Identification of predictive biomarker for pseudoprogression after immunotherapy

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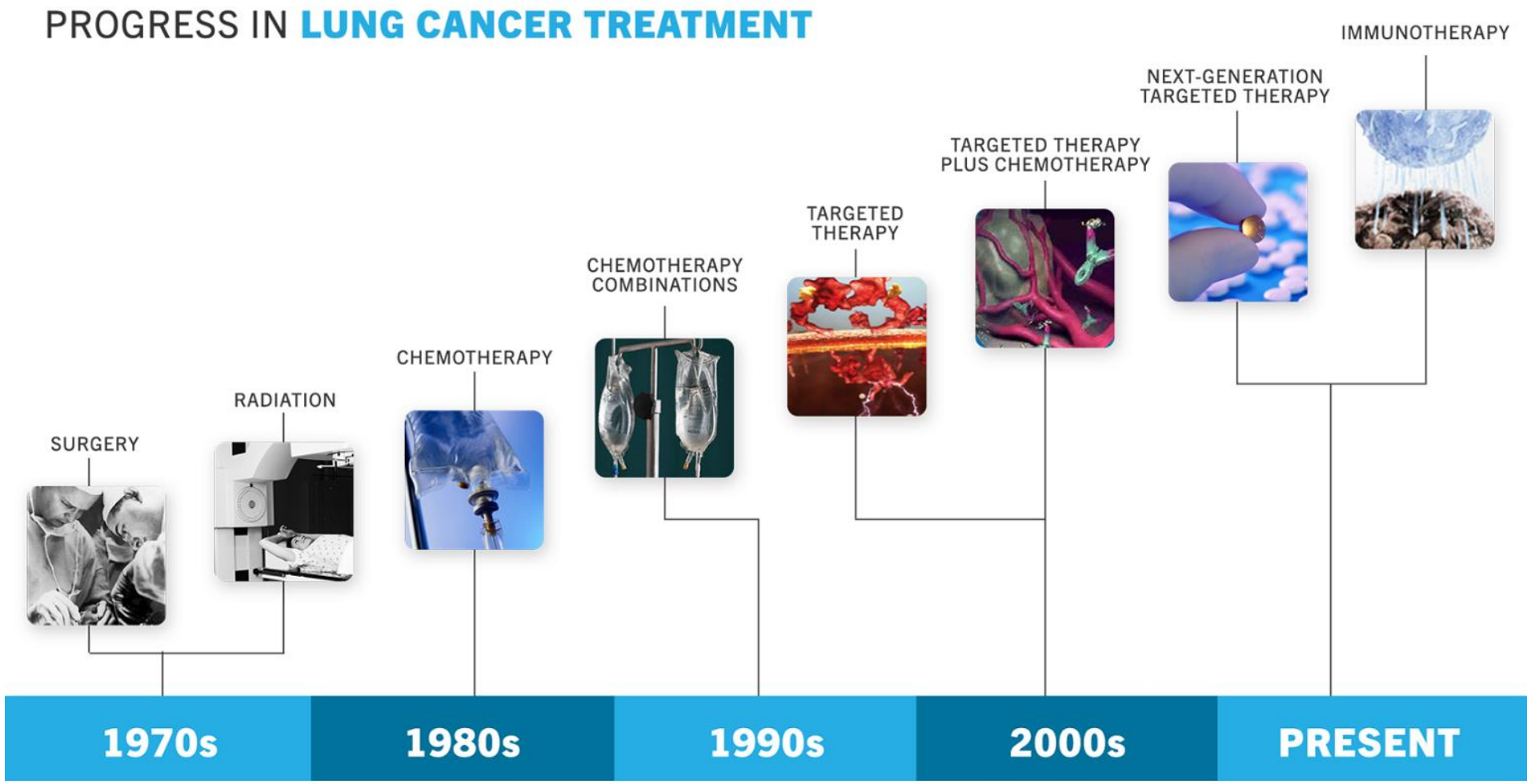
1. 연구의 배경

Lung Cancer Treatment Paradigm

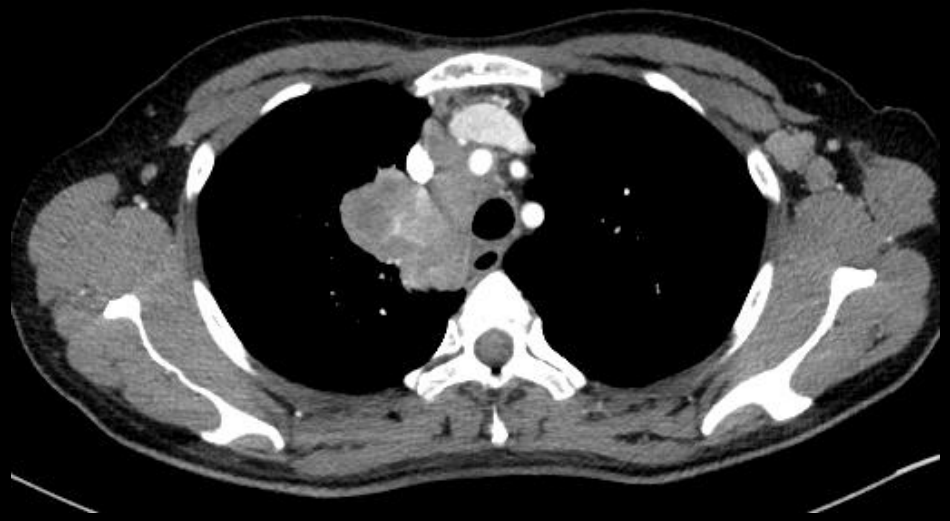


http://www.thelungcancerproject.org/

1. 연구의 배경

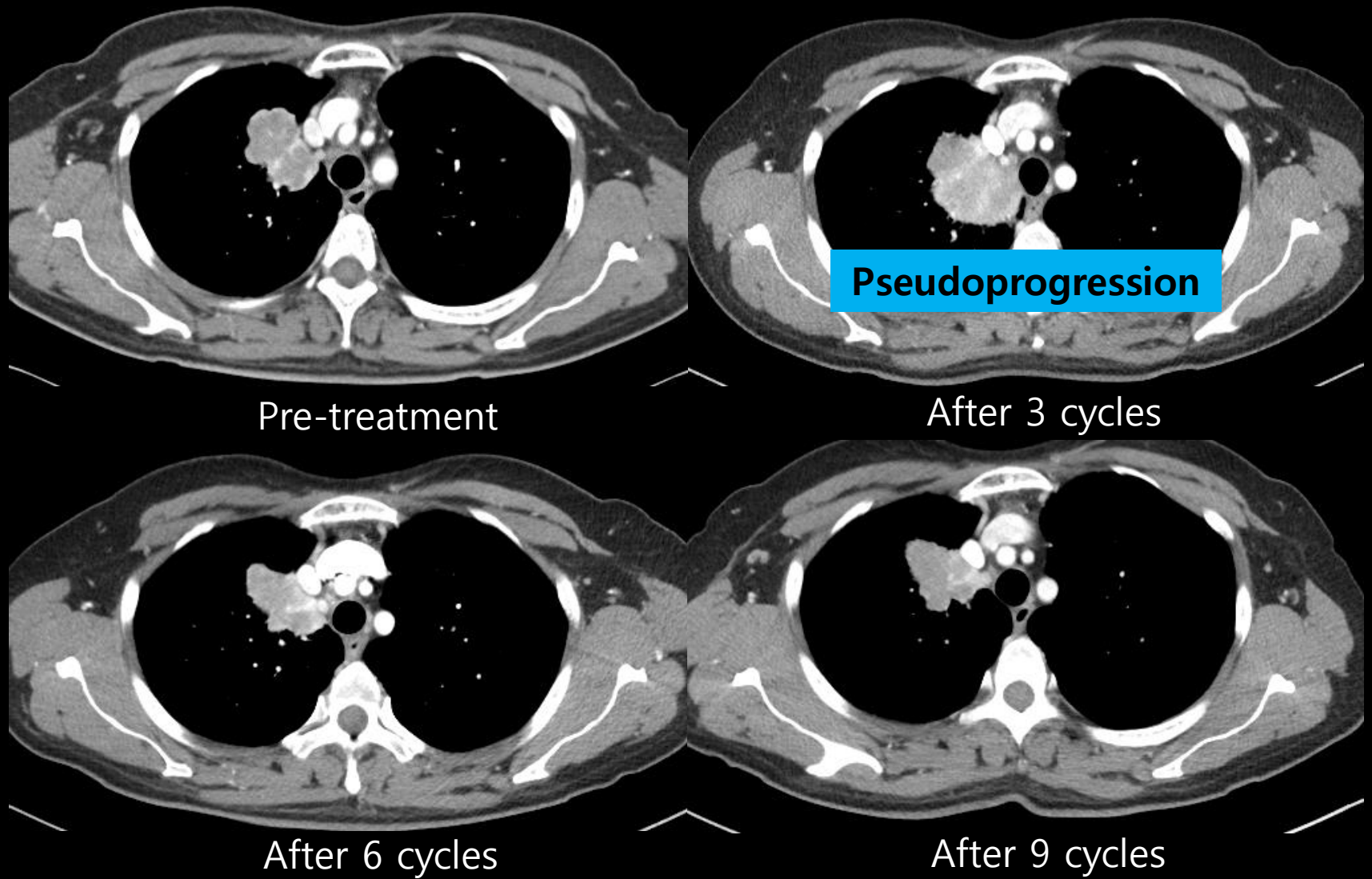
CNUH CASE #1

- 55/F, Past medical history (-)
- 2016.05) Lt. SCLN Bx : metastatic adenocarcinoma of lung origin, EGFR WT, ALK (-), Stage IV (bone)
- 2016.05-2017.02) #1-4. cis+alimta, alimta maintenance (#1-9) → PD



1. 연구의 배경

CNUH CASE #1



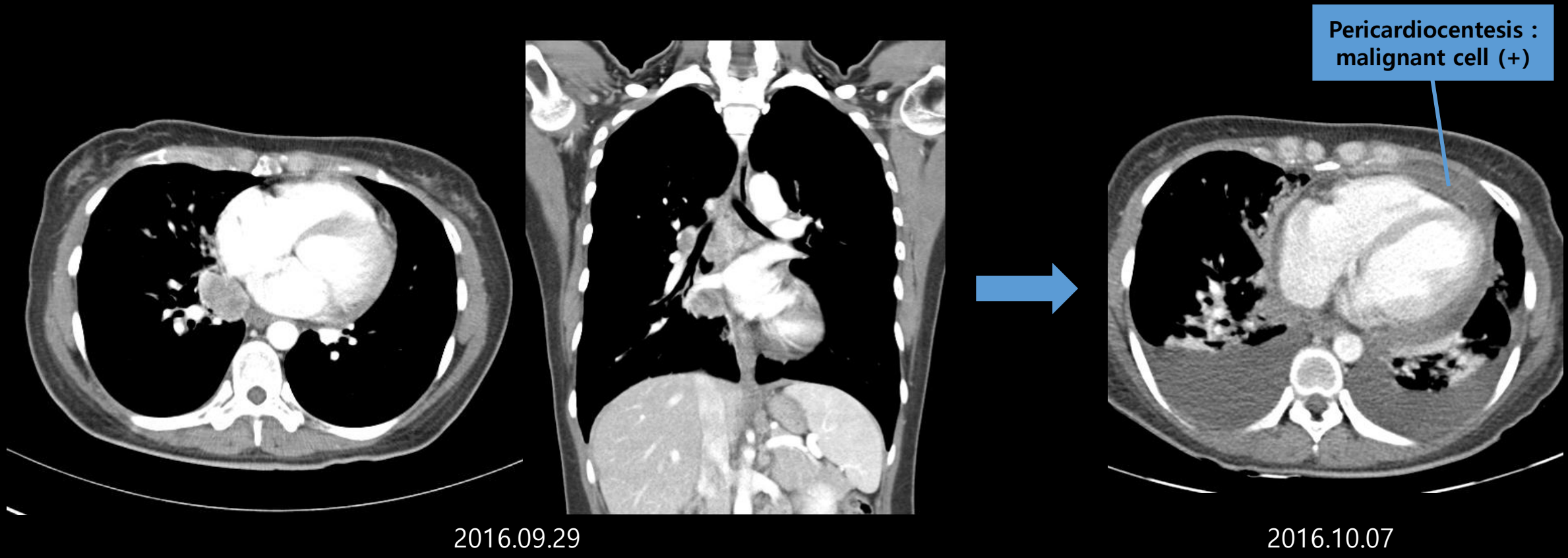
- 55/F, adenocarcinoma, stage IV
- high PD-L1 expression (TPS≥50%)
- 2nd line, pembrolizumab

- Ongoing 14 cycles

1. 연구의 배경

CNUH CASE #2

- 34/F, Past medical history (-)
- 2016.10) EBUS Bx : adenocarcinoma, EGFR WT, ALK (-), Stage IV (pericardial effusion)
- 2016.10~2017.04) #1-4. cis+alimta, alimta maintenance (#1-3) → PD



1. 연구의 배경

CNUH CASE #2

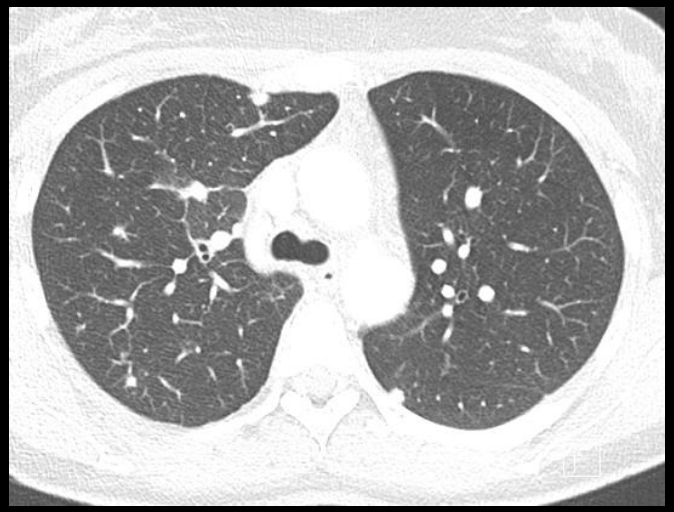
Pericardiostomy
- Cytology : malignant cell (-)
- Biopsy : acute and chronic inflammation without tumor

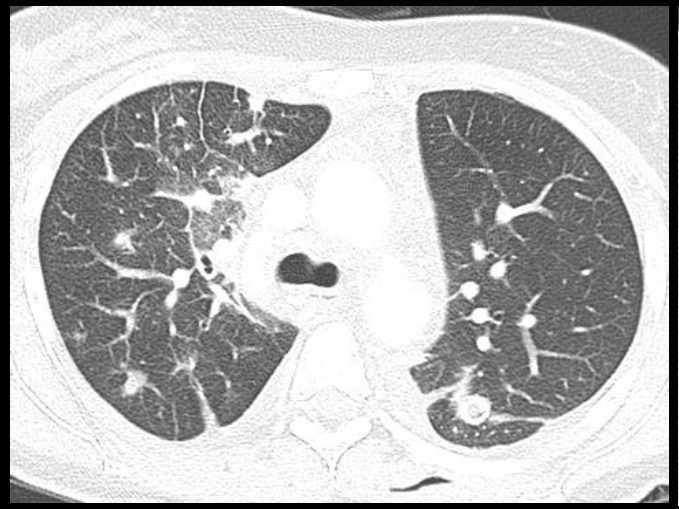
Pre-treatment

Pseudoprogression

After 2 months

- 34/F, adenoca, stage IV
- high PD-L1 expression (TPS≥50%)
- 2nd line, pembrolizumab





- Death after 3 months

1. 연구의 배경

1. 연구의 배경

Pseudoprogression with Immunotherapy

- Transient increase in the size of existing tumor lesions or the appearance of new lesions from treatment effect rather than true disease progression

- ≥25% increase of the tumor burden or a new lesion

  - Early pseudoprogression : at 12 weeks, first imaging assessment
  - Delayed pseudoprogression : after the first imaging assessment

Journal of Clinical Oncology 33.31 (2015): 3541-3543.

1. 연구의 배경

Pseudoprogression with Immunotherapy

- Incidence
  - 8.9% in patients with melanoma treated with ipilimumab
    (early pseudoprogression 4.6%, delayed pseudoprogression 4.3%)
  - 7% in patients with melanoma treated with pembrolizumab
    (early pseudoprogression 4.6%, delayed pseudoprogression 2.8%)

- Pathophysiology

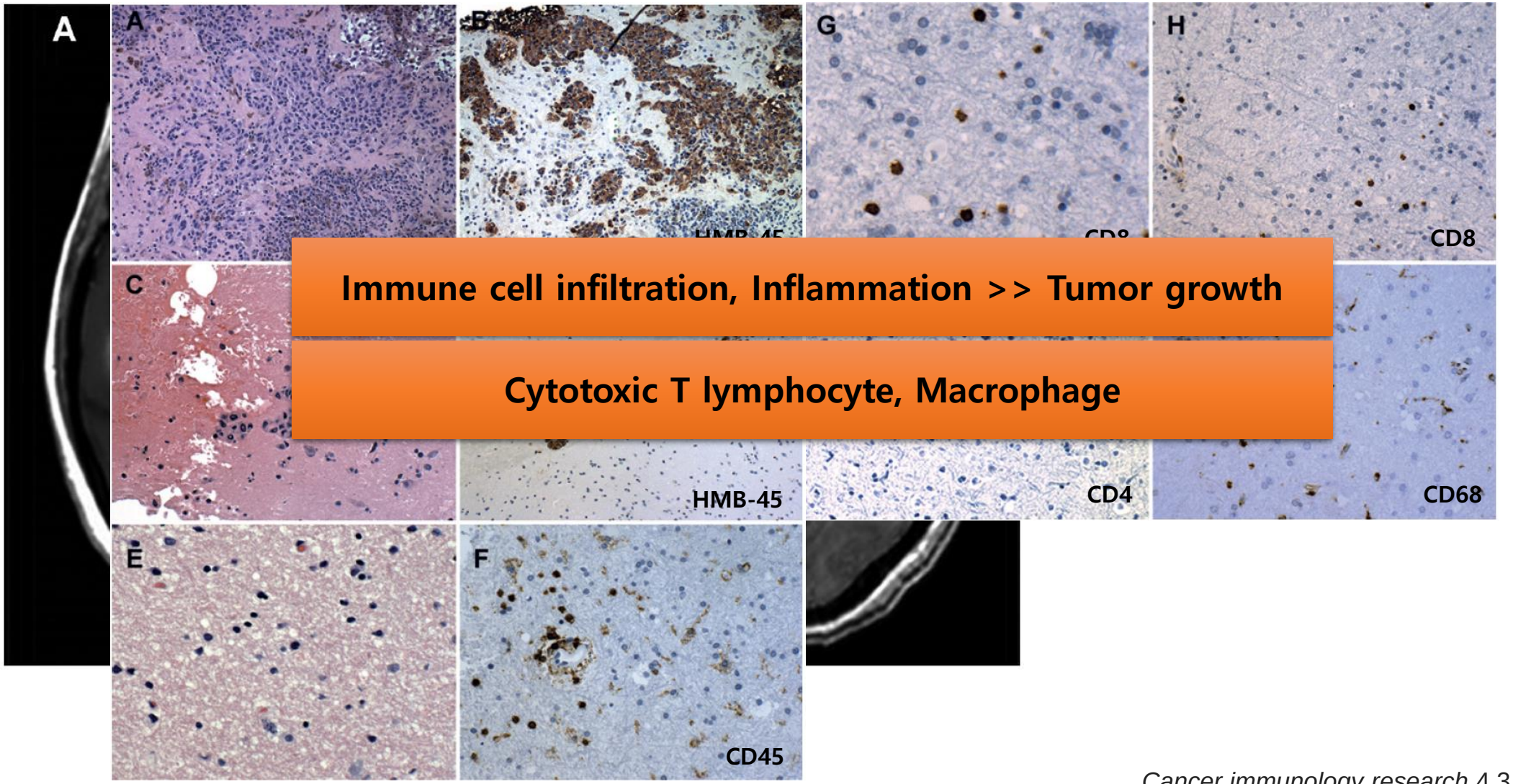
  1) Transient immune cell infiltration with or without edema

  2) Late effective immune response
     (Continuing tumor growth until development of a sufficient immune response)

Journal of Clinical Oncology 33.31 (2015): 3541-3543.

1. 연구의 배경

Melanoma Brain Metastasis Pseudoprogression



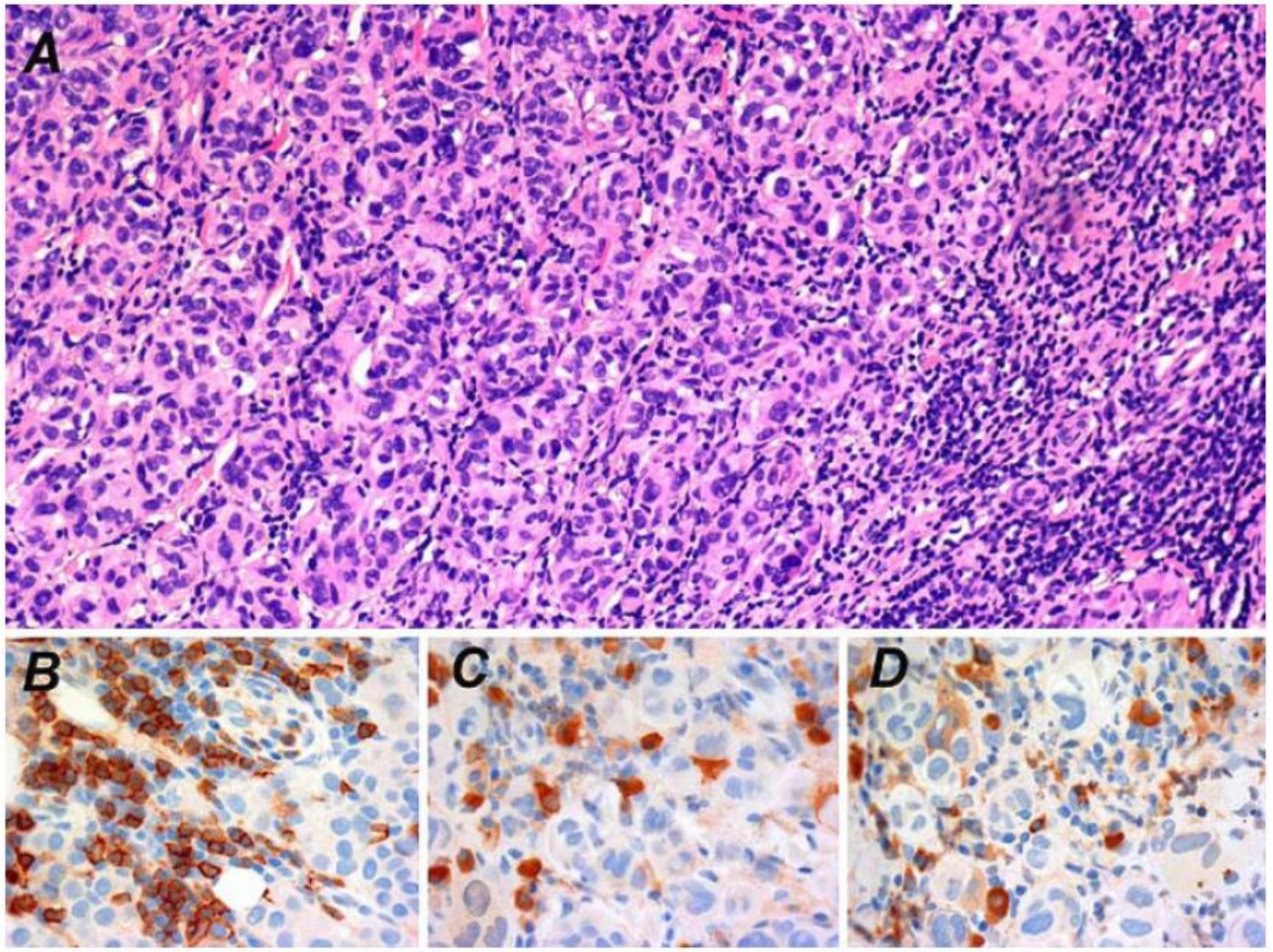
Immune cell infiltration, Inflammation >> Tumor growth

Cytotoxic T lymphocyte, Macrophage

Cancer immunology research 4.3 (2016): 179-182

1. 연구의 배경

Melanoma Cutaneous Lesion Pseudoprogression



(A) Melanoma-cell nest with abundant mononuclear cell infiltrate

(B) Activated cytotoxic lymphocytes (CD8)

(C) TIA-1 (apoptosis promoting protein)

(D) Granzyme B

Cancer immunology, immunotherapy 58.8 (2009): 1297-1306.

1. 연구의 배경

Pseudoprogression with Immunotherapy

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Pseudoprogression in cancer immunotherapy: Rates, time course and patient outcomes.

- Cohort, retrospective study
- Phase I and II trials from March 2008 to July 2015
  (214 melanoma, 103 NSCLC, 6 SCLC, 33 Others)
- Pseudoprogression : progression from nadir followed by response from peak

	RECIST	irRC
Incidence (%)	7/356 (2%)	21/356 (6%)
Mean days (range)		
Baseline to progression	74	88
Baseline to response	169	187
Interventing time	94	99

1. 연구의 배경

Pseudoprogression with Immunotherapy in Lung Cancer

- **Non-conventional benefit criteria** (CheckMate 017 & 057)

  - Patients who had not experienced PR or CR prior to initial progression (RECIST v1.1)

  1) new lesion followed by decrease from baseline of at least 10% in sum of target lesions
  2) initial increase ≥20% in sum of target lesions followed by reduction from baseline of at least 30%
  3) initial increase ≥20% in sum of target lesions followed by at least 2 tumor assessments showing no further progression

	Patients Treated After Initial RECIST v1.1-defined Progression	Non-conventional benefit criteria
CheckMate 017	20.7% (28/135)	6.7% (9/135)
CheckMate 057	24.3% (71/292)	5.5% (16/292)

1. 연구의 배경

Pseudoprogression with Immunotherapy in Lung Cancer

Reports	Year	Journal	Case	Clinical course
Immunotherapy and pseudoprogression in lung adenocarcinoma	2017	Canadian journal of respiratory, critical care, and sleep medicine	59/F, Adeno, PD-L1 (-) Nivolumab, 2nd line	After 5 cycles : PD
Report of two cases of pseudoprogression in patients with NSCLC treated with nivolumab	2016	Lung cancer	64/M, Adeno Nivolumab, 2nd line	
			75/F, Adeno Nivolumab, 7th line	
Subcutaneous pseudoprogression in lung squamous cell carcinoma treated with nivolumab	2017	Clinical case report	68/F, Squamous NSCLC Nivolumab, 3rd line	
Symptomatic pseudoprogression followed by significant treatment response in two lung cancer patients with immunotherapy	2017	Lung cancer	63/M, Adeno, high PD-L1 Pembrolizumab, 2nd line	
			63/F, Adeno Pembrolizumab, 2nd line	After 2 months : lung lesions resolved

1. 연구의 배경

Pseudoprogression with Immunotherapy in Lung Cancer

- Tumor size increase or new tumor lesion

  → Pseudoprogression vs. True disease progression ?

Contents

2. 연구의 목표 및 내용

Purpose of Study

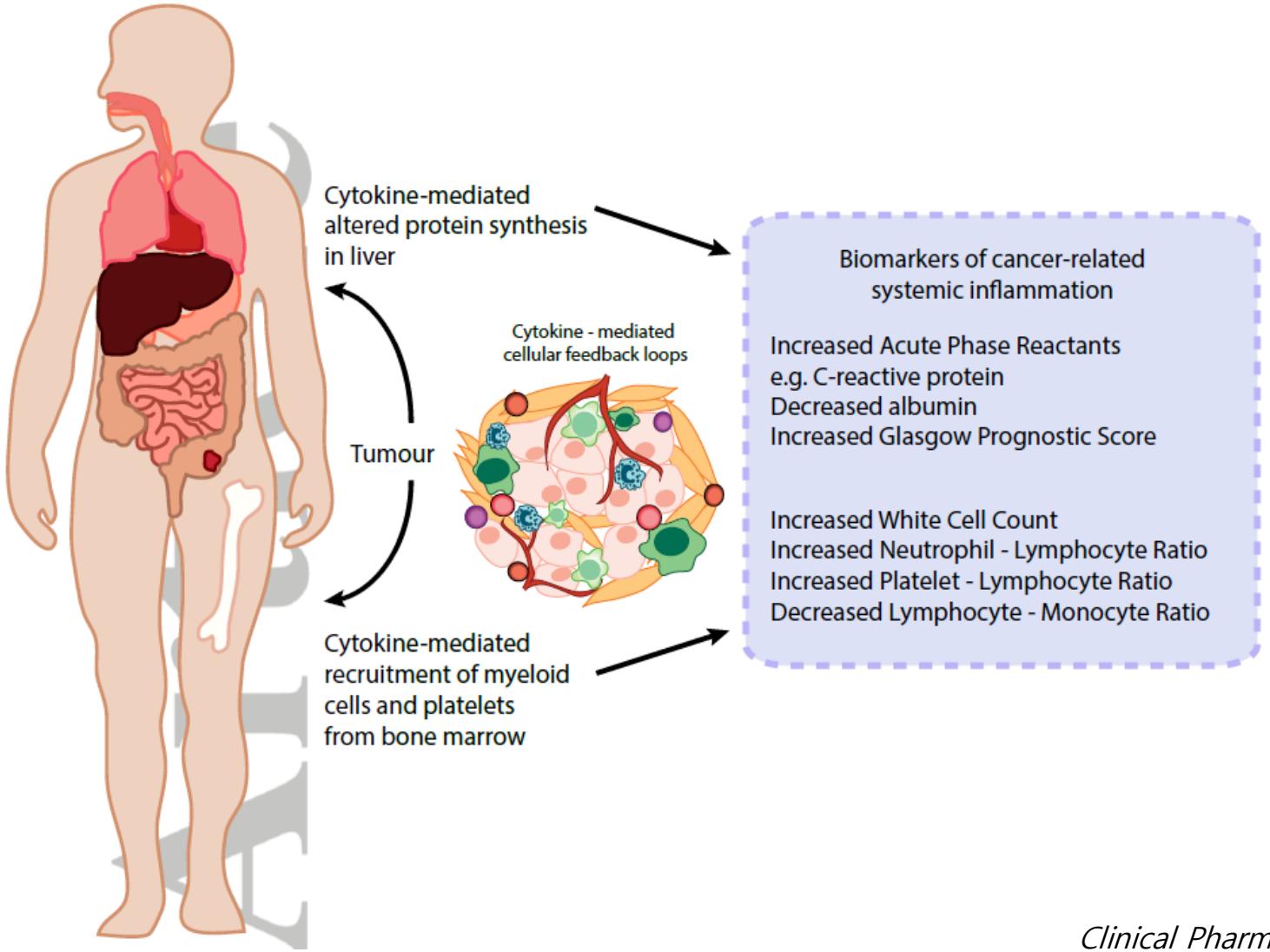
- **Predictive biomarker for pseudoprogression after immunotherapy**

  1) Peripheral blood biomarker

  2) Imaging modality

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

Relationship between tumor and host cells



Clinical Pharmacology & Therapeutics (2017).

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

Available blood markers predictive of ICI outcomes

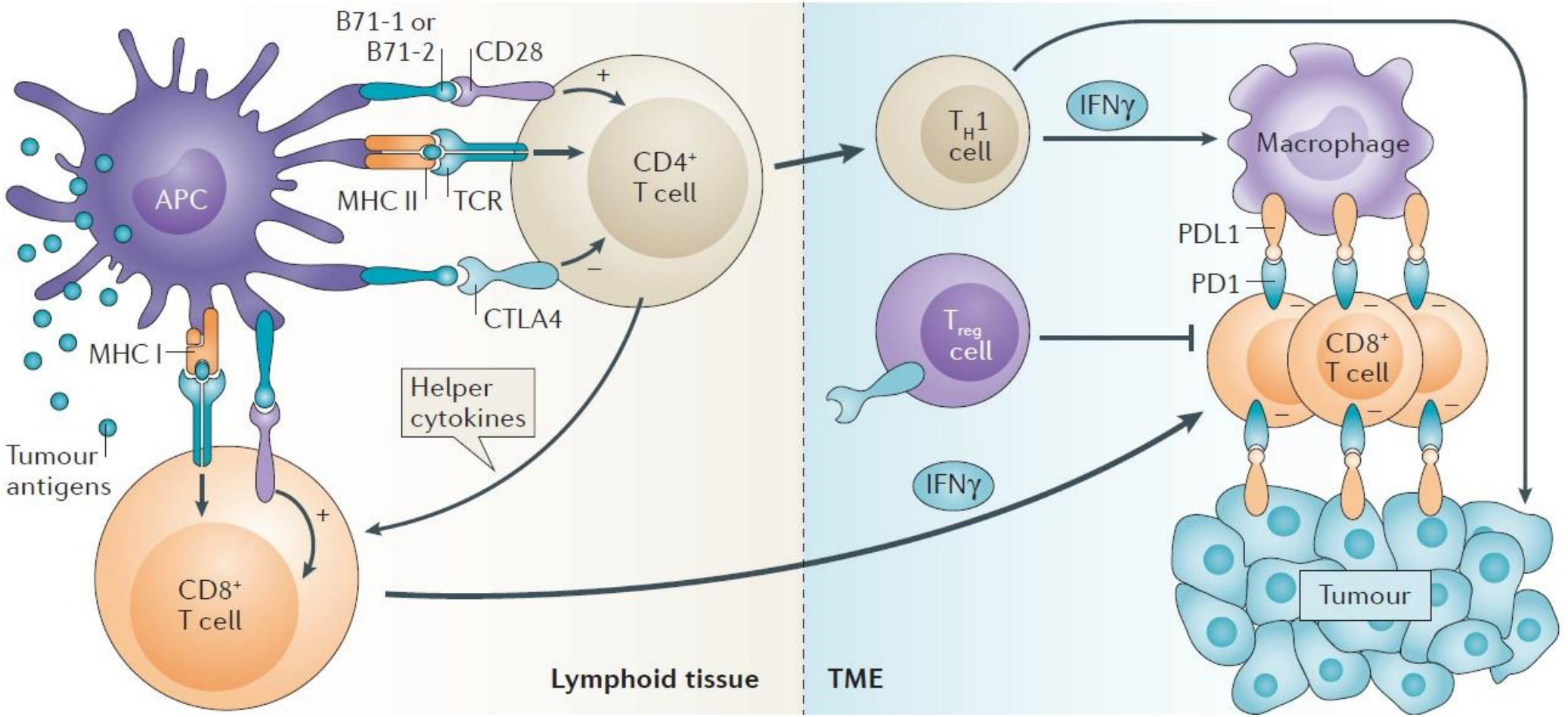
Marker	ICI therapy	Cancer	Study results
Lymphocyte count	Ipilimumab, Pembrolizumab	Melanoma	≥1000/㎕ at week 3-6 → ↑ OS ↑ At week 12 vs baseline → ↑ OS
Relative lymphocyte count	Ipilimumab, Pembrolizumab	Melanoma	↑ Baseline → ↑ OS
Total leukocyte count	Ipilimumab	Melanoma	↓ Baseline → ↑ response
Eosinophil count	Ipilimumab	Melanoma	↑ At week 3 vs baseline → ↑ response ↑ At week 6 vs baseline → ↑ OS
Relative eosinophil count			OS
Neutrophil count			OS, PFS, response ek 3-6 → ↑ OS
Neutrophil/lymphocyte ratio	Ipilimumab	Melanoma	↓ Baseline → ↑ OS, PFS
	Nivolumab	NSCLC	↓ Baseline → ↑ OS
Derived neutrophil/lymphocyte ratio	Ipilimumab	Melanoma	↓ Baseline → ↑ OS, PFS
Monocyte count	Ipilimumab	Melanoma	↓ Baseline → ↑ OS
LDH	Ipilimumab, Nivolumab, Pembrolizumab	Melanoma	↓ Baseline → ↑ OS ↑ At week 12 vs baseline → ↓ response, OS ↓ At week 12 → ↑ response, OS
CRP	Ipilimumab	Melanoma	↓ At week 12 → ↑ response, OS

Outcome ≠ Pseudoprogression

British journal of cancer 117.7 (2017): 913.

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

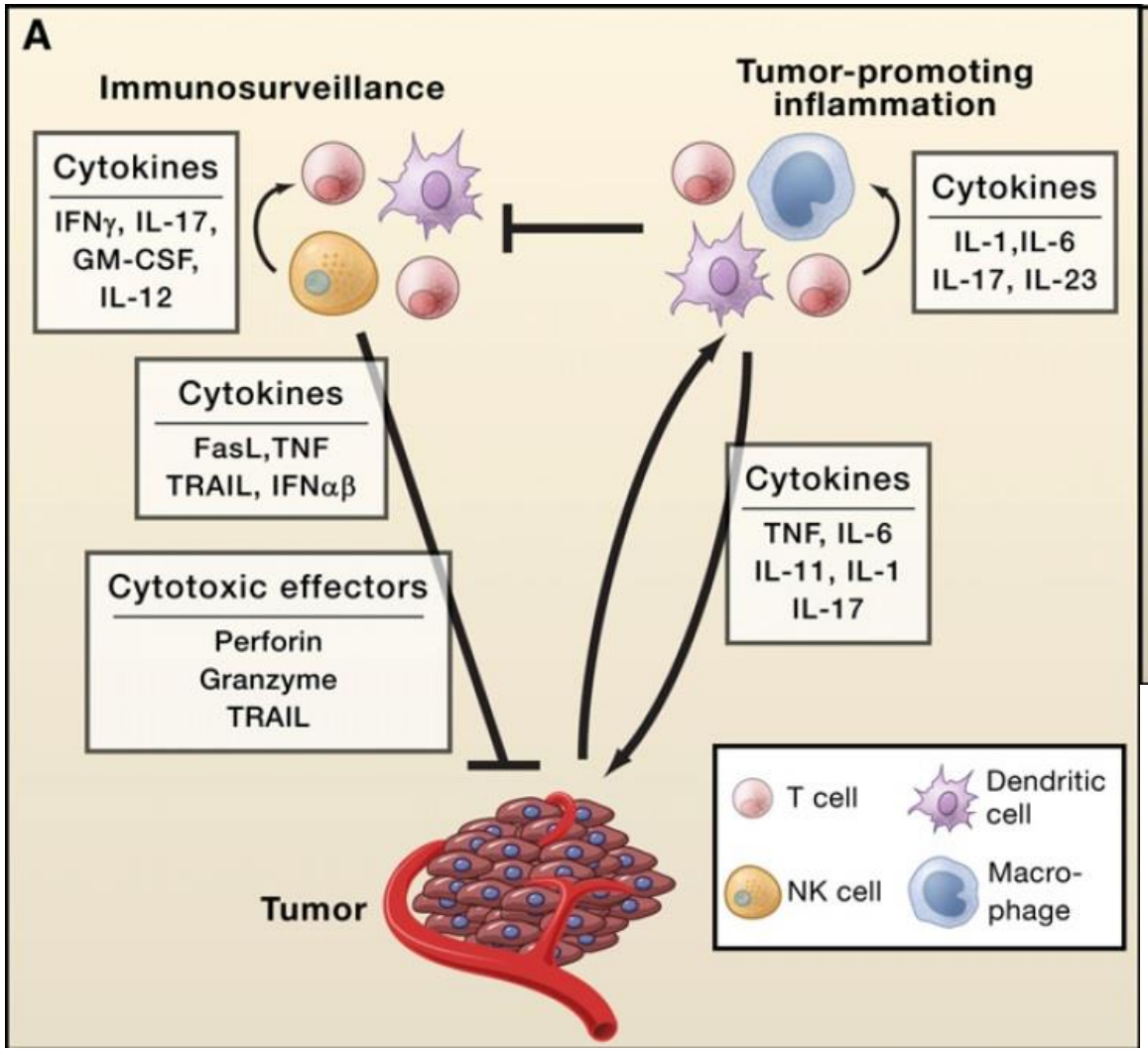
Immune checkpoint pathway

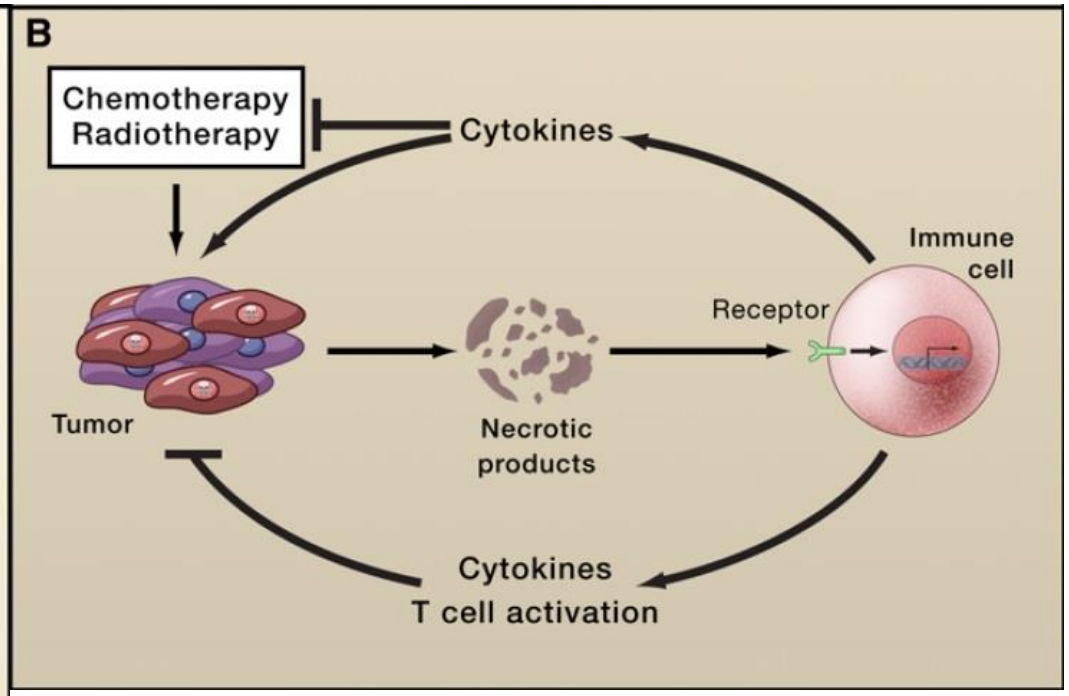


Nature Reviews Cancer 16.5 (2016): 275.

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

Tumor microenvironment



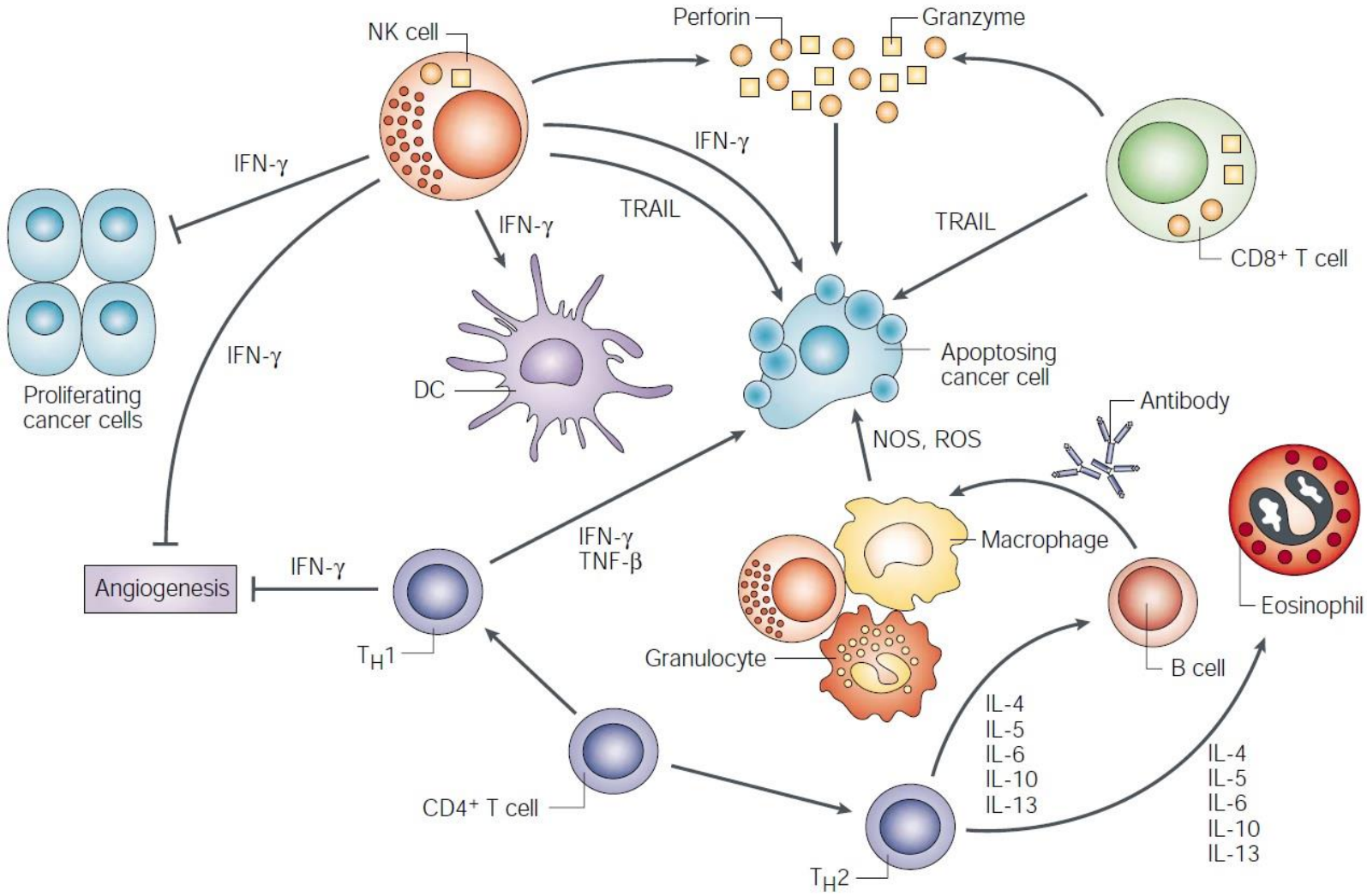


Therapy-Induced Inflammation

Cell 140.6 (2010): 883-899.

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

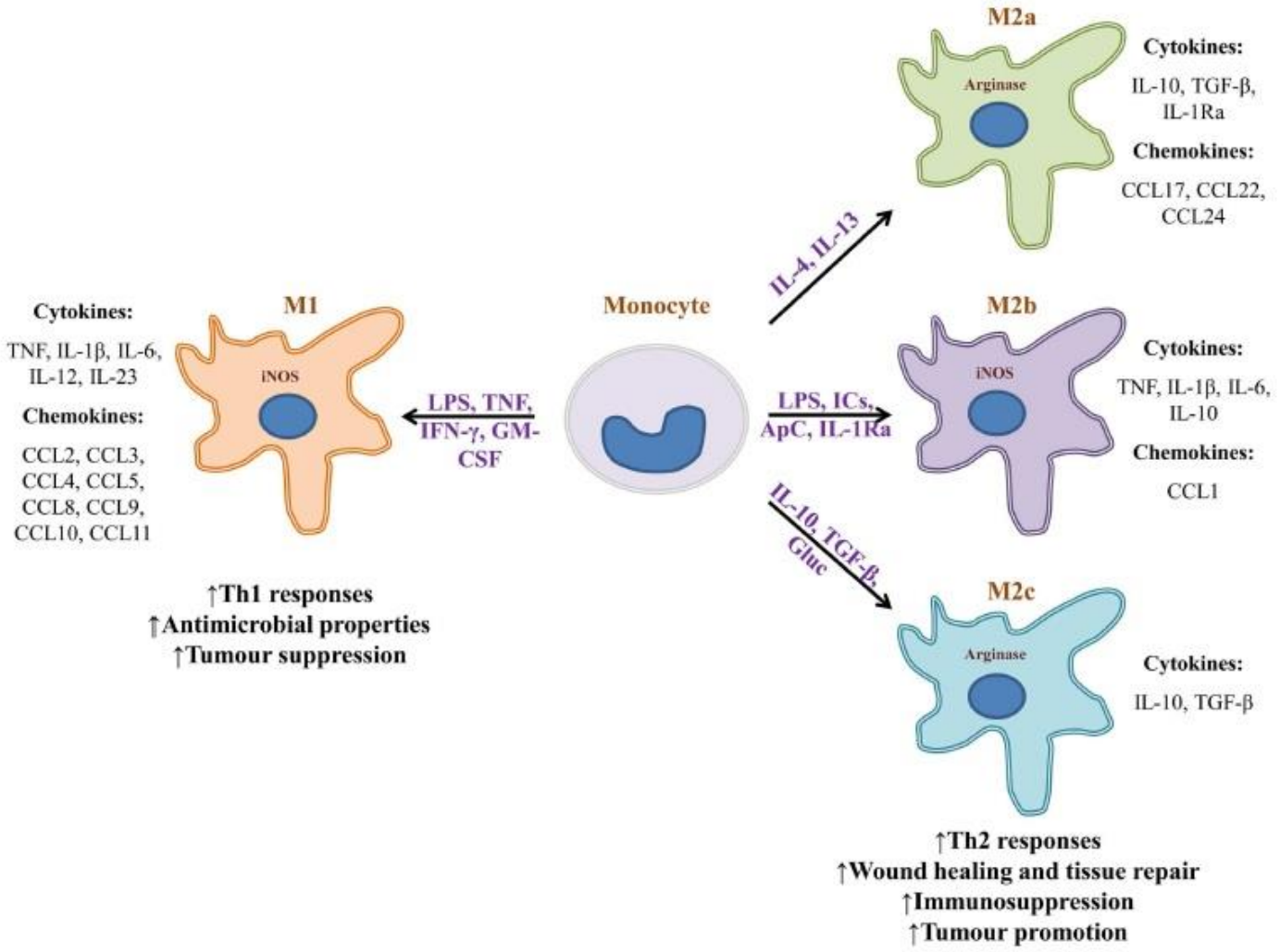
Cytokines in tumor destruction



Nature Reviews Cancer 4.1 (2004): 11.

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

Macrophage cytokines



Frontiers in immunology 5 (2014): 491.

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

Emerging blood-based biomarkers of ICI response, prognosis, and toxicity

Candidate biomarker	Assay	ICI therapy	Cancer	Study results
Eosinophil count	Absolute eosinophil count	Ipilimumab or pembrolizumab	Melanoma	↑ AEC → ↑ Survival REC<1.5 → ↑ Death
		Atezolizumab, pembrolizumab, or nivolumab	Lung cancer	Baseline eosinophil : toxicity
Neutrophils and lymphocytes	ALC, ANC, or NLR	Ipilimumab	Melanoma	Baseline ALC, ANC : prognostic value
		Nivolimab	Lung cancer	NLR >3 : progression, death
Peripheral blood cytokines	Plasma IL-6, cytoscore	Nivolumab	Lung cancer	↑ IL-6 : Inflammatory tumor microenvironment ↓ Cytoscore → ↓ Survival
Peripheral T cells	FOXP3+ Tregs, CD4 & CD8 T cells	Ipilimumab	Melanoma	↑ Treg (baseline, after Tx) : ↓ Survival ↑ CD4, CD8 T cell after Tx : ↑ Survival

Annals of translational medicine 5.18 (2017).

2. 연구의 목표 및 내용 - 1) Peripheral blood biomarker

Key Points

Pseudoprogression

Immune cell infiltration, Inflammation >> Tumor growth

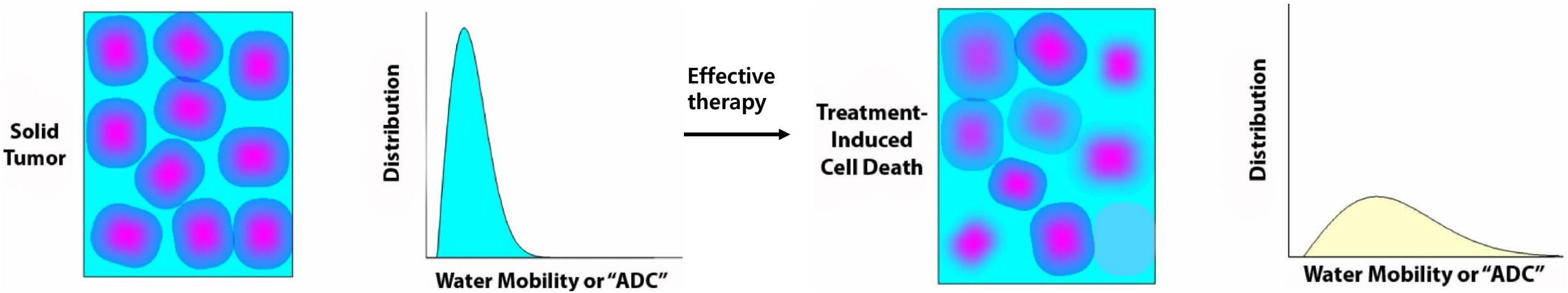
Cytotoxic T lymphocyte, Macrophage

(Circulating) Immune cells, Inflammatory cytokines

2. 연구의 목표 및 내용 - 2) Imaging Modality

Diffusion-weighted MRI

- Increase in ADC following therapy

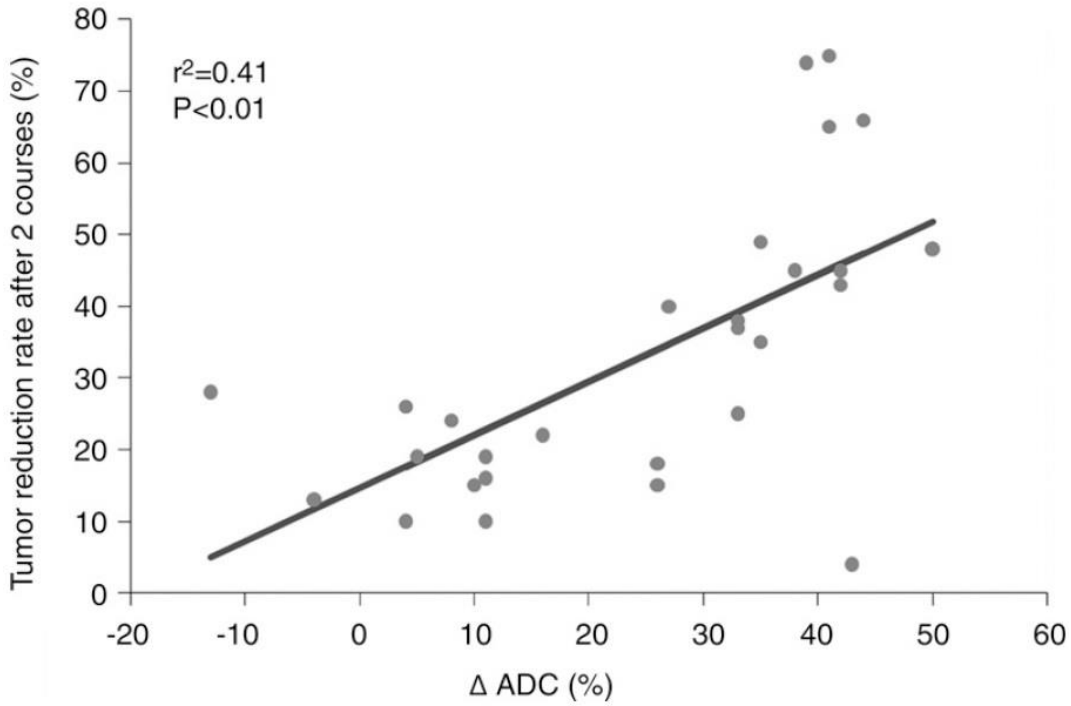


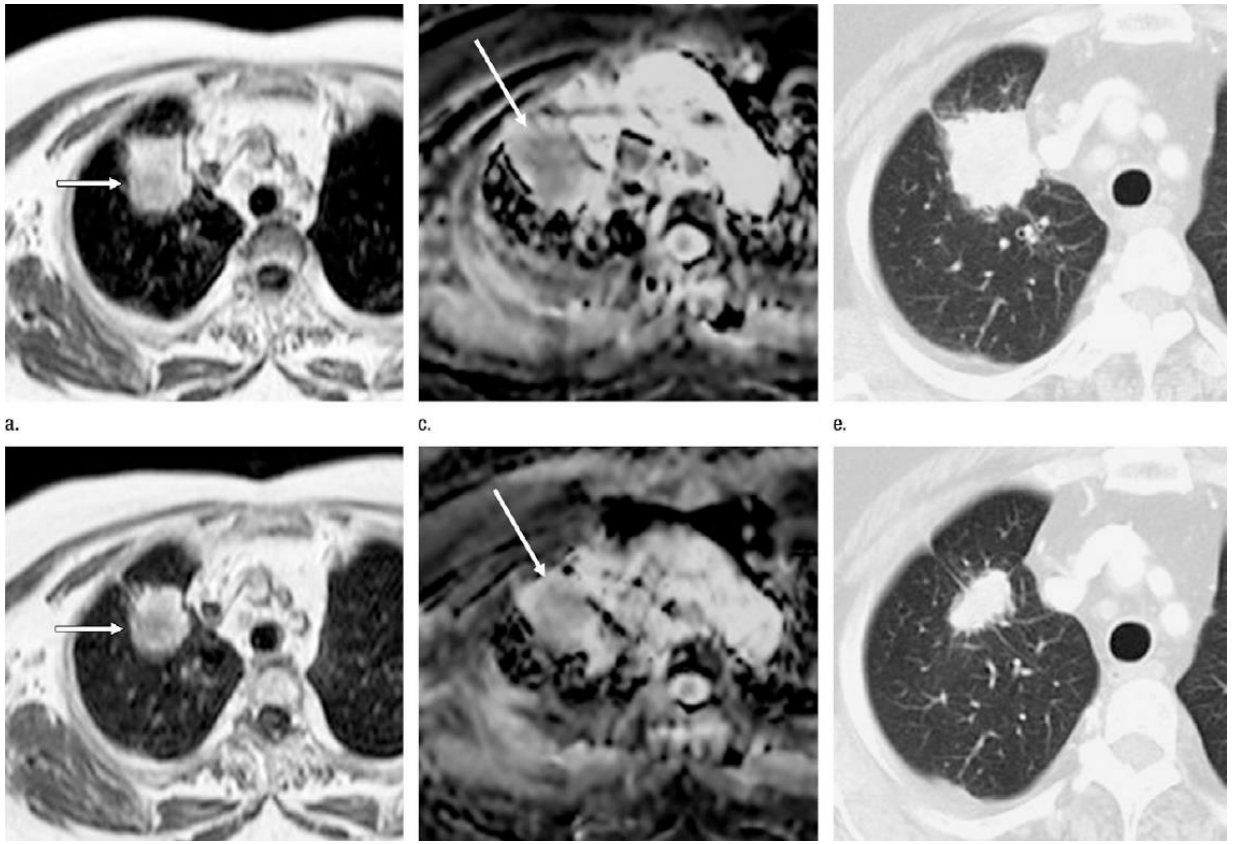
Journal of Magnetic Resonance Imaging 32.1 (2010): 2-16.

2. 연구의 목표 및 내용 - 2) Imaging Modality

Diffusion-weighted MRI

- Detection of Early Response to Chemotherapy in NSCLC



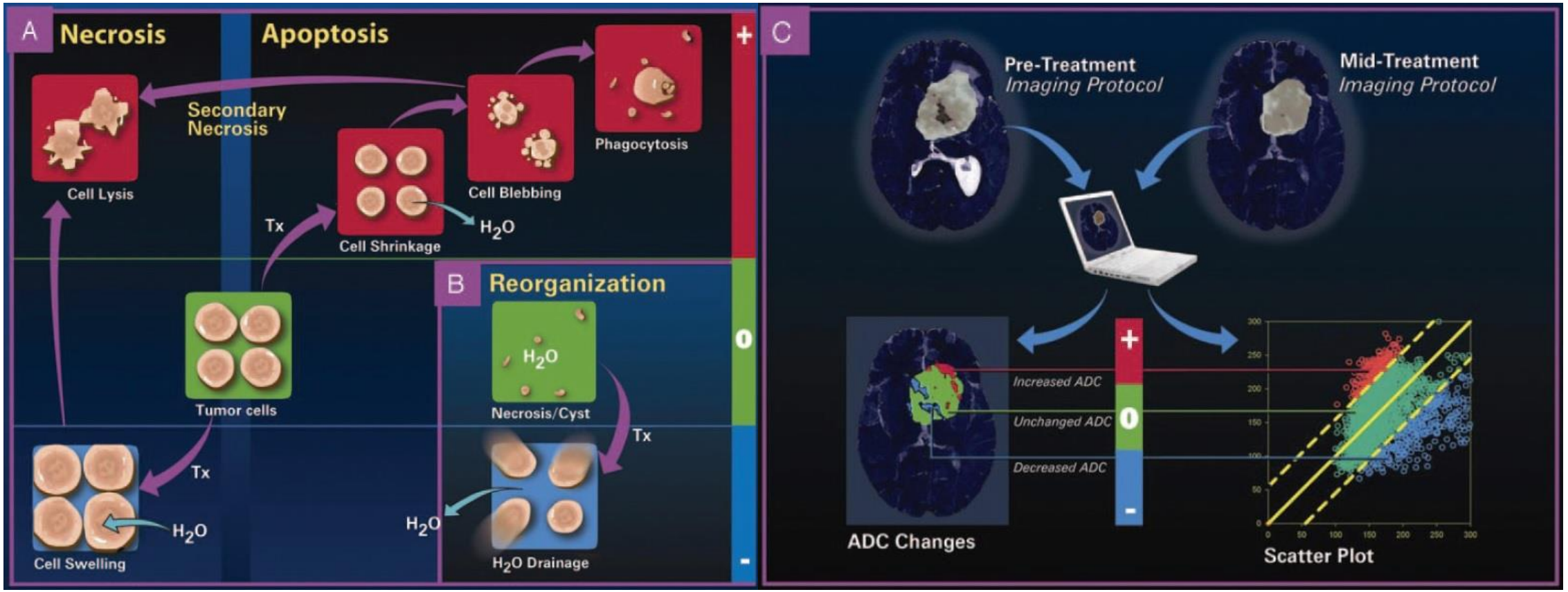


Radiology 261.2 (2011): 598-604.

2. 연구의 목표 및 내용 - 2) Imaging Modality

Functional diffusion map in Brain tumor

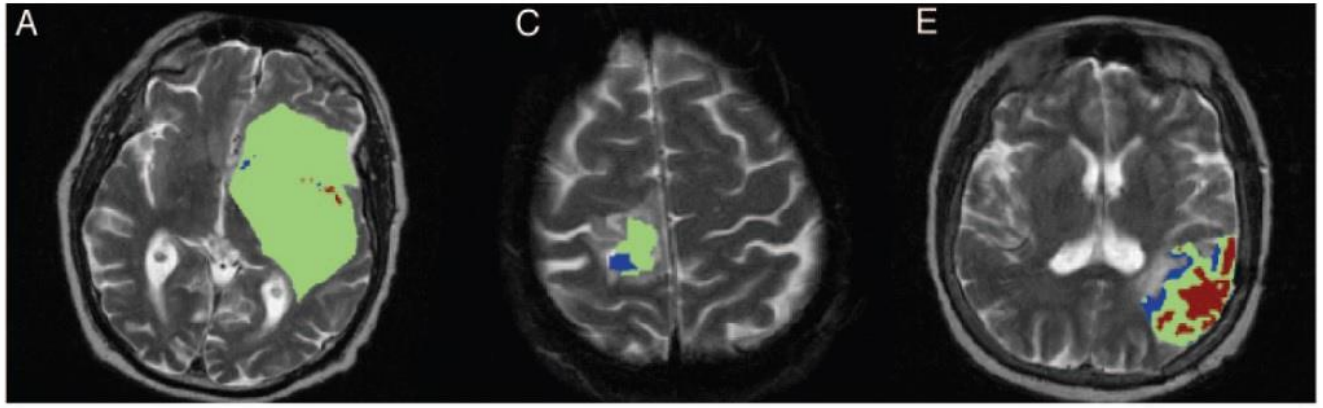
- Changes in tumor water diffusion values : clinical brain tumor response

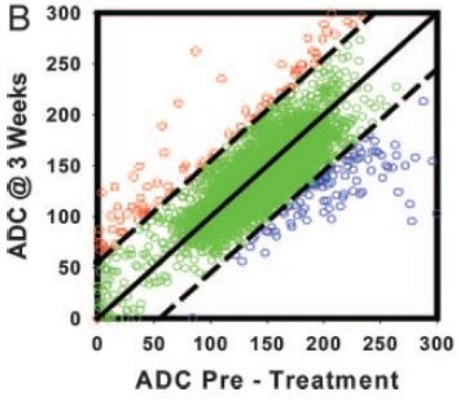


Proceedings of the National Academy of Sciences of the United States of America 102.15 (2005): 5524-5529.

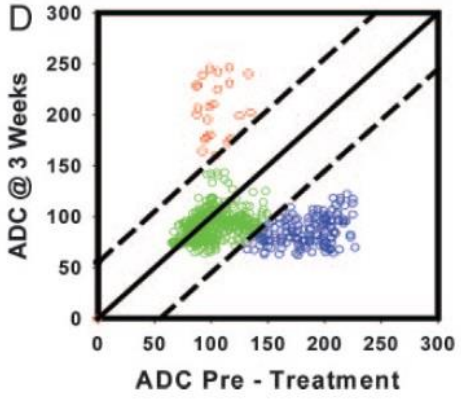
2. 연구의 목표 및 내용 - 2) Imaging Modality

Functional diffusion map in Brain tumor

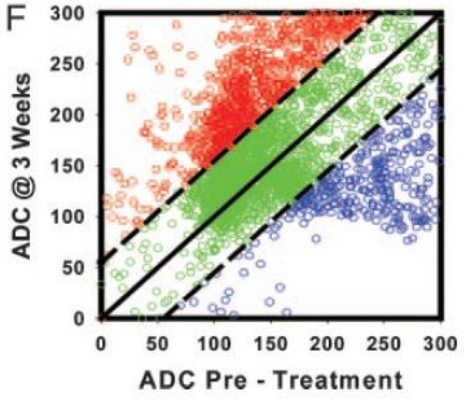




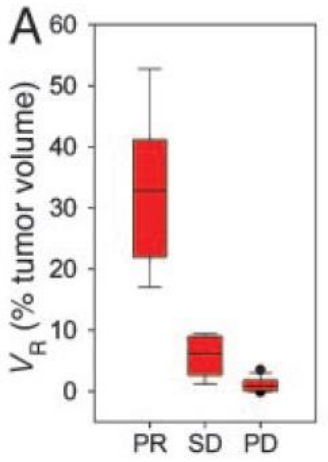
PD

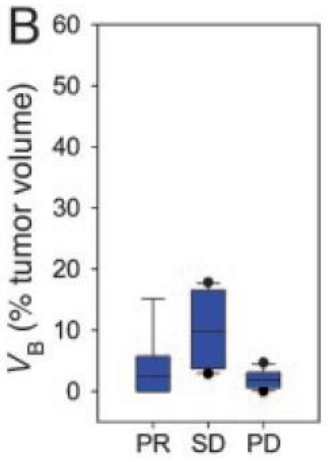


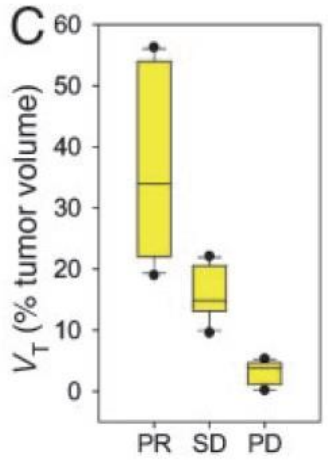
SD



PR







Proceedings of the National Academy of Sciences of the United States of America 102.15 (2005): 5524-5529.

2. 연구의 목표 및 내용 - 2) Imaging Modality

Key Points

Pseudoprogression

Immune cell infiltration, Inflammation >> Tumor growth

Cytotoxic T lymphocyte, Macrophage

(Circulating) Immune cells, Inflammatory cytokines

\+ Diffusion-weighted MRI (Functional diffusion map)

Contents

3. 연구의 방법

Patient Number & Time

- **Participants** : 200 patients with advanced NSCLC
- **Study duration :** 3 years
- **Sampling Time**
  - Pre-treatment
  - Just before every cycle until the 2nd response assessment
  - At every response assessment
  - At initial RECIST v1.1-defined progression or events suspecting progression

3. 연구의 방법

Patient Number & Time

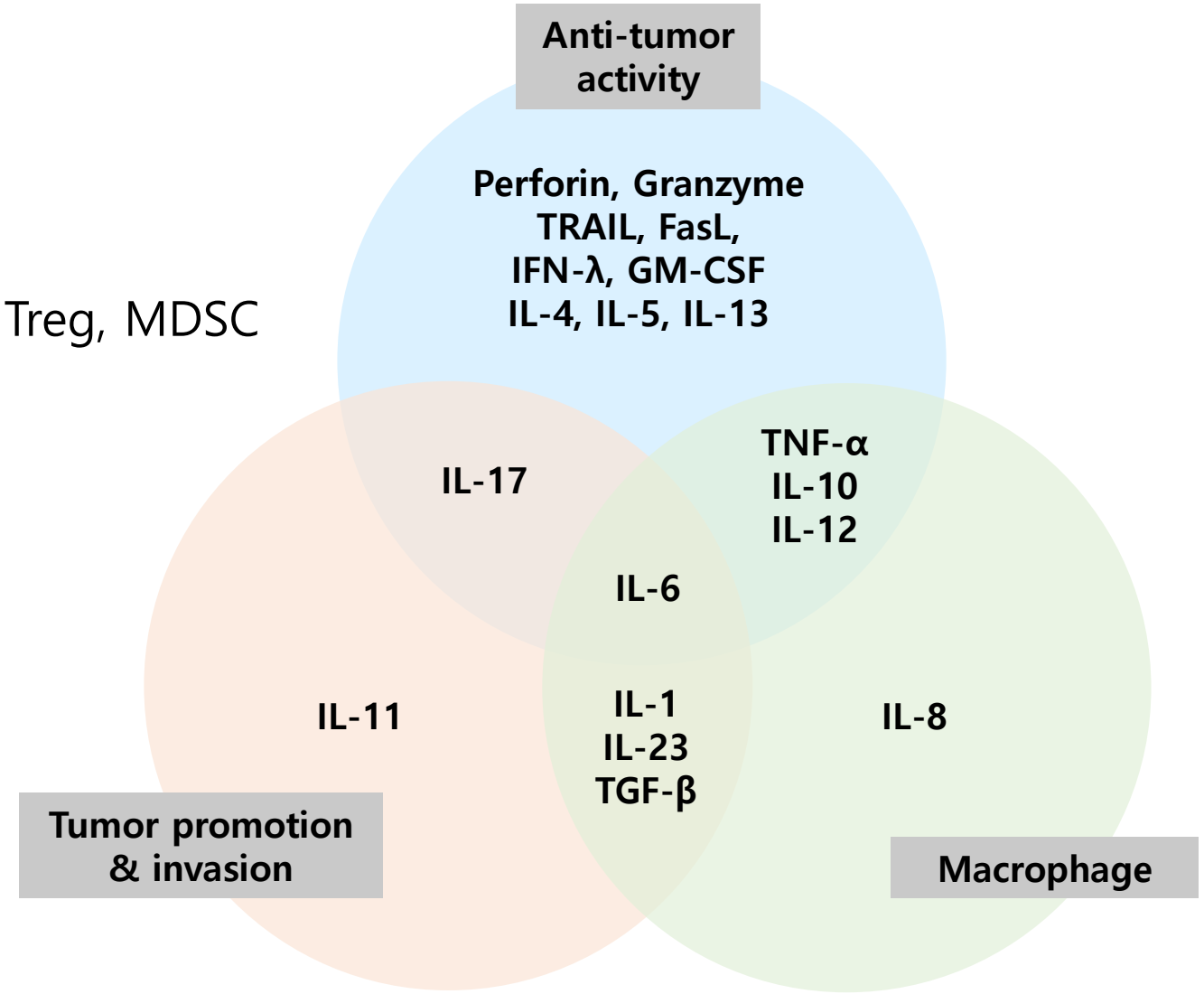
- **Imaging Time**
  - Pre-treatment
  - At the 1st response assessment : no CR or PR
  - At the 2nd response assessment
  - At initial RECIST v1.1-defined progression or events suspecting progression

3. 연구의 방법

Analysis

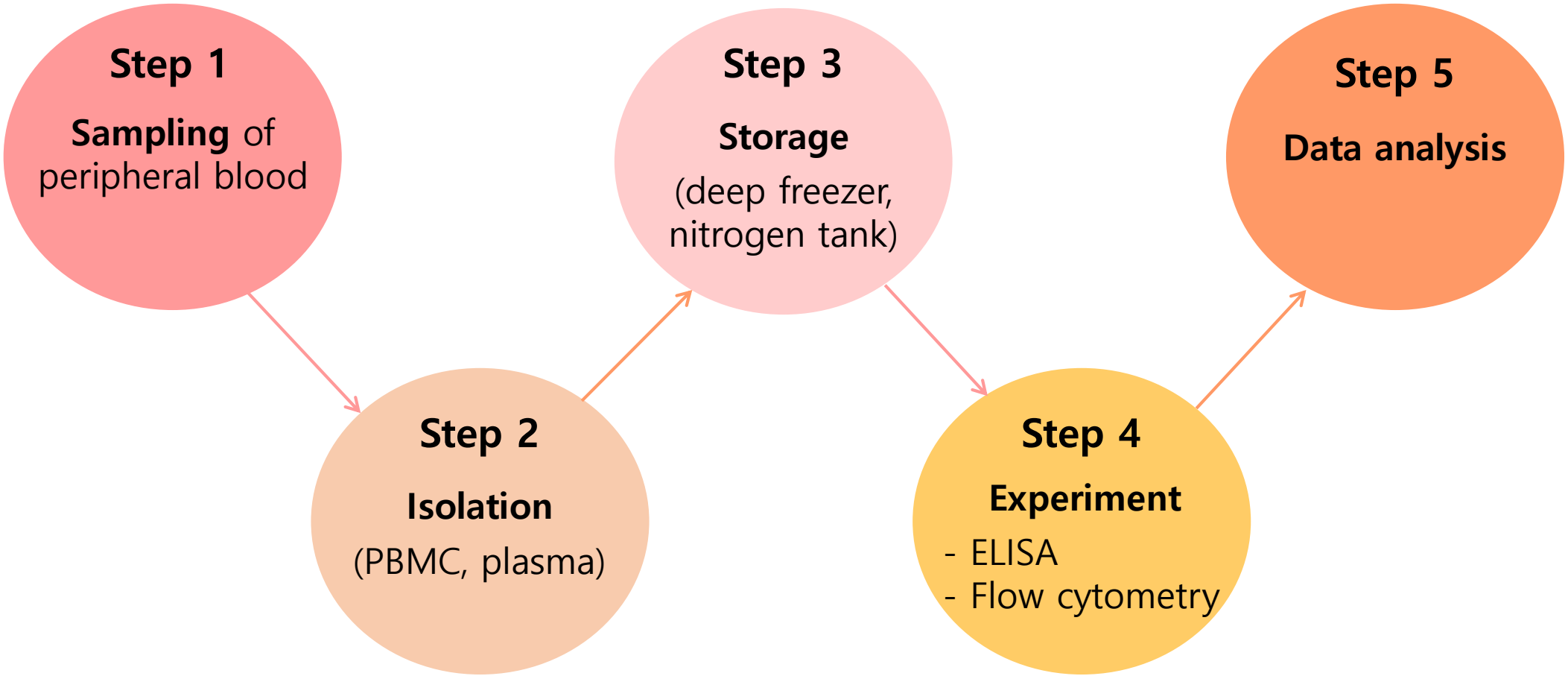
- **Peripheral blood biomarker**
  - ELISA : Inflammatory cytokines
  - Flow cytometry : CD4/CD8 T cell, Treg, MDSC

- **Imaging modality**
  - Diffusion-weighted MRI



3. 연구의 방법

Method for peripheral blood biomarker



THANK YOU FOR YOUR ATTENTION