Roche
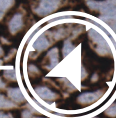
VENTANA PD-L1 (SP142) Assay
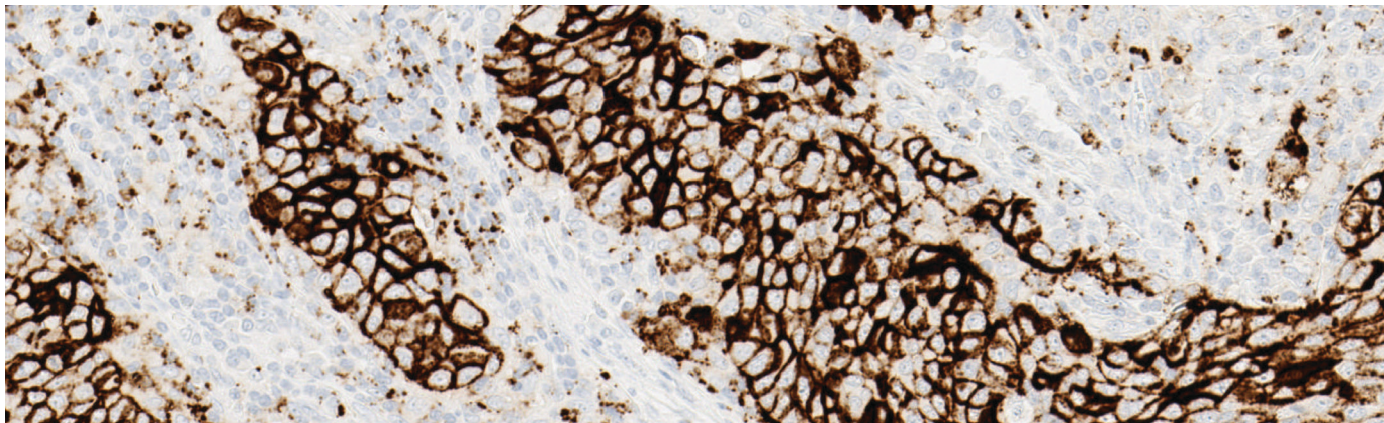## *Guiding immunotherapy in NSCLC*

PD-L1

Hiker's path: VENTANA PD-L1 (SP142) Assay
on non–small cell lung cancer tissue
Location: Point Conception, CA

VENTANA PD-L1 (SP142) Assay

Assess NSCLC patient benefit from TECENTRIQ

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

Intended use statement

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).

PD-L1 diagnostic confidence

Using the right test to determine PD-L1 status for immunotherapy options is important, and the VENTANA PD-L1 (SP142) Assay is the only FDA approved test for TECENTRIQ. This innovative assay is the first to evaluate patient PD-L1 expression using both tumor cell (TC) and tumor-infiltrating immune cell (IC) staining. Determining a patient's PD-L1 expression level can give insight to the overall survival that may be achieved from TECENTRIQ.*

The VENTANA PD-L1 (SP142) Assay

- FDA approved to assess NSCLC patient treatment benefit from TECENTRIQ
- Informative for the clinician of a patient's potential overall survival
- Novel scoring algorithm using PD-L1 staining in both TC and IC
- Designed to enhance visual contrast of immune cell staining within the tumor microenvironment

The PD-L1 (SP142) Assay gives you the confidence to guide immunotherapy decisions in NSCLC.

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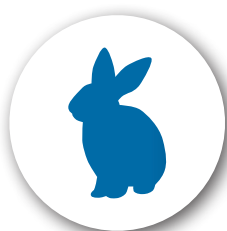
Rabbit
Monoclonal

IHC antibody developed by Spring Bioscience Corporation

Fully
Automated

With specific and robust signal

Highly
Reproducible

Accurate scoring and educational resources

About PD-L1

PD-L1 is a transmembrane protein that down-regulates immune responses through binding to its two inhibitory receptors, programmed death-1 (PD-1) and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer.[1] Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen presenting cells can mediate down-regulation of immune responses, including inhibition of T-cell activation and cytokine production.[2] PD-L1 expression has been observed in immune cells and tumor cells.[3, 4] Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion.[1] Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity suppressed by the expression of PD-L1 in the tumor microenvironment.
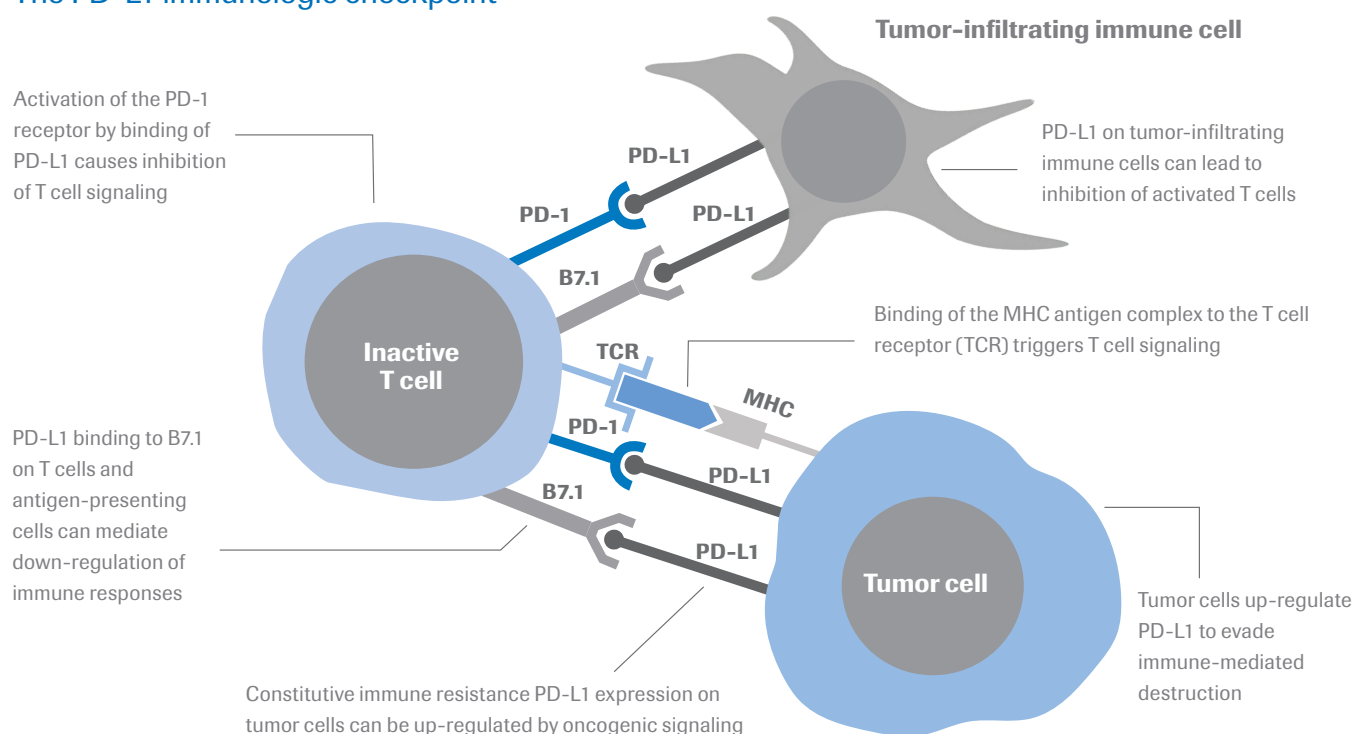
About non-small cell lung cancer

Lung cancer has been the most common cancer in the world for several decades and remains the leading cause of cancer deaths worldwide. It is estimated to account for 12.9% of all new cancer cases and is responsible for nearly 1.59 million deaths annually worldwide, or approximately one in five cancer-related deaths.[5] In the United States alone, approximately 224,390 new cases of lung cancer and 158,080 lung cancer-related deaths are predicted for 2016.[6] Although improvements have been made in diagnosis and therapy options, prognosis remains poor with low long-term survival rates for all stages. Over the past three decades, lung cancer has shown among the least improvement in survival rates when compared with other cancers.[7]

Non-small cell lung cancer (NSCLC), one of the two major types of lung cancer, accounts for approximately 85% of all lung cancer cases.[8] In more than half of patients newly diagnosed with NSCLC, the disease has already metastasized, greatly decreasing the likelihood of survival. The five-year relative survival rate for NSCLC diagnosed as distant disease is 4.7%.[8]
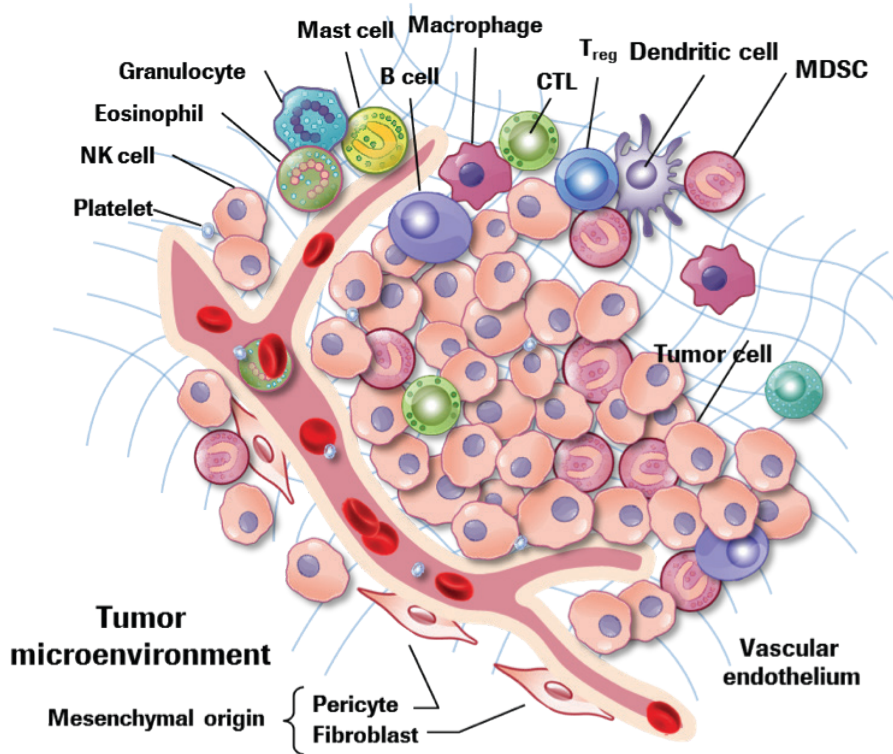The majority of patients with NSCLC present with inoperable, locally advanced disease (Stage IIIB) or metastatic disease (Stage IV), neither of which currently has any curative treatment options. On average, these patients die within a year of diagnosis. Improvement in the clinical outcome of lung cancer is likely to be achieved through better understanding of the molecular events that underlie its pathogenesis, identifying new biomarker targets and developing new treatment options.

The PD-L1 immunologic checkpoint

Tumor-infiltrating immune cell

Activation of the PD-1 receptor by binding of PD-L1 causes inhibition of T cell signaling

PD-L1 on tumor-infiltrating immune cells can lead to inhibition of activated T cells

Binding of the MHC antigen complex to the T cell receptor (TCR) triggers T cell signaling

PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate down-regulation of immune responses

Tumor cells up-regulate PD-L1 to evade immune-mediated destruction

Constitutive immune resistance PD-L1 expression on tumor cells can be up-regulated by oncogenic signaling

PD-1 · PD-L1 · B7.1 · TCR · MHC · Inactive T cell · Tumor cell

The tumor microenvironment

A key player in tumor progression

Tumor microenvironment diagram with labels: Granulocyte, Eosinophil, NK cell, Platelet, Mast cell, B cell, Macrophage, CTL, Treg, Dendritic cell, MDSC, Tumor cell, Vascular endothelium, Tumor microenvironment, Mesenchymal origin { Pericyte, Fibroblast }

The PD-L1 (SP142) Assay stain highlights a heterogeneous population of immune cells. The majority of these cells are morphologically consistent with lymphocytes, macrophages, dendritic cells and granulocytes.

What is the tumor microenvironment (TME)?

The tumor microenvironment (TME) consists of different cells, including immune cells and non-cellular components in and around the tumor. The TME has been recognized to play a significant role in tumor progression. [9,10]

Why is the TME important?

The TME shapes tumor evolution (whether the tumor regresses, develops resistance, evades the immune system and/or metastasizes) and consequently impacts patient outcomes. [11] An association has been observed between the levels of tumor infiltrating immune cells, key components of the TME and outcome in lung cancer patients. A meta-analysis showed that high levels of CD8+ lymphocyte tumor stroma infiltration was associated with better overall survival (Hazard ratio = 0.76 95% confidence interval 0.62-0.93), high levels of CD4+ lymphocyte tumor stroma infiltration was also associated with better overall survival (Hazard ratio = 0.65 95% confidence interval 0.46-0.91, P 0.013). In contrast, high levels of FOXP3P+ T lymphocyte stroma infiltration was associated with poor progression-free survival (Hazard ratio = 2.67 95% confidence interval 1.74-4.08, P value < 0.001). [12]

What is the role of PD-L1 in the TME?

Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion. [13] Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity suppressed by the expression of PD-L1 in the tumor and in the tumor microenvironment. This approach has proven effective: PD-L1 expression on immune cells in the tumor microenvironment has been shown to help assess NSCLC patient benefit from TECENTRIQ, an anti-PD-L1 drug. [14]
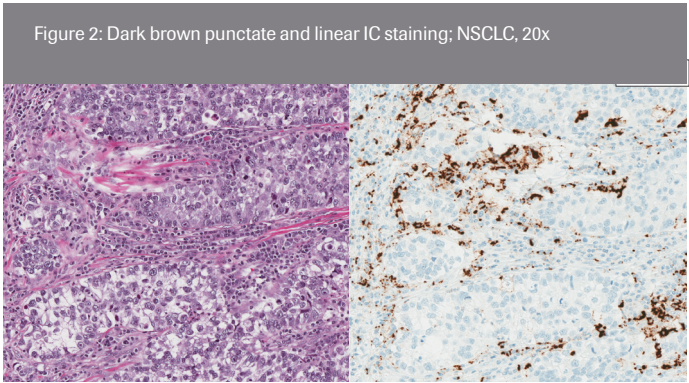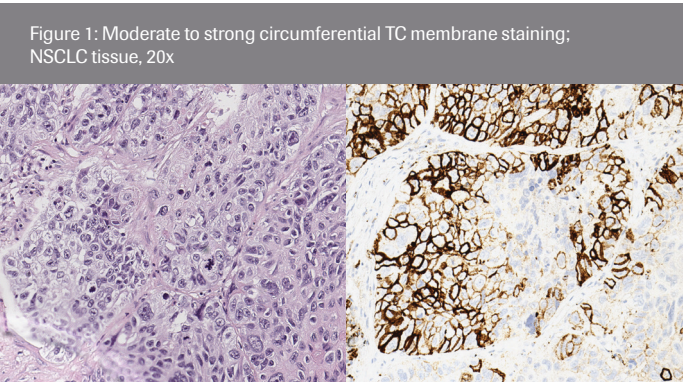
Scoring of VENTANA PD-L1 (SP142) Assay
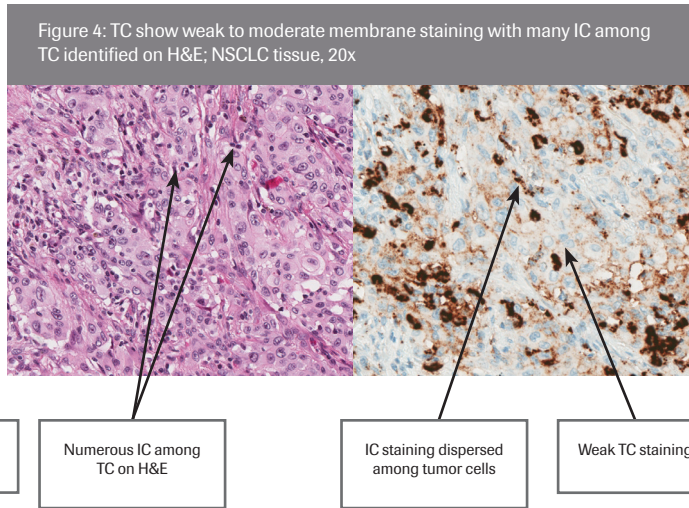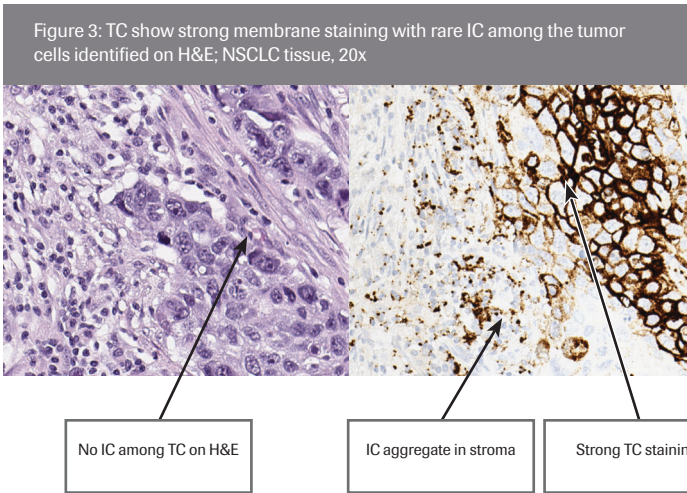
General guidelines

Immunohistochemical (IHC) staining with the VENTANA PD-L1 (SP142) Assay demonstrates staining in tumor cells (TC, Figure 1) as well as tumor-infiltrating immune cells (IC, Figure 2).

A patient's tumor tissue stained with the VENTANA PD-L1 (SP142) Assay is evaluated for TC and/or IC staining. TC are scored as the proportion of viable tumor cells showing PD-L1 membrane staining of any intensity. IC are scored as the proportion of tumor area that is occupied by PD-L1 staining IC of any intensity.

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

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

Differentiation of TC and IC Staining

TC staining can be observed in association with IC staining. Review of the corresponding H&E slide will help in identifying IC among TC. This along with a high magnification review of the PD-L1 stained slide may aid in differentiating between TC and IC staining. The following images demonstrate different commonly observed patterns encountered in clinical practice, when TC and IC staining is observed together.

Figure 3: TC show strong membrane staining with rare IC among the tumor cells identified on H&E; NSCLC tissue, 20x

No IC among TC on H&E

IC aggregate in stroma

Strong TC staining

Figure 4: TC show weak to moderate membrane staining with many IC among TC identified on H&E; NSCLC tissue, 20x

Numerous IC among TC on H&E

IC staining dispersed among tumor cells

Weak TC staining

VENTANA PD-L1 (SP142) Assay scoring approach – NSCLC

NSCLC tissue stained with the VENTANA PD-L1 (SP142) Assay will be scored using a stepwise approach according to the criteria outlined in Table 1. TC are scored as the proportion of viable tumor cells showing PD-L1 membrane staining of any intensity. IC are scored as the proportion of tumor area that is occupied by PD-L1 staining IC of any intensity. VENTANA PD-L1 (SP142) Assay-stained slides will first be evaluated for TC staining (Step 1 in Table 1). If the specimen contains any discernible PD-L1 membrane staining of any intensity in ≥ 50% TC, the case will be assigned a PD-L1 expression level of ≥ 50% TC. If the specimen contains < 50% TC staining, the slide will then be evaluated for IC staining (Step 2 in Table 1). If the specimen contains PD-L1 staining of any intensity in IC occupying ≥ 10% of tumor area, the case will be assigned a PD-L1 expression level of > 10% IC. If the specimen contains PD-L1 staining of any intensity in IC covering < 10% of tumor area, the case will be assigned a PD-L1 expression level of < 50% TC and < 10% IC.
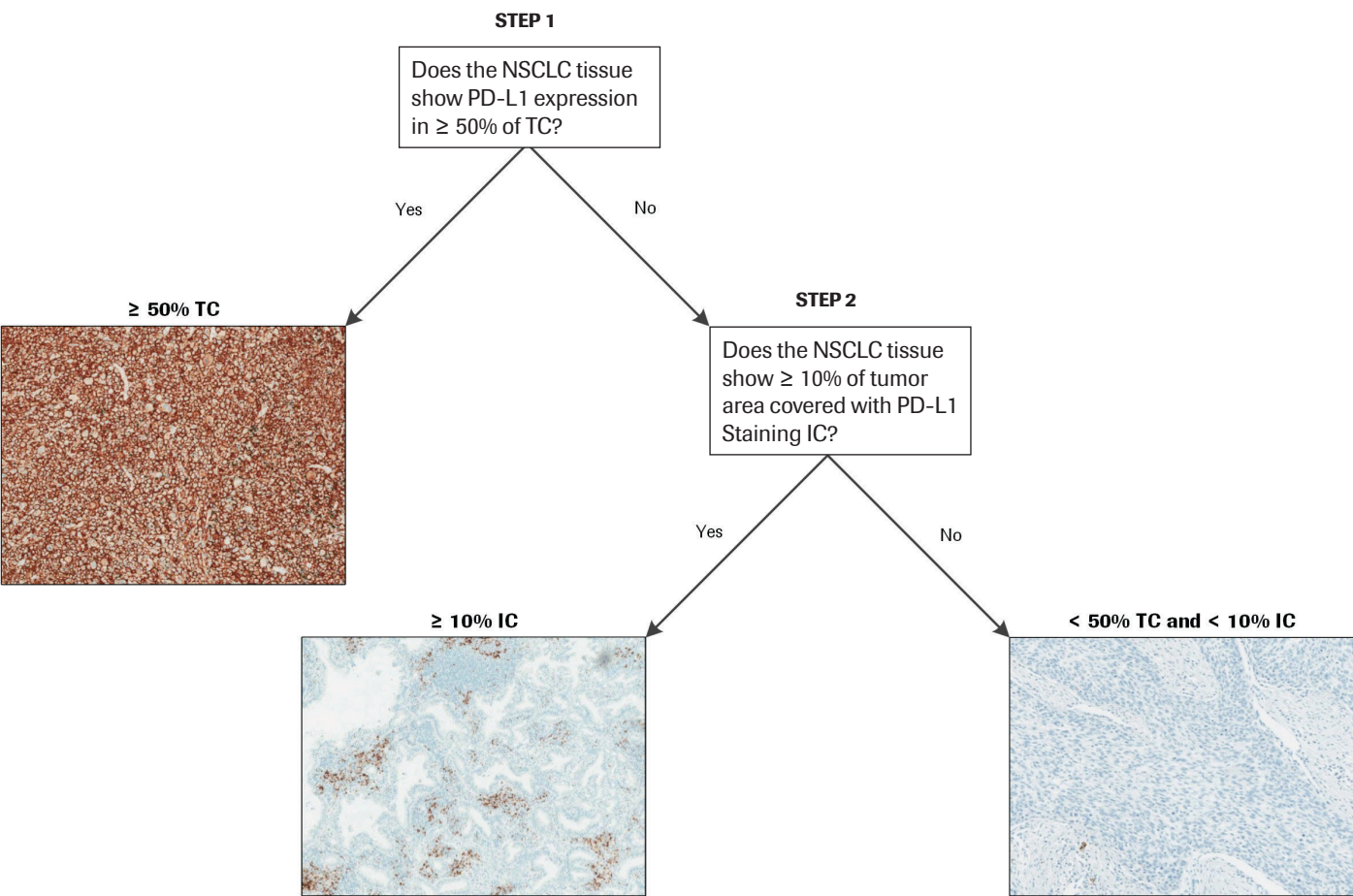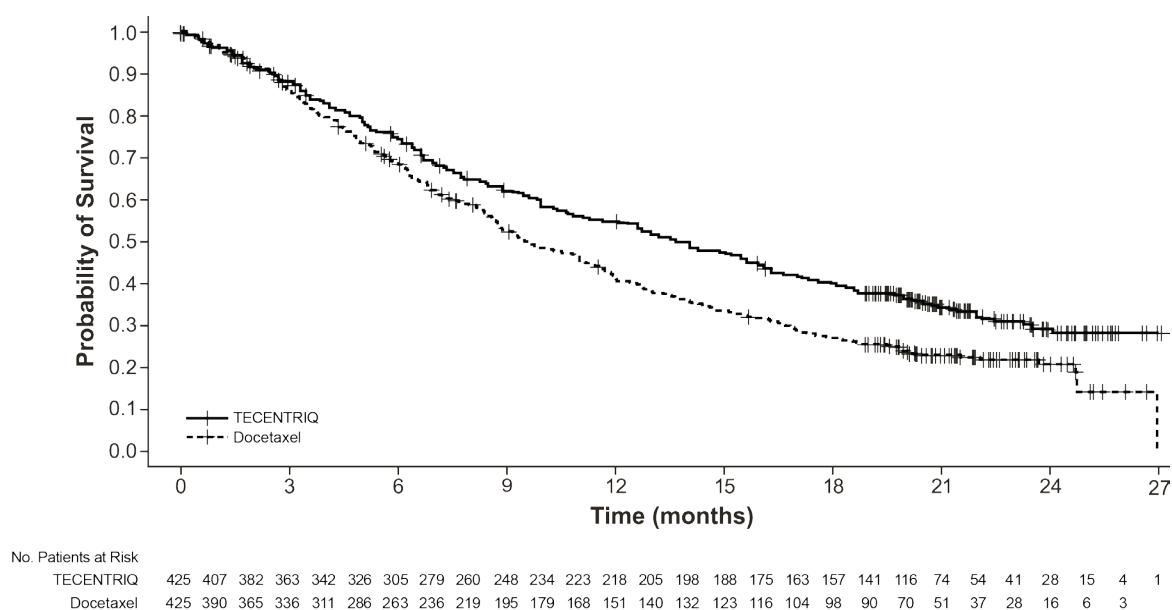

Stepwise scoring process – VENTANA PD-L1 (SP142) Assay in NSCLC tissues (images 10x magnification).

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% TC
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

VENTANA PD-L1 (SP142) Assay results from clinical trials

Results from the OAK trial[*, 14]

No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3

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

Efficacy Results in the Primary Analysis Population from the Phase III Study		
Overall Survival	**TECENTRIQ (n=425)**	**Docetaxel (n=425)**
Deaths (%)	271 (64%)	298 (70%)
Median, months (95% CI)	13.8 (11.8, 15.7)	9.6 (8.6, 11.2)
Hazard ratio* (95% CI)	0.74 (0.63, 0.87)	
p-value**	0.0004	

Stratified by PD-L1 expression in tumor-infiltrating immune cells, the number of prior chemotherapy regimens, and histology
**Based on the stratified log-rank test*
CI = confidence interval

Tumor specimens were evaluated prospectively using VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

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	OptiView DAB IHC Detection Kit	OptiView Amplification Kit	Negative Reagent Control
Catalog number	**740-4859** 07709374001	**760-700** 06396500001	**860-099** 06718663001	**790-4795** 06683380001
Quantity	50 tests	250 tests	250 tests	50 tests
Positive control	Tonsil			
Species	Rabbit			
Localization	Membranous and/or Cytoplasmic			

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