Lung Cancer Update on Pathology

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DISCLOSURE

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Speaker's bureau/honoraria: Pfizer, Roche, Boehringer Ingelheim, AstraZeneca, Merck Canada, Novartis, Bristol-Myers Squibb

Objectives:

- To review the changes in the 2015 WHO lung carcinoma classification
- To describe molecular profiling in lung cancer
- To introduce lung cancer immunotherapy with its implication in pathology

WHO Lung Adenocarcinoma

1967	1981	2004	2015
Acinar	Acinar ADC	BAC	Adenocarcinoma in situ
Papillary	Papillary ADC	Mixed	Minimally invasive
BAC	BAC	Clear cell	Lepidic
	Solid with mucus	Acinar	Acinar
		Papillary	Papillary
		Signet-ring	Micropapillary
		Solid with mucin	Solid
		Mucinous (Colloid)	Invasive mucimous
			Colloid
		Fetal	Fetal
		Mucinous-cystadenocarcinoma	Enteric

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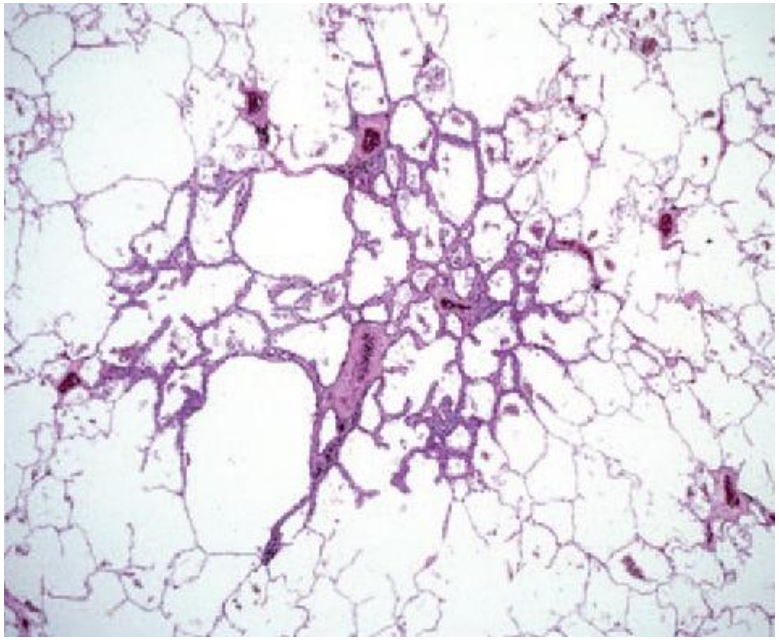
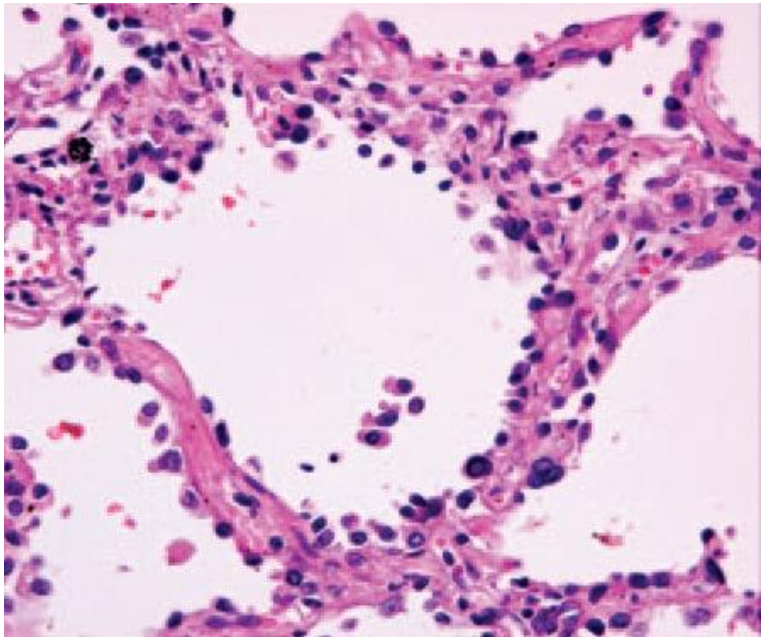
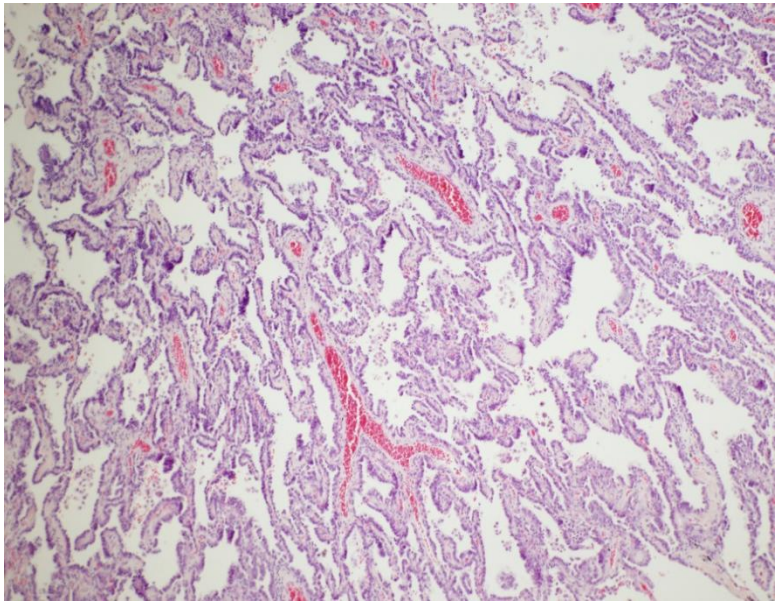
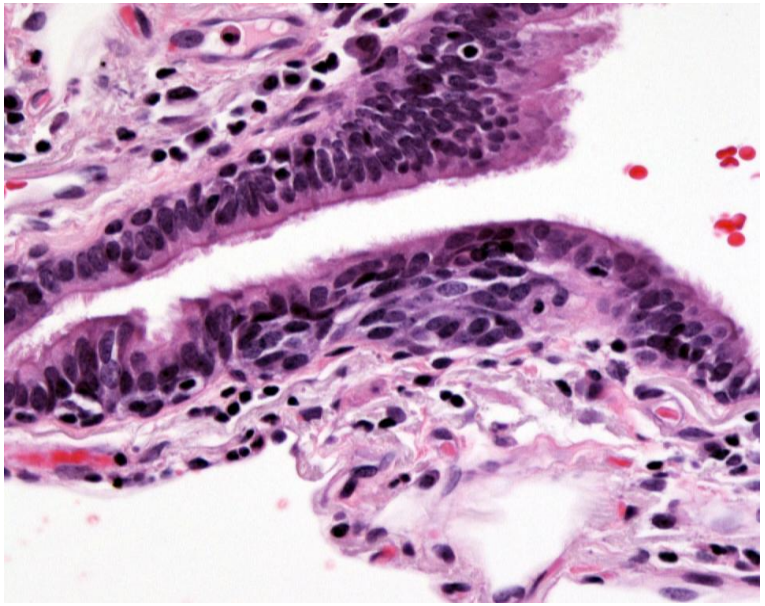
Preinvasive lesions

- For adenocarcinoma
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ
- For squamous cell carcinoma
  - Squamous cell carcinoma in situ
- For neuroendocrine tumors
  - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

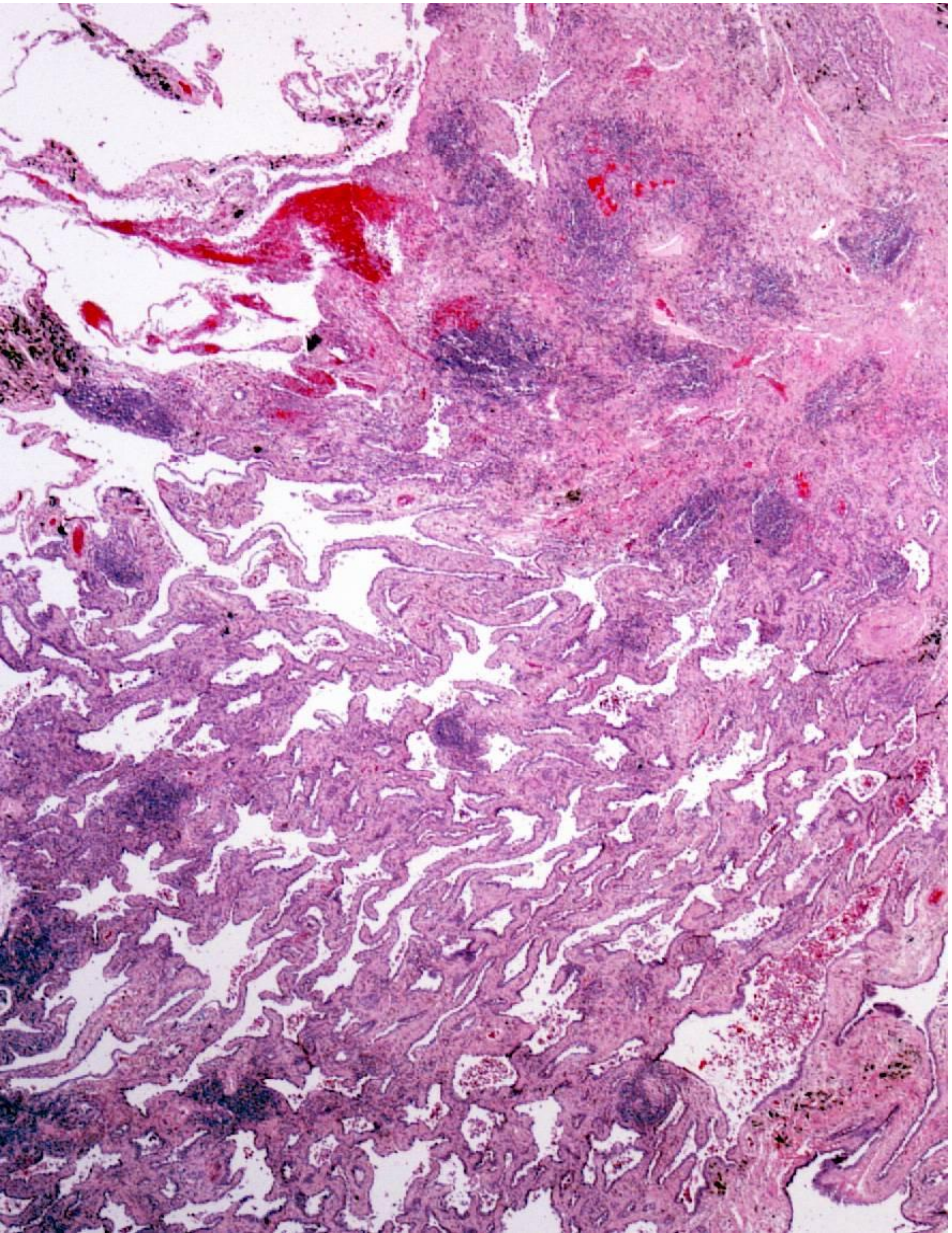


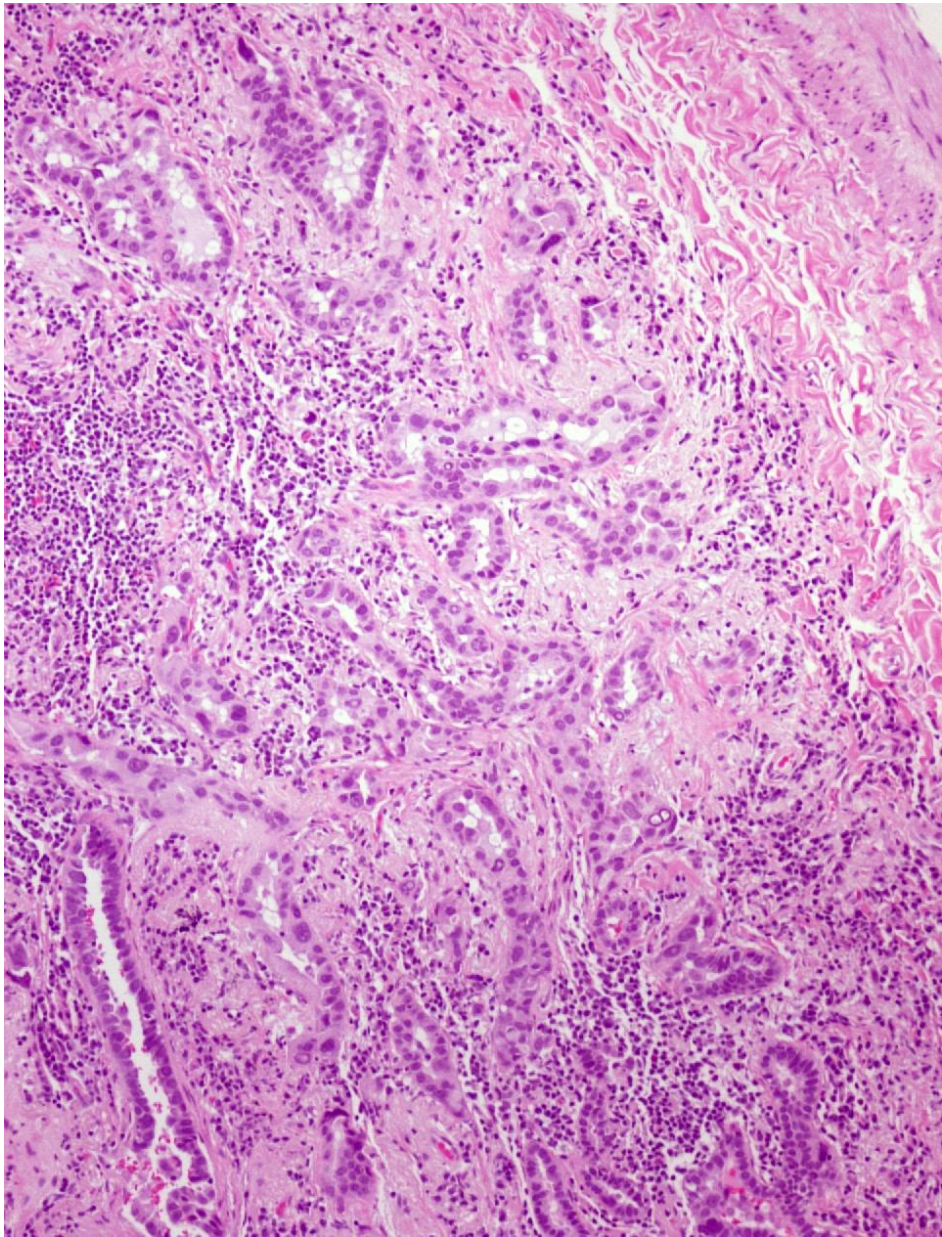




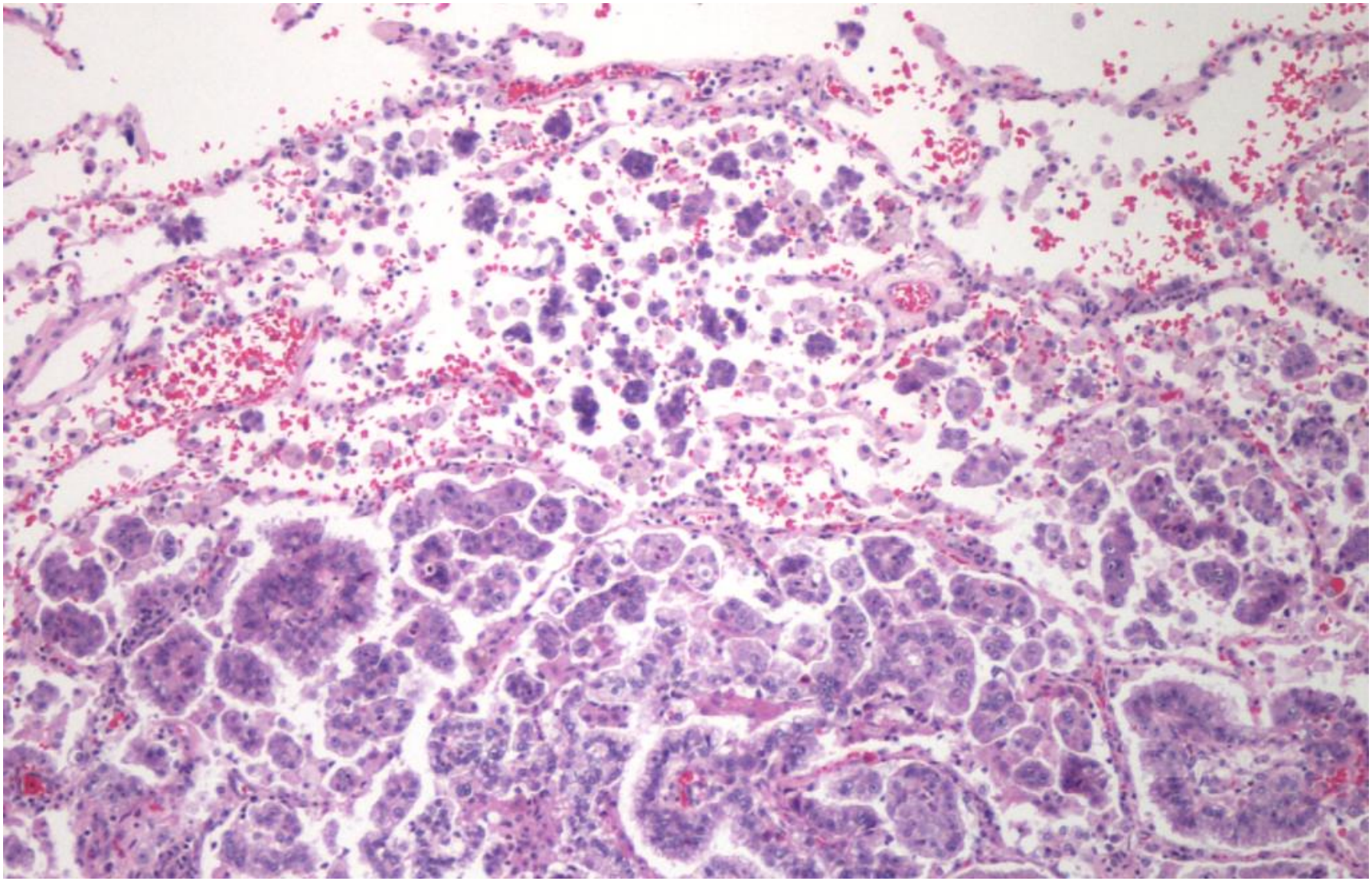


Minimally invasive/Lepidic





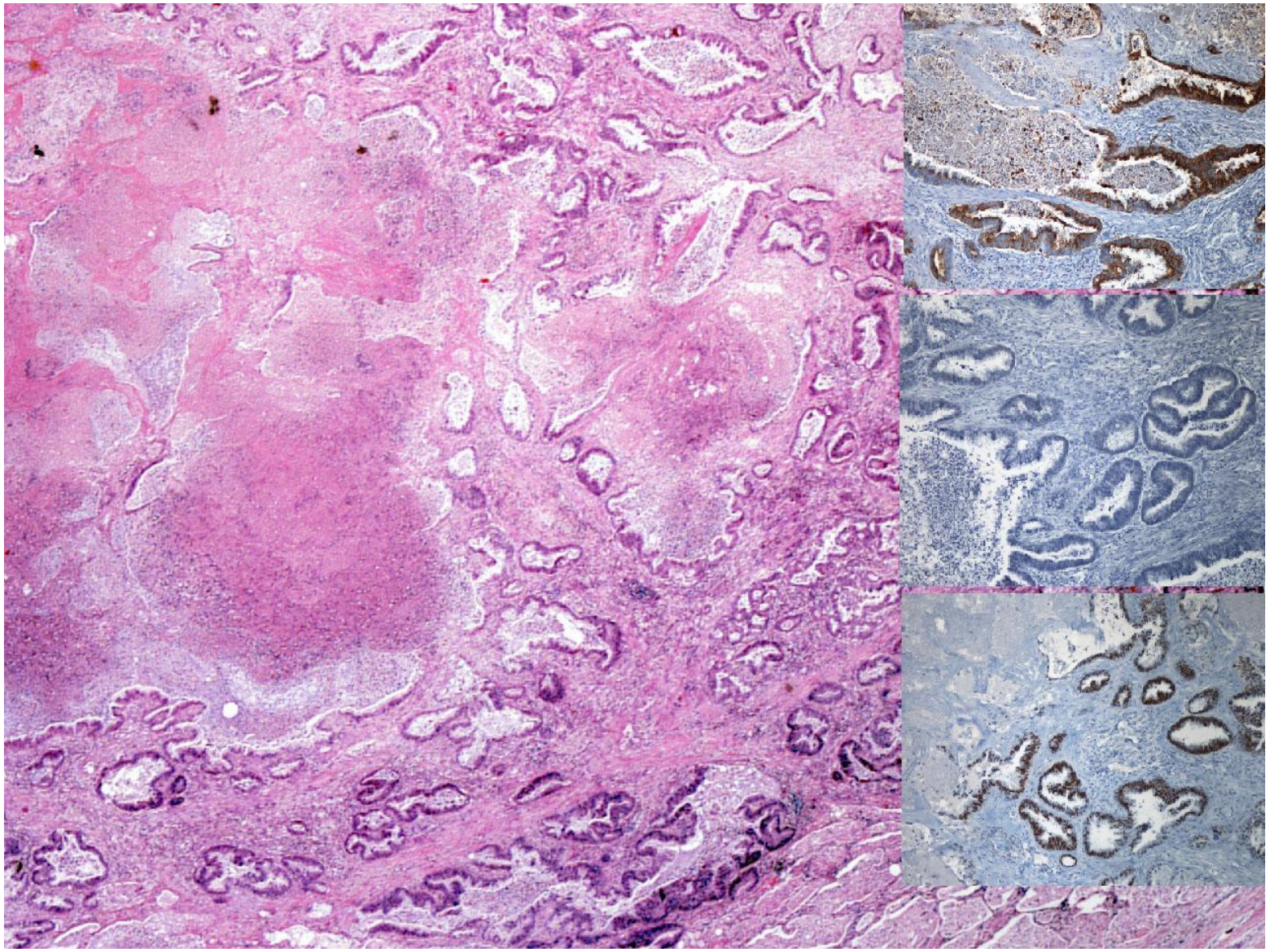
Micropapillary adenocarcinoma



Enteric adenocarcinoma

- It resembles colorectal adenocarcinoma
- The enteric pattern > 50%
- IHC may be identical to or different from colorectal adenocarcinoma (CK7, CK20, CDX2, TTF-1)
- Clinical correlation

Enteric adenocarcinoma



WHO Lung Squamous Cell Carcinoma

1967	1981	2004	2015
Epidermoid	Sq Ca (epidermoid)	Sq Ca Papillary	Keratinizing Sq Ca Non-keratinizing Sq Ca
	Spindle cell	Clear cell	Bsaloid
		Small cell	
		Basaloid	

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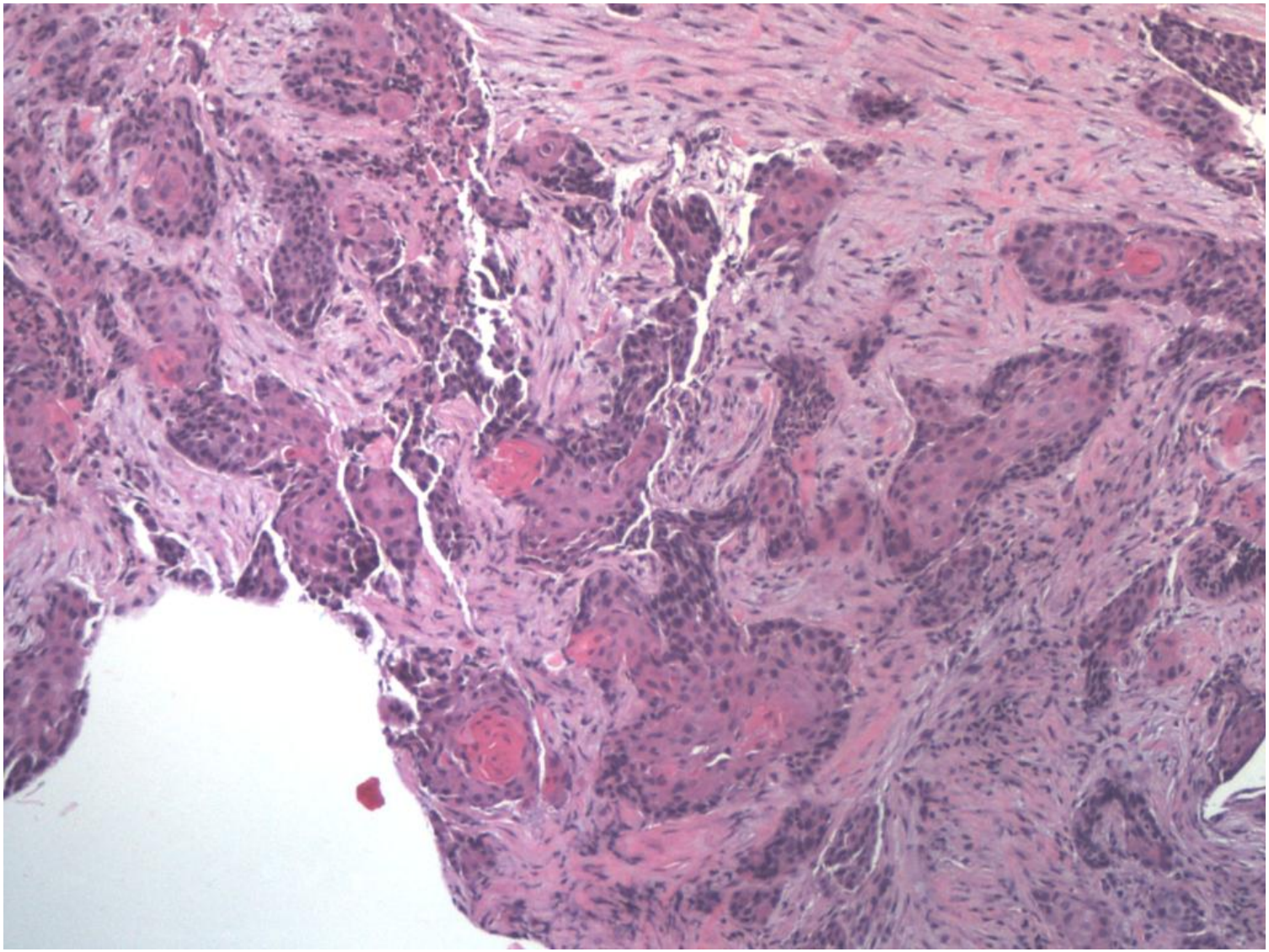
Squamous Cell Carcinoma



WHO Large Cell Carcinoma

1967	1981	2004	2015
Large cell	Large cell	Large cell	Large cell
	Giant cell	LCNEC	
	Clear cell	Basaloid	
		Lymphoepithelioma-like	
		Clear cell	
		Rhabdoid	

WHO Large Cell Carcinoma

1967	1981	2004	2015
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	Giant cell	LCNEC	
	Clear cell	Basaloid	
		Lymphoepithelioma-like	
		Clear cell	
		Rhabdoid	

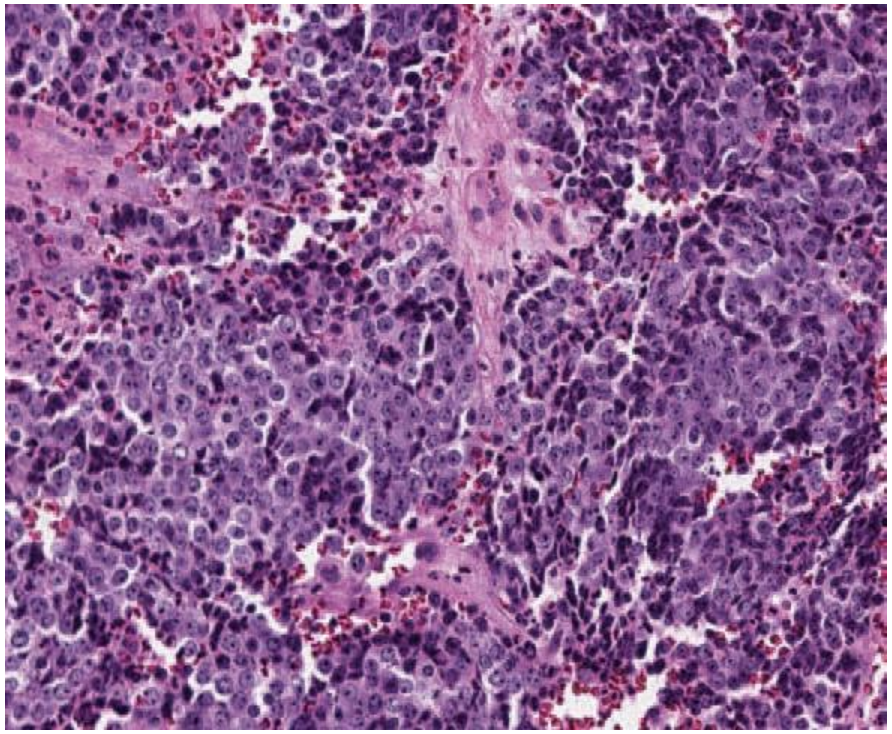
Neuroendocrine tumors

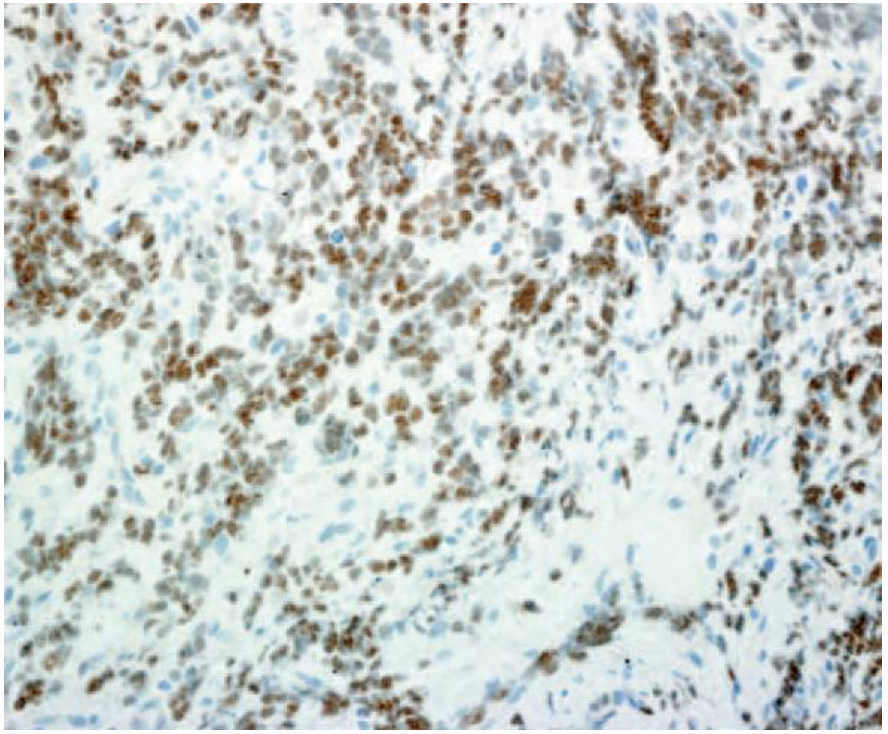
- Typical carcinoid
- Atypical carcinoid
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

Other/Unclassified

- **Lymphoepthelioma-like carcinoma**
- **NUT carcinoma**
  - **An aggressive tumor with NUT (nuclear protein in testis) gene rearrangement t(15;19), t(15;9)**
  - **Sheets and nests of monomorphic small to intermediate cells**
  - **Abrupt foci of keratinization**
  - **Positive for NUT antibody, CK, P63/P40, CD34**
  - **May also positive for neuroendocrine markers, TTF-1**

NUT carcinoma



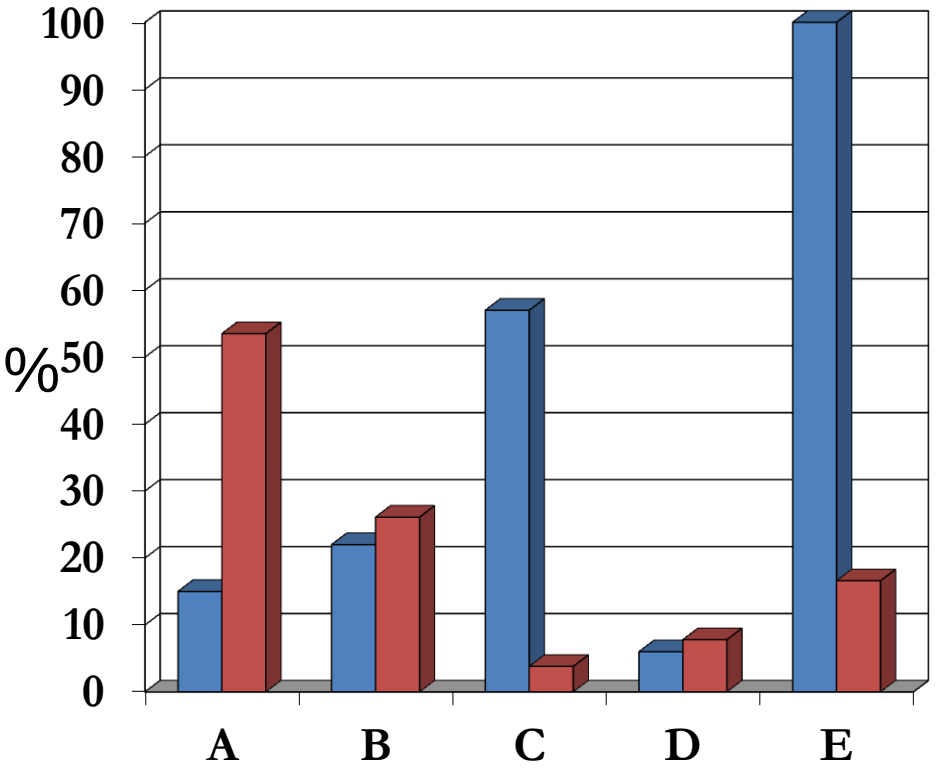


Five-year relative survival (%)

SITE	1975-77	1984-86	1996-98	2005-11
All sites	49	52	63	67
Lung and bronchus	**12**	**13**	**15**	**18**
Breast (female)	75	79	88	91
Prostate	68	75	97	99
Colon & rectum	50	58	62	66
Stomach	15	18	22	30
Pancreas	3	3	4	8
Leukemia	34	41	48	62
Melanoma	82	87	91	93
Non-Hodgkin lymphoma	47	52	59	70
Ovary	36	38	44	46
Urinary bladder	72	77	79	79
Mesothelioma	10	7	10	9
Esophagus	5	10	13	20
Livre	3	6	9	18
Kidney	50	55	63	74
Uterus	87	82	84	83
Cervix	69	67	73	69

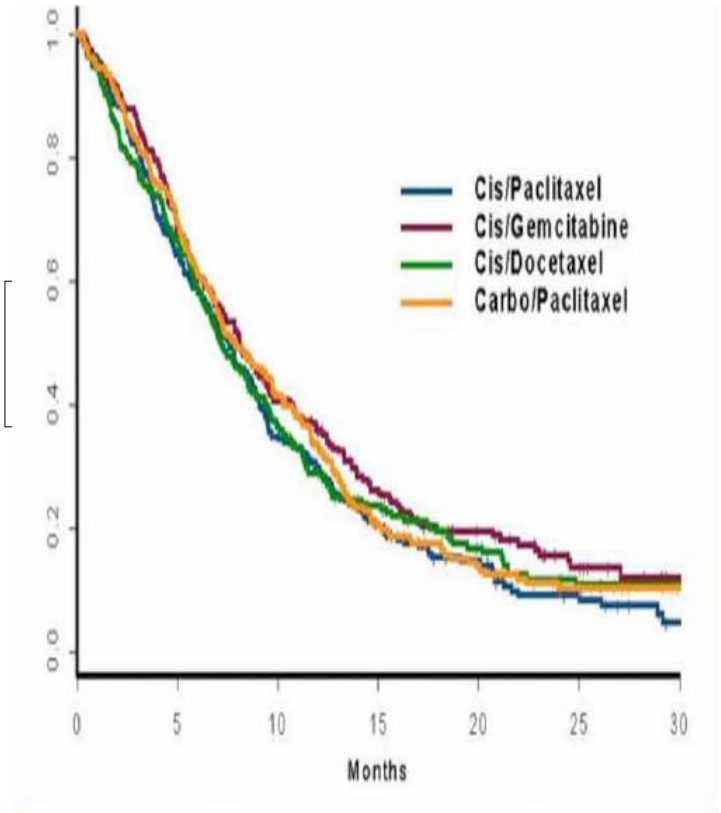
Source: Surveillance, Epidemiology, and End Results (SEER)1975-2012, National Cancer Institute.

Lung cancer survival rates



Blue – cases Red -5 year survival

A – Localized
B – Regional node metastasis or directly beyond primary site
C - Distant metastasis
D - Unknown stage
E - Overall



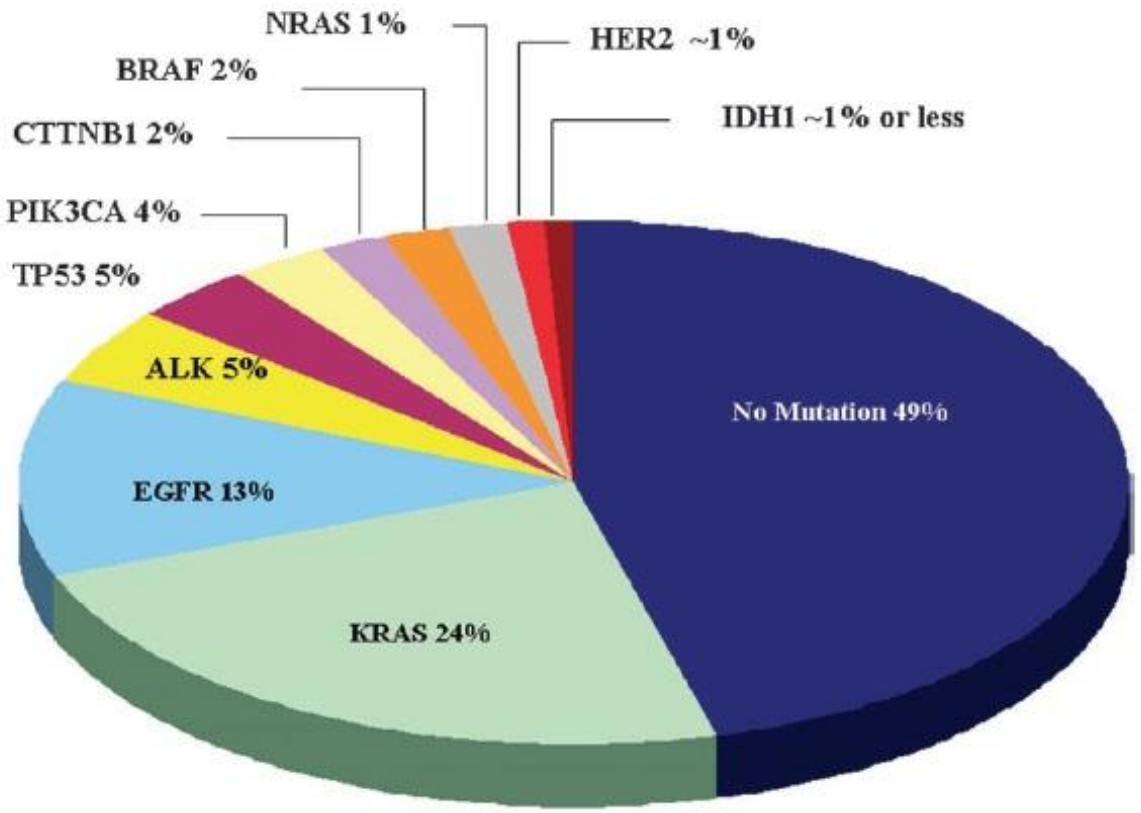
Median survival 8 months, 1 year survival 30 %

Schiller JH et al. NEJM Jan. 2002

What do we learn from the history?

- Surgical treatment is effective but has limitations
- Majority of the lung cancer cases with no surgical indications at the time of diagnosis
- Chemotherapy / radiation is palliative
- Solutions
  - Prevention
  - Early detection
  - New modalities

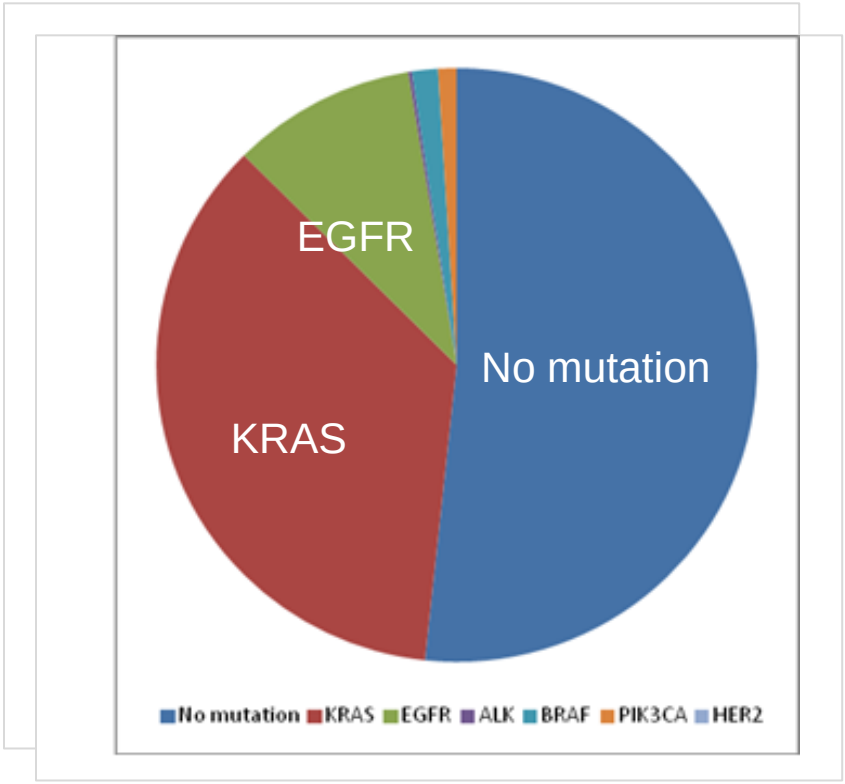
Relevant mutations in Non-small cell lung carcinoma



Sequist et al. 2011

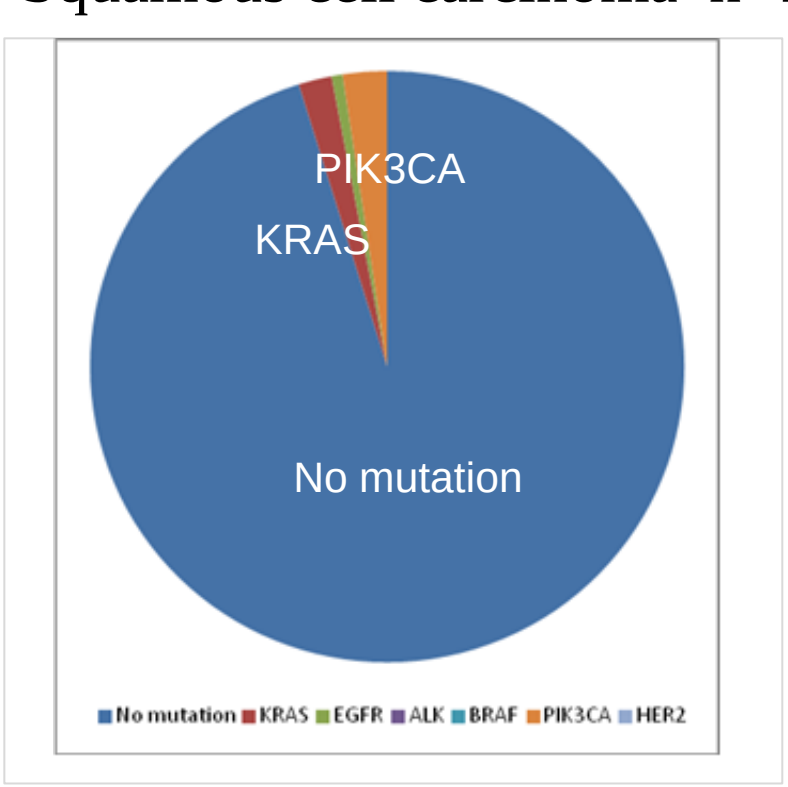
Mutations in cancer types

Adenocarcinoma n=438



EGFR 10%, KRAS 36%, BRAF 1%, PIK3CA 1%, ALK 0.2%, HER2 0% No mutation 52%

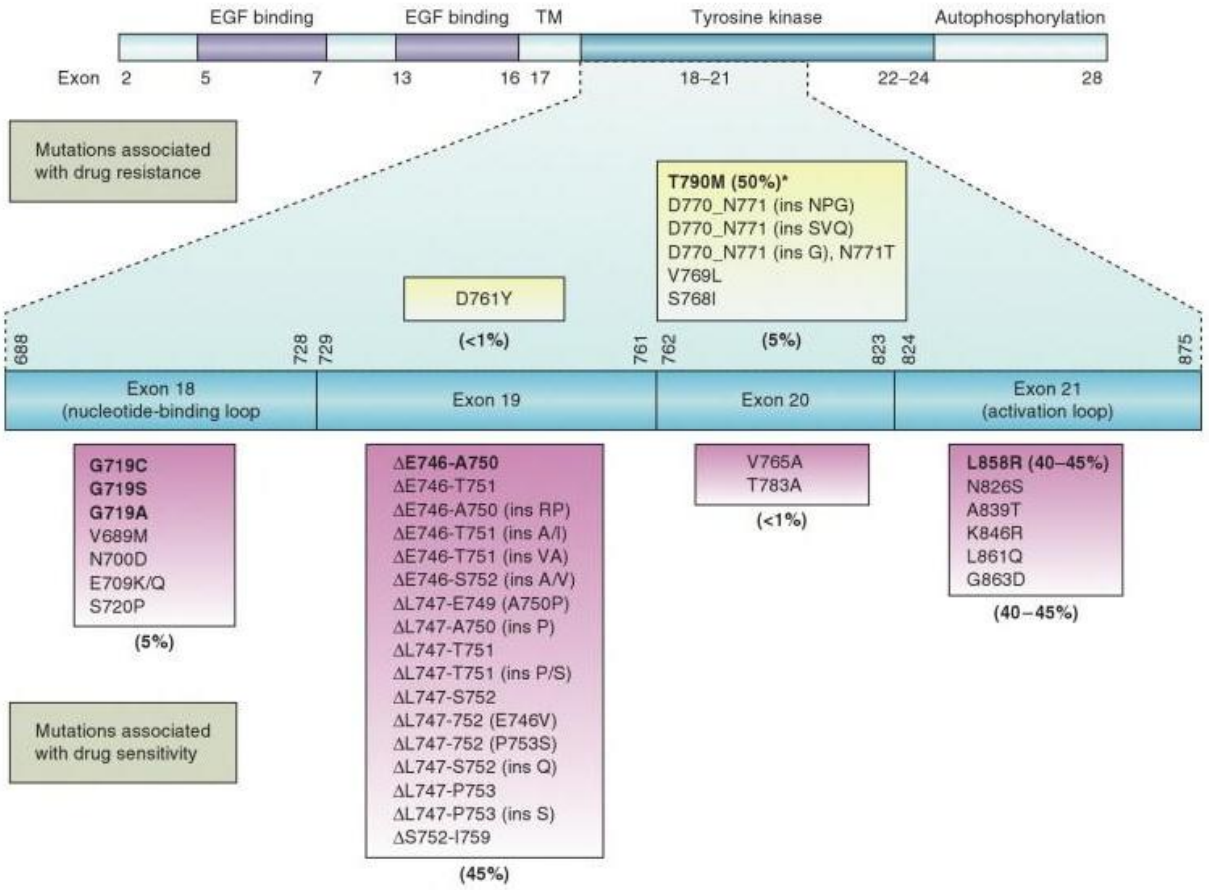
Squamous cell carcinoma n=166



EGFR 0.6%, KRAS 1.8%, BRAF 0%, PIK3CA 2.4%, ALK 0%, HER2 0% No mutation 95%

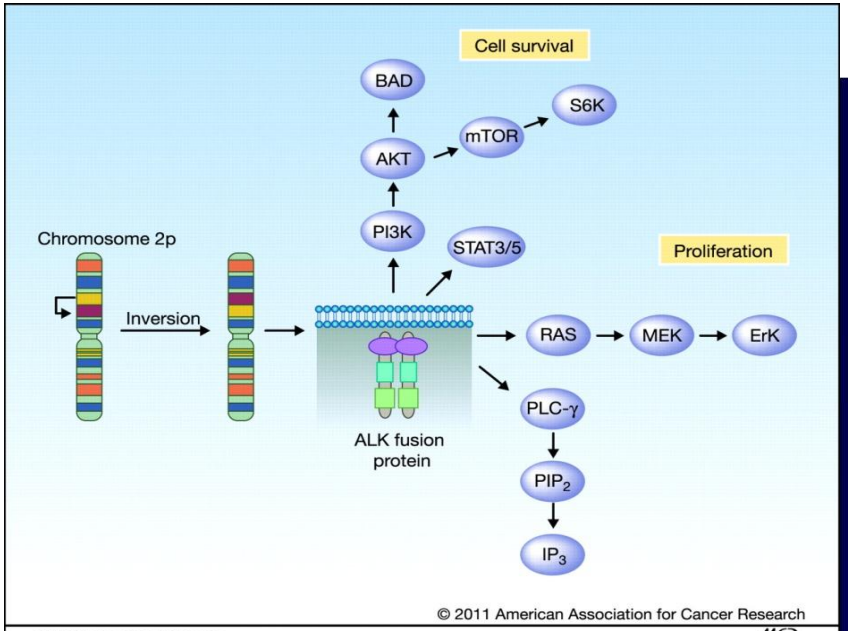
QEII HSC data unpublished

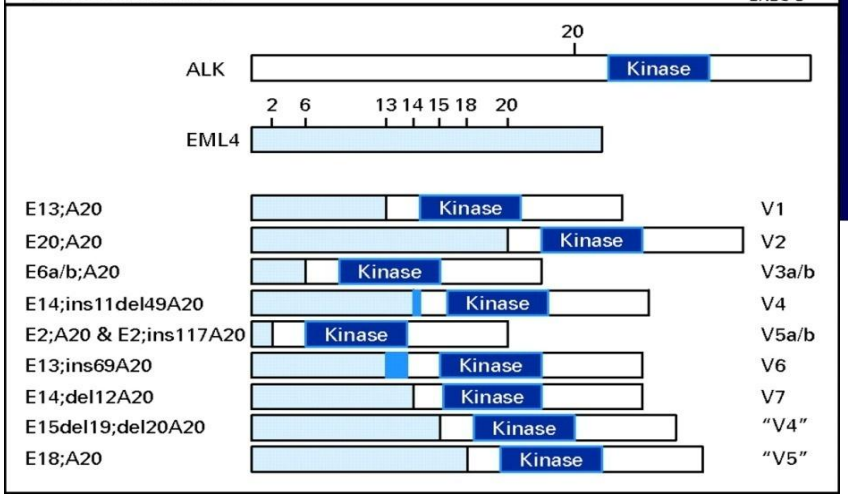
EGFR mutations



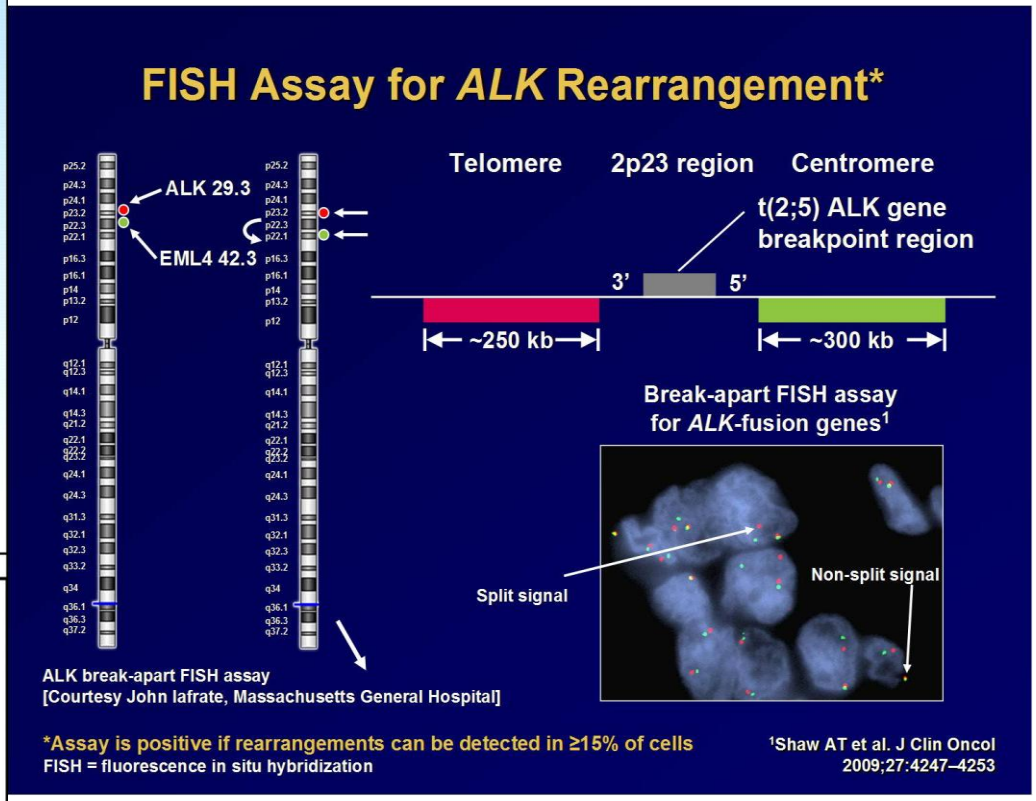
Sharma et al. 2007

EML4-ALK gene rearrangement





Horn L , Pao W JCO 2009;27:4232-4235



TKI Targeted therapy

- **EGFR mutations**
  - TKIs – gefitinib, erlotinib, afatinib, AZD9291, CO-1686
  - ORR 68%, DCR 86%, median PFS 12 m, OS 23.3 m
  - ↑PFS, quality of life, safety profile, convenience
  - EGFR exon 19 deletion in which afatinib vs chemotherapy median survival 31.7 : 20.7 m $p<0.0001$

- **ALK gene rearrangement**
  - ALK TKI – crizotinib, ceritinib, alectinib
  - In 1st line setting vs chemotherapy: ORR 74% vs 45%, PFS 10.9 vs 7.0 m, but no OS benefit
  - Phase 3 in 2nd line setting vs chemotherapy: ORR 65% vs 20%, PFS 7.7 vs 3.0 m but no OS benefit

Atlantic Molecular Profiling Network

- Role of central lab (Atlantic Canada Molecular Oncology Centre)
- Started lung cancer molecular tests since Sept. 2012
- Multiplexed genotyping
- Tests including EGFR, KRAS, BRAF, PIK3CA, Her2 and ALK
- Volume of molecular tests
  - About 2400 cases in total (2012-2015)
  - QE II 50%, all other centers 50%
  - >90 % are for adenocarcinoma
- Reflexive testing

Case distribution

	2012	2013	2014	2015	Total	
QE II HSC	53	311	492	361	1217	(49.7%)
Atlantic (-QEII)	43	410	400	381	1234	(50.3%)
Nova Scotia	*56*	*381*	*564*	*422*	*1423*	*(58.1%)*
NL	*4*	*130*	*133*	*158*	*425*	*(17.3%)*
NB	*36*	*191*	*165*	*135*	*527*	*(21.5%)*
PEI	*0*	*19*	*30*	*27*	*76*	*(3.1%)*
Total	96	721	892	742	2451	(100%)

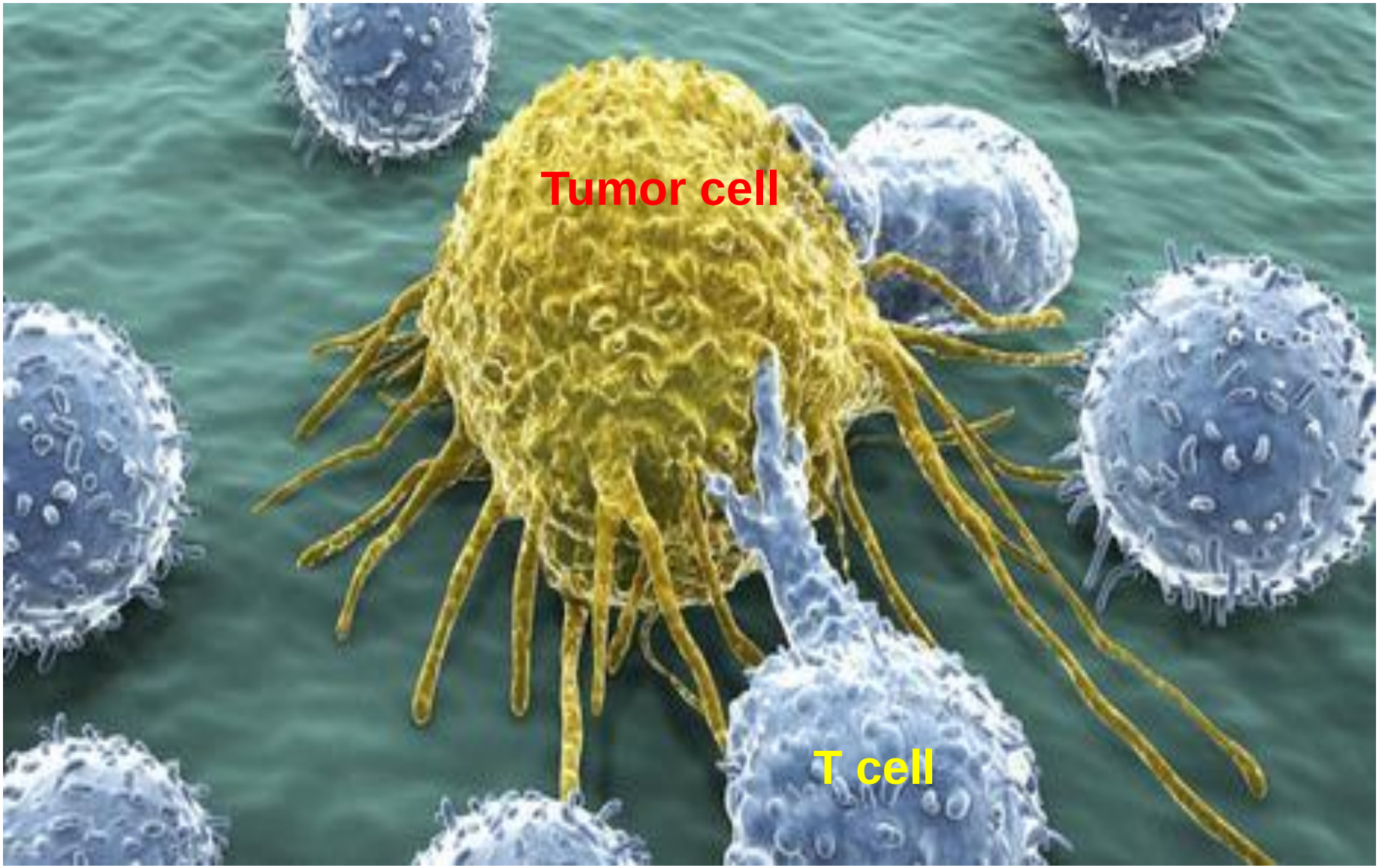
Consideration for lung cancer molecular profiling

- Testing all bronchogenic adenocarcinoma cases
- Testing squamous cell carcinoma if a non-smoker, young age, family history
- Neuroendocrine carcinoma almost always negative
- Multiplexed genotyping approach
- Next generation sequencing
- Reflexive testing
- Consent issue
- Sample requirement
- Turn around time (2-3 w)

Specimen requirement

- **Biopsy specimen**
  - **Formalin fixed paraffin embedded tissue**
  - **Tumor size ≥ 1mm², tumor cells ≥ 10% for molecular tests**
  - **Formalin fixation time 8-36 h**
- **Cytology specimen (FNA)**
  - **Formalin fixative**
  - **Cell block**
  - **Enough tumor cells available**
- **Tissue precessing / cutting**
  - **Routine histology preparation**
  - **Consideration for possible tests**
  - **Consecutive cutting at once if possible**

PD-L1/PD1 in immunotherapy



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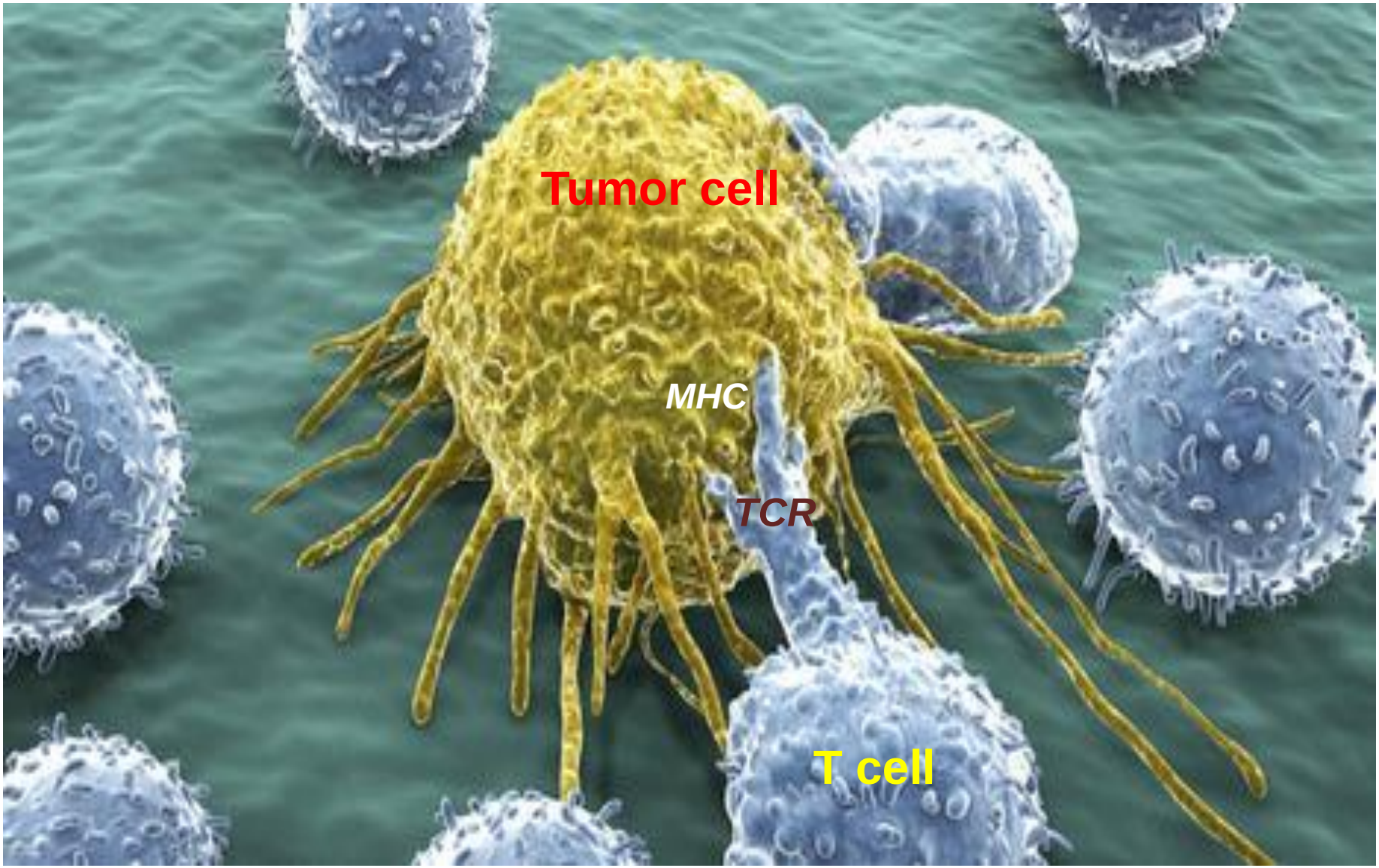

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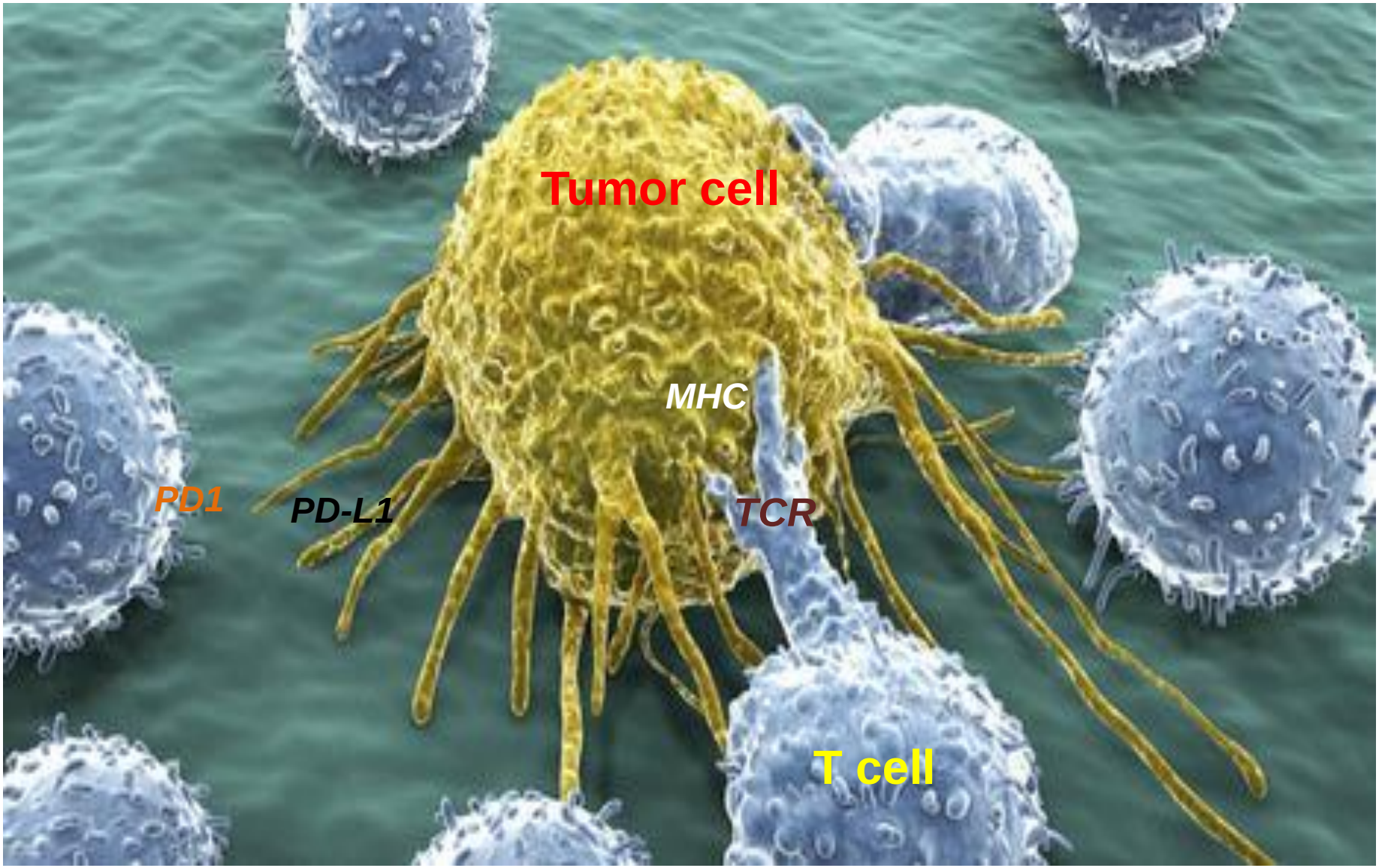

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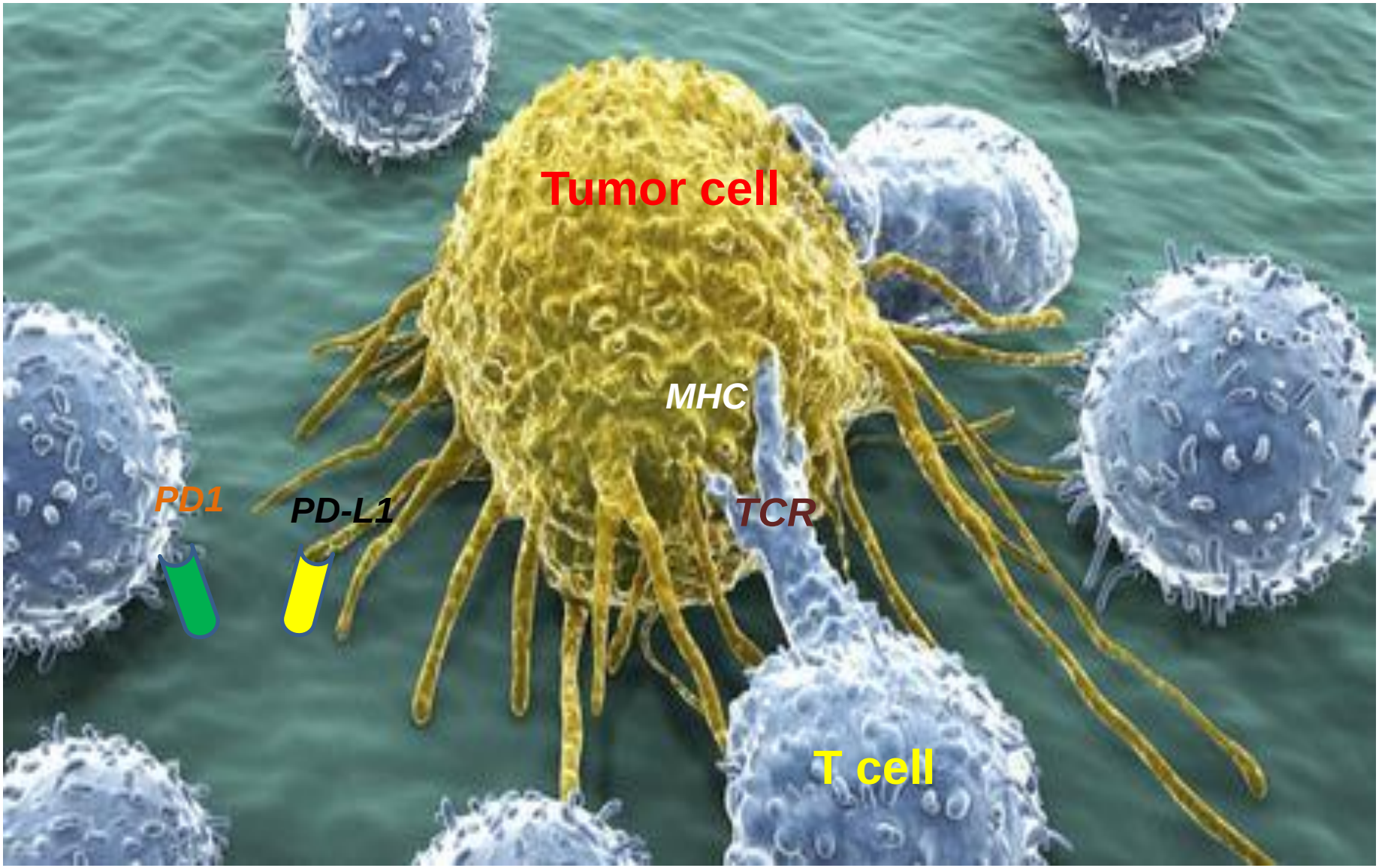

PD1/PD-L1 in immunotherapy

- PD1 expressed in cytotoxic T cells
- PD-L1 expressed in tumor cells
- PD1 bingding to PD-L1 inactivates cytotoxic T cells
- Blocking PD1/PD-L1 binding resumes T cell's cytotoxic function
- Either blocking PD1 or PD-L1 is effective in anticancer effect
- PD-L1 tests
  - Two diagnostic platforms
  - Five companion diagnostics

PD-L1 testing in clinical trials

	Nivolumab	Pembrolizumab	Atezolizumab	Avelumab	Durvalumab
Antibody	28-8	22C3	SP142	Not released	SP263
Platform	Dako	Dako	Ventana	Dako	Ventana
Pharma	BMS	Merck	Roche	Pfizer/Merck Group	AstraZeneca
Cells scored	Tumor cells	Tumor cells	Tumor and immune cells	Tumor and immune cells	Tumor cells
Detailed cut-off	≥ 1% ≥ 5% ≥ 10%	< 1% 1-49% ≥ 50%	TC3 (≥ 50%) or IC3 (≥ 1)%) TC2/3 (≥ 5%) or IC2/3 (≥ 5%) TC1-3 (≥ 1%) or IC1-3 (≥ 1%) TC0 (< 1%) and IC0 (< 1%)	TC (≥ 1%) TC (≥ 5%) TC (≥ 25%) IC (≥ 10%)	25%
Health Canada	NSCLC Melanoma	NSCLC Melanoma	No	No	No
FDA	NSCLC, Malanoma Advanced RCC	NSCLC Melanoma	"Breakthrough" for bladder and lung cancer	"Breakthrough" for Merkel cell carcinoma	"Breakthrough" for bladder cancer

Blueprint proposal

- FDA, AACR, ASCO convened a workshop titled “Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies”on March 24, 2015
- An industry work group volunteered to develop a blueprint proposal
- The goal: to agree and deliver a package of information /data upon which analytic comparison of the various diagnostic assays may be conducted, potentially paving the way for post-market standardization and/or practice guideline development as appropriate.
- Blueprint Working Group Members:
  - Steven Averbuch, VP, Bristol-Myers Squibb
  - Kenneth Emancipator, Executive Medical Director, Merck Research Laboratories
  - Ian McCaffery, Head, Companion Diagnostic Development, Genentech
  - Abigail McElhinny, VP, Ventana Medical Systems Inc.
  - Dave Stanforth, Director, Companion Diagnostics, Agilent Technologies
  - Jill Walker, Executive Director, Companion Diagnostic Development, AstraZeneca
  - Doug Ward VP & General Manager, Ventana Medical Systems Inc.

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Blueprint preliminary results

- **Compaired 4 assays: Dako 28-8 (BMS), 22C3 (Merck), and Ventana SP263 (AstraZeneca), Ventana SP124 (Roche)**
- **Approximately 39 tumor biopsy samples from patients with NSCLC were assessed.**
- **3 assays (Dako/BMS, Dako/Merck, and Ventana/AstraZeneca) had a high degree of concordance comparing each other.**
- **The results of this preliminary study should not alter current guidelines as indicated for each therapeutic-diagnostic validated combination pair.**

Consideration for PD-L1 testing

- Testing PD-L1 for non-small cell lung cancer cases
- Along with other molecular tests if possible
- Reflexive testing approach
- Using validated companion diagnostics
  - Antibody
  - Assay protocol
  - Assessment
- Turn around time 2-3 d

Prospective cancer diagnosis