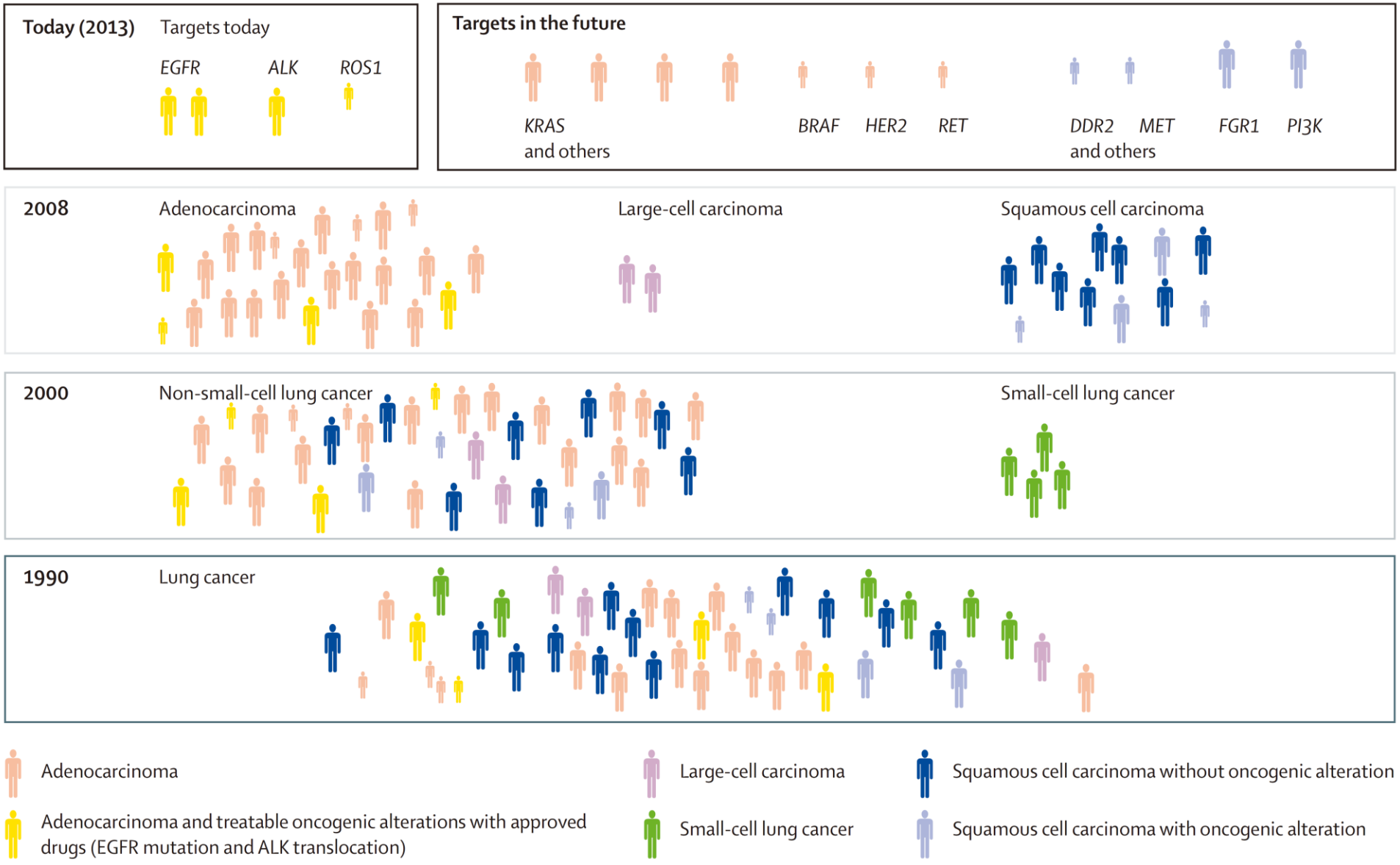
The Korean Academy of Tuberculosis and Respiratory Diseases
Lung Cancer School 2017
일자 : 2017년 7월 22일(토)
장소 : 백범 김구 기념관 컨벤션홀

Case Oriented Clinical Applications of Lung Cancer

- EGFR Mutation Positive Patients -

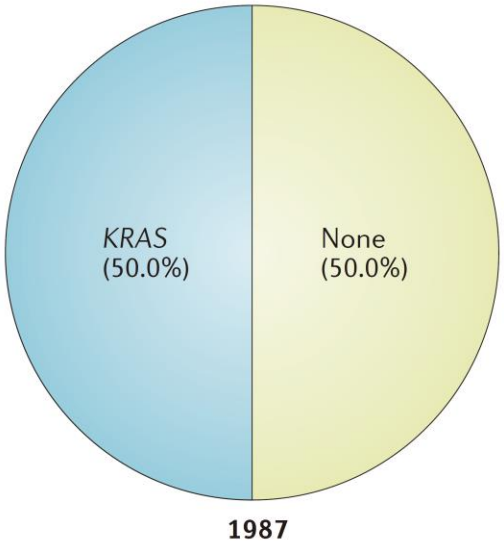
가톨릭의과대학 서울성모병원
김 승 준

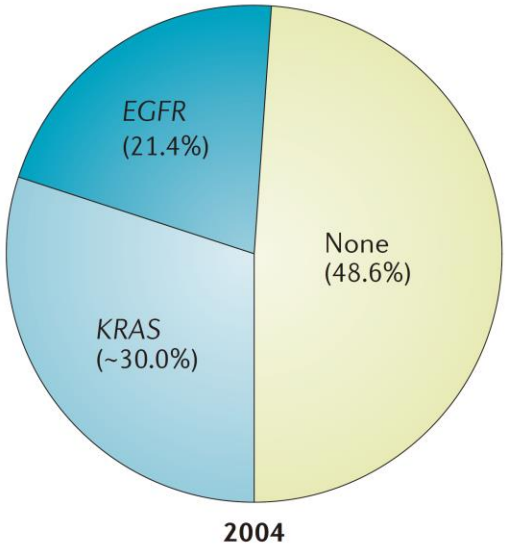
Evolution of lung cancer histology over time

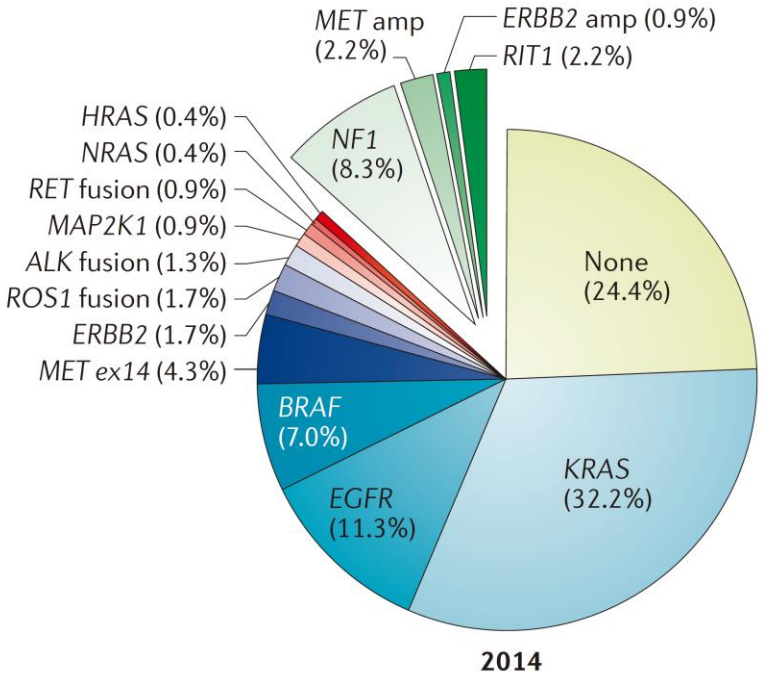


Reck, M., et al., Lancet, 2013. **382**(9893): p. 709-19.

Knowledge of non-small cell lung adenocarcinoma has evolved in recent decades

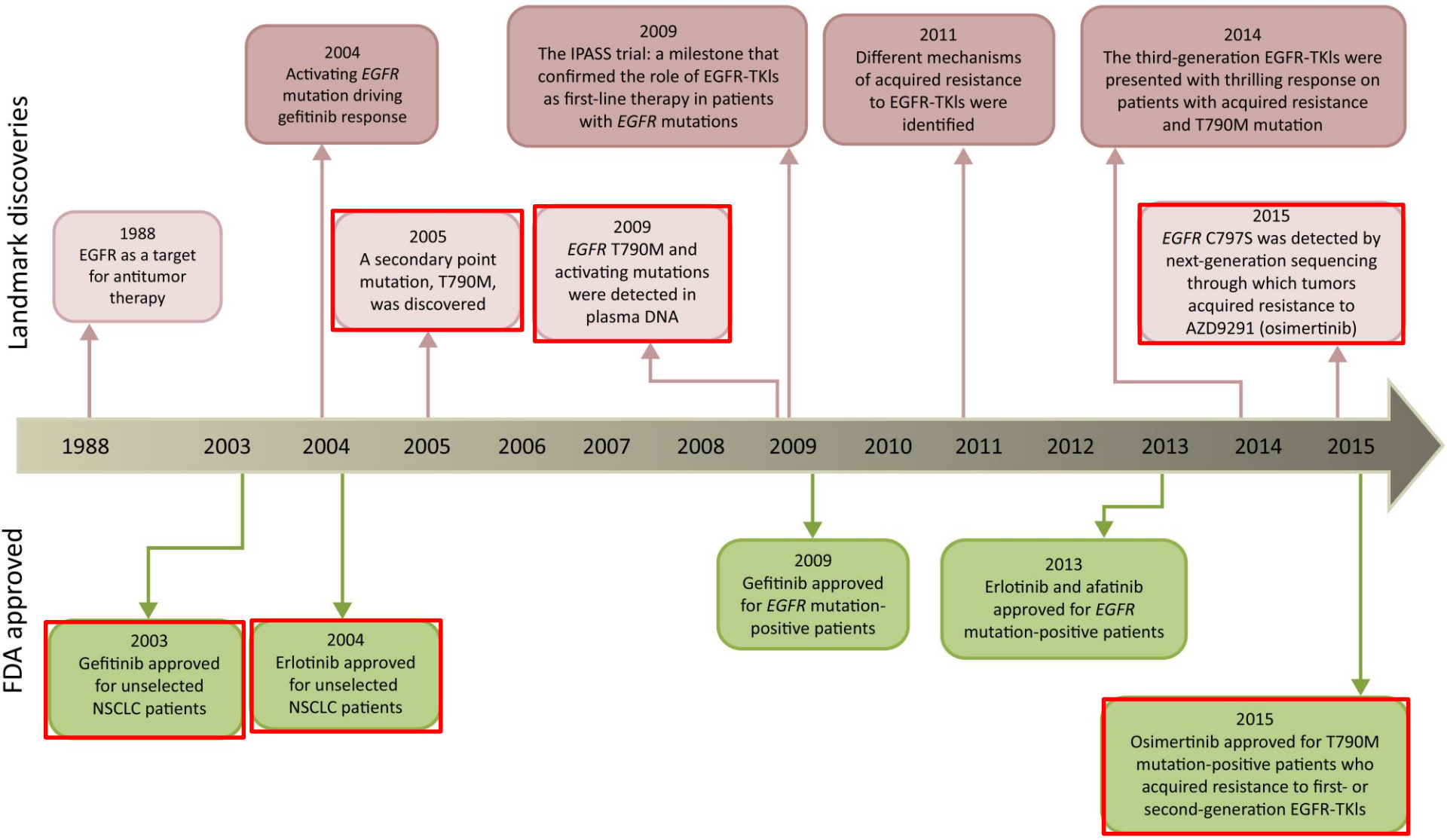






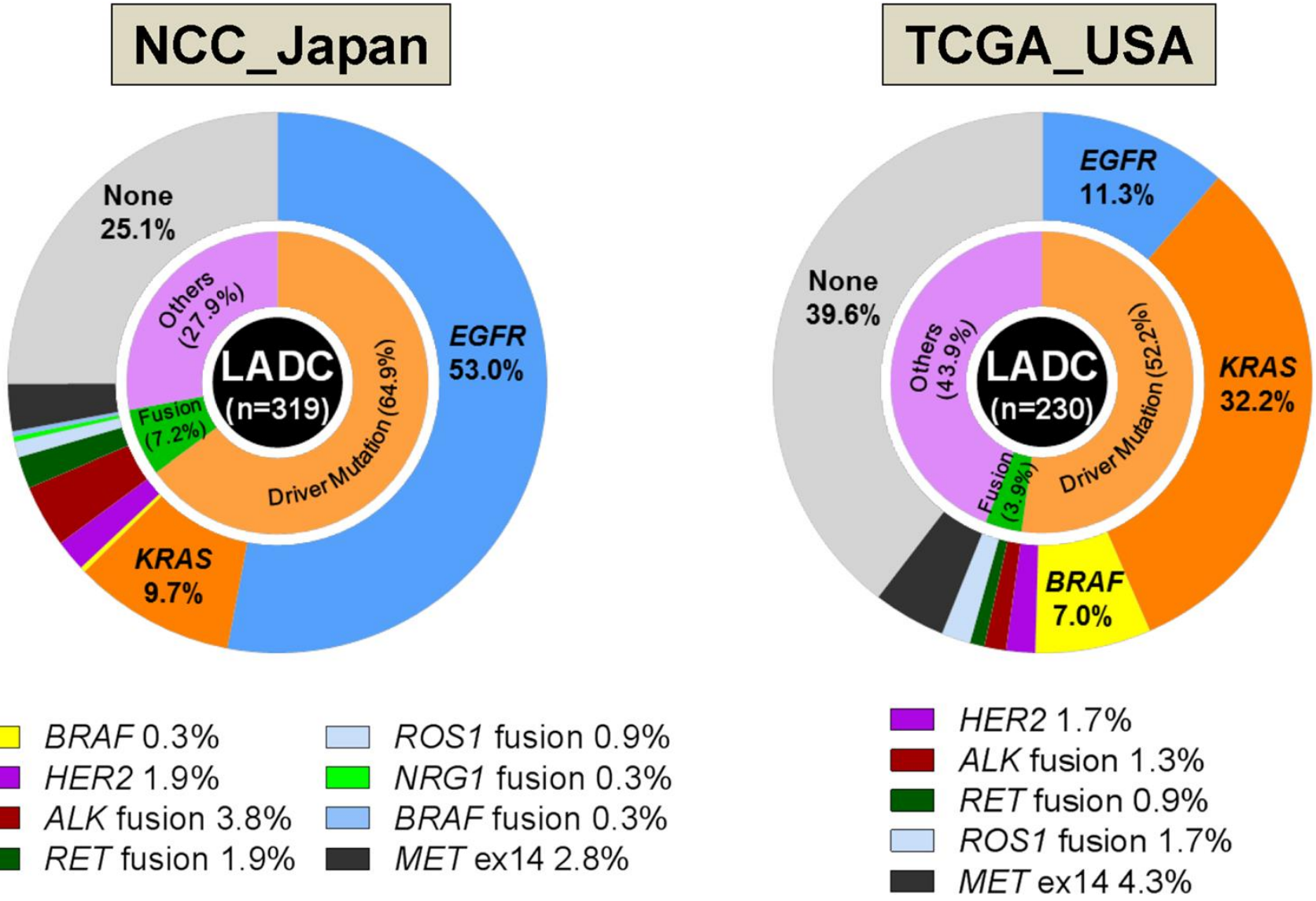
Vargas, A.J. and C.C. Harris, Nat Rev Cancer, 2016. **16**(8): p. 525-37.

Timeline of major progress made in targeting EGFR in management of lung cancer



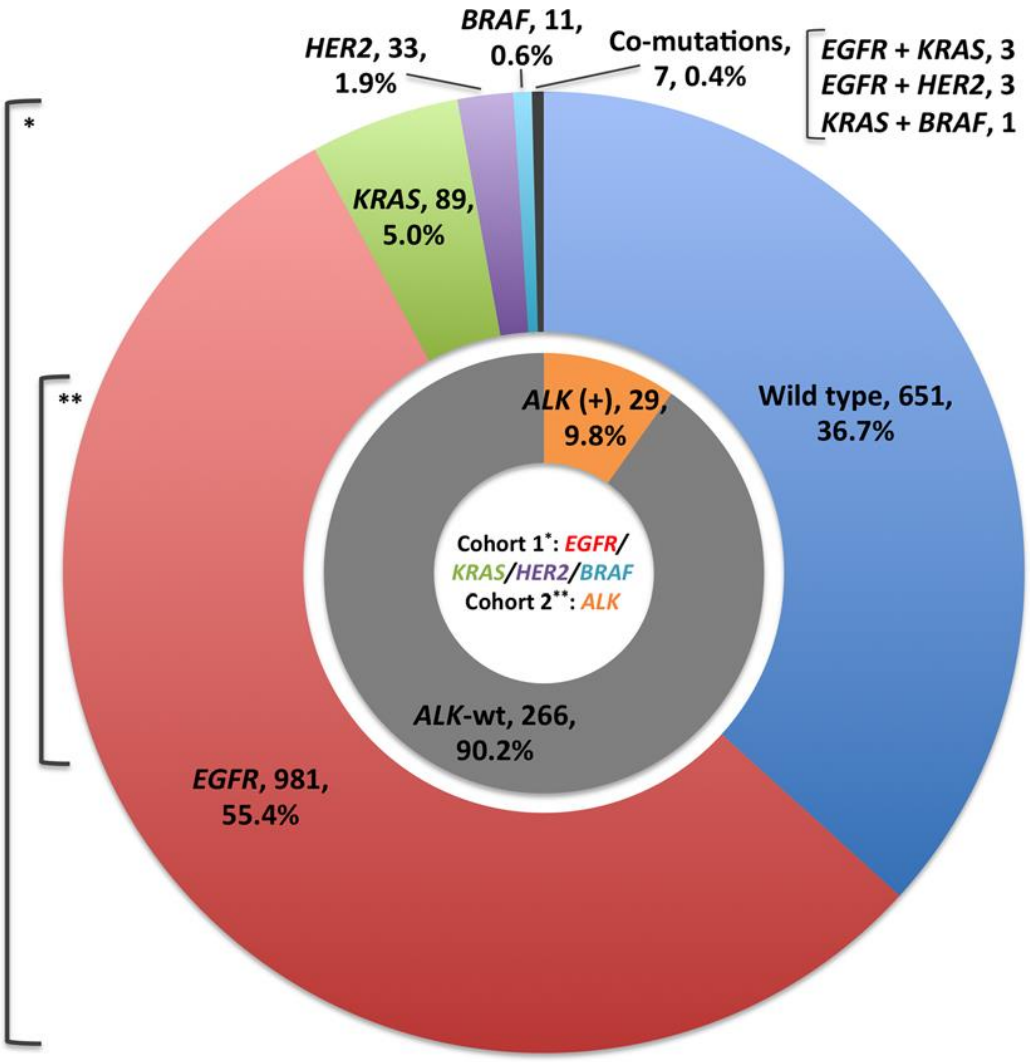
Ke, E.E. and Y.L. Wu, Trends Pharmacol Sci, 2016. **37**(11): p. 887-903.

Genetic alterations of lung adenocarcinoma



Saito, M., et al., Surg Today, 2017.

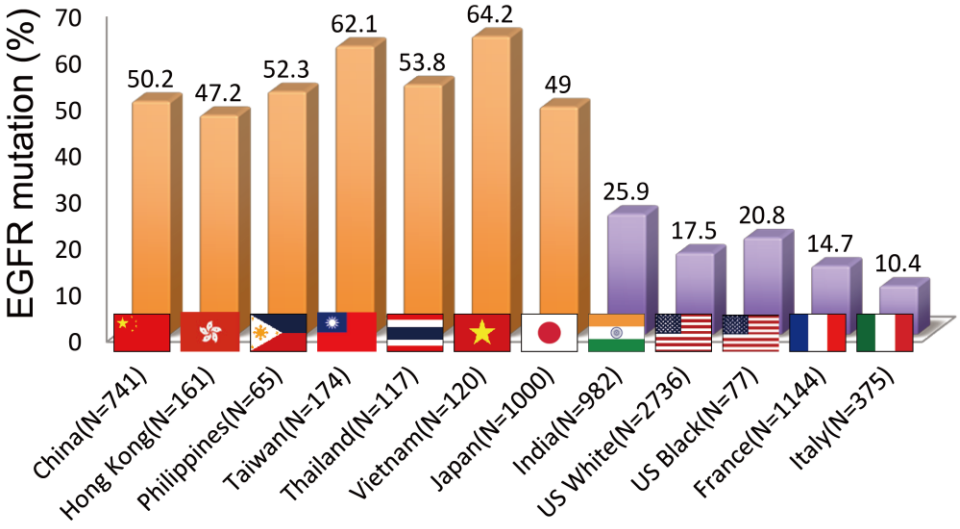
Genetic alterations of lung adenocarcinoma in Taiwan

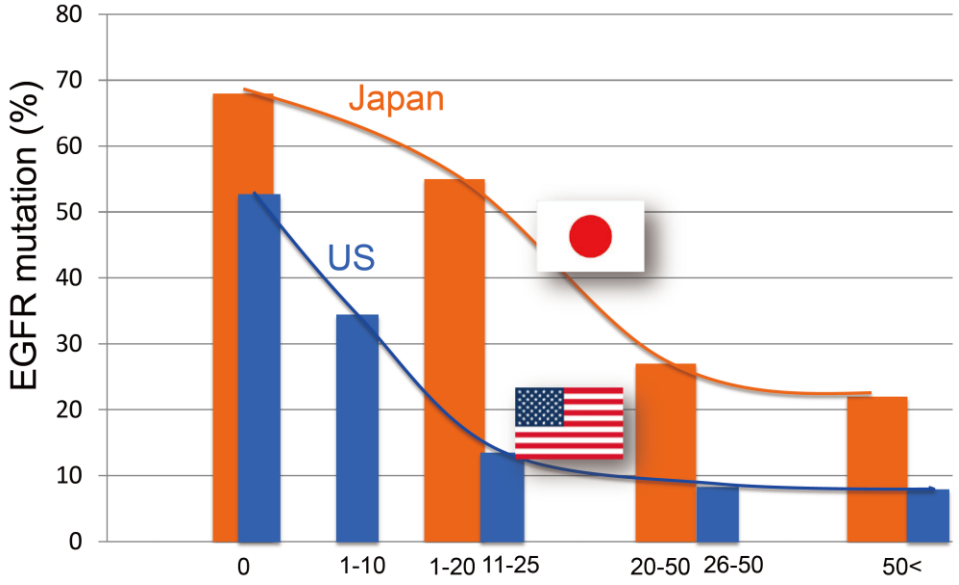


*Cohort 1 (n=1772 lung adenocarcinoma): testing of *EGFR/KRAS/HER2/BRAF*.
**Cohort 2 (n=295 *EGFR*-wt lung adenocarcinoma): testing of *ALK*.

Hsu, K.H., et al., PLoS One, 2015. **10**(3): p. e0120852.

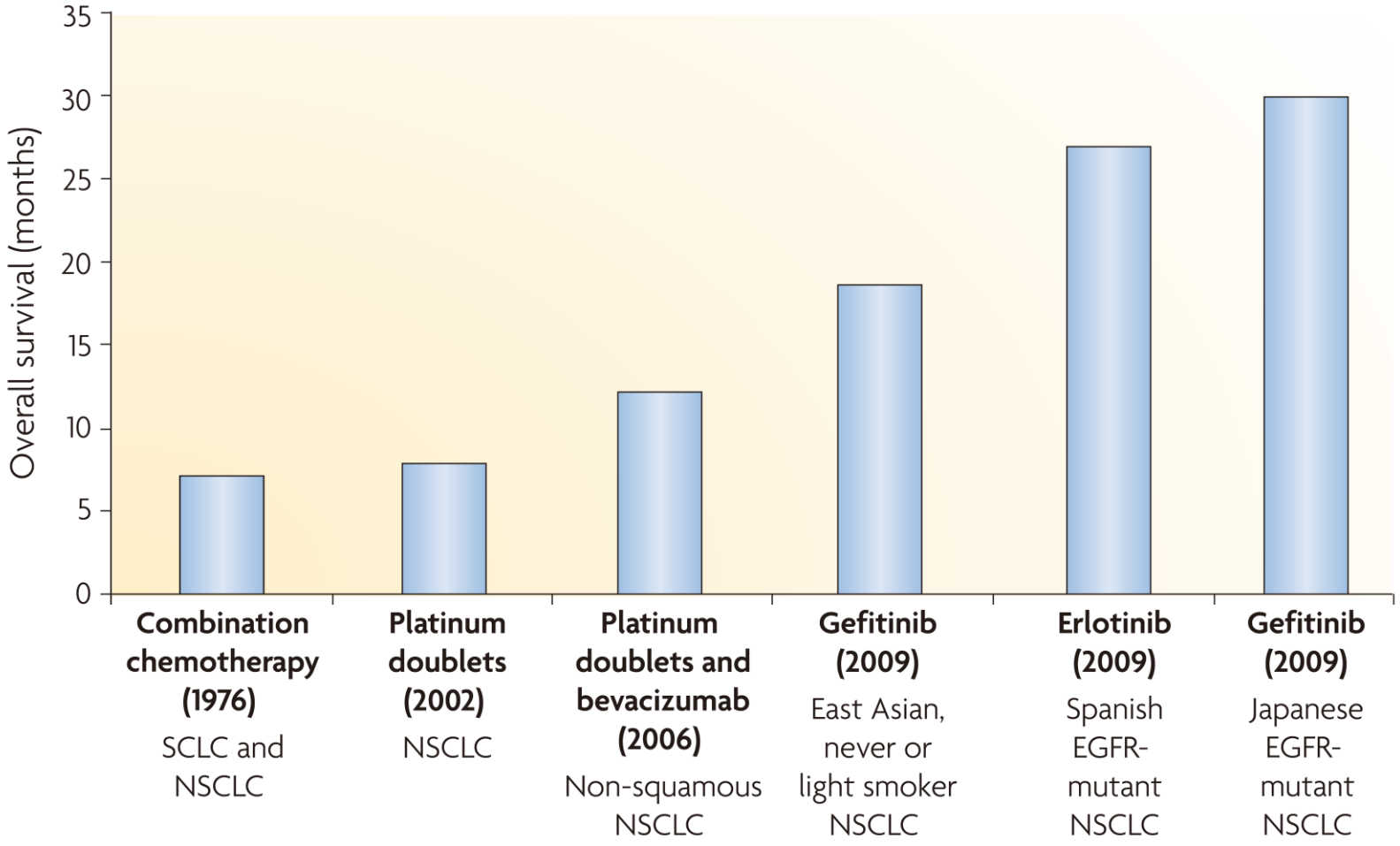
Frequency of EGFR mutations in lung cancer according to ethnic, geographic & smoking backgrounds





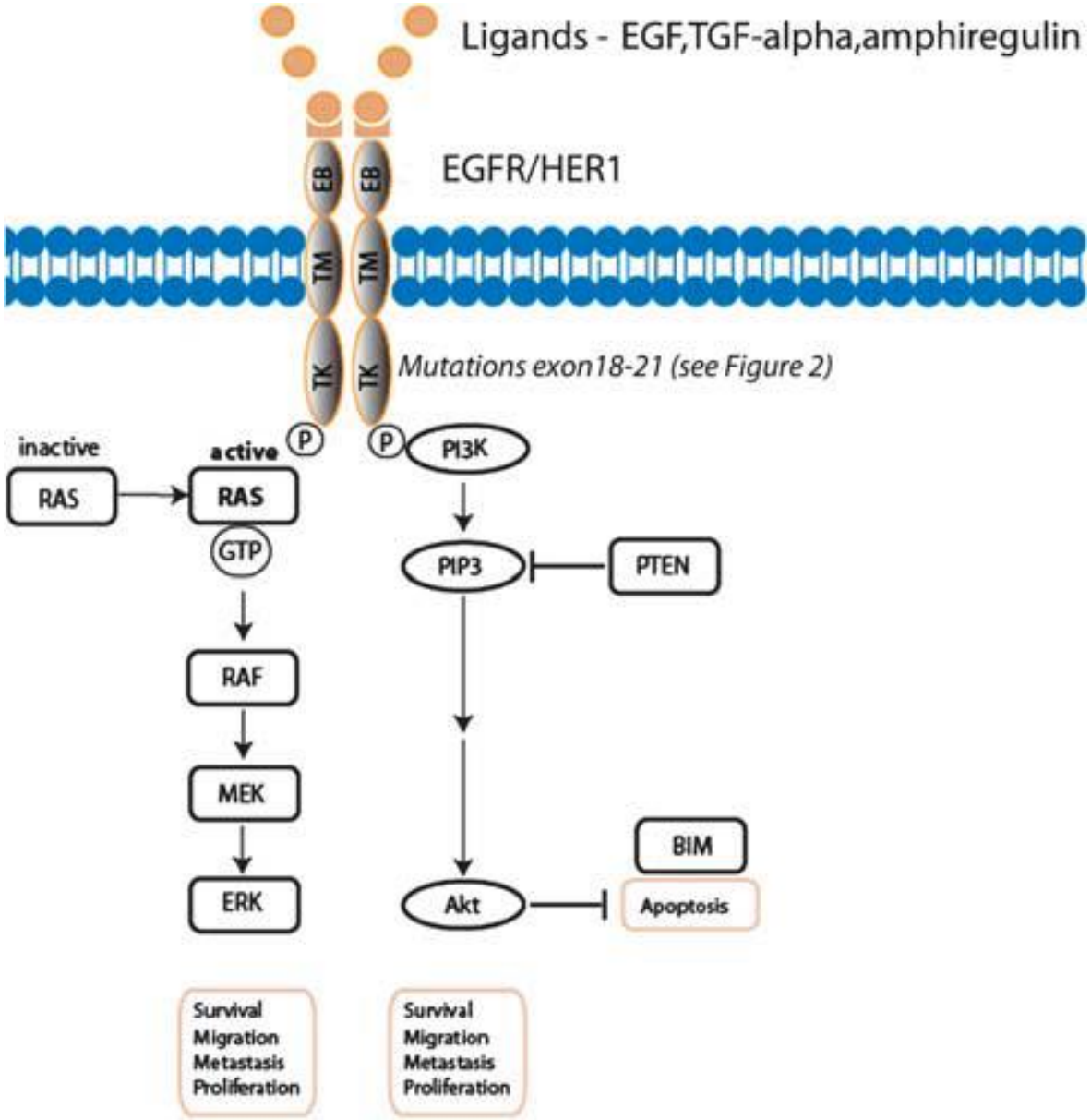
Mitsudomi, T., Transl Lung Cancer Res, 2014. **3**(4): p. 205-11.

Progress in the treatment of metastatic lung cancer



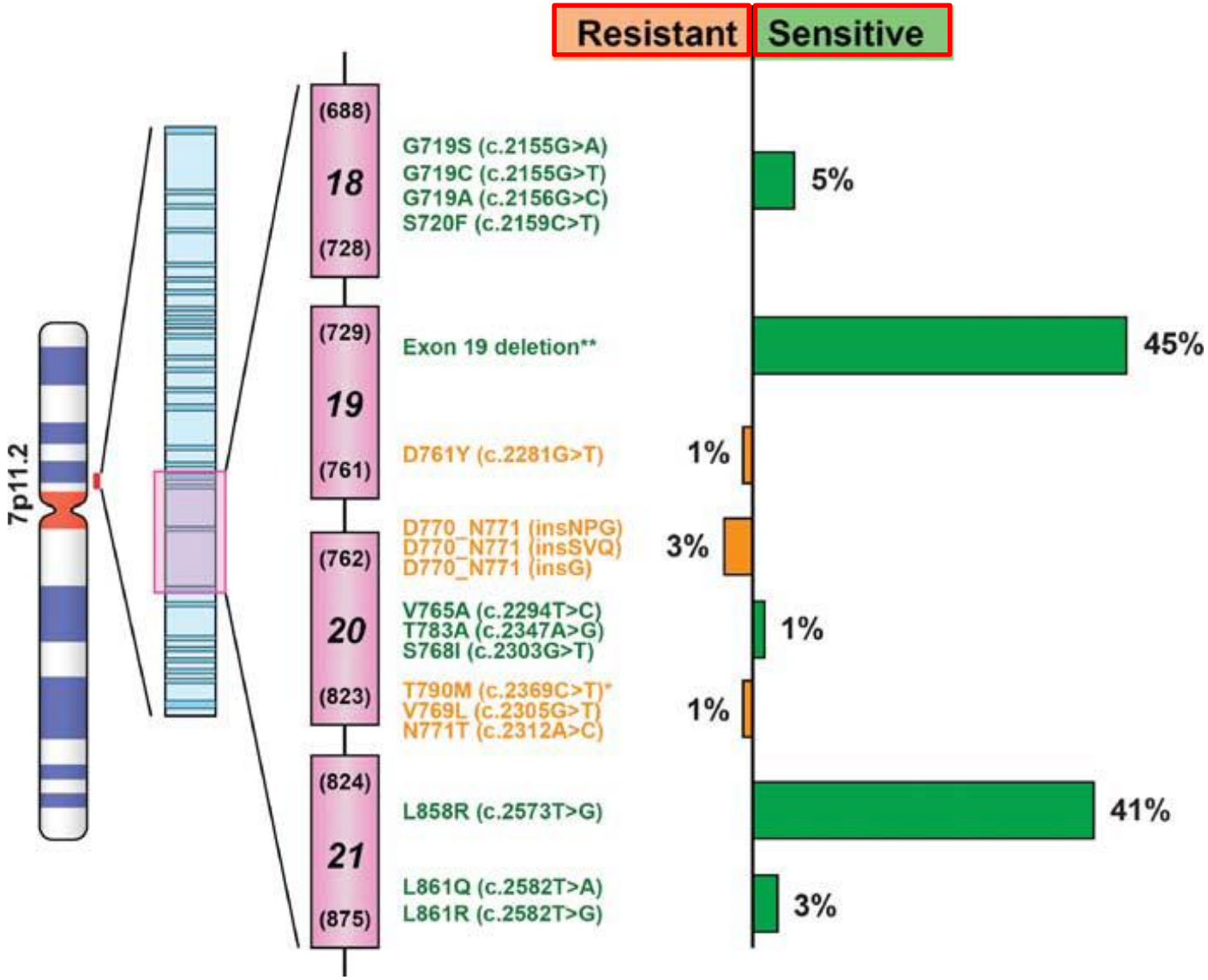
Pao, W. and J. Chmielecki, Nat Rev Cancer, 2010. **10**(11): p. 760-74.

Epidermal growth factor receptor (EGFR) pathway



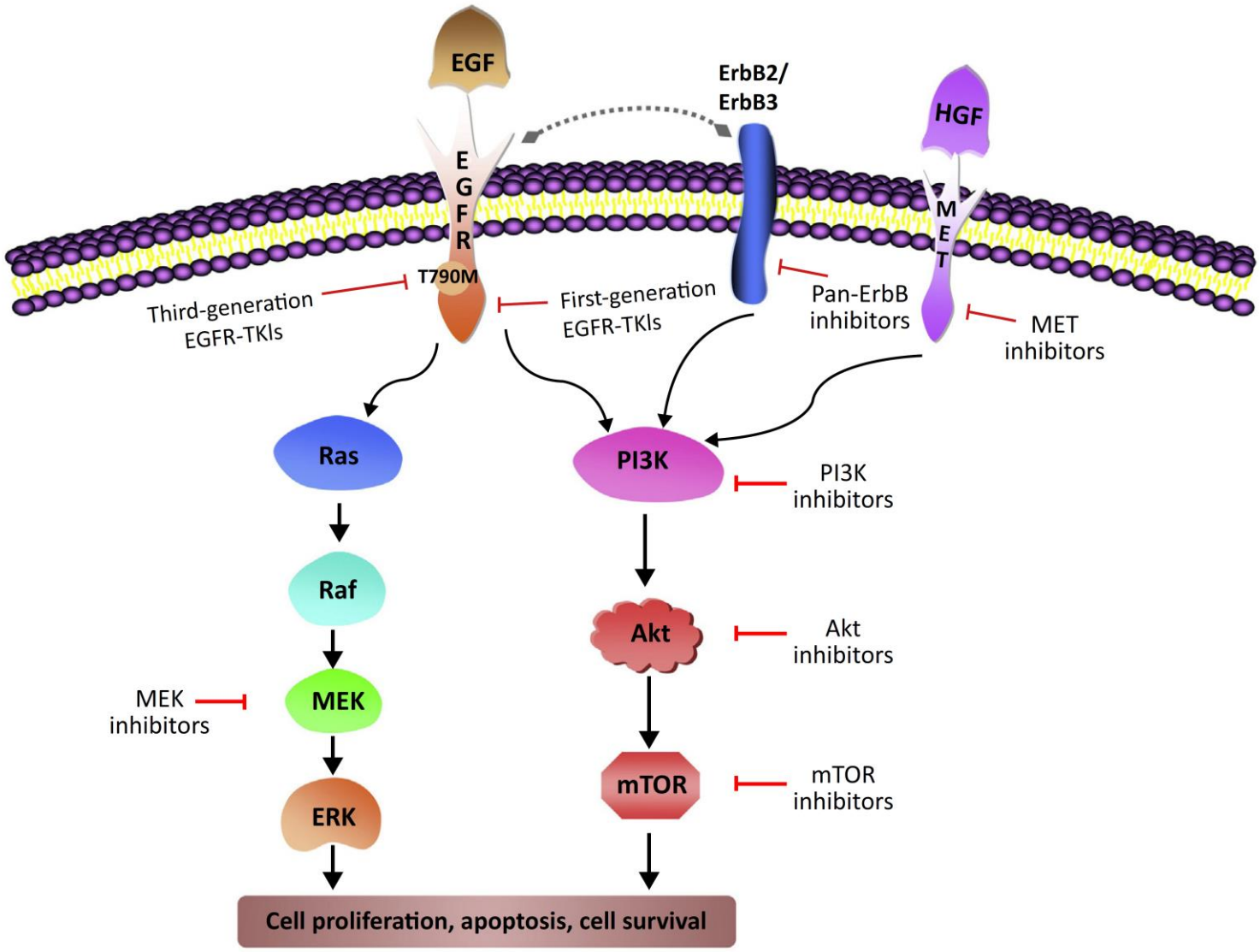
Siegelin, M.D. and A.C. Borczuk, Lab Invest, 2014. **94**(2): p. 129-37.

Frequency of mutations in exons 18-21 of EGFR gene & association with responsiveness to EGFR targeted therapy



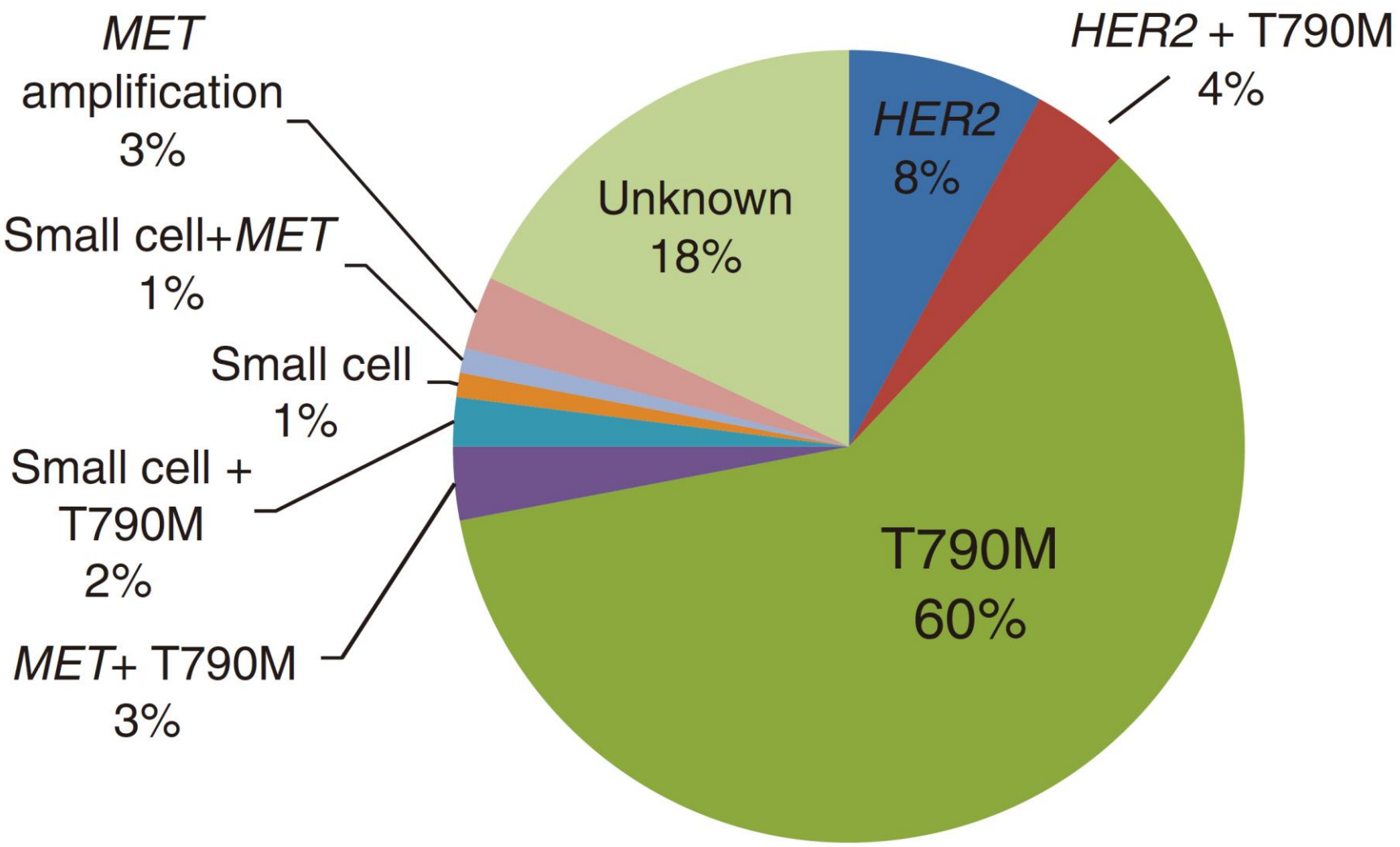
Cheng, L., et al., Mod Pathol, 2012. **25**(3): p. 347-69.

Mechanisms of acquired resistance to EGFR-TKIs & agents used to overcome resistance



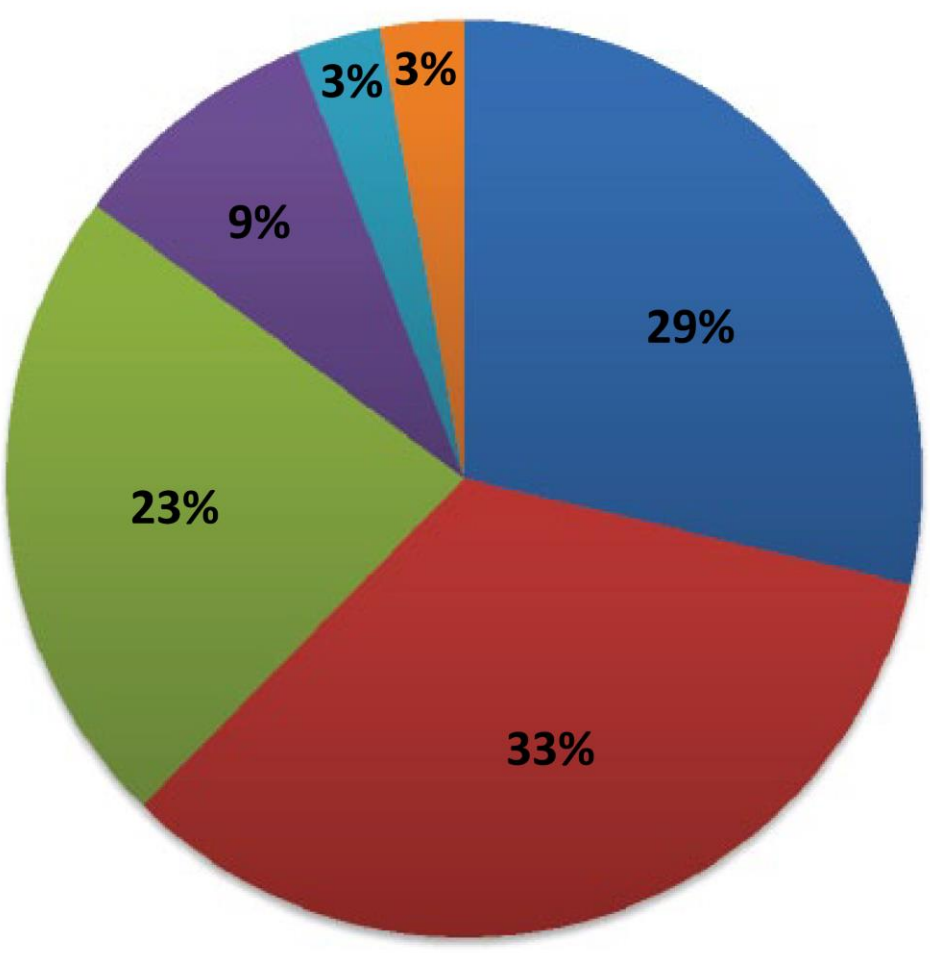
Ke, E.E. and Y.L. Wu, Trends Pharmacol Sci, 2016. **37**(11): p. 887-903.

Relative frequencies of acquired resistance mechanisms



Yu, H.A., et al., Clin Cancer Res, 2013. **19**(8): p. 2240-7.

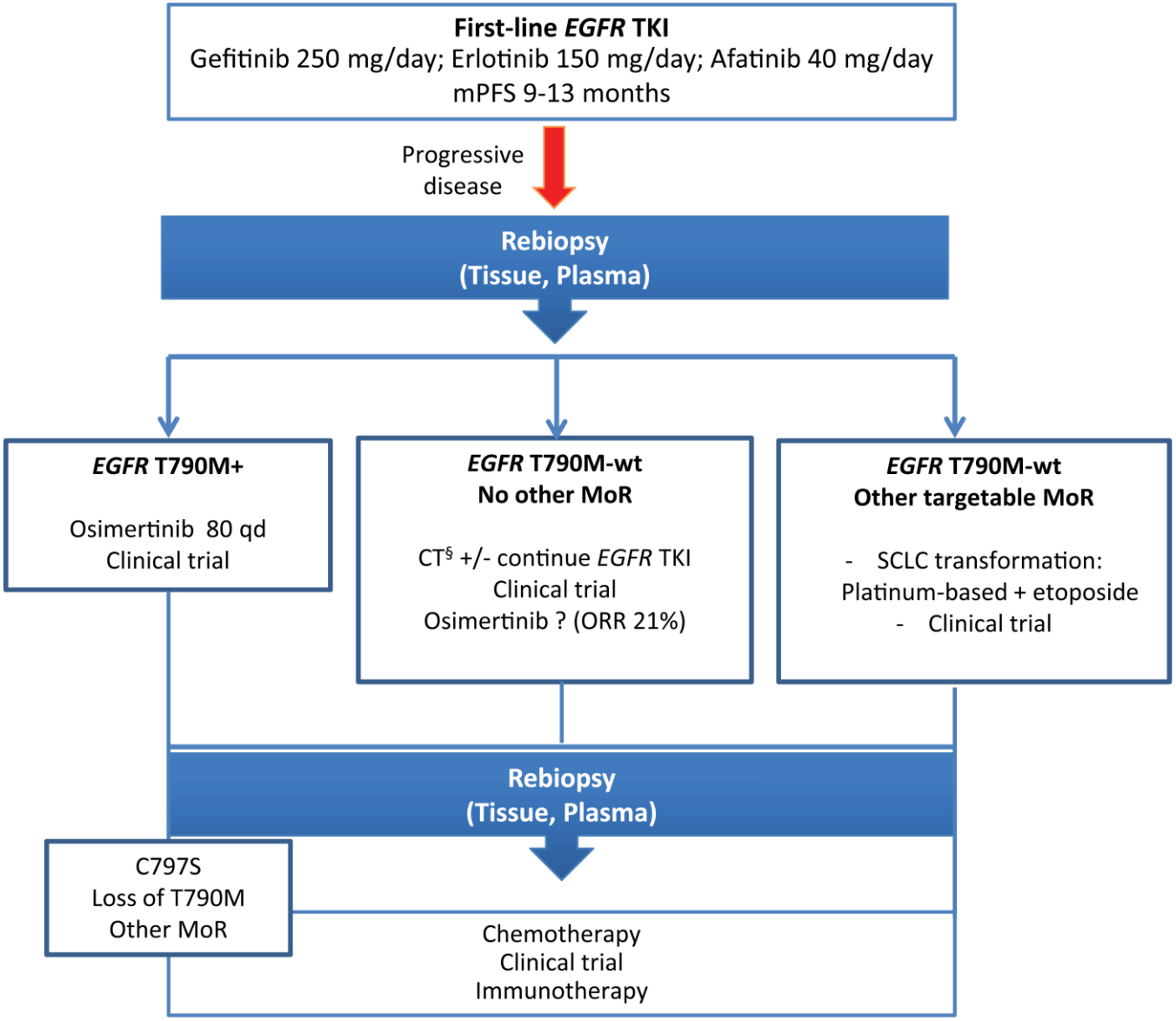
Mechanisms of resistance to 3rd-generation EGFR TKIs



- T790M "loss"
- T790M "maintained" (no resistance mechanism identified)
- C797S/T790M-positive
- SCLC/T790-wild-type
- *HER2* amp/T790-wild-type
- *MET* amp/T790-wild-type

Sullivan, I. and D. Planchard, Ther Adv Respir Dis, 2016. **10**(6): p. 549-565.

Potential treatment algorithm for EGFR-mutated advanced NSCLC



Sullivan, I. and D. Planchard, Ther Adv Respir Dis, 2016. **10**(6): p. 549-565.

최 OO, F/75

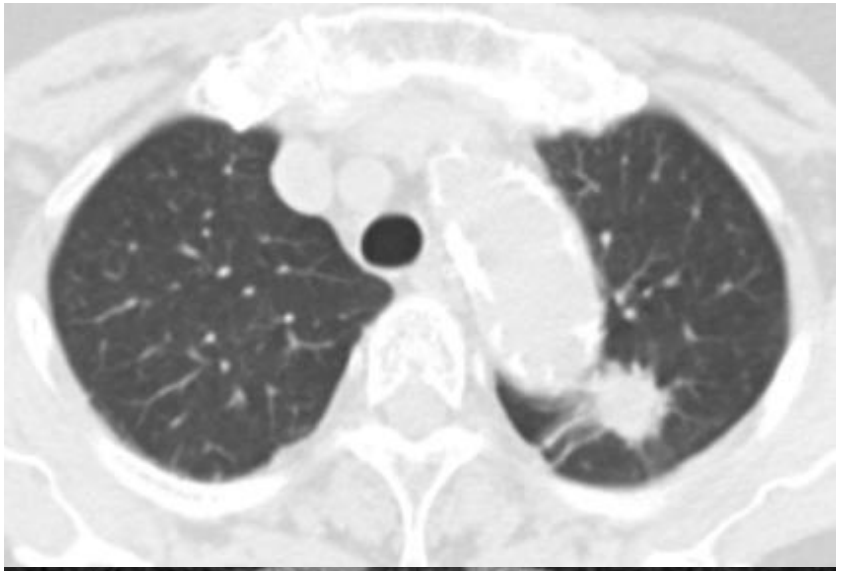
- 주 증상: 한 달 간 두통과 몸이 한 쪽으로 기우는

  증상으로 타 병원 흉부사진 상 폐암 의심 소견으로

  외래통해 입원

- Smoking Hx (-)

흉부사진



PET-CT

Brain MRI

Necrotic enhancing mass in Rt. cerebellar hemisphere
: R/O metastasis

진행 결과

- CT-guided lung Bx: Adenocarcinoma
- 병기: Stage IV, T1N0M1b
- 수행능력: ECOG 1

본 환자의 다음 치료 계획은?

1. EGFR 돌연변이 결과를 기다린다.

2. Platinum-based chemotherapy

3. Whole brain RT

4. Stereotactic body radiation therapy (뇌, SBRT)

5. 신경외과 의뢰 뇌 종양 제거술

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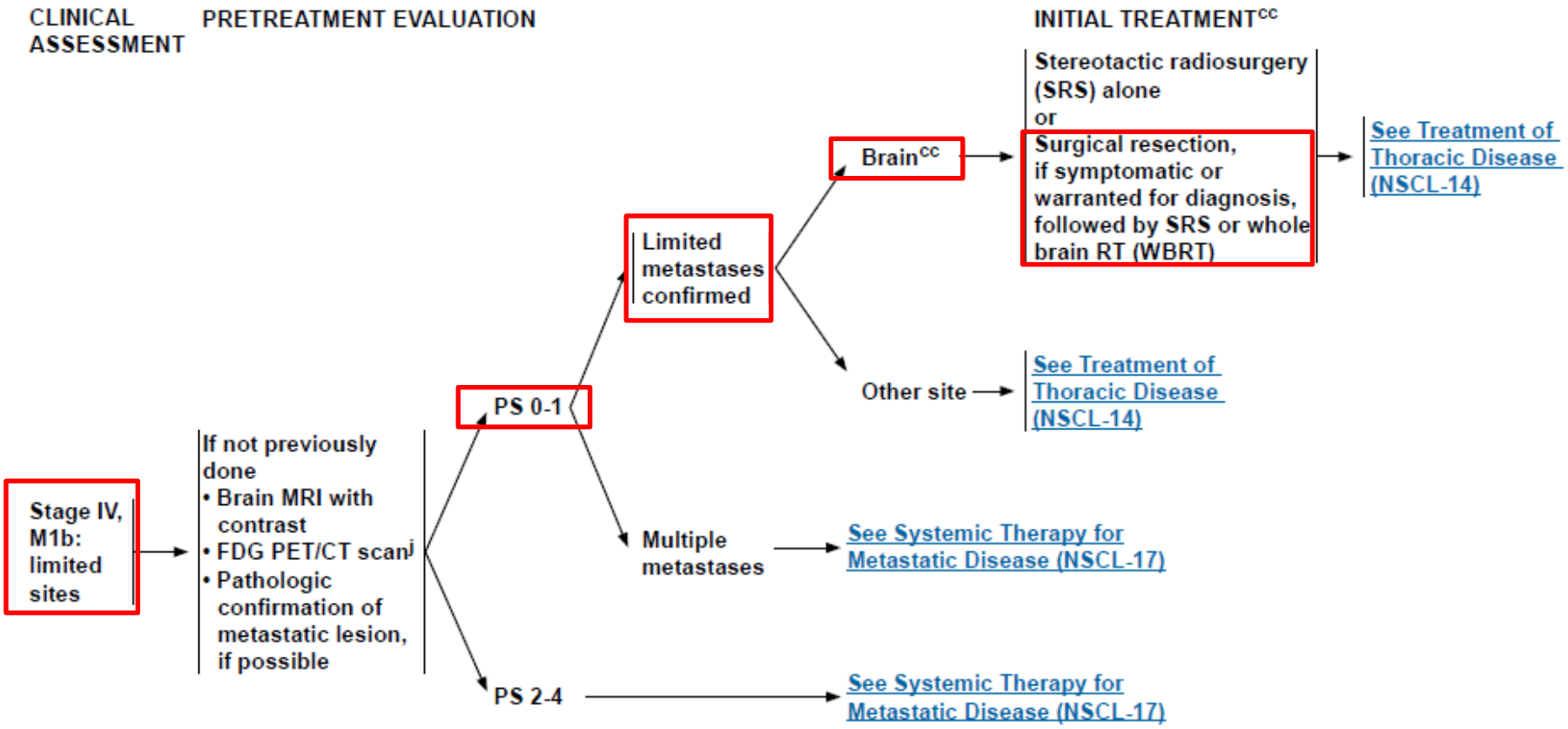

[j]PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation.
[cc]See NCCN Guidelines for Central Nervous System Cancers.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

추가 결과

- CT-guided lung Bx: Adenocarcinoma
- 돌연변이 결과: EGFR (+, exon21 p.L858R or p.L861Q)/ALK (-)
- 뇌 수술 조직: Adenocarcinoma

```
[IMMUNOHISTOCHEMISTRY]
     IH14-006588     Ki-67                    70 %
     IH14-006593     CK-7                     positive
     IH14-006593     CK-20                    negative
     IH14-006593     TTF-1                    positive
     IH14-006593     CDX-2                    negative

Additional Report 1      S14-037842      *진  단  일 : 20141014
     [DIAGNOSIS 1]
     Brain, cerebrum, excision:
        Adenocarcinoma, moderately differentiated, metastatic.

[COMMENT 1]
     폐 기원의 선암종이 전이한 것으로 생각합니다.
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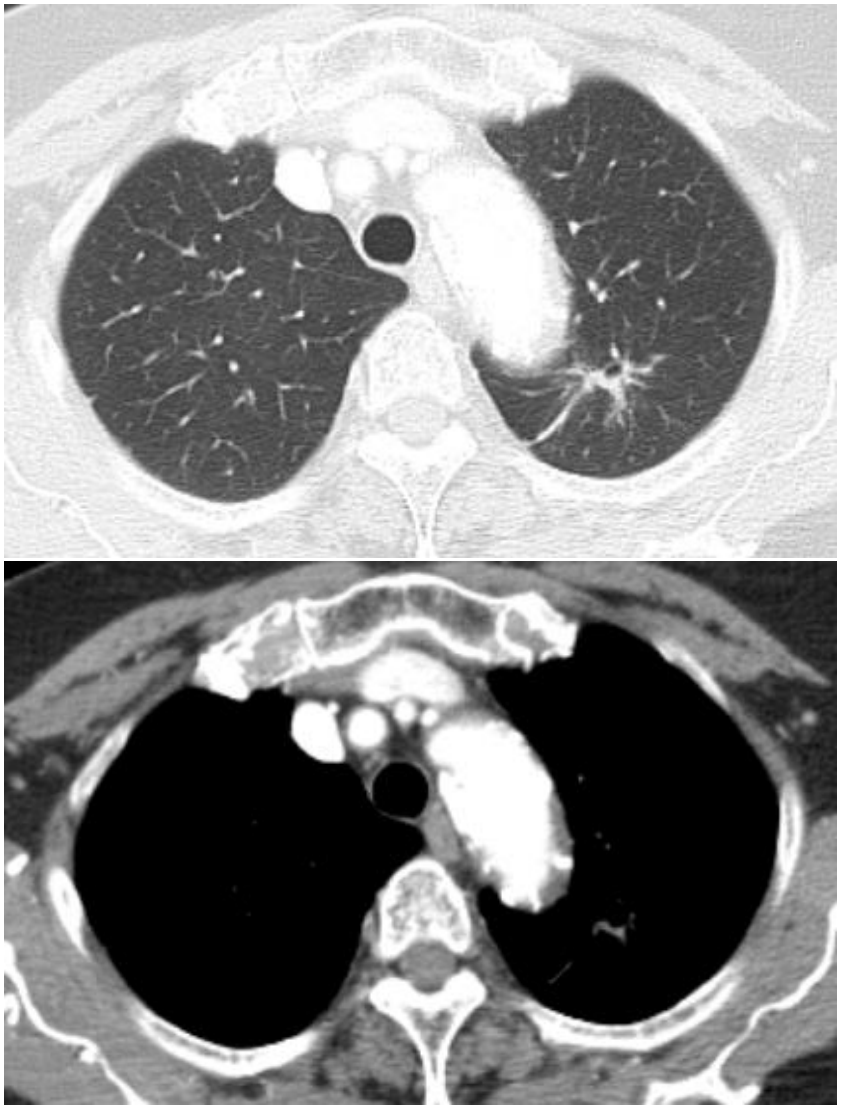
뇌 수술 및 타세바 10개월 치료 후



본 환자의 다음 치료 계획은?

1. 타세바 치료 유지

2. Platinum-based chemotherapy로 변경

3. Stereotactic body radiation therapy (폐, SBRT)

4. 폐 절제술

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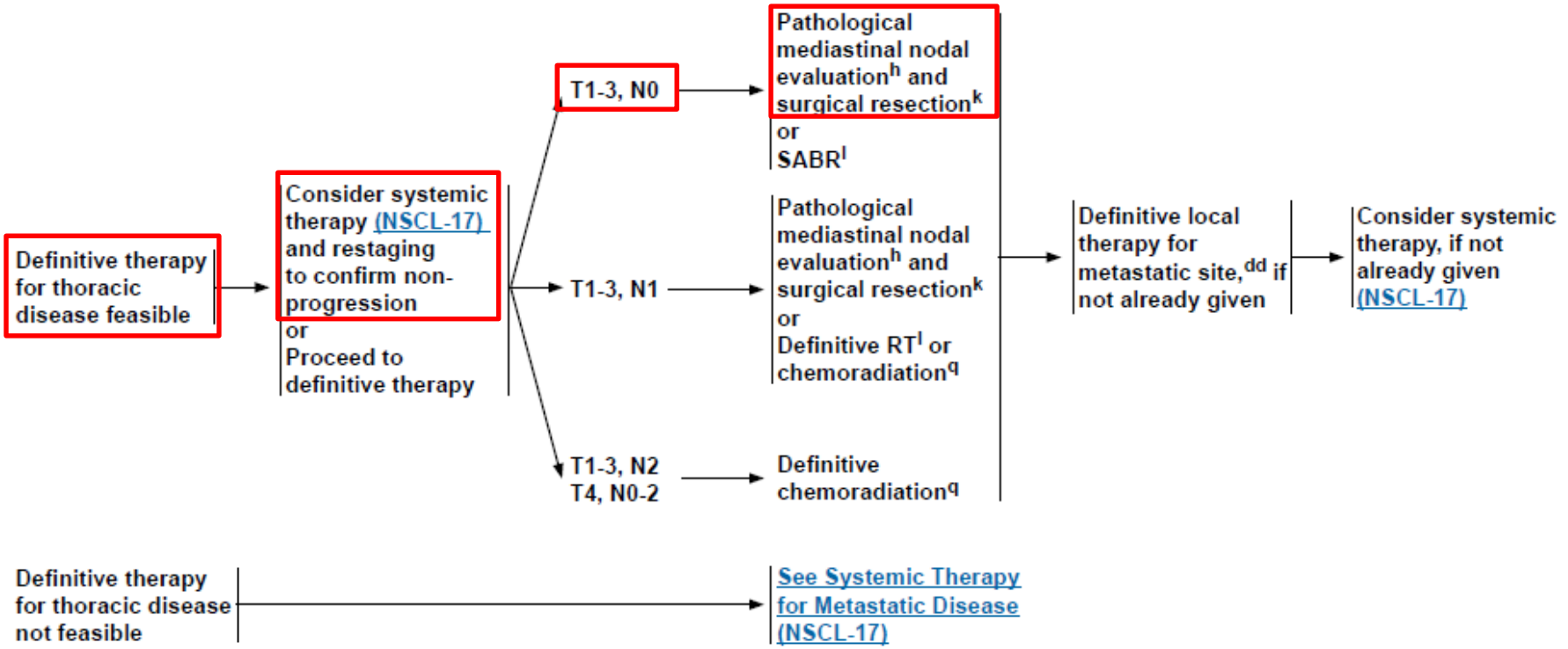
4. 폐 절제술

TREATMENT OF THORACIC DISEASE



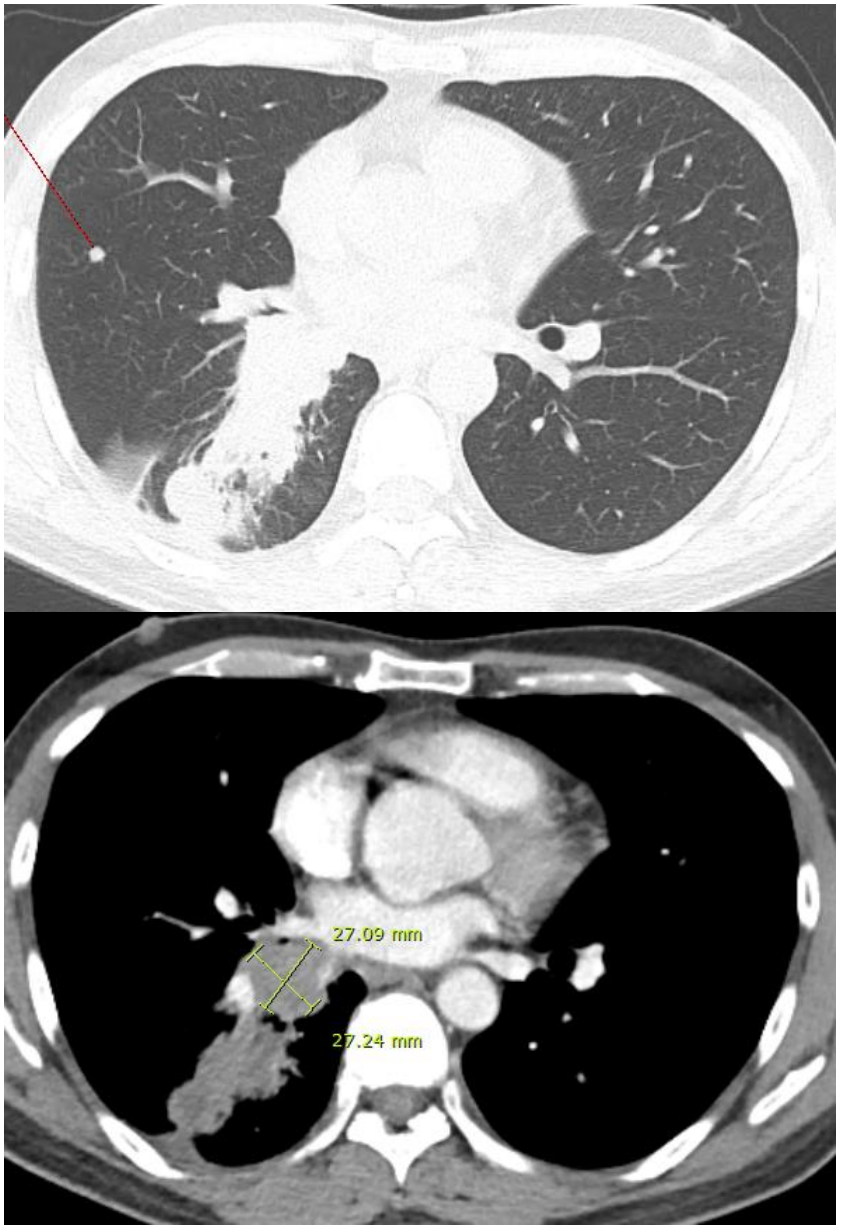
[h]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[dd]Typically, RT (including SABR) or surgical resection.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

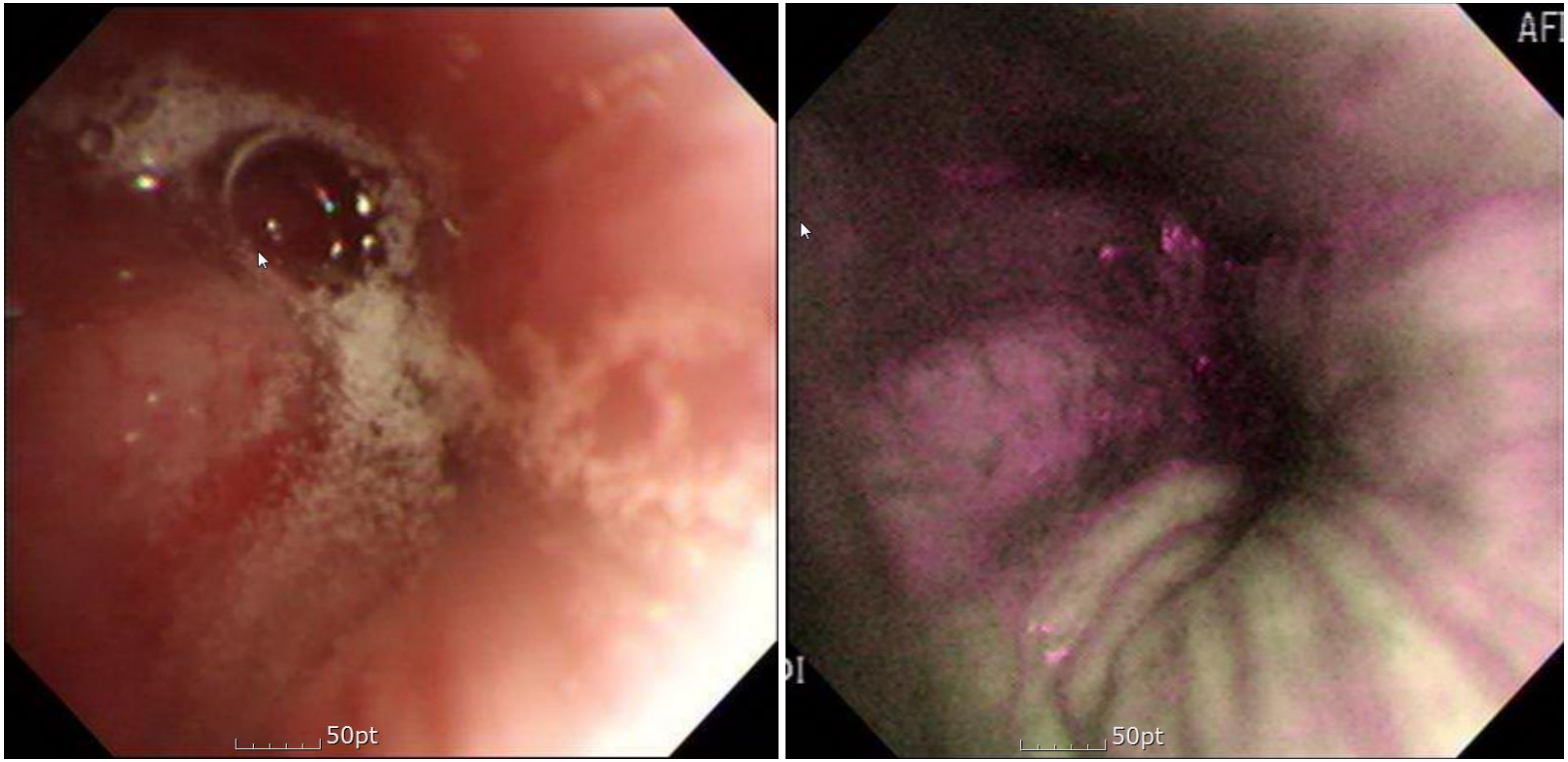
주 OO, M/43

- 주 증상: 감기 및 기침 증상으로 오랫동안 치료를 받아도 호전이 안되어 타 병원에서 흉부 CT 및 기관지내시경 검사 후 폐암 진단 받고 향후 치료위해 외래통해 입원
- Smoking Hx: 2년 반 전부터 금연, 그 전에는 8년 간 하루 평균 1/3갑 정도 흡연

흉부사진



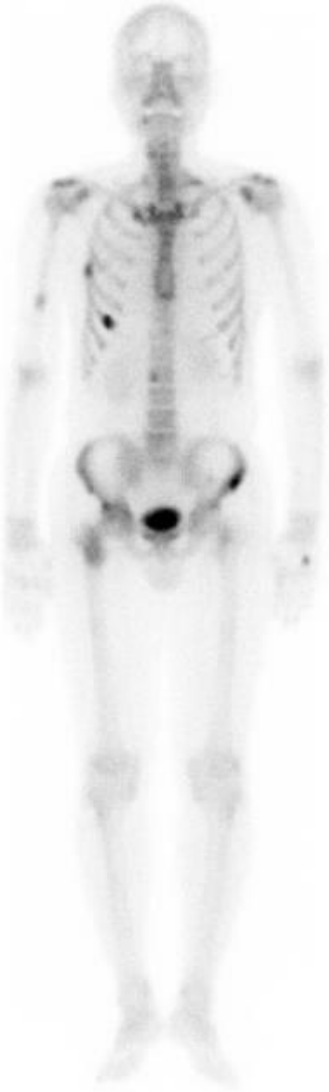
기관지내시경 검사

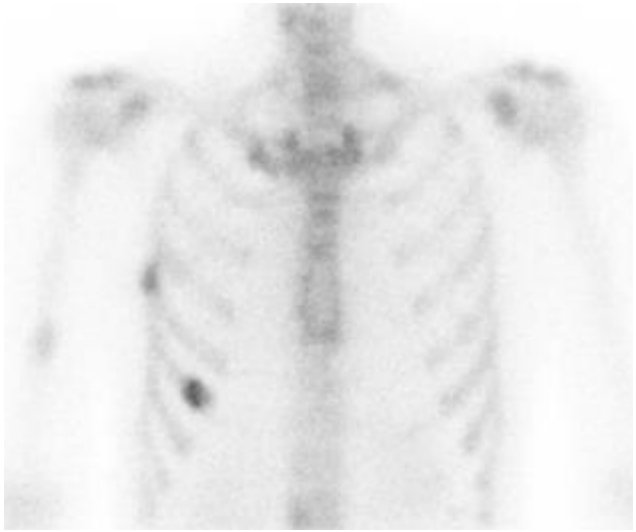


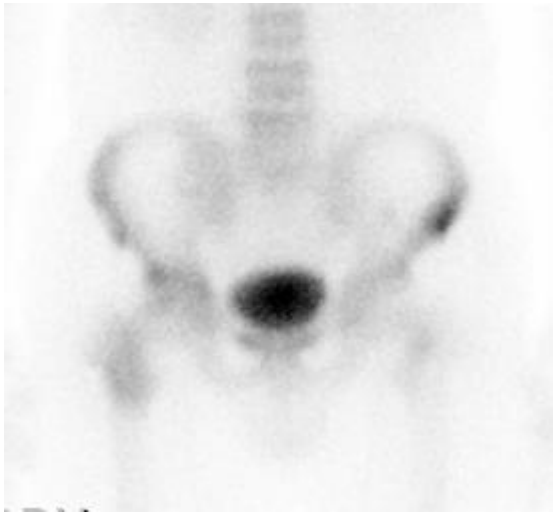
Rt. intermedius bronchus

PET-CT

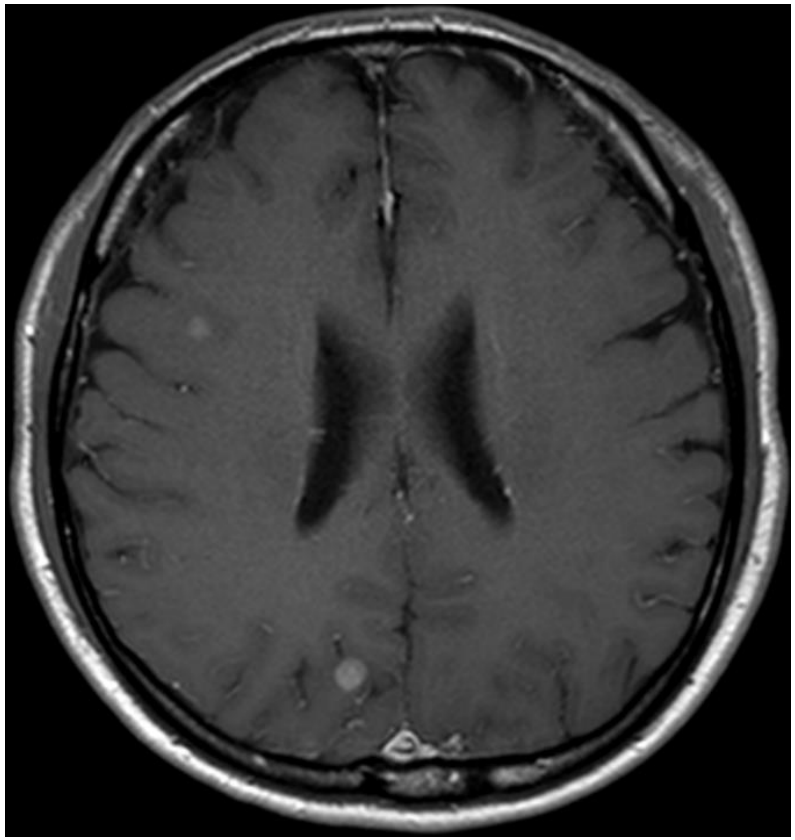
Bone scan

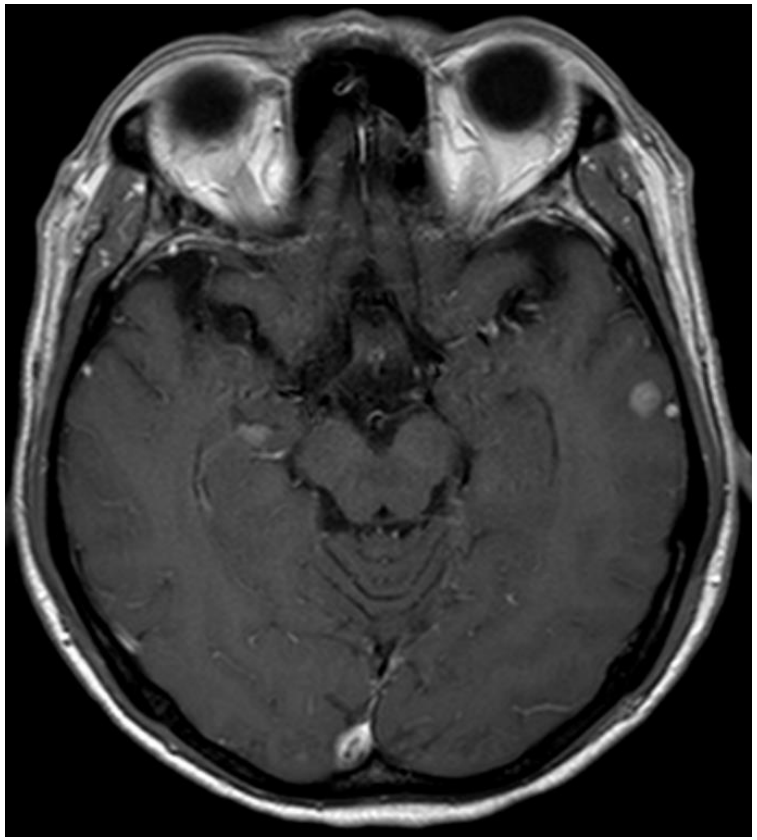






Brain MRI





Multifocal enhancing lesions with mild perilesional edema in both cerebral hemisphere: Brain metastasis

진행 결과

- Bronchoscopic Bx: Adenocarcinoma
- 병기: Stage IV, T4N3M1b
- 수행능력: ECOG 0

본 환자의 다음 치료 계획은?

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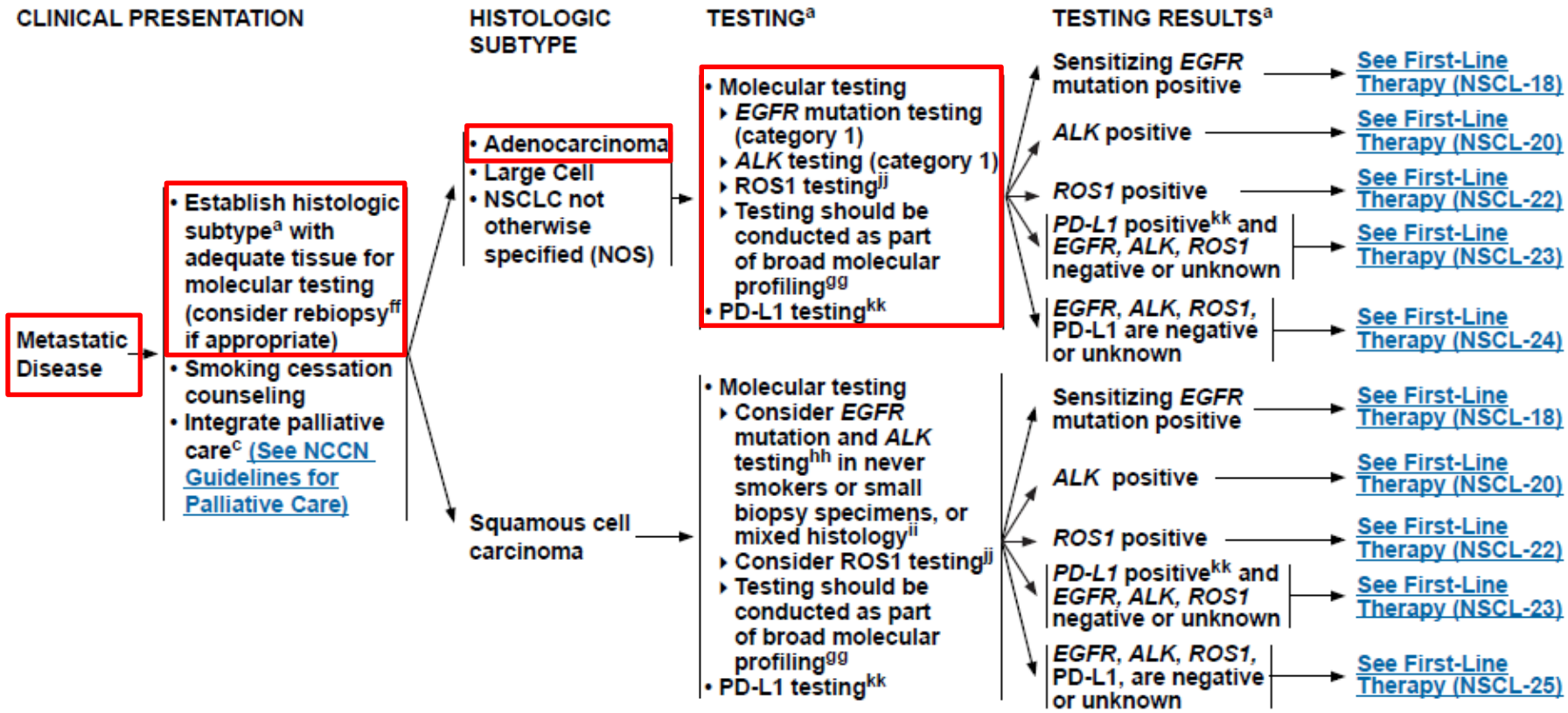

[a] See Principles of Pathologic Review (NSCL-A).

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[ff] If repeat biopsy is not feasible, plasma biopsy should be considered.

[gg] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

[hh] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

[ii] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[jj] Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

[kk] PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.
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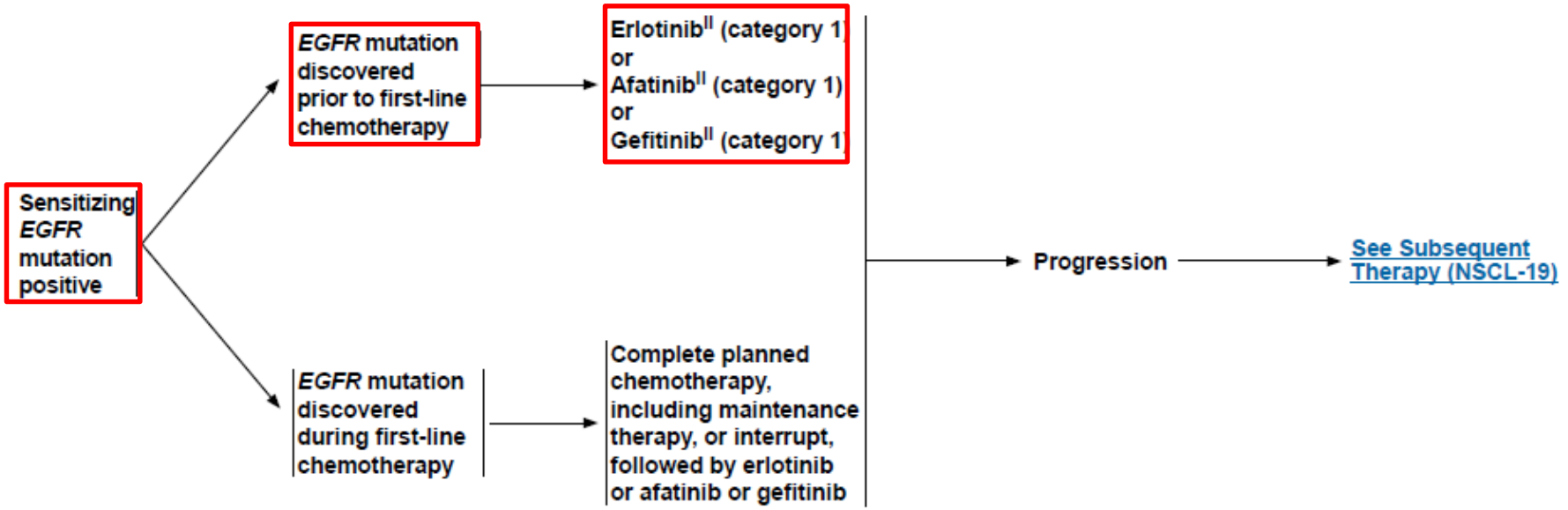
추가 결과

- Bronchoscopic Bx: Adenocarcinoma

- 돌연변이 결과: EGFR (+, exon19 deletion)/ALK (-)

SENSITIZING EGFR MUTATION POSITIVE[a]

FIRST-LINE THERAPY



[a] See Principles of Pathologic Review (NSCL-A).
[II] For performance status 0-4.

Note: All recommendations are category 2A unless otherwise indicated.
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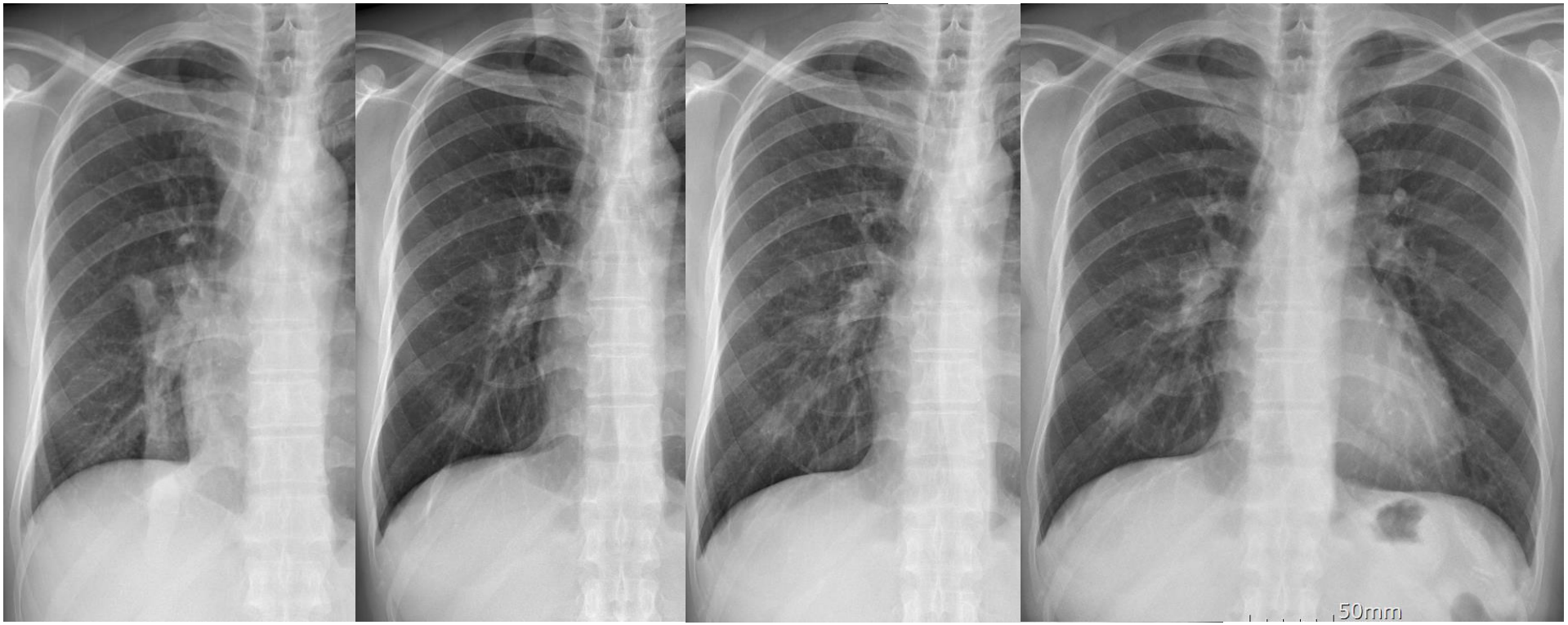
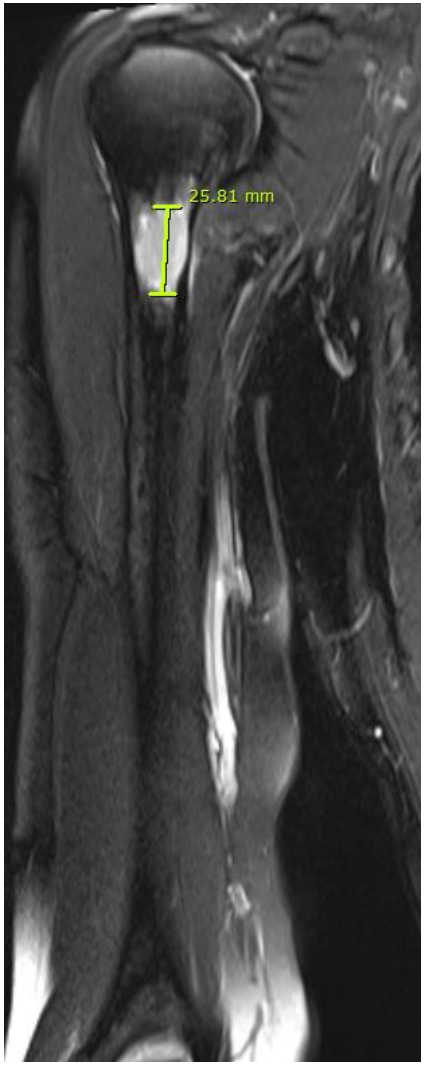
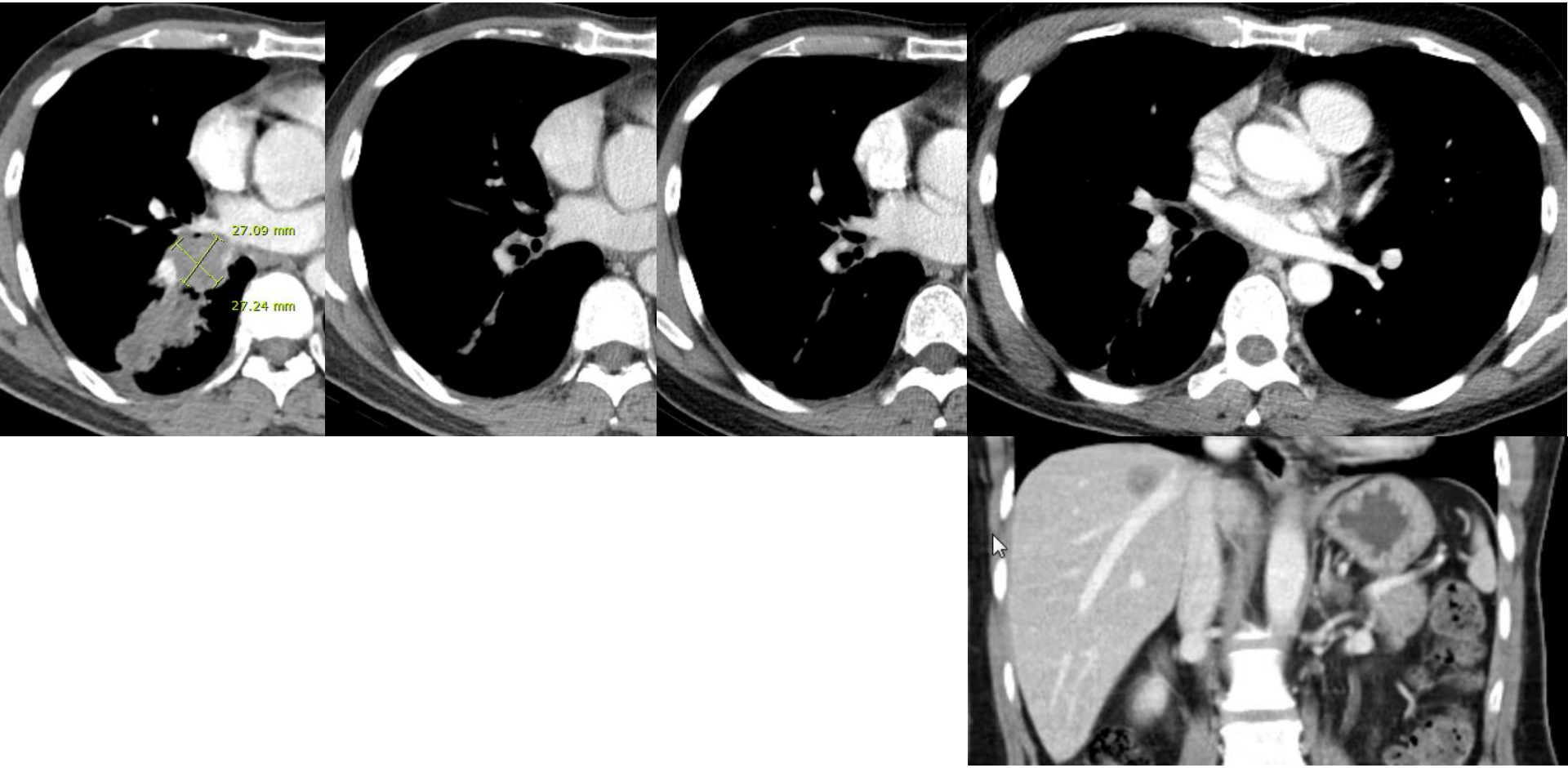
타세바 11개월 치료 후 흉부 X선



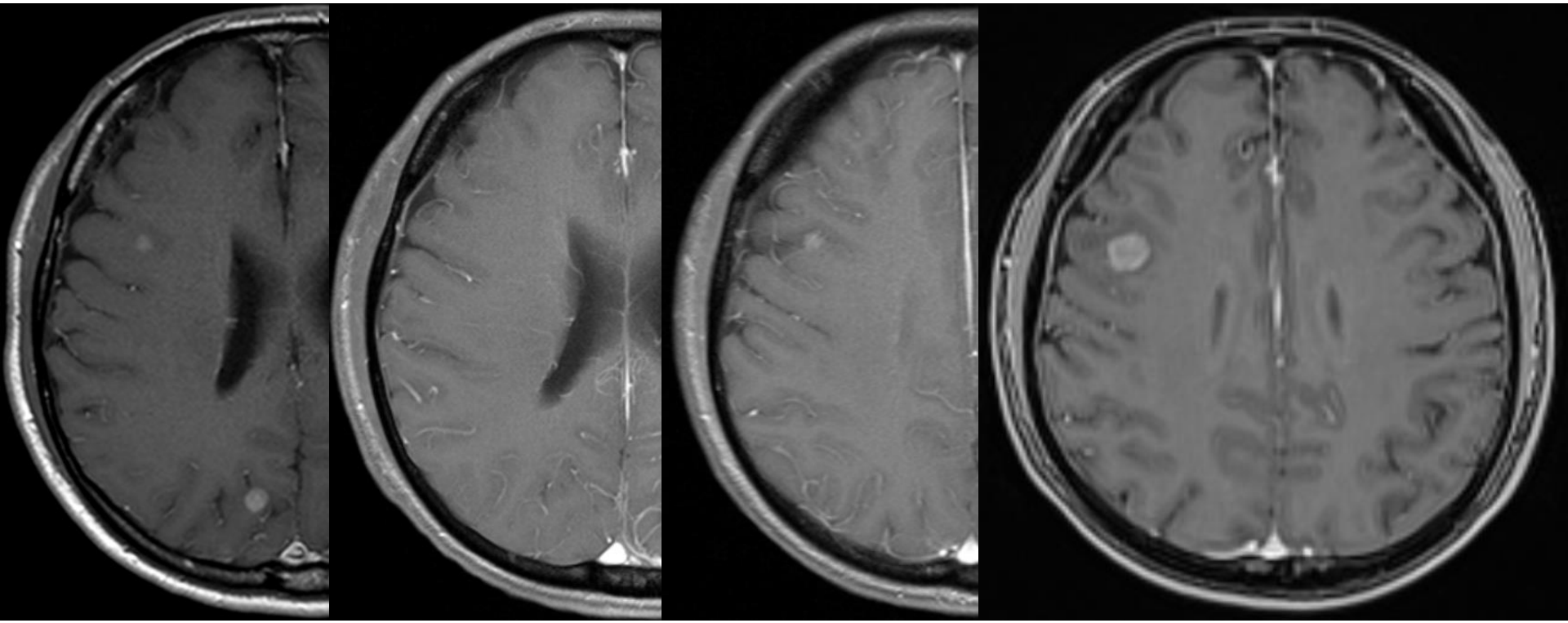
타세바 11개월 치료 후 Bone X선 & CT 사진
- 우측 팔에 가끔 통증이 있습니다. -



타세바 11개월 치료 후 흉부 및 복부 CT



타세바 11개월 치료 후 brain MRI



본 환자의 다음 치료 계획은?

1. 적절한 종양 부위에서 재조직검사
2. Platinum-based chemotherapy
3. 뼈 전이 치료
4. 뇌 전이 치료
5. 간 전이 치료

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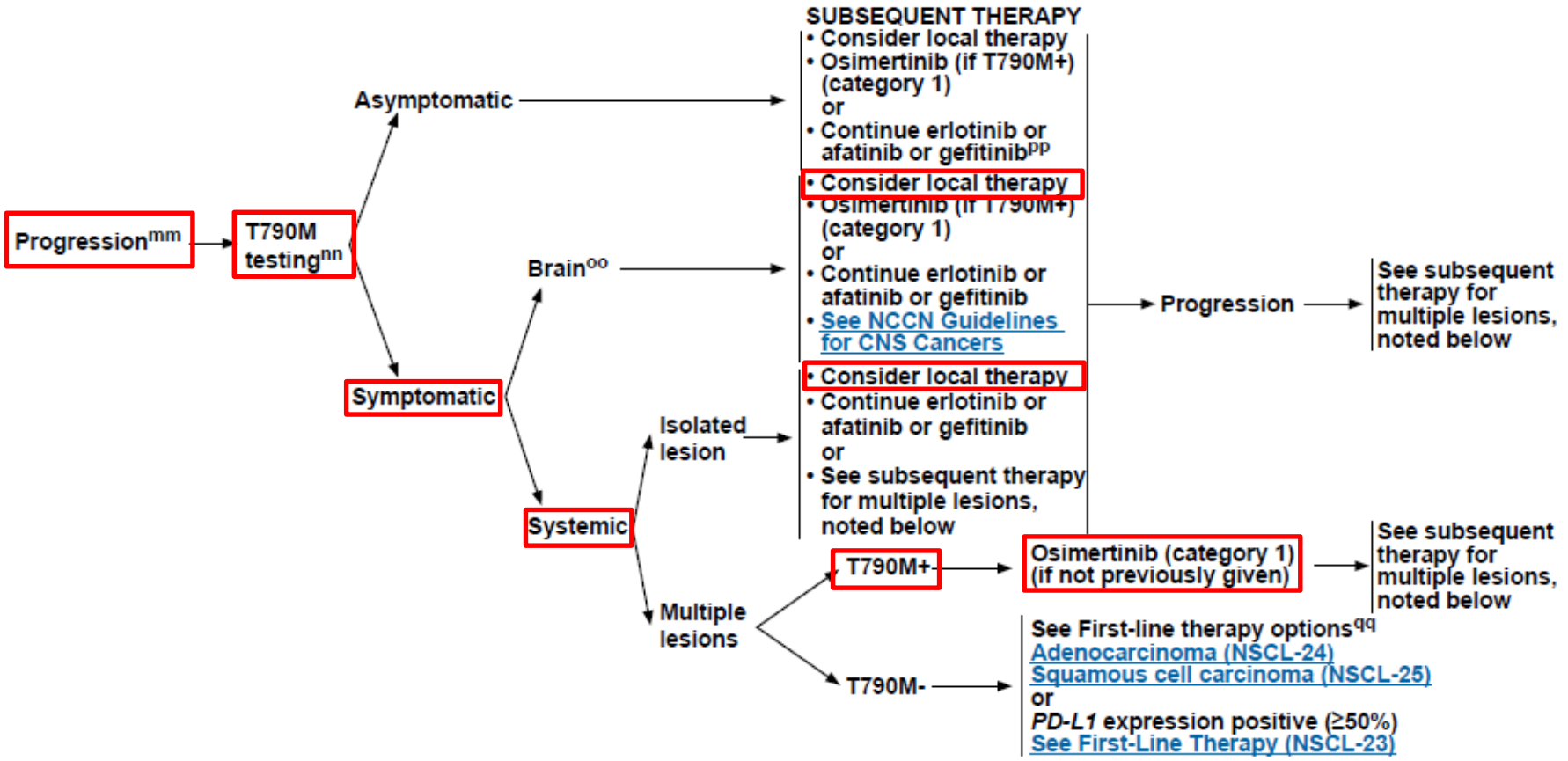
4. 뇌 전이 치료
5. 간 전이 치료

SENSITIZING EGFR MUTATION POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[mm] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[nn] If tissue biopsy is not feasible, plasma biopsy should be considered. Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.
[oo] Consider pulse erlotinib for carcinomatosis meningitis.
[pp] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
[qq] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

치료 경과 (정형외과 & 방종)

- Extended curettage & cementation

  I/F with Philos plate & screws 후 palliative ERT

- 뇌 전이 병변 – Cyberknife (3 Fx, 2200 cGy)

- Bone meta부위 soft tissue: EGFR mutation 결과

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EGFR PNAClamp 유전자돌연변이검사 결과입니다.
Mutation : Positive - (1) exon19 deletion입니다.
                      (2) exon20 p.T790M mutation입니다.
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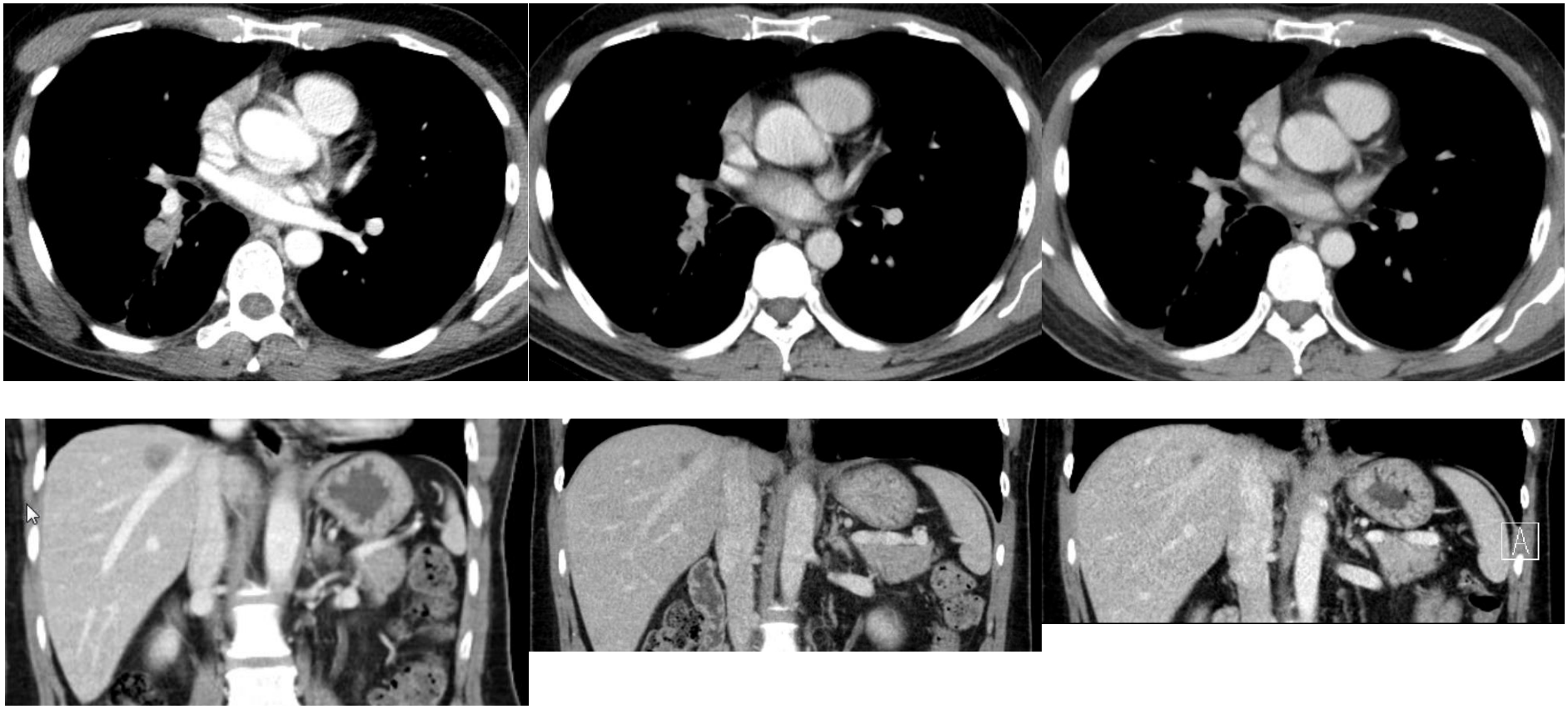
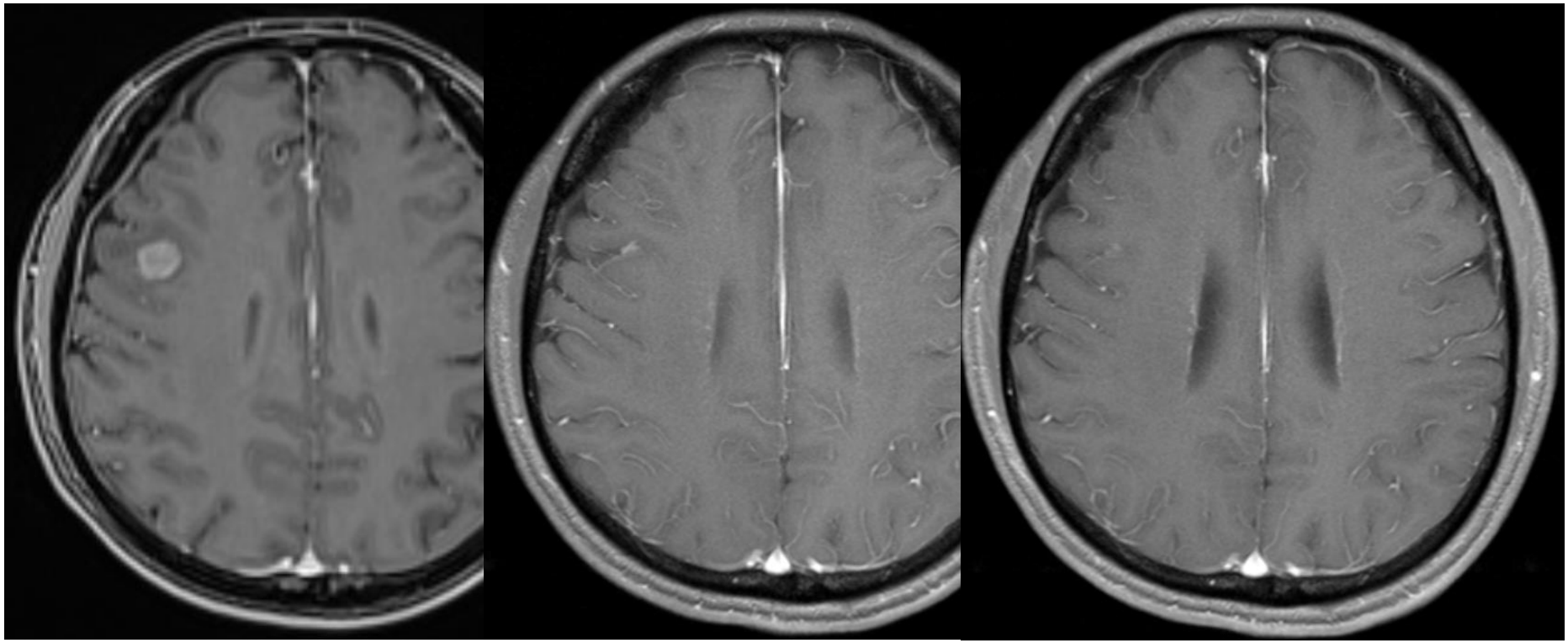
올리타 5개월 치료 후 흉부 및 복부 CT



Cyberknife 및 올리타 5개월 치료 후 brain MRI



경청해 주셔서 감사합니다!