTANA PD-L1 (SP142) Assay in **NSCLC** tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab).

This product is intended for in vitro diagnostic (IVD) use.



Positive NSCLC tissue stained with PD-L1 (SP142) assay, 10x

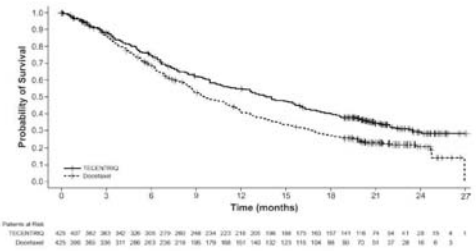
What is the Rationale for PD-L1 Testing

*A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab compared with docetaxel in patients with non-small cell lung cancer after failure with platinum containing chemotherapy.

Clinicaltrials.gov number NCT0202008227

VENTANA PD-L1 (SP142) assay: NSCLC OAK Trial Data

- In 2nd line setting all patients had longer overall survival
- Clinical trial data consistently demonstrates that if you have higher PD-L1 expression you have higher response rates



- All randomized patients in a NSCLC phase III study observed benefit from TECENTRIQ regardless of PD-L1 status.

VENTANA PD-L1 (S142) Assay

NSCLC Interpretation

Figure 1: Moderate to strong circumferential TC membrane staining; NSCLC tissue, 20x

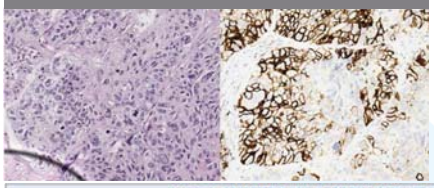


Figure 2: Dark brown punctate and linear IC staining; NSCLC, 20x

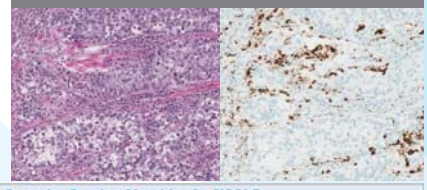


Table 1: VENTANA PD-L1 (SP142) Assay Stepwise Scoring Algorithm for NSCLC

Step 1: Tumor Cell (TC) Staining Assessment	PD-L1 Expression
Presence of discernible PD-L1 membrane staining of any intensity in ≥ 50% of tumor cells	≥ 50% TC
Absence of any discernible PD-L1 staining (OR) Presence of discernible PD-L1 membrane staining of any intensity in < 50% of tumor cells.	Proceed to Step 2
Step 2: Tumor Infiltrating Immune Cell (IC) Staining Assessment	**PD-L1 Expression**
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma	≥ 10% IC
Absence of any discernible PD-L1 staining (OR) Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering < 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma	< 50% TC and < 10% IC

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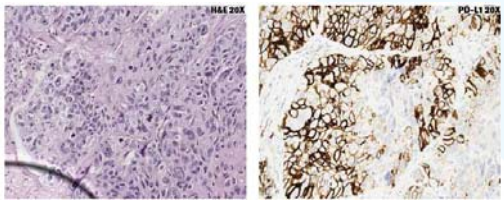
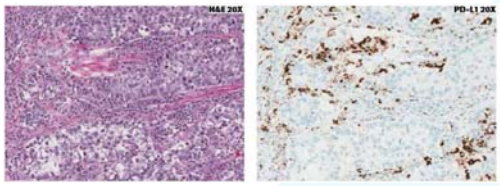
VENTANA PD-L1 (SP142) Assay

Examples of NSCLC Staining

Tumor Biopsy with PD-L1 Immunostaining



NSCLC tissue showing moderate to strong circumferential TC membrane staining



NSCLC tissue showing dark brown punctate and linear IC staining

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VENTANA PD-L1 (SP142) Assay

NSCLC Specimen and Assay Needs

SPECIMEN TYPES

- Acceptable UC tissue:
  - Resection, Excisions, Core needle and other biopsies
  - Primary or metastatic sites
- Adequacy:
  - Contains at least 50 viable tumor cells
  - Tumor-associated stroma is not required for TC scoring
  - Presence of tumor-associated stroma is essential for scoring IC
- Unacceptable tissues: cytology or decalcified bone

NUMBER OF SLIDES REQUIRED

- Three serial sections from each case:
  - H&E, Negative control staining, PD-L1 (SP142) staining

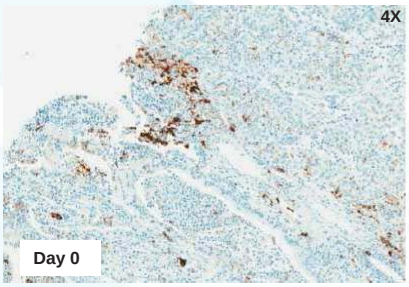
CONTROL TISSUE

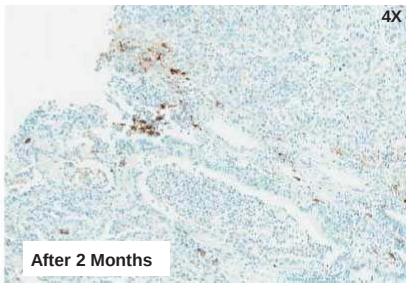
- Pre-qualified benign tonsil tissue

73

VENTANA PD-L1 (SP142) Assay

NSCLC Specimen antigen stability





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PD-L1 Testing Landscape

Approved Therapies		IMFINZI durvalumab	TECENTRIQ atezolizumab	KEYTRUDA pembrolizumab	OPDIVO nivolumab
Diagnostic Clone	Ventana SP263	Ventana SP263	Ventana SP142	Dako 22C3	Dako 28-8
Assay Status	Descriptive	Complementary	Complementary	Companion	Complement ary
Scoring	N/A	Tumor Cells (TC) Immune Cells (IC)	Tumor Cells (TC) Immune Cells (IC)	Tumor Cells (TC) Immune Cells (IC)*	Tumor Cells (TC)
Approved Indications	N/A	2L UC	1L/2L UC, 2L NSCLC	1L/2L NSCLC, 1L Mel, 2L mUC, 2L cHL, 2L HNSCC 3L Gastric*	1L Mel, 2L NSq NSCLC, 2L RCC, 2L cHL, 2L mUC, 2L SCCHN
Assay Components	BenchMark XT BenchMark ULTRA	OptiView BenchMark ULTRA	OptiView + Amp BenchMark ULTRA	EnVision FLEX+ Autostainer Link 48	EnVision FLEX+ Autostainer Link 48
Classification	Class I	Class III PMA Approved	Class III PMA Approved	Class III PMA Approved	Class III PMA Approved

+

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Your vision and expertise

29
Years of IHC automation

300
Ready-to-use reagents

>200
Ongoing projects

= *Personalized care for patients*

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