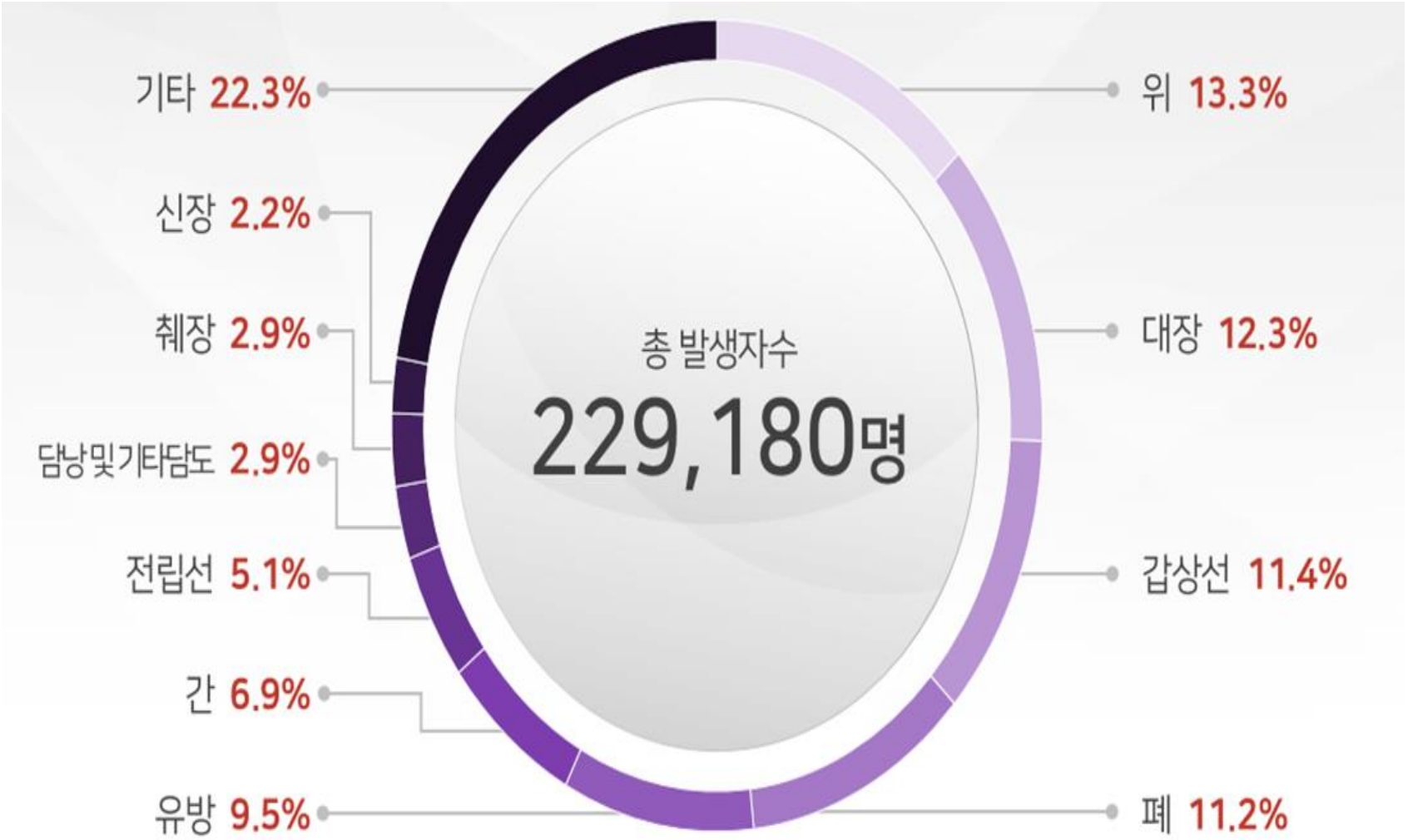
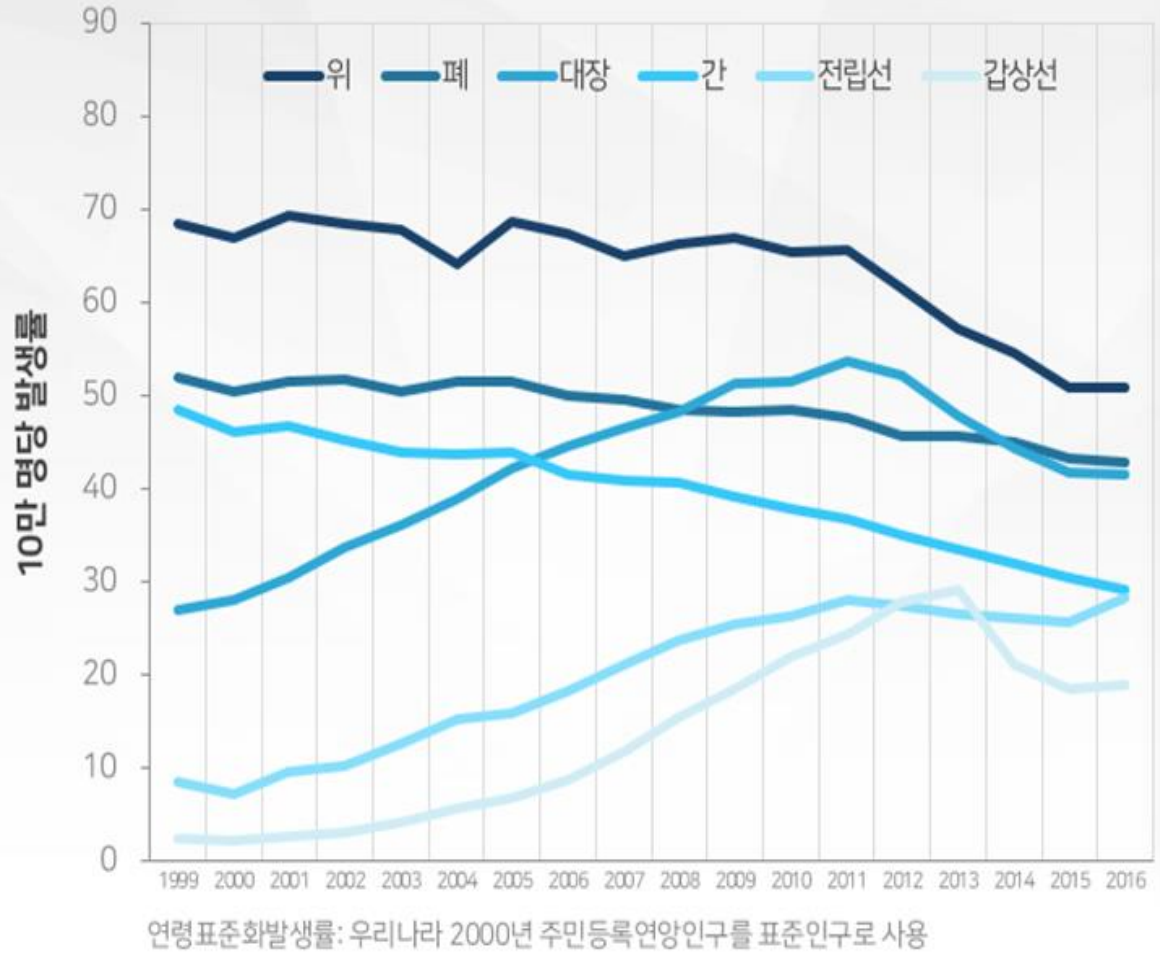
증례로 알아보는
암 치료의 변화

동아의대 혈액종양내과 이수이

주요 암종 발생분율, 2016



주요 암종의 연령표준화 발생율 - 남자

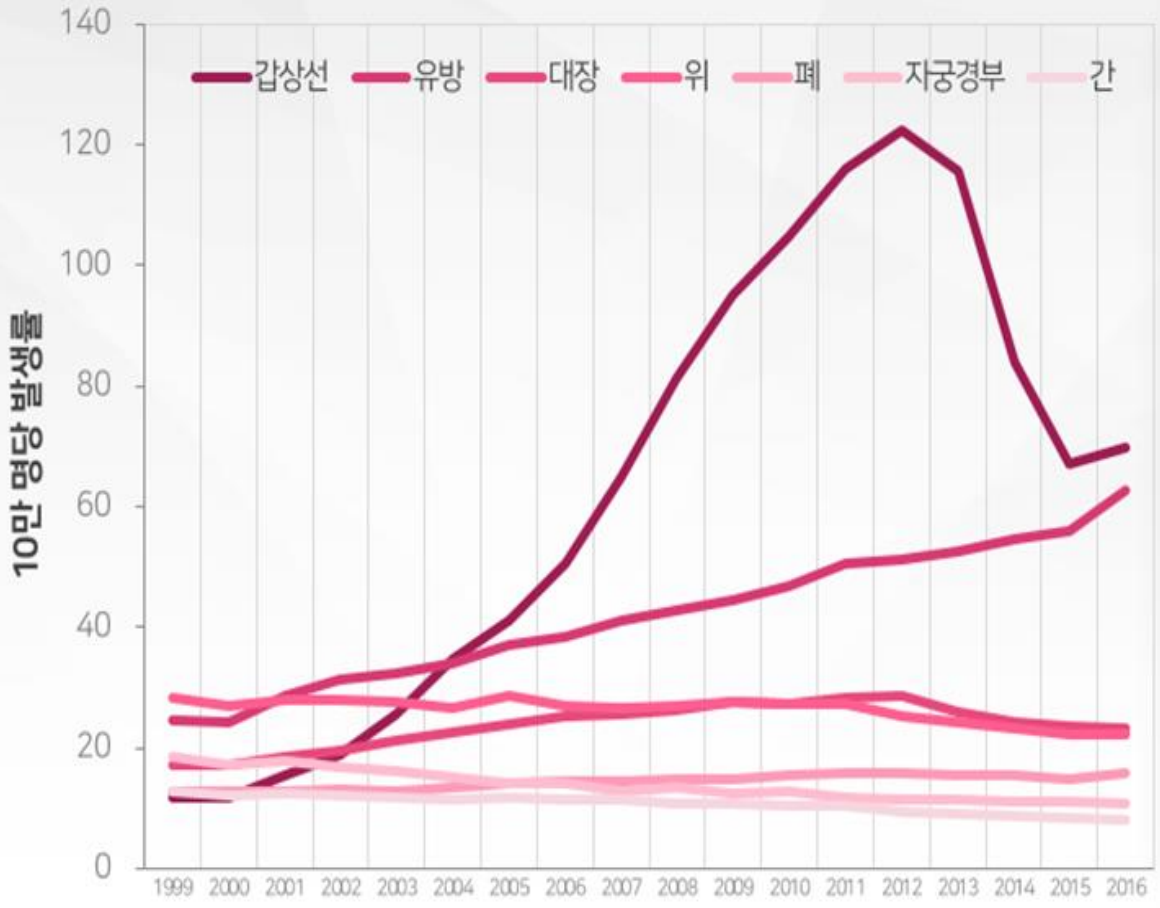


연령표준화발생률: 우리나라 2000년 주민등록연앙인구를 표준인구로 사용

암종	추이 1		추이 2	
	발생 기간	연간% 변화율	발생 기간	연간% 변화율
위	1999-2011	-0.4*	2011-2016	-5.4*
폐	1999-2005	0.0	2005-2016	-1.6*
대장	1999-2010	6.4*	2010-2016	-4.9*
전립선	1999-2009	13.3*	2009-2016	0.2
간	1999-2009	-1.9*	2009-2016	-4.2*
갑상선	1999-2012	23.3*	2012-2016	-13.7*

* $p < 0.05$

주요 암종의 연령표준화 발생율 - 여자

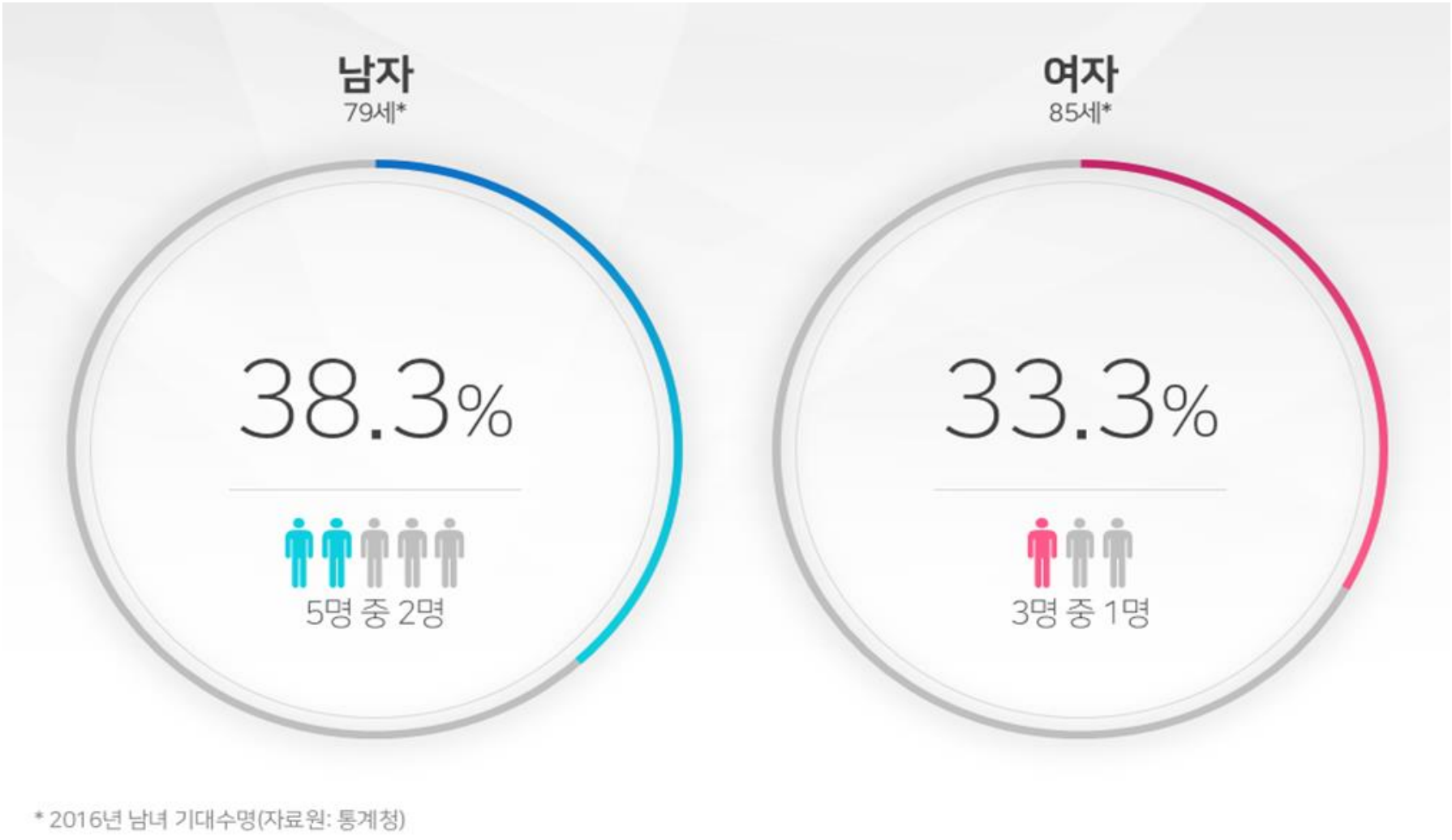


암종	추이 1		추이 2	
	발생 기간	연간% 변화율	발생 기간	연간% 변화율
유방	1999-2005	7.5*	2005-2016	4.5*
갑상선	1999-2011	22.5*	2011-2016	-13.2*
대장	1999-2010	4.9*	2010-2016	-3.8*
위	1999-2011	-0.3	2011-2016	-4.4*
폐	1999-2011	1.9*	2011-2016	-0.2
자궁경부	1999-2007	-4.3*	2007-2016	-2.5*
간	1999-2010	-1.5*	2010-2016	-4.7*

* $p < 0.05$

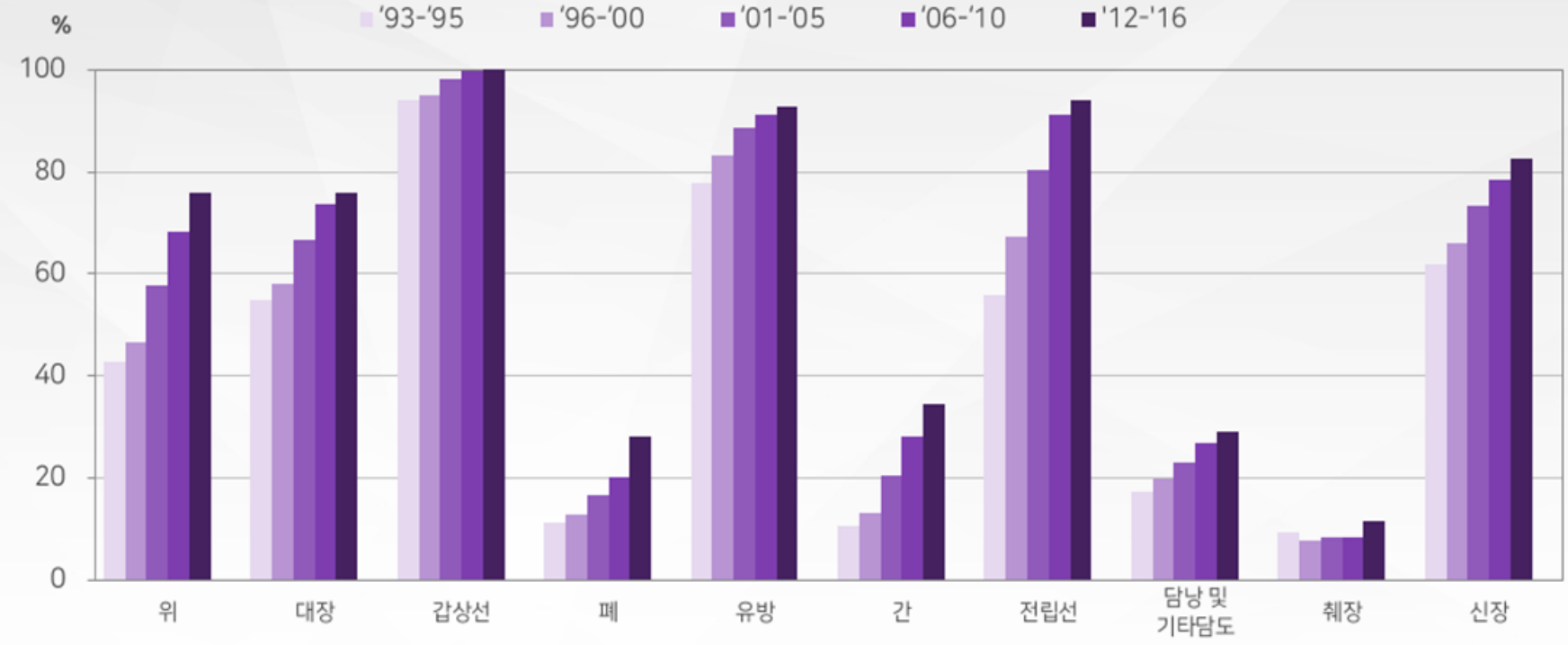
연령표준화발생률: 우리나라 2000년 주민등록연앙인구를 표준인구로 사용

기대수명까지 생존 시 암발생 확률



* 2016년 남녀 기대수명(자료원: 통계청)

우리나라 주요 암의 5년 생존율 변화



	위	대장	갑상선	폐	유방	간	전립선	담낭 및 기타담도	췌장	신장
'93-'95	42.8	54.8	94.2	11.3	77.9	10.7	55.9	17.3	9.4	62.0
'96-'00	46.6	58.0	94.9	12.7	83.2	13.2	67.2	19.7	7.6	66.1
'01-'05	57.8	66.7	98.3	16.5	88.6	20.4	80.4	23.0	8.4	73.5
'06-'10	68.1	73.6	99.9	20.1	91.1	28.1	91.1	26.7	8.4	78.3
'12-'16	76.0	75.9	100.2	28.2	92.7	34.6	93.9	29.0	11.4	82.7
증감*	33.2	21.1	6.0	16.9	14.8	23.9	38.0	11.7	2.0	20.7

* 증감: '93-'95년 대비 '12-'16년 암발생자의 생존율 차이

주요 암의 5년 생존율 국제비교

(단위: %)

암종	한국 ('96-'00)	한국 ('06-'10)	한국 ('12-'16)	미국[1] ('08-'14)	캐나다[2] ('06-'08)	일본[3] ('06-'08)
모든 암	44.0	65.2	70.6	69.2	60	62.1
위	46.6	35.1	76.0	32.1	25	64.6
대장	58.0	73.6	75.9	66.2	64	71.1
갑상선	94.9	99.9	100.2	98.3	98	93.7
폐	12.7	20.1	28.2	19.9	17	31.9
유방	83.2	91.1	92.7	91.1	87	91.1
간	13.2	28.1	34.6	18.8	19	32.6
전립선	67.2	91.1	93.9	98.9	95	97.5
췌장	7.6	8.4	11.4	9.1	8	7.7
자궁경부	80.0	80.6	79.8	68.9	73	73.4

암 치료의 발전

- 암 예방
- 조기 진단 – 암 검진
- 수술 기술의 발전
- **항암 치료의 발전 : 표적치료, 정밀의료**

항암치료의 종류

- **Cytotoxic chemotherapy**
- **Hormone therapy : breast and prostate cancer**
- **Target therapy**
  - Monoclonal Antibody : -mab
  - Small molecular blocker : -nib, -lib
- **Immunotherapy**
  - Immune Checkpoint inhibitor

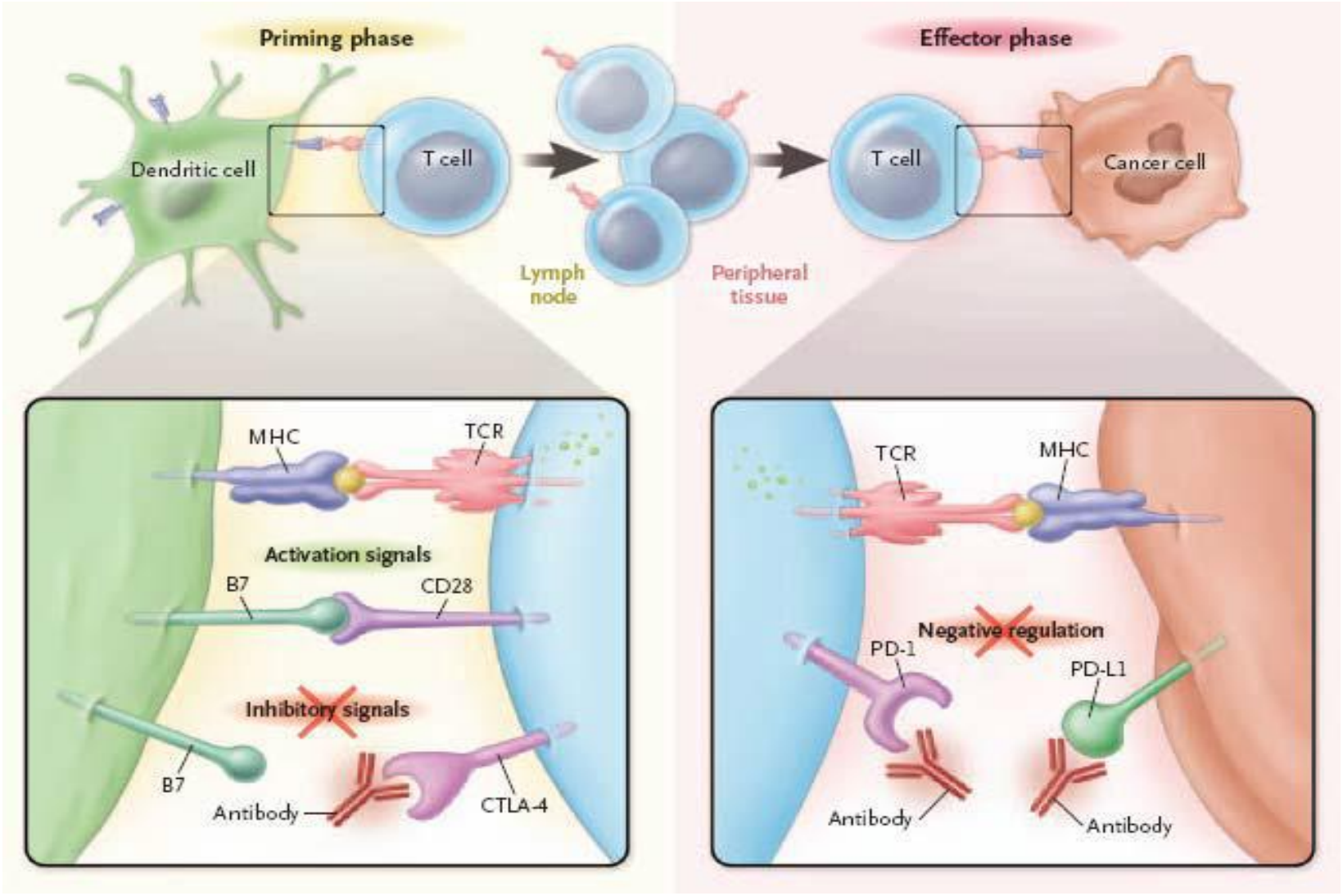
Monoclonal Antibody

Monoclonal Antibodies Alone			
Trastuzumab	HER2/neu (ERBB2)	Breast cancer	Binds HER2 on tumor cell surface and induces receptor internalization
Pertuzumab	HER2/neu (ERBB2)	Breast cancer	Binds HER2 on tumor cell surface at distinct site from trastuzumab and prevents binding to other receptors
Cetuximab	EGFR	Colon cancer, squamous cell carcinoma of the head and neck	Binds extracellular domain of EGFR and blocks binding of EGF and TGF-α; induces receptor internalization; potentiates the efficacy of chemotherapy and radiotherapy
Panitumumab	EGFR	Colon cancer	Similar to cetuximab but fully humanized rather than chimeric
Rituximab	CD20	B cell lymphomas and leukemias that express CD20	Multiple potential mechanisms, including direct induction of tumor cell apoptosis and immune mechanisms
Alemtuzumab	CD52	Chronic lymphocytic leukemia and CD52-expressing lymphoid tumors	Immune mechanisms
Bevacizumab	VEGF	Colorectal, lung cancers, RCC, glioblastoma, cervical cancer	Inhibits angiogenesis by high-affinity binding to VEGF
Ziv-aflibercept	VEGF-A, VEGF-B, PLGF	Colorectal cancers	Inhibits angiogenesis by high-affinity binding to VEGF-A, VEGF-B, and PLGF
Ipilimumab	CTLA-4	Melanoma	Blocks CTLA-4, preventing interaction with CD80/86 and T cell inhibition
Denosumab	RANK ligand	Breast, prostate cancer	Inhibits RANK ligand, the primary signal for bone removal
Pembrolizumab	PD-1	Melanoma	Blocks PD-1 preventing interaction with PD-L1 T cell inhibition
Antibody-Chemotherapy Conjugates			
Brentuximab vedotin	CD30	Hodgkin's disease, anaplastic lymphoma	Delivery of chemotherapeutic agent (MMAE) to CD30-expressing tumor cells
Ado-trastuzumab emtansine	HER2	Breast cancer	Delivery of chemotherapeutic agent emtansine to HER2-expressing breast cancer cells

Small Molecular Blocker

Drug	Molecular Target	Disease	Mechanism of Action
All-*trans* retinoic acid	PML-RARα oncogene	Acute promyelocytic leukemia M3 AML; t(15;17)	Inhibits transcriptional repression by PML-RARα
Imatinib	Bcr-Abl, c-Abl, c-Kit, PDGFR-α/β	Chronic myeloid leukemia; GIST	Blocks ATP binding to tyrosine kinase active site
Dasatinib, nilotinib, ponatinib, bosutinib	Bcr-Abl (primarily)	Chronic myeloid leukemia	Blocks ATP binding to tyrosine kinase active site
Sunitinib	c-Kit, VEGFR-2, PDGFR-β, Flt-3	GIST; renal cell cancer	Inhibits activated c-Kit and PDGFR in GIST; inhibits VEGFR in RCC
Sorafenib	RAF, VEGFR-2, PDGFR-α/β, Flt-3, c-Kit	RCC; hepatocellular carcinoma; TC	Targets VEGFR pathways in RCC. Possible activity against BRAF in thyroid cancer
Regorafenib	VEGFR-1 to -3, TIE-2, FGFR1, KIT, RET, PDGFR	Colorectal cancer; GIST	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases
Axitinib	VEGFR-1 to -3	RCC	Competitive inhibitor of ATP binding site of tyrosine kinase domain VEGF receptors
Erlotinib	EGFR	Non-small-cell lung cancer; pancreatic cancer	Competitive inhibitor of the ATP-binding site of the EGFR
Afatinib	EGFR (and other HER family)	Non-small-cell lung cancer	Irreversible inhibitor of ATP-binding site of HER family members
Lapatinib	HER2/neu	Breast cancer	Competitive inhibitor of the ATP binding site of HER2
Crizotinib (Xalkori)	ALK	Non-small-cell lung cancer	Inhibitor of ALK tyrosine kinase
Bortezomib, carfilzomib	Proteasome	Multiple myeloma	Inhibits proteolytic degradation of multiple cellular proteins
Vemurafenib, dabrafenib	BRAF	Melanoma	Inhibitor of serine-threonine kinase domain of V600E mutant of BRAF
Trametinib	MEK	Melanoma	Inhibitor of serine-threonine kinase domain of V600E mutant of MEK
Cabozantinib	RET, MET, VEGFR	MTC	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases
Vandetanib	RET, VEGFR, EGFR	MTC	Competitive inhibitor of ATP binding site of tyrosine kinase domain

Immunotherapy: Immune Checkpoint



Immune Checkpoint Inhibitor

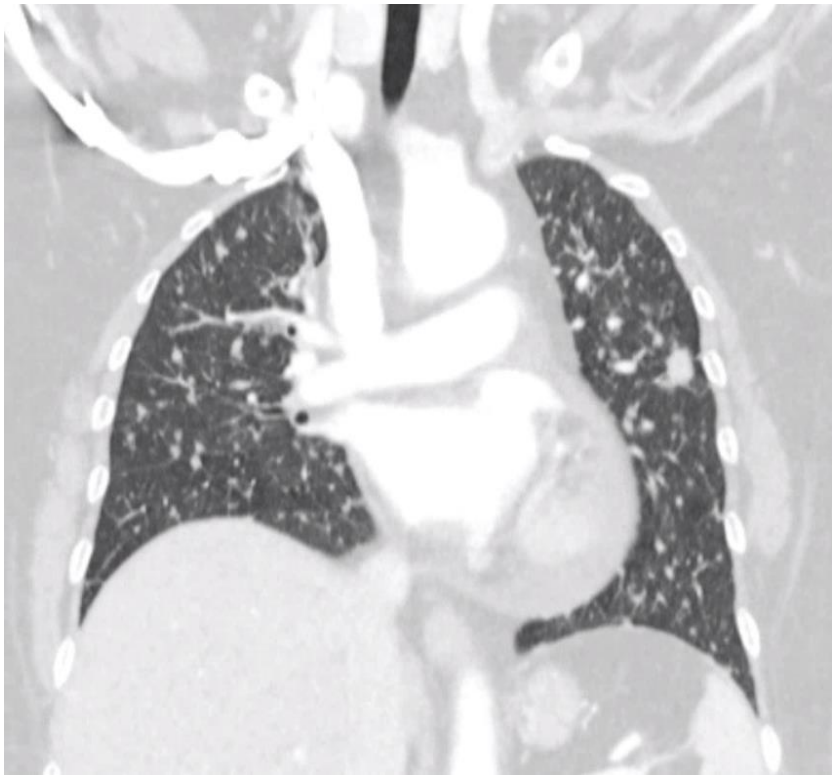
Target	Agent
CTLA-4	Ipilimumab Tremelimumab
PD-1	Nivolumab Pembrolizumab
PD-L1	Avelumab Atezolizumab Durvalumab

Case 1 (F/60)

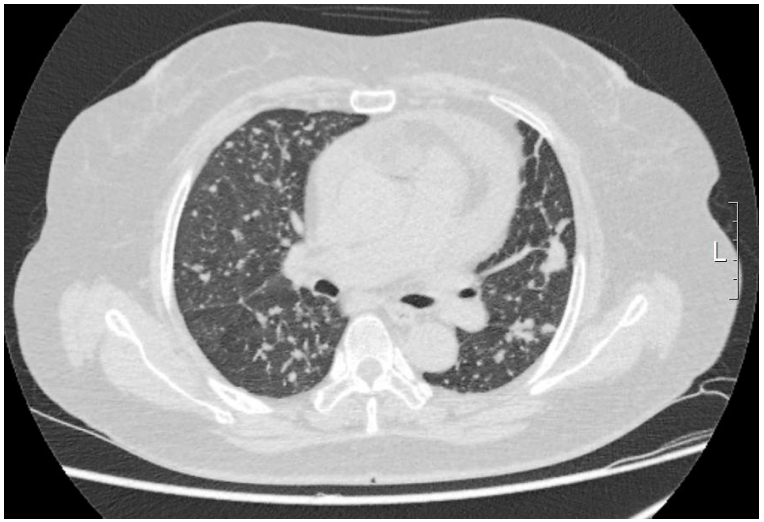
- 2019.7.8. acute dyspnea onset

→ Local clinic : cardiac tamopande

: pericardiocentesis- cytology: adenocarcinoma



Case 1 (F/60)



Case 1 (F/60)

- 2019.7.23. Lung, upper lobe, right, transbronchial lung biopsy: Adenocarcinoma (IHC) TTF-1: positive

➔ Stage IV, NSCLC (adenocarcinoma), lung/pericardium metastasis

Case 1 (F/60)

- 2019.7.23. Lung, upper lobe, right, transbronchial lung biopsy: Adenocarcinoma (IHC) TTF-1: positive

- 2019.7.26. Lung, lower lobe, left, VATS wedge resection

  adenocarcinoma, papillary
  - EGFR mutation
  - Ventana anti-ALK IHC stain or ALK FISH
  - ROS-1 fusion gene
  - Ventana PD-L1 (SP263)

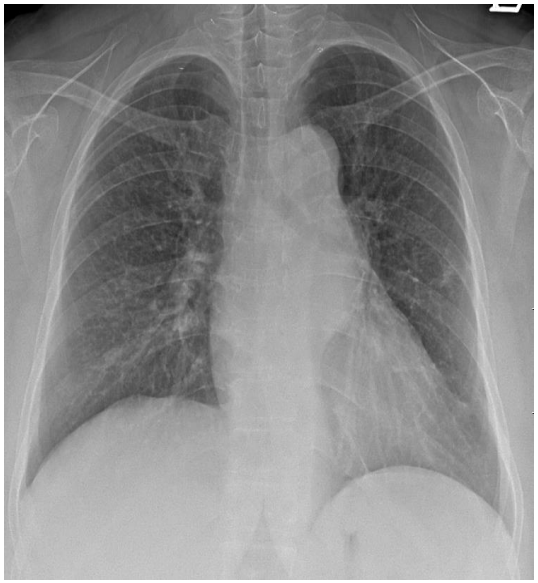
Case 1 (F/60)

- 2019.7.23. Lung, upper lobe, right, transbronchial lung biopsy: Adenocarcinoma (IHC) TTF-1: positive

- 2019.7.26. Lung, lower lobe, left, VATS wedge resection
  adenocarcinoma, papillary
  - EGFR mutation : **L858R mutant**
  - Ventana anti-ALK IHC stain : negative
  - ROS-1 fusion gene : negative
  - Ventana PD-L1 (SP263) : positive 1%

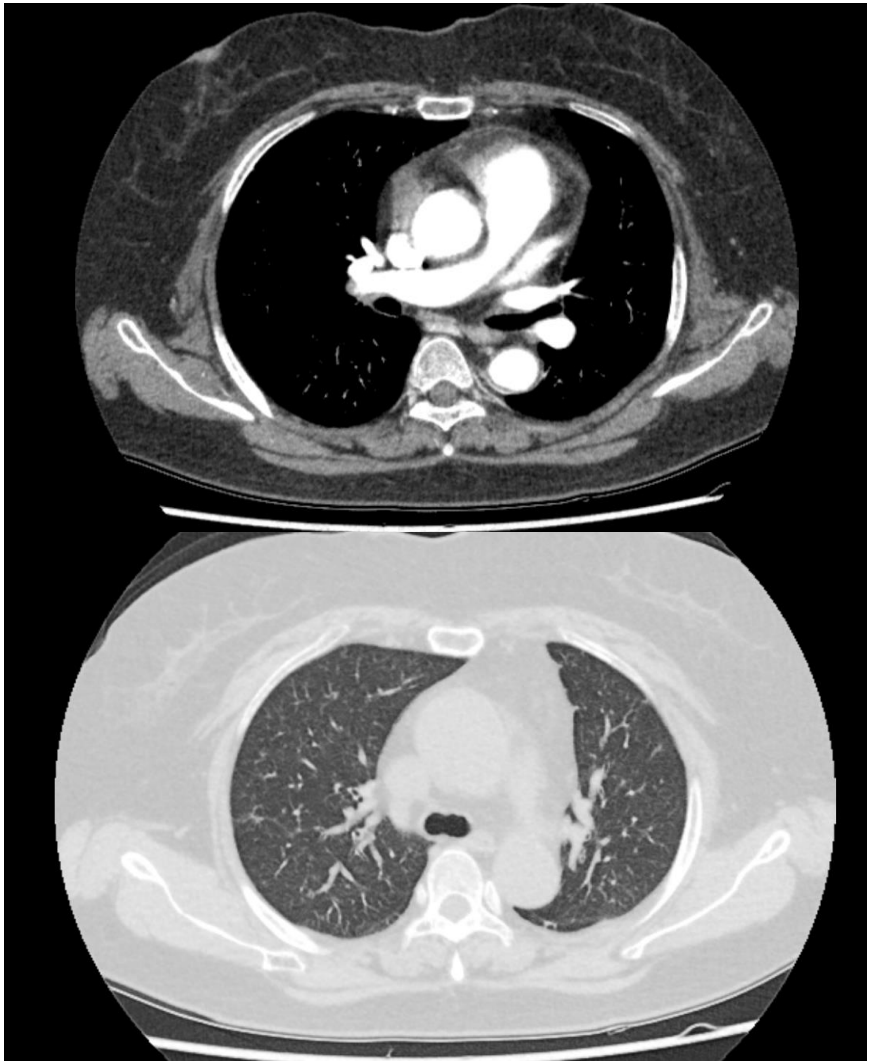
- 2019.8.20. **Erlotinib**

Case 1 (F/60)



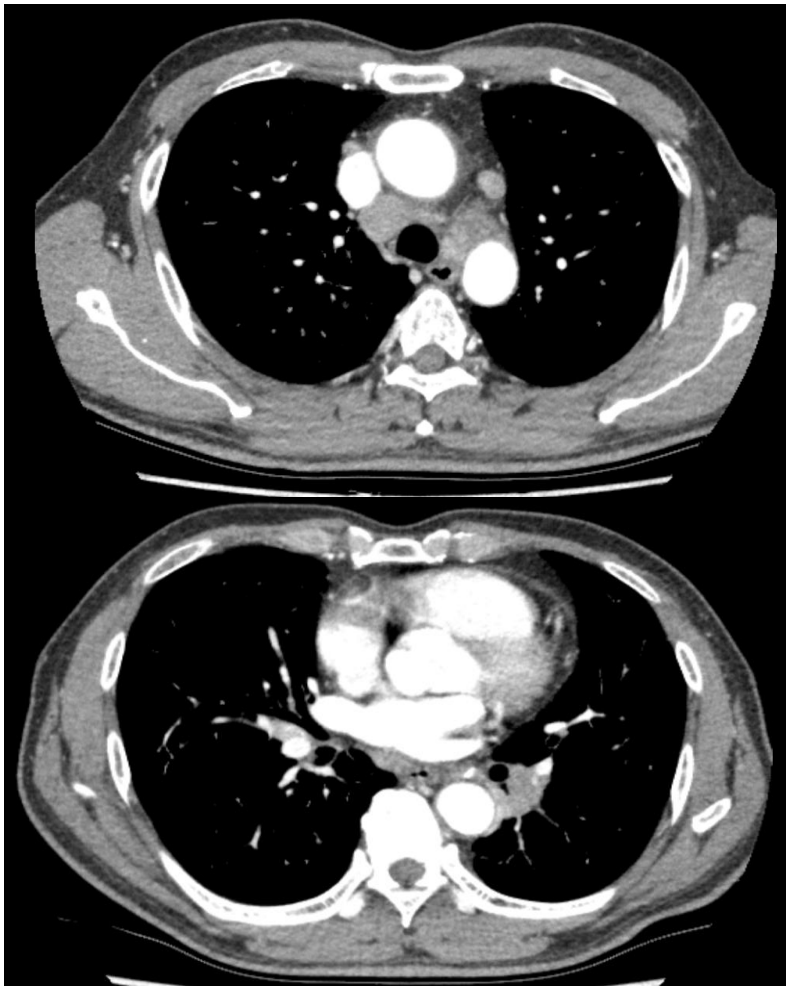
Monthly, regular F/U CXR
➔ Rapid response to target agent, Erlotinib

Case 1 (F/60)



Case 2 (M/71)

- 2018.3.5. recurrent cough for 2 months



Case 2 (M/71)

- Lung, left lobe, EBUS-guided, liquid based cytology & cell block:

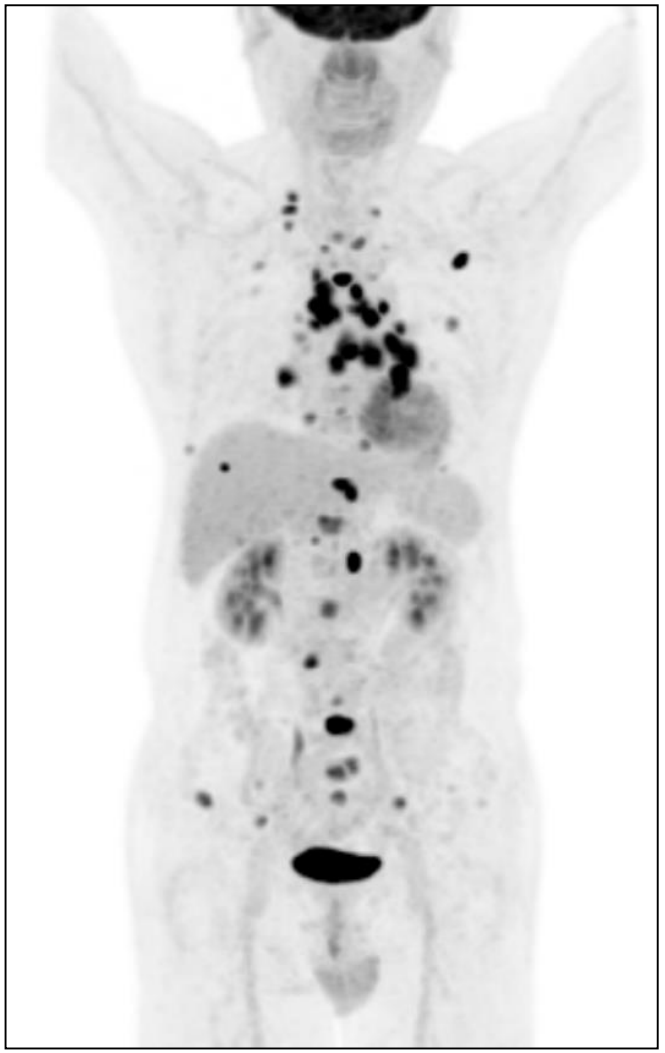
  Positive for malignancy

  Non-small cell carcinoma,

  consistent with adenocarcinoma

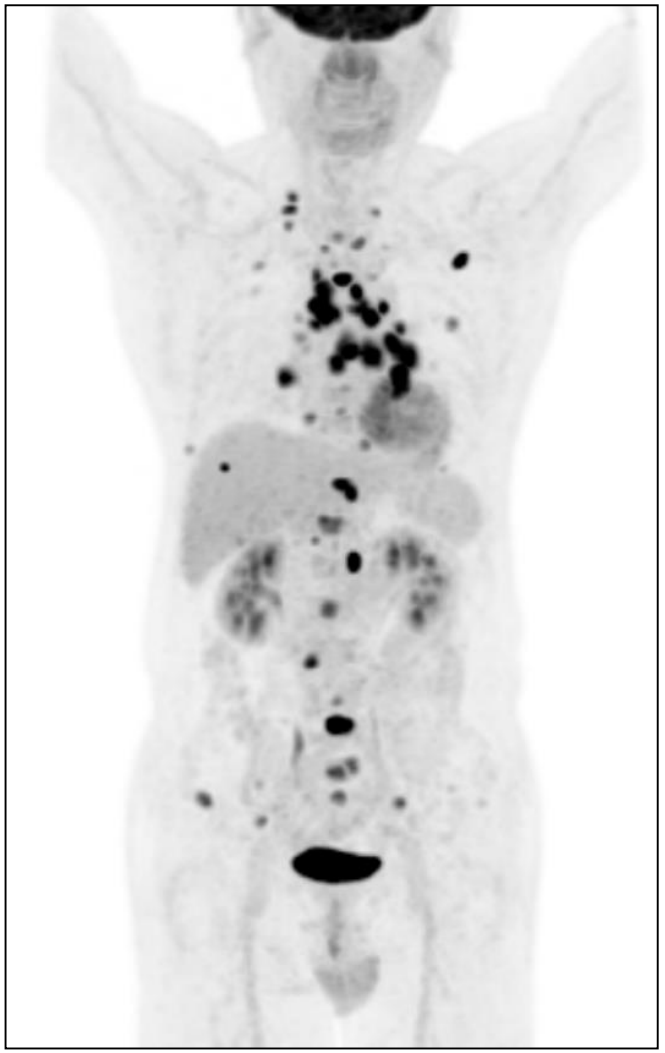
- 2018.3.20. PET :

  1. Hypermetabolic lung malignancy in LLL with invasion to segmental bronchus
  2. Multiple metastatic LNs in both supraclavicular & mediastinal areas
  3. Multiple bone & lung metastases



Case 2 (M/71)

- Stage IV, NSCLC (adenocarcinoma) with bone/lung metastasis
- EGFR mutation : wild type
- Refer to SNUH →
  ALK IHC stain (+++) →
  ALK FISH : translocation (+)
- 2018.4.18 – **Crizotinib**

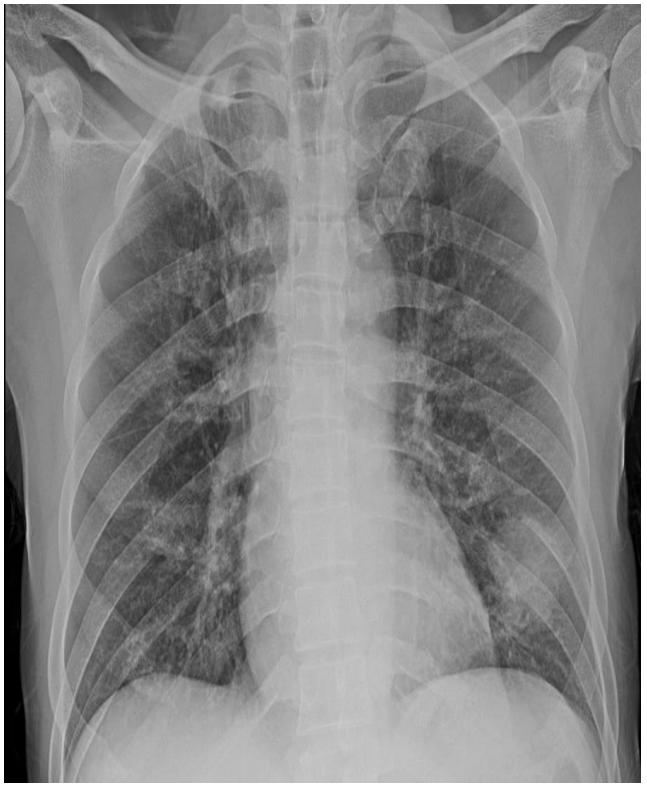


Case 2 (M/71)

- Until now, 18 months treatment of crizotinib

Case 3 (M/51)

- 2018.12.29. increasing mass in Lt. neck for 2 months
  Rt. femur pain → ER



Case 3 (M/51)

Case 3 (M/51)

- 2019.1.4. Skin, shoulder, left, incisional biopsy:
  Carcinoma (c/w adenocarcinoma), metastatic

- 2019.1.7. CT-guided liquid based cytology & cell block
  Positive for malignancy
  NSCLC, consistent with adenocarcinoma

➔ Stage IV, NSCLC (adenocarcinoma)
bone/skin/muscle/adrenal/kidney metastasis

Case 3 (M/51)

- 2019.1.10 – 2018.1.27. palliative RTx to Rt. Femur, acetabulum
  - EGFR mutation : wild type
  - ALK FISH : negative
  - Ventana PD-L1 (SP263) : 80%
  - **PD-L1 IHC 22C3 pharmDx : positive 80%**
- 2019.1.30. Pembrolizumab/pemetrexed/cisplatin

  100% self-funded ➔ cost problem
- 2019.7.16. #8. Pembrolizumab/pemetrexed, last treatment

Case 3 (M/51)

2019.6.19. F/U PET

2019.10.2. F/U CT

CASE for NSCLC

- NSCLC (adenocarcinoma)
  - EGFR mutation test
  - ALK rearrangement
  - ROS-1 rearrangement
  - PD-L1 test
- NSCLC (squamous cell carcinoma)
  - PD-L1 test

CASE for NSCLC

- NSCLC (adenocarcinoma)
  - EGFR mutation test : Erlotinib, Afatinib, Gefitinib
    ➔ T790M mutation : Osimertinib
  - ALK rearrangement : Crizotinib, Alectinib, Ceritinib
    ➔ PD : Alectinib, Ceritinib, brigatinib
  - ROS-1 rearrangement : Crizotinib
  - PD-L1 test : ≥ 50% - Pembrolizumab
    - Pembrolizumab/platinum/pemetrexed

Case 4 (F/77)

- 2012. Rt. breast cancer Dx → No treatment
- 2017.6.9. Dyspnea onset

Case 4 (F/77)

- 2017.6.11. Rt. Thoracentesis and O2 supply
- 2017.6.15. Breast Biopsy : invasive ductal carcinoma

  ER/PR/HER2 (+/+/-)

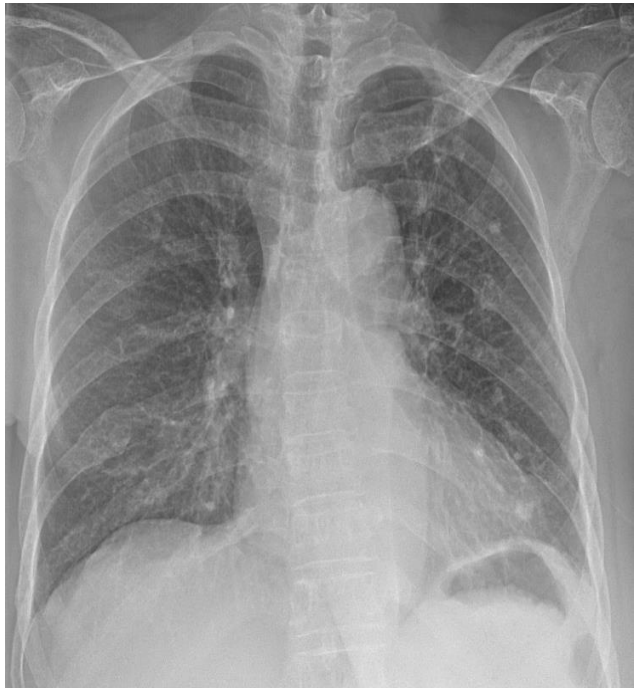
  ➔ Stage IV Breast cancer, Hormone positive, HER2 negative with pleura, bone, liver metastasis

Case 4 (F/77)

- 2017.6.19. **Palbociclib (CDK4/6 inhibitor)** + Letrozole

  Bone metastasis → Zoledronic acid

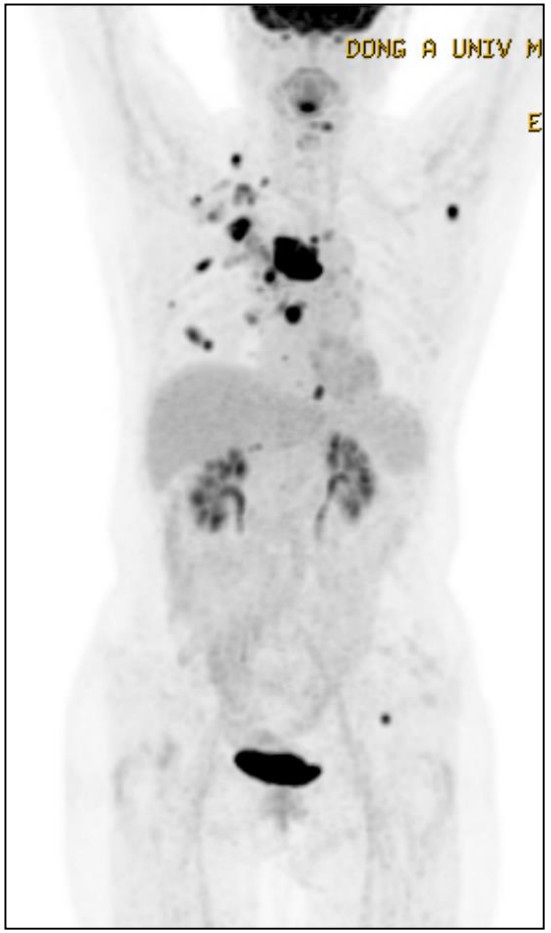
- Until now, 29 months treatment



Case 5 (F/67)

- 2003.10. Rt. MRM → Adjuvant FAC #6 cycles
- 2015.2.13. Rt. palpable neck LN
- Neck LN biopsy : invasive ductal carcinoma

  ER/PR/HER2 (-/-/+++)



Case 5 (F/67)

- Relapsed breast cancer with bone/LN metastasis
  Hormone negative, HER2 positive Breast cancer

- 2015.2.26 – Pertuzumab/Trastuzumab/Docetaxel
  Bone metastasis → Zoledronic acid
  After #9, Pertuzumab/Trastuzumab maintenance

- Recurrent GI problem → stop pertuzumab

- 2019.8.2 – Trastuzumab maintenance

→ **1st line treatment : for 56 months**

CASE for Breast Cancer

- Hormone Receptor (+), HER2 (-)
- Hormone Receptor (+), HER2 (+)
- Hormone Receptor (-), HER2 (+)
- Hormone Receptor (-), HER2 (-)

CASE for Breast Cancer

- Hormone Receptor (+), HER2 (-)
  - **CDK4/6 inhibitor (palbociclib)** + letrozole
    for postmenopausal state
- Hormone Receptor (+), HER2 (+)
  - **Pertuzumab + trastuzumab** + docetaxel
  - **Trastuzumab** + anastrozole
- Hormone Receptor (-), HER2 (+)
  - **Pertuzumab + trastuzumab** + docetaxel
    ➔ PD : **trastuzumab emtansine**

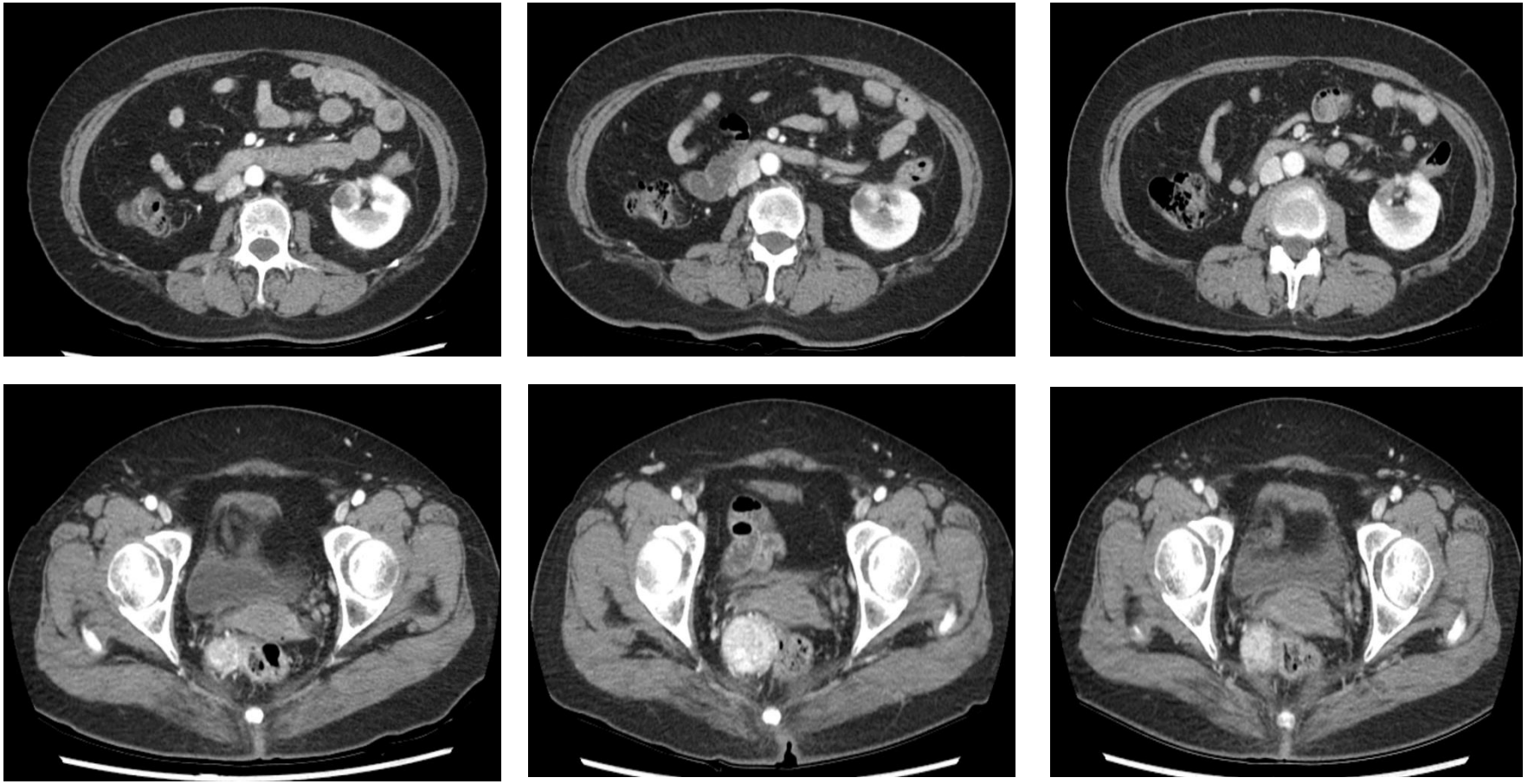
Case 6 (F/60) : RCC

- 2013.2.28. Rt. RCC → Radical Nephrectomy, Rt. (clear cell type)
- 2016.8.9. Lung VATS : metastasis from RCC
- 2016.8.16. Lt. kidney metastasis : RFA
- 2016.12.8. Brain metastais → Removal of tumor
- 2016.12.27, 2017.4.18, 2017.5.23 – Novalis for Brain metastasis

- 2017.9.11 – 2018.11.11. Pazopanib: PR → PD
- 2018.11.24 – Nivolumab (self)

Case 6 (F/60) : RCC

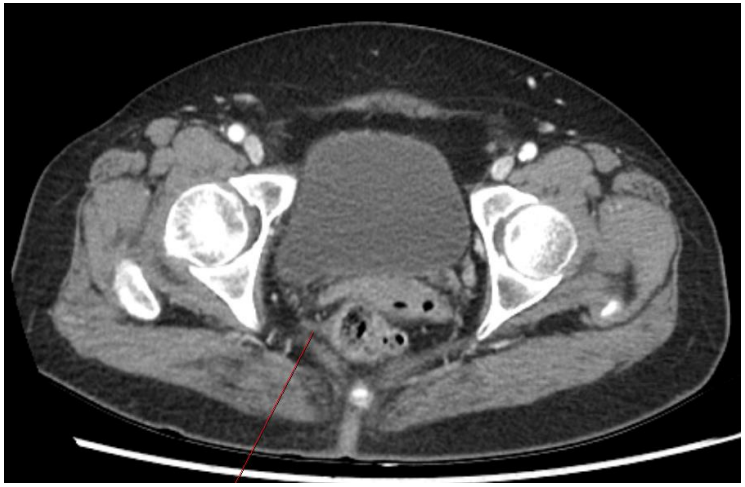
2018.11.11. **2019.1.11.** **2019.2.25.**



Case 6 (F/60) : RCC

- Nivolumab → pseudoprogression
- Until now, nivolumab maintenance

2019.10.18.



Case 7 (M/63) : Colon Cancer

- 2017.4.12. Laparoscopic converted to open extended right hemicolectomy : adenocarcinoma, moderately differentiated

  peritoneum biospy: adenocarcinoma, metastatic

  EGFR positive, K-ras: mutant type, N-ras: wild type

- 2017.5.11 - 2018.2.23 #20. Bevacizumab-FOLFOX
- 2018.3.16 - 2018.10.19 #12. Bevacizumab-FOLFIRI

- 2018.11.16. Whipple's operation for wide local recurrence
- 2019.4.1. Excision of abdominal wall metastasis

- Further treatment ???

Case 7 (M/63) : Colon Cancer

- 2019.5.1 – 2019.5.28. #2. FP : PD

- Biopsy Review :

  EGFR : positive

  MLH1 : Positive

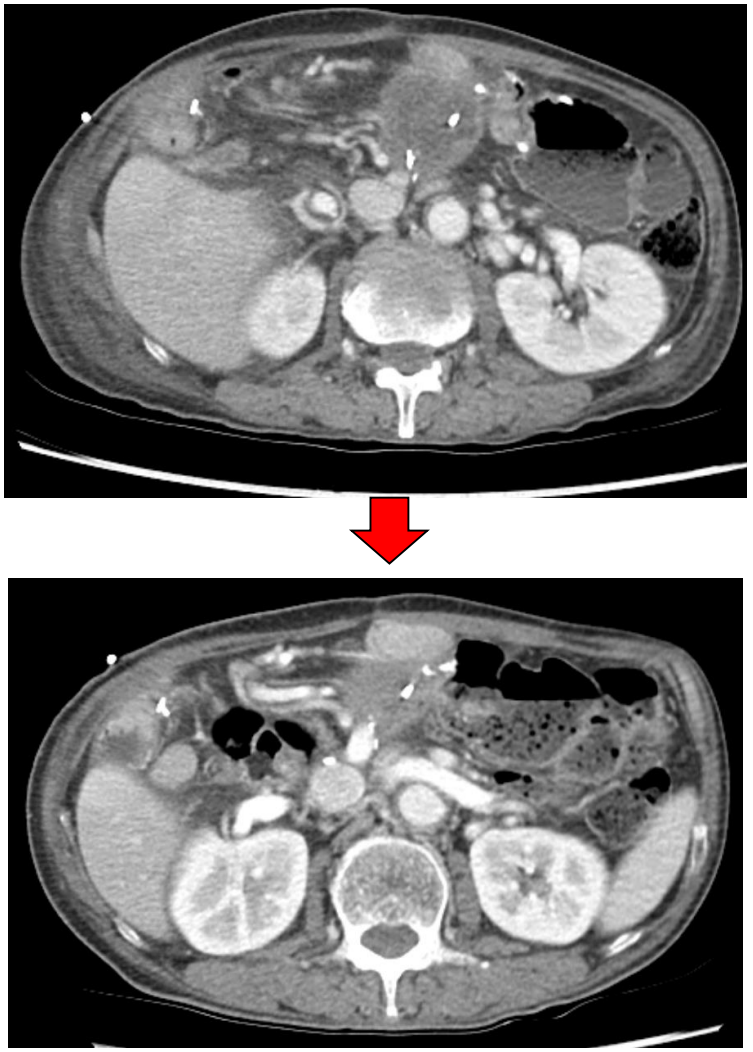
  MSH2 : Negative

  MSH6 : Negative

  p53 : Positive

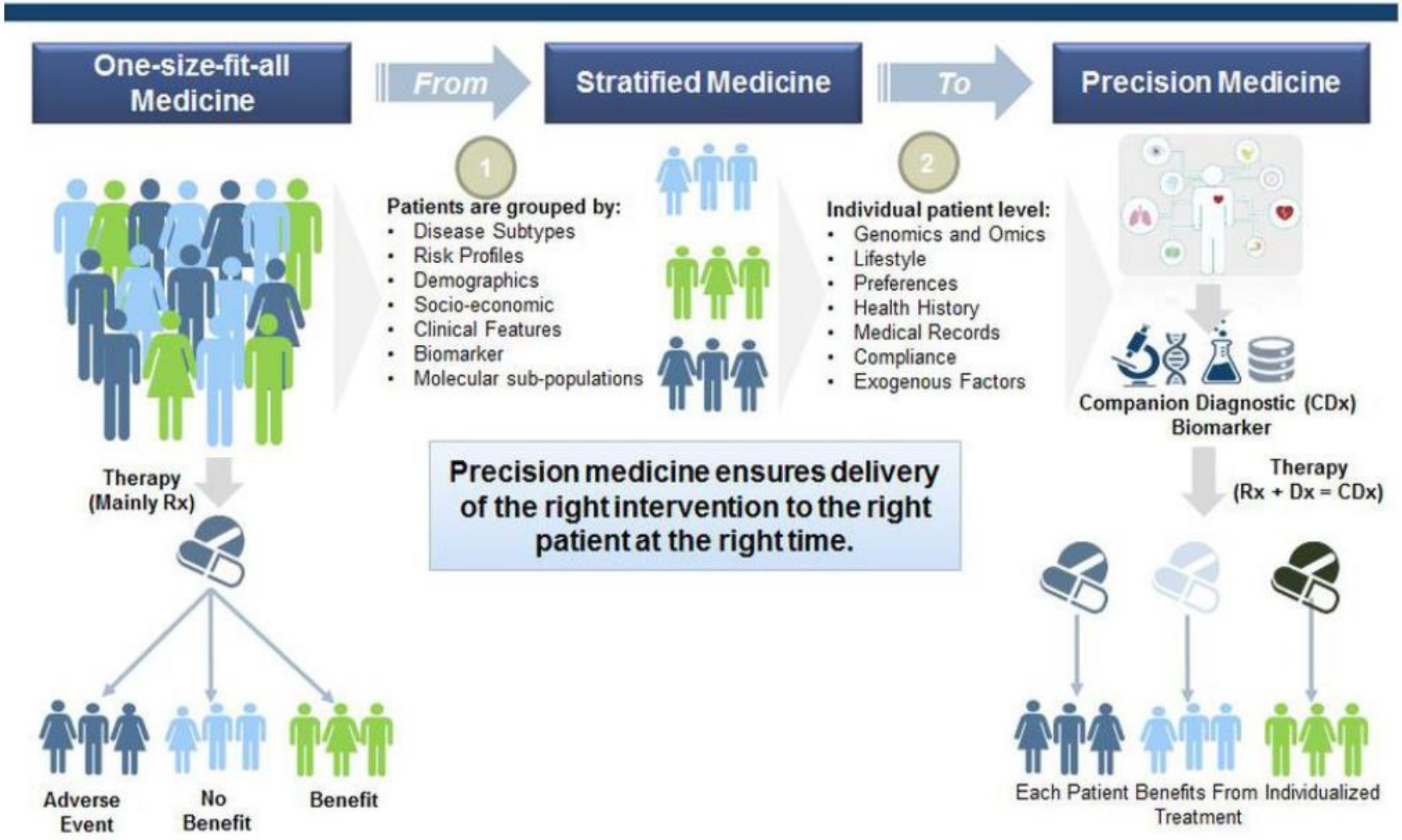
- 2019.8.6 – Nivolumab montherapy

MSI-H detection for Immunotherapy
MLH1, PMS2, MSH2, MSH6



정밀의료 (Precision Medicine)

치료의 새로운 변화들


One-size-fit-all Medicine
From
Stratified Medicine
To
Precision Medicine
1
Patients are grouped by:
• Disease Subtypes
• Risk Profiles
• Demographics
• Socio-economic
• Clinical Features
• Biomarker
• Molecular sub-populations
2
Individual patient level:
• Genomics and Omics
• Lifestyle
• Preferences
• Health History
• Medical Records
• Compliance
• Exogenous Factors
Companion Diagnostic (CDx) Biomarker
Therapy (Mainly Rx)
Therapy (Rx + Dx = CDx)
Precision medicine ensures delivery of the right intervention to the right patient at the right time.
Adverse Event
No Benefit
Benefit
Each Patient Benefits From Individualized Treatment

Thank you for your attention.