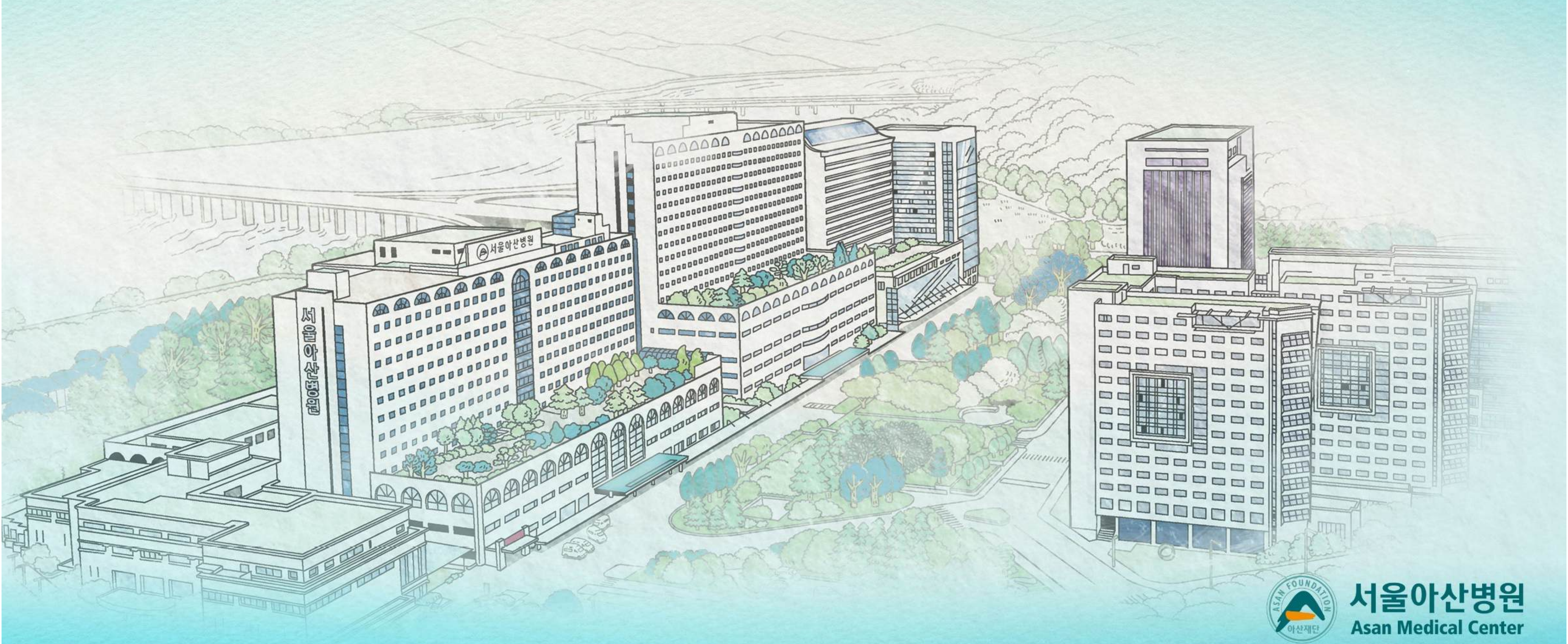


호흡기내과 의사가 설계하는 폐암의 항암치료



서울아산병원
Asan Medical Center



‘외도’하는 의사, 서울아산병원 최창민 교수

TV 의학 드라마에 생명 불어 넣는 ‘숨은PD’

박태근 식음료전문기자
tpark@joongang.co.kr

서울아산병원 호흡기내과 최창민(42)교수는 “부담이 TV 드라마의 의학 자문이다. ‘고양수다’, ‘동행병영’, ‘메디컬 탑팀’, ‘응급남녀’ 등 내 견의 드라마에 참여했다. 직접 출연도 했다. ‘응급남녀’에선 환자에게 임상연구 용의서를 받는 의사 역, ‘고양수다’에선 주인공인 장혜미 수술하는 장면에서 보조 의사 역을 맡았다. 그는 의학드라마는 의학교육이나 환자 교육자료가 아닌 단순 사상을 잘 인식하고 있다. 그래서 드라마가 시청자의 흥미를 높이기 위해 실제 병원 분위기와 약간 다르게 묘사하는 것에 대해서도 이해하는 편이다. 연구실 책상에 의학 서적과 함께 ‘EMR’ 그램이 나와 있다. ‘오! 골든타임’, ‘외과야 불쌍해!’ 등 국내의 의학 드라마와 영화 드라마가 줄줄이 끊인 것이 드라마에 대한 그의 애정을 짐작하게 한다. 최근 최 교수와 의료 드라마와 그의 전문인 과암에 대해 대화를 나눴다.

-의료 드라마 자문을 시작한 계기는
“2006년 당시 의사협회에서 신문 기사와 드라마에 의학적으로 잘못된 내용이 나오면 기사나 작가에게 알리고 ‘다 알면 너 신경 써 달라’고 외도에 하는 말을 들었다. 그 무렵 아나운서로서 있던 ‘외도’와 ‘병원’이 ‘실로자’에서 드라마에 나오는 ‘외도’에 대해 강의했다. 그 행사에

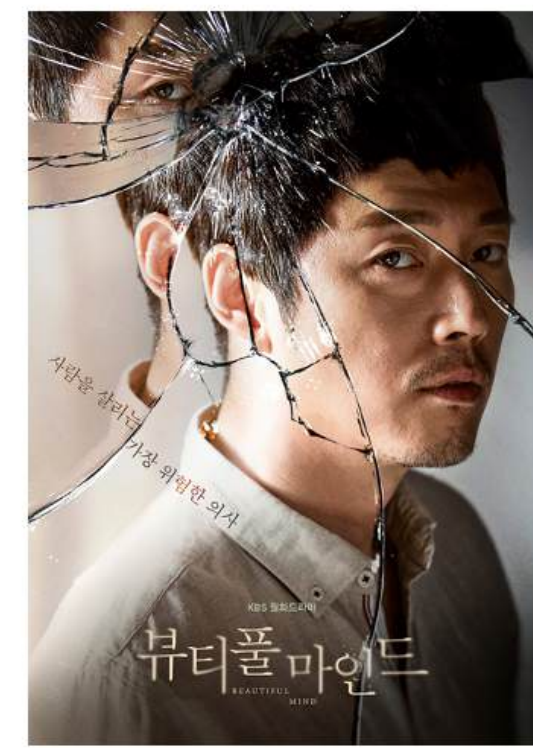


주사 바늘을 꽂아도 물이 빠지지 않으면 의사에선 긴급하는 응급상황이다. 그러다 내 시계를 이용해 돌을 빼면 의사들은 응급상황은 넘겨주고 본다. 반면 일반인들에게 내 시계이나 주사기로 볼 때는 장면을 보여줘 봤자 긴박감이 전달되지 않는다. 몇몇년 심장을 의사가 손으로 직접 만져 다시 쥐게 하면 진짜 괴물하더라 드라마에 몰입한다. 환자 심장을 손으로 만지는 것은 의사를 어떤 난코스냐”

-드라마를 자문한 뒤 보람을 느낀 적은
“장학후원의 ‘고양수다’엔 수술로 예이츠에 감염된 아기가 나온다. 이 드라마를 통해 예이츠 감염자에 대한 편견을 어느 정도 없애줄 수 있겠다고 생각했다. 예이츠는 뇌종양과 신경학에 의해 감염되기 쉬우며 일상 생활에서 전염되지 않고 전염할 경우 매우 치명적이다”

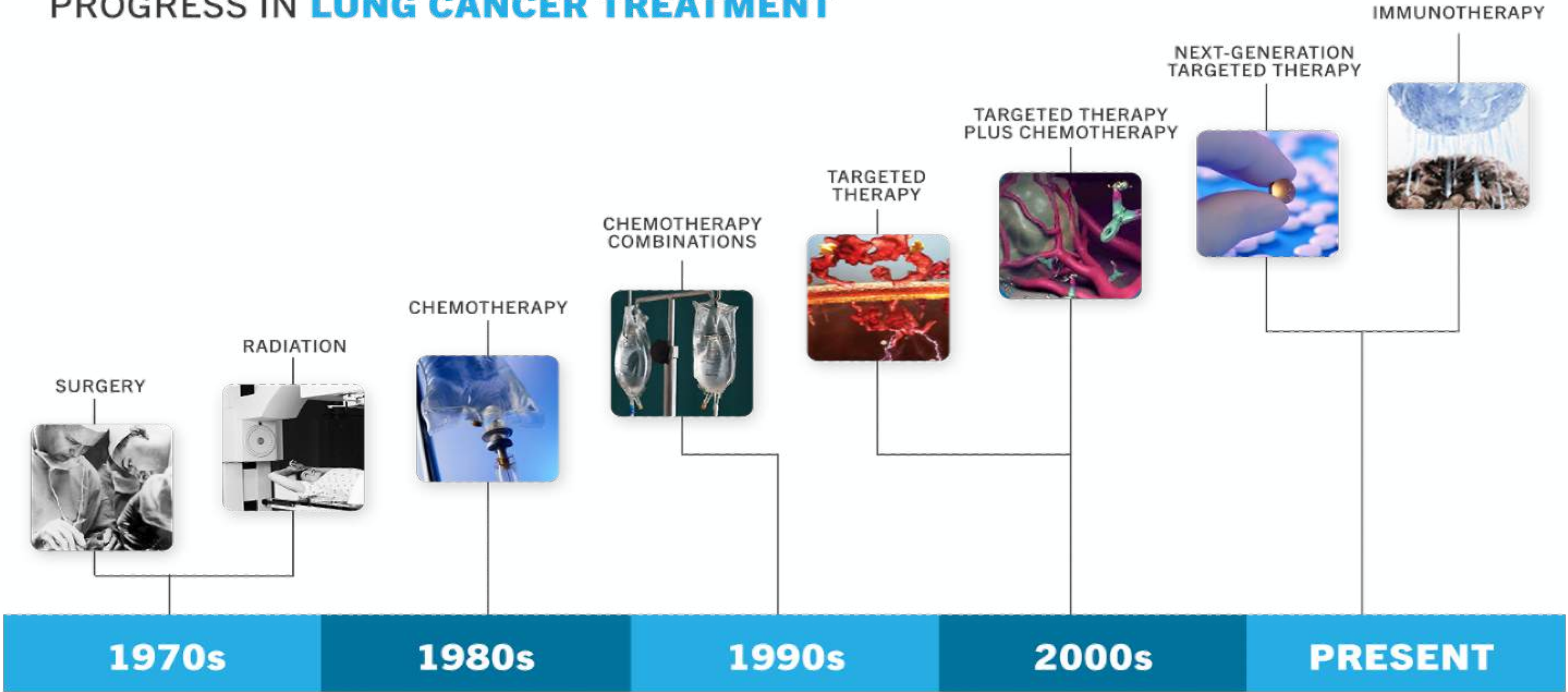
-이후 의료 드라마에선 암학적인 불륜 물이 있다는데
“가족에서 뇌사 판정을 받은 환자 가족에겐 장기이식을 권유한다. 치료에 대한 최종 결정은 환자 가족이나 주변 사람이 아닌 환자 자신이 내리는 것으로 그려진다. 암과 같은 중대한 병이 있으면 환자에게 바를 일깨우는 교사의 임무도 따른다.”

-‘외도’ 전담 사수를 황지에게 맡겼다.
“‘외도’도 전담 사수가 시끄러워 전담. 전담했다. 환자가 나중에 일면 거짓말한 의사를 믿지 않는다.”

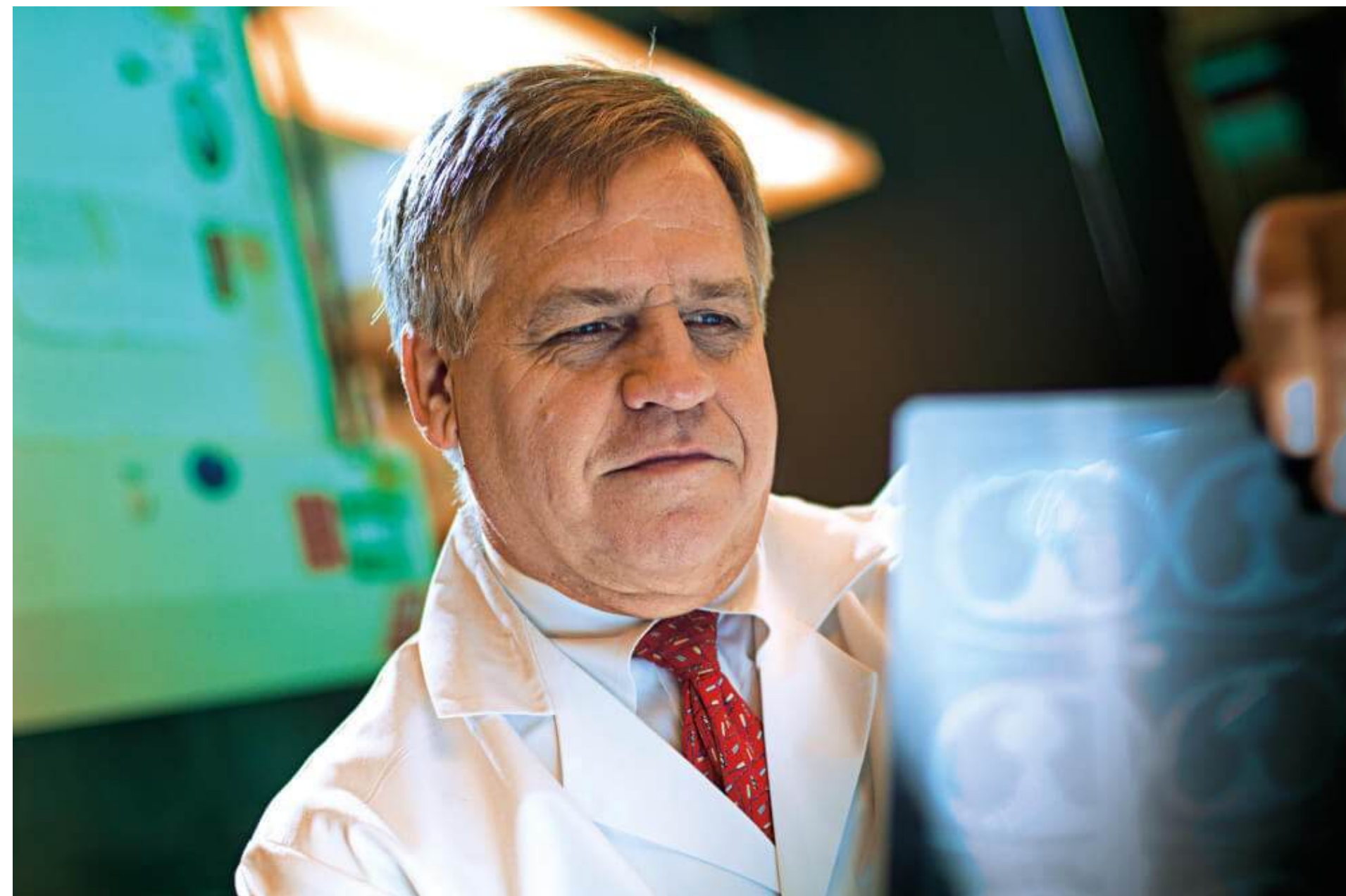


서울아산병원 호흡기내과/종양내과 교수

PROGRESS IN LUNG CANCER TREATMENT



When is Immunotherapy the Right Treatment for Lung Cancer?

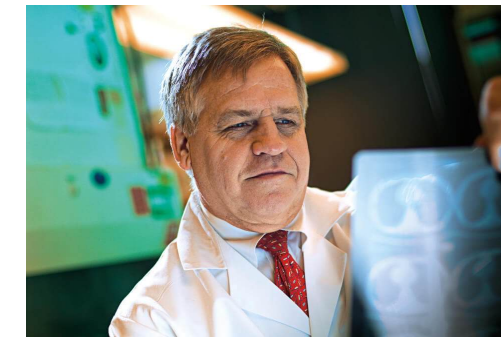


Bruce Johnson, MD

“dramatic transformation”

“Today, nearly **half** of all patients presenting with lung cancer can be **initially treated** with **targeted agents or immunotherapy** rather than chemotherapy.”

“The estimated three-year survival rates are 17 percent and the curve remains relatively flat out toward five years,”

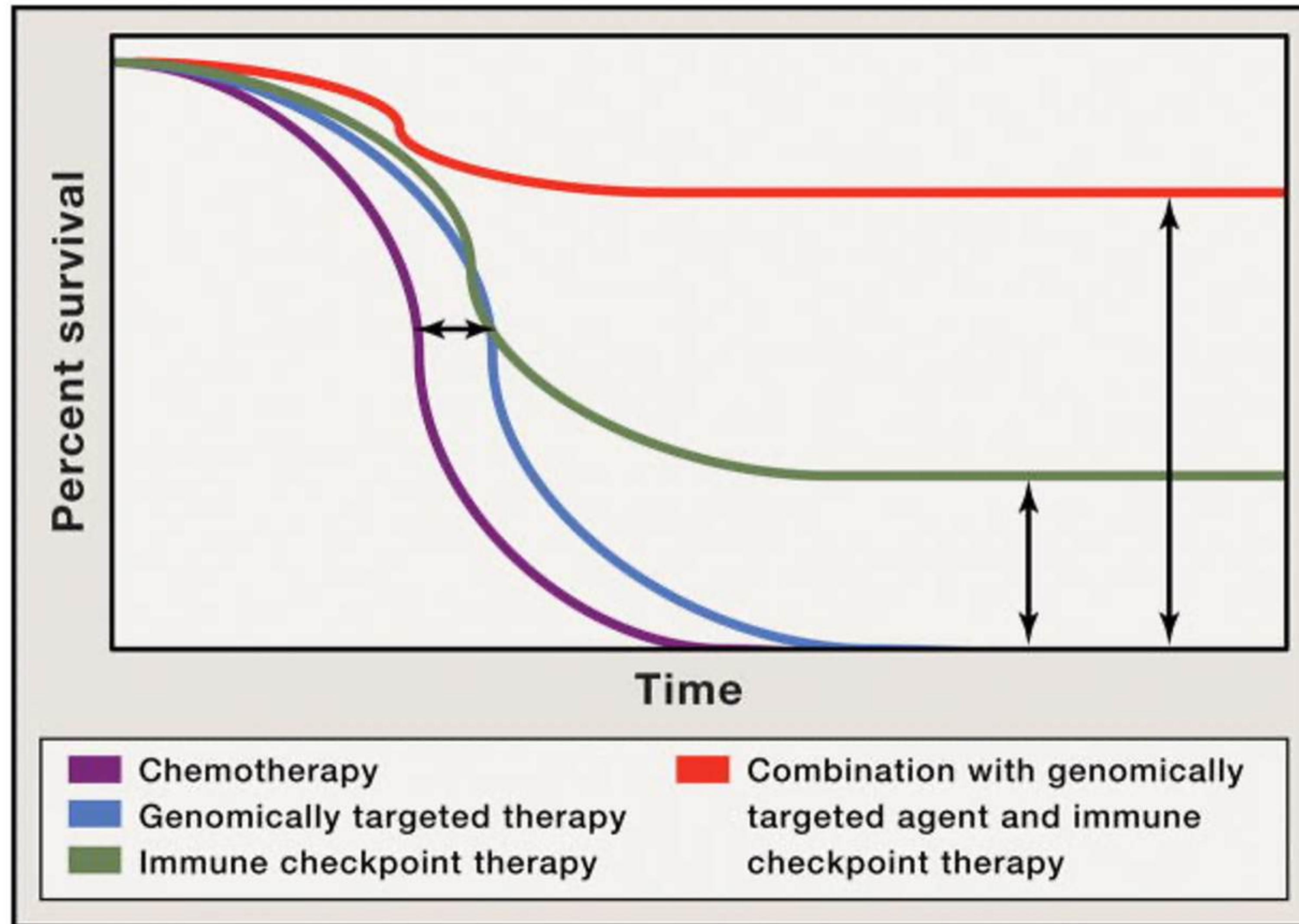


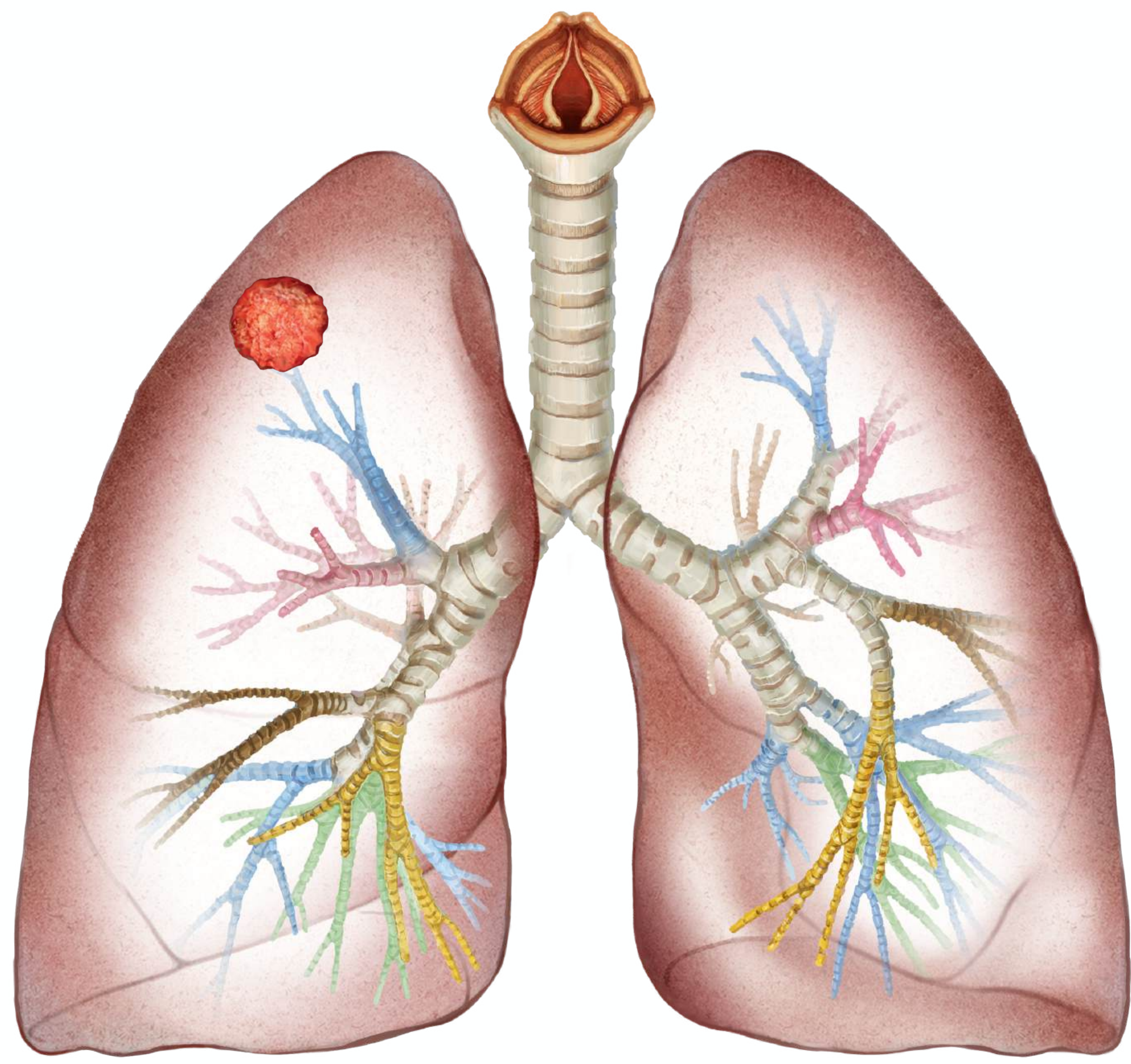
Bruce Johnson, MD

“dramatic transformation”

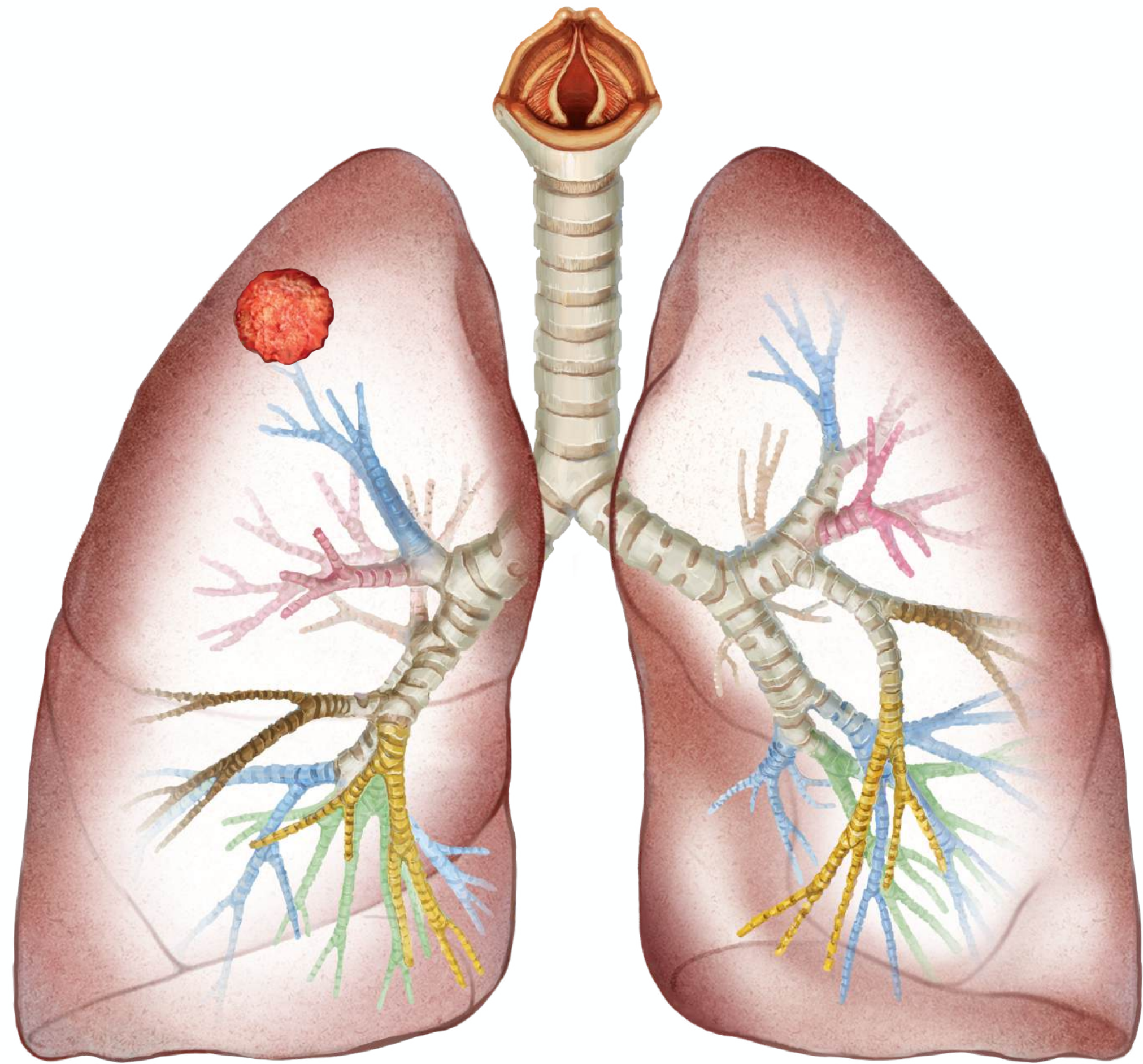
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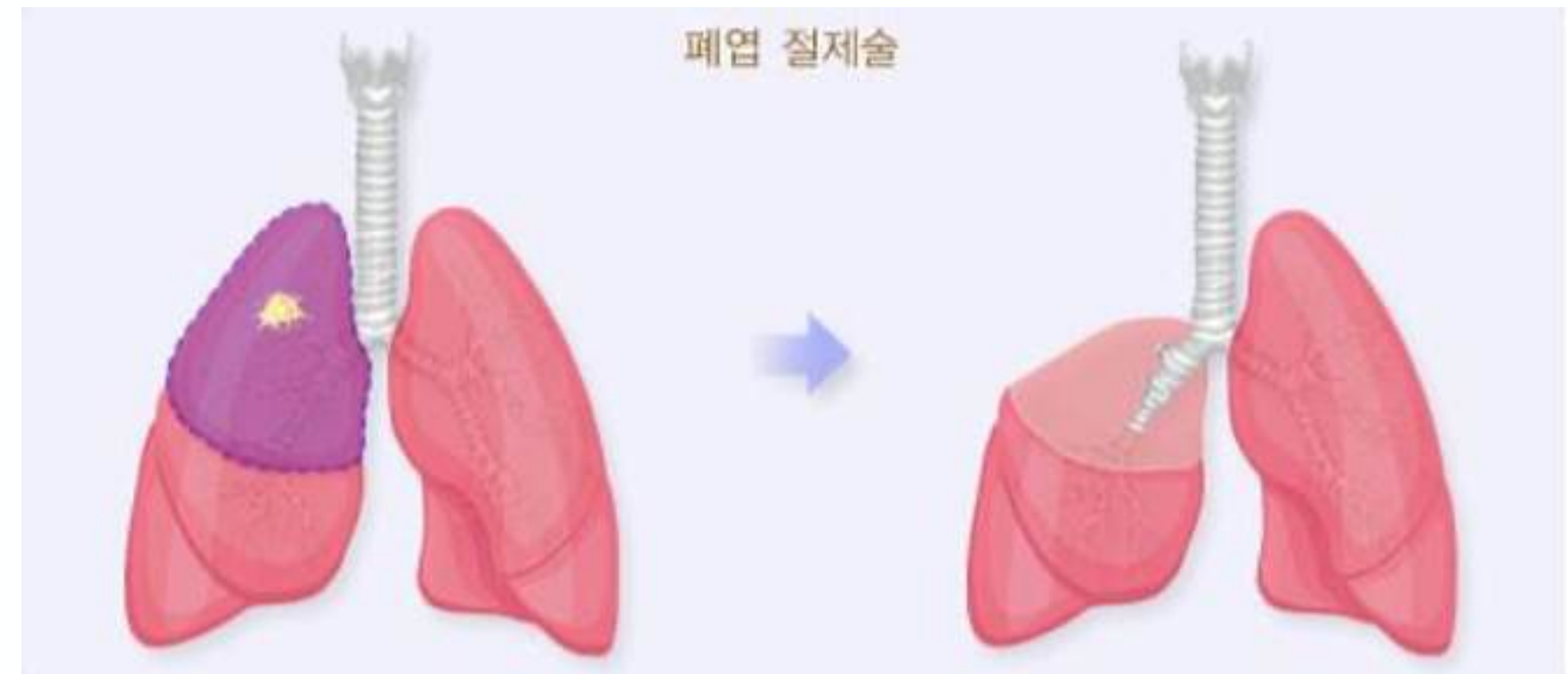
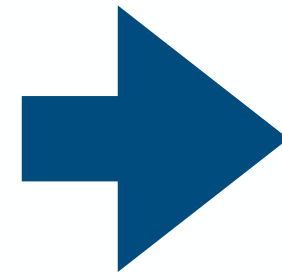


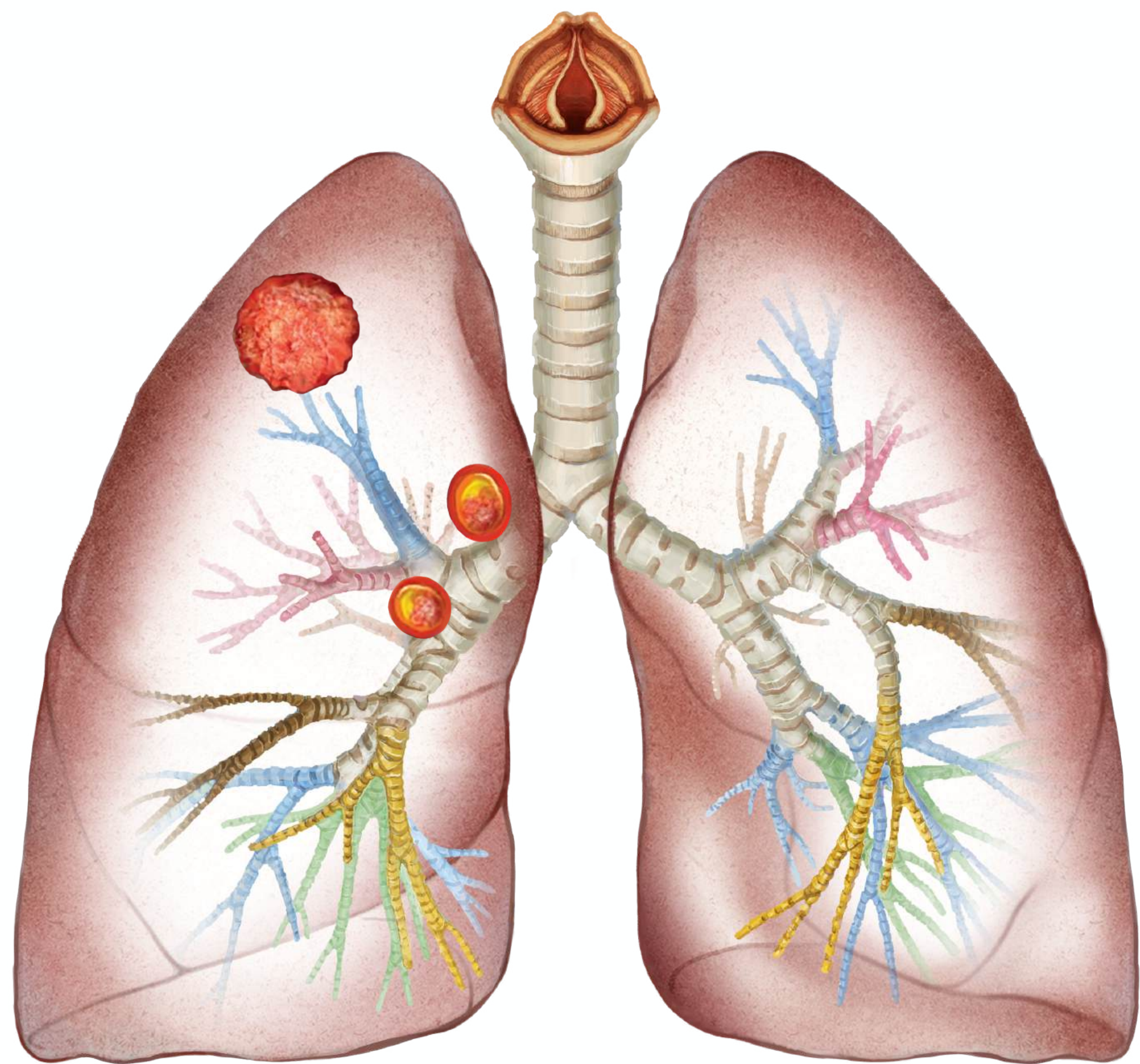


Stage I



Stage I

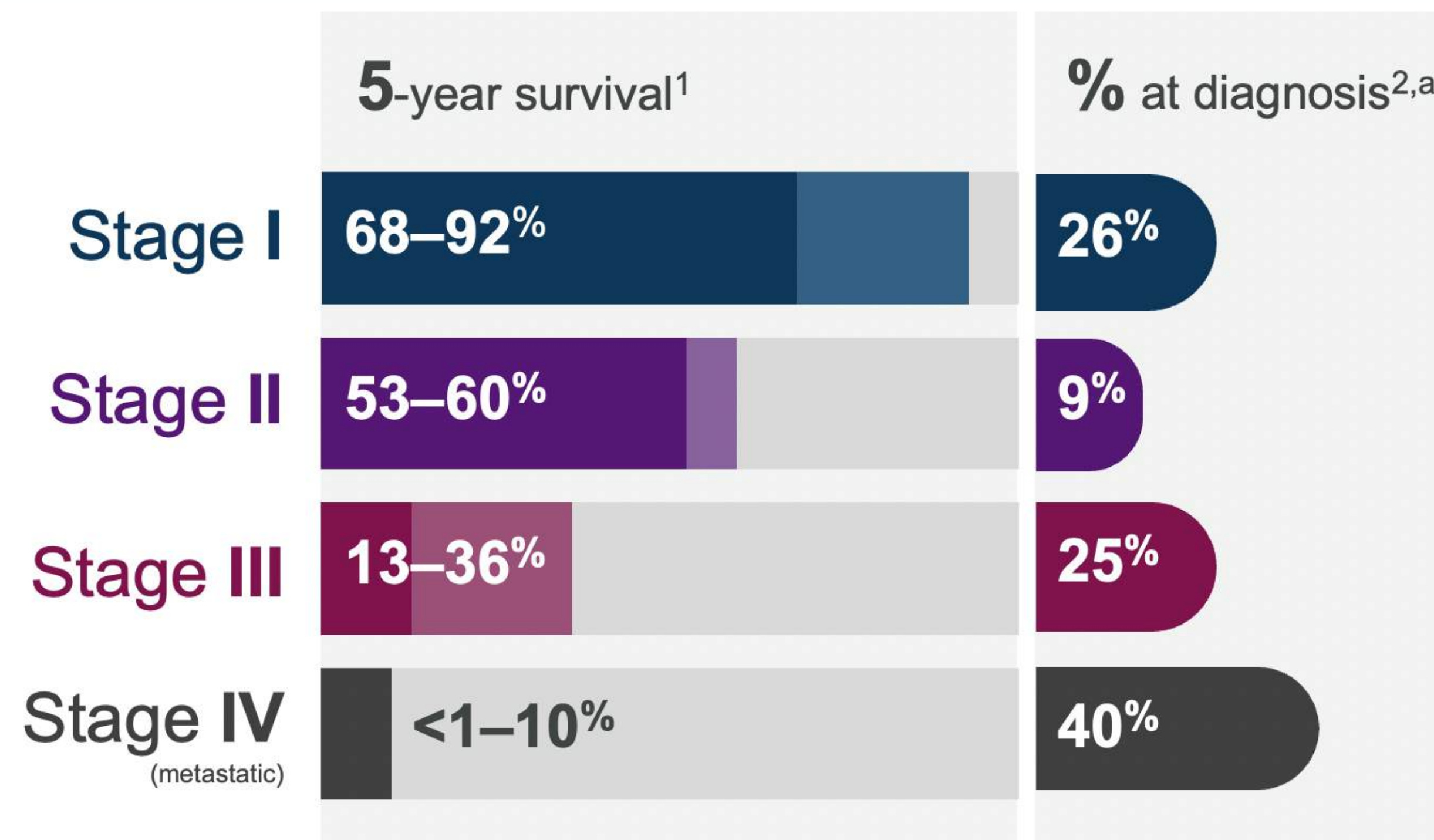
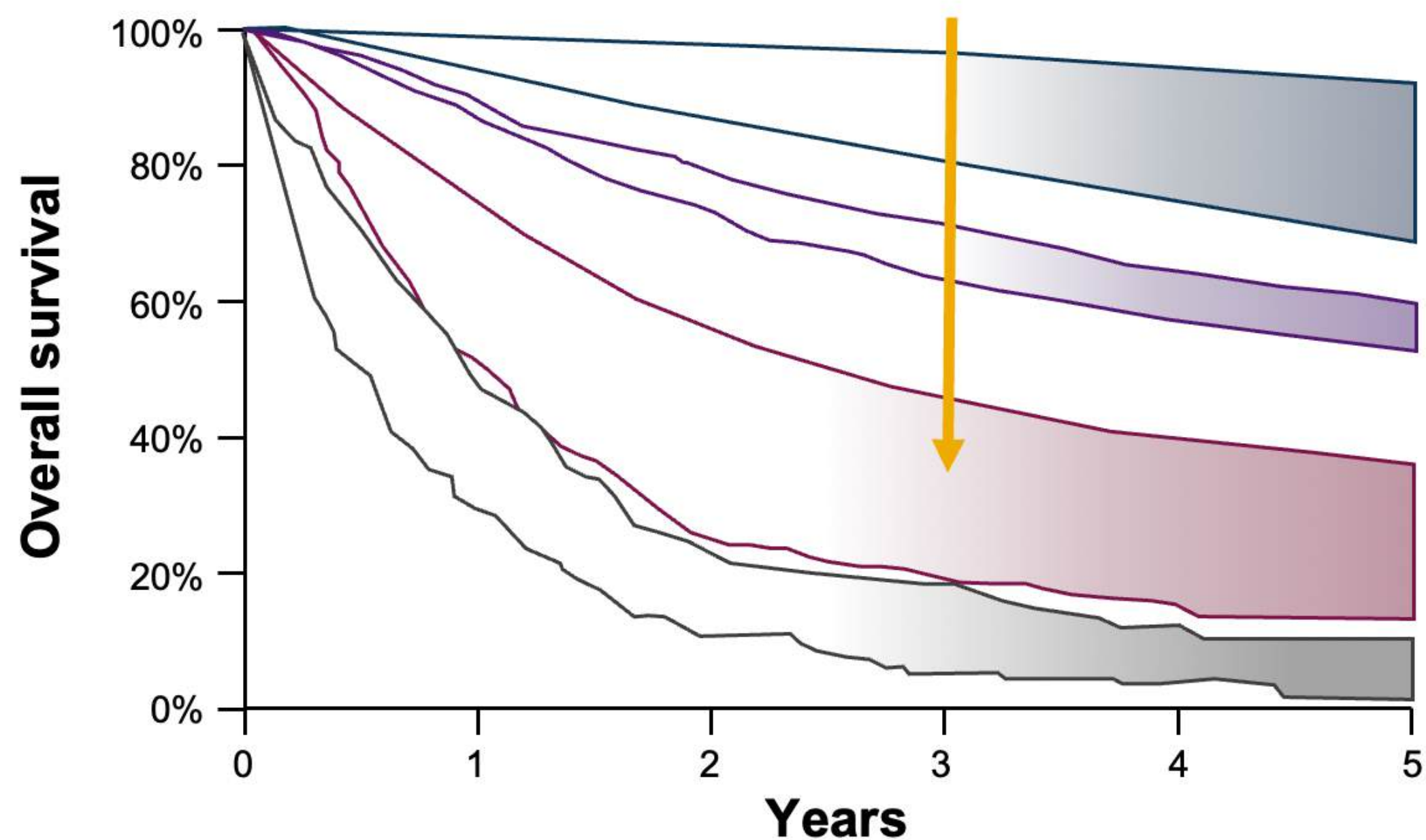




Stage II

Surgery + Adjuvant Chemotherapy
Neoadjuvant Chemotherapy

5-year NSCLC survival rates by stage at diagnosis¹



- Lung cancer is responsible for the largest number of cancer deaths (more than 1.7 million/year) worldwide³
- The overall 5-year survival rate for lung cancer is 18% and varies by stage²
- NSCLC represents 85% of all lung cancer cases⁴
- Approximately 30% of patients with NSCL present with resectable disease at diagnosis⁵⁻⁷

Adapted from Global Data. 2016.

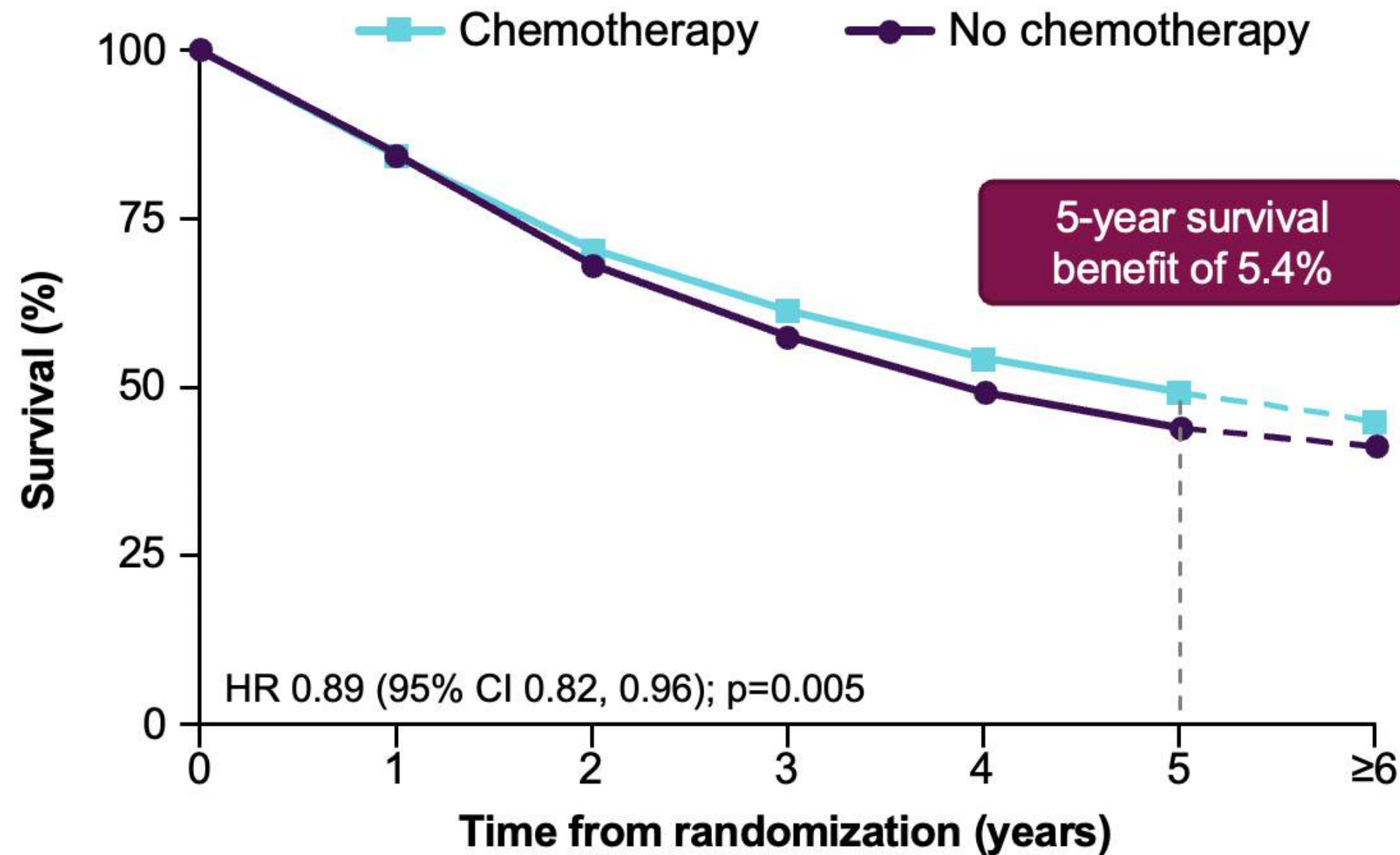
^aDiagnosis statistics based on 7 major market countries (EU5, US, and Japan).

EU-5 = European Union Five (France, Germany, Italy, Spain, and United Kingdom); NSCLC = non-small cell lung cancer; US = United States.

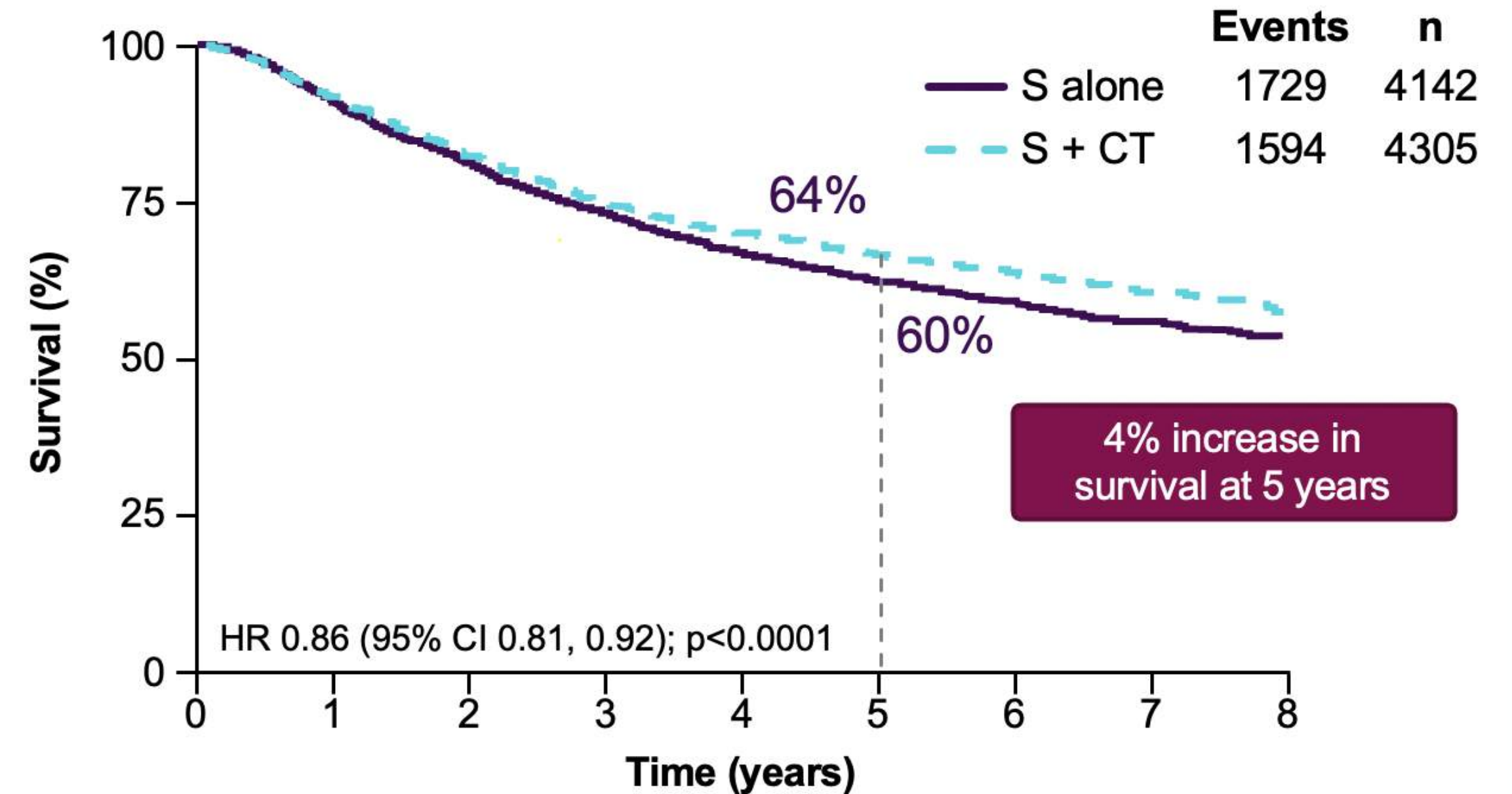
1. Deslypere G et al. *Ther Adv Med Oncol*. 2018;10:1758835918772810. 2. GlobalData EpiCast. NSCLC Epidemiology Forecast to 2025. Nov. 2016. 3. World Health Organization. Cancer. 2018. Accessed May 20, 2020. 4. Cancer.org. Available at: <https://www.cancer.org/content/dam/cancer-org/cancer-control/en/cancer-types/non-small-cell-lung-cancer-complete.pdf>. Accessed May 14, 2020. 5. Datta D et al. *Chest*. 2003;123:2096-2103. 6. Le Chevalier et al. *Ann Oncol*. 2010;21:vii196-vii198. 7. Cagle PT et al. *Arch Pathol Lab Med*. 2013;137:1191-1198.

Adjuvant Platinum-Based Doublet Chemotherapy is Standard of Care in Patients with Resected Stage II–III NSCLC and Select Patients with Stage IB Disease¹

LACE pooled analysis of 5 randomized adjuvant cisplatin trials performed since 1995 (n=4584)²



Meta-analysis of randomized adjuvant chemotherapy trials performed since 1965 (n=8447)³



Number at risk

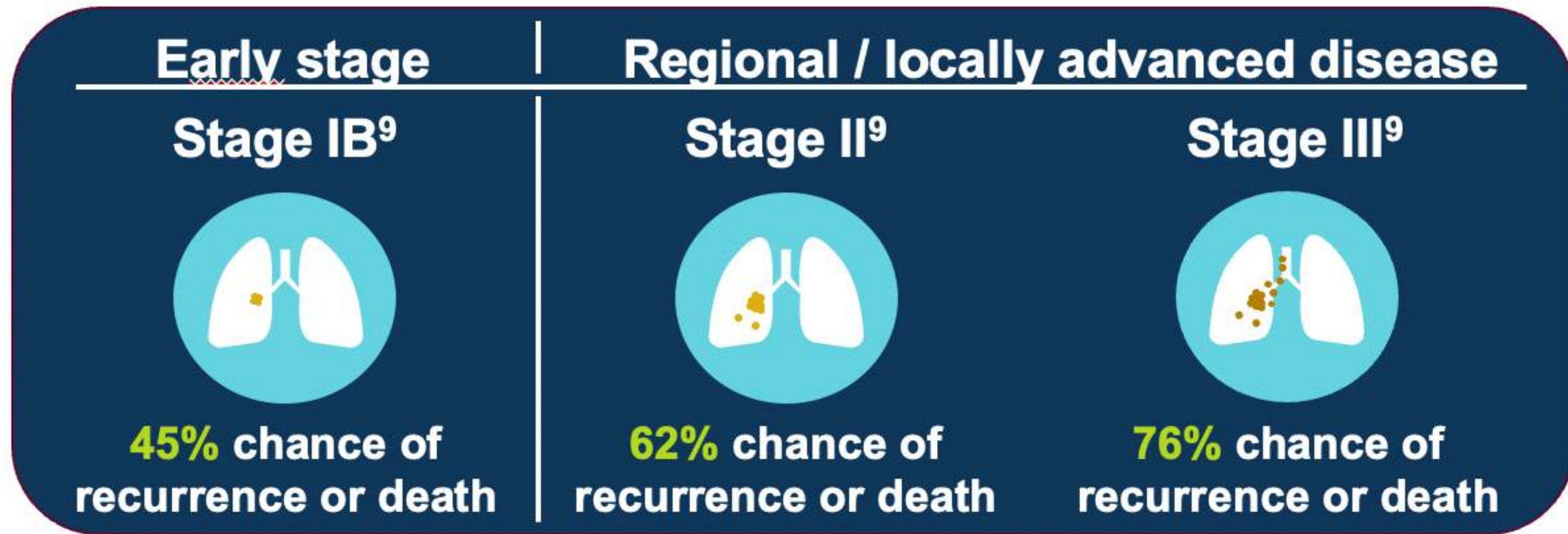
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---------|------|------|------|------|------|------|-----|-----|-----|
| S alone | 4142 | 3648 | 3102 | 2584 | 2083 | 1601 | 841 | 407 | 148 |
| S + CT | 4305 | 3809 | 3261 | 2746 | 2278 | 1785 | 936 | 473 | 165 |

Results from large randomised trials^{4,5} and meta-analyses^{2,3} have shown a statistically significant OS benefit (~5% at 5 years) only in patients with stage II-III disease

CI = confidence interval; CT = chemotherapy; HR = hazard ratio; NSCLC = non-small cell lung cancer; PORT = postoperative radiotherapy; RT = radiotherapy; S = surgery.

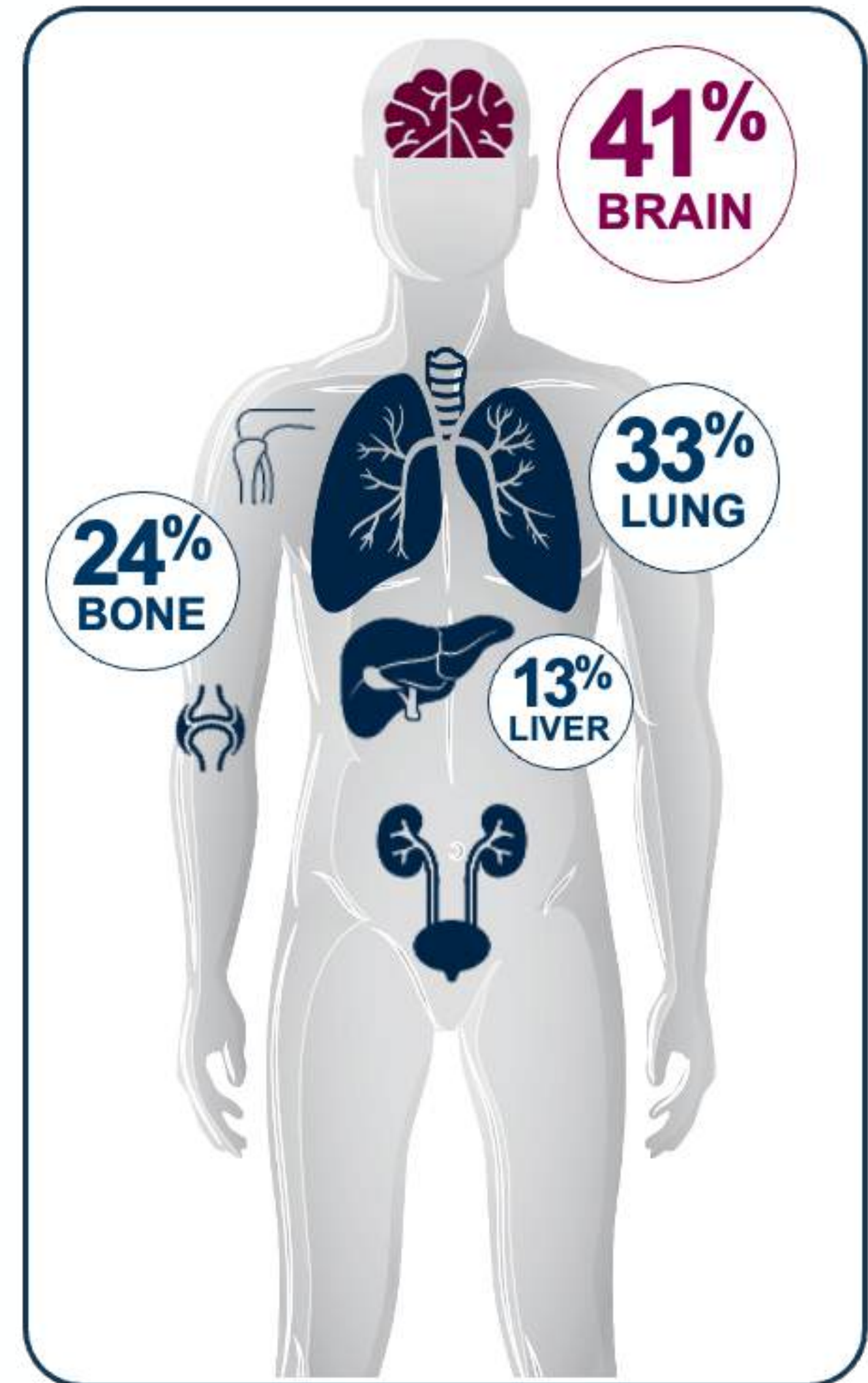
1. Kris MG et al. *J Clin Oncol*. 2017;35:2960-2974. 2. Pignon JP et al. *J Clin Oncol*. 2008;26:3552-3559. 3. NSCLC Meta-analyses Collaborative Group.

Lancet. 2010;375:1267-1277. 4. Arriagada R et al. *N Engl J Med*. 2004;350:351-360. 5. Winton T et al. *N Engl J Med*. 2005;352:2589-2597.



⁹Median follow-up: 5.2 years, data based on AJCC Staging Manual 6th edition.

Pignon JP et al. *J Clin Oncol*.



Chouaid C et al. *Lung Cancer*. 2018;124:310-316.

Following IDMC recommendation, the study was unblinded at a trial level two years early due to evidence of efficacy benefit. At the time of unblinding, the study had completed enrollment and all patients were followed up for at least 1 year.

ADAURA: Study Design

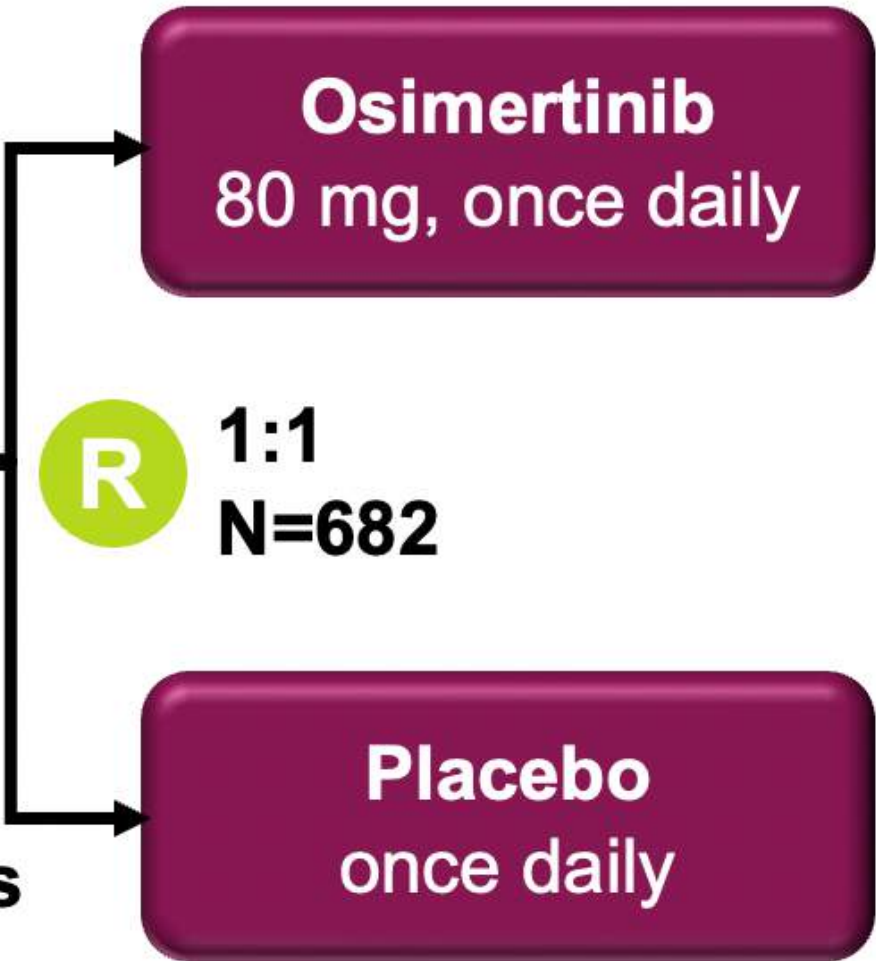
Phase III, double-blind, randomized, placebo-controlled, multicenter study

Patients with completely resected Stage^a IB, II, IIIA NSCLC, with or without adjuvant chemotherapy^b

Key inclusion criteria:

- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R^c
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins^d
- Maximum interval between surgery and randomization:
 - 10 weeks without adjuvant chemotherapy
 - 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFR^m (Ex19del vs L858R)
Race (Asian vs non-Asian)



Planned treatment duration: 3 years

Treatment continues until:

- Disease recurrence, treatment completed, or discontinuation criterion met

Follow up:

- Until recurrence: week 12 and 24, then every 24 weeks to 5 years, then yearly after recurrence: every 24 weeks for 5 years, then yearly

Primary Endpoint:

- DFS, by investigator assessment, in stage II/IIIA patients^e

Secondary Endpoints:

- DFS in the overall population^f
- OS
- HRQoL
- Safety

Exploratory Endpoints:

- Sites of recurrence
- Time to CNS recurrence

Upon early unblinding cross-over was allowed after confirmed disease recurrence

Data cut-off: January 17, 2020.

AJCC = American Joint Committee on Cancer; CNS = central nervous system; CT = computed tomography; DFS = disease-free survival; EGFR^m = epidermal growth factor receptor mutation positive; ex19del = exon 19 deletion; HR = hazard ratio; IDMC = Independent Data Monitoring Committee; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; OS = overall survival;

PS = Performance status; WHO = World Health Organization.

^aAJCC 7th edition; postsurgical, pathology-based. ^bPrior, post, or planned radiotherapy was **not** allowed. ^cCentrally confirmed in tissue. ^dPatients received a CT scan after resection and within 28 days prior to treatment. ^eDesigned for superiority under the assumed DFS HR of 0.70. ^fStage IB / II / IIIA.

Wu Y-L et al. *N Engl J Med* 2020; 383:1711-1723.

ADAURA: DFS by Stage

ADAURA: Study Design

Phase III, double-blind, randomized, placebo-controlled, multicenter study

Patients with completely resected Stage^a IB, II, IIIA NSCLC, with or without adjuvant chemotherapy^b

Stratification by: Stage (IB vs II vs IIIA), EGFR^c (Ex19del vs L858R), Race (Asian vs non-Asian)

1:1 N=682

Osimertinib 80 mg, once daily

Placebo once daily

Planned treatment duration: 3 years

Treatment continues until: Disease recurrence, treatment completed, or discontinuation criterion met

Follow up: Until recurrence: week 12 and 24, then every 24 weeks to 5 years, then yearly after recurrence: every 24 weeks for 5 years, then yearly

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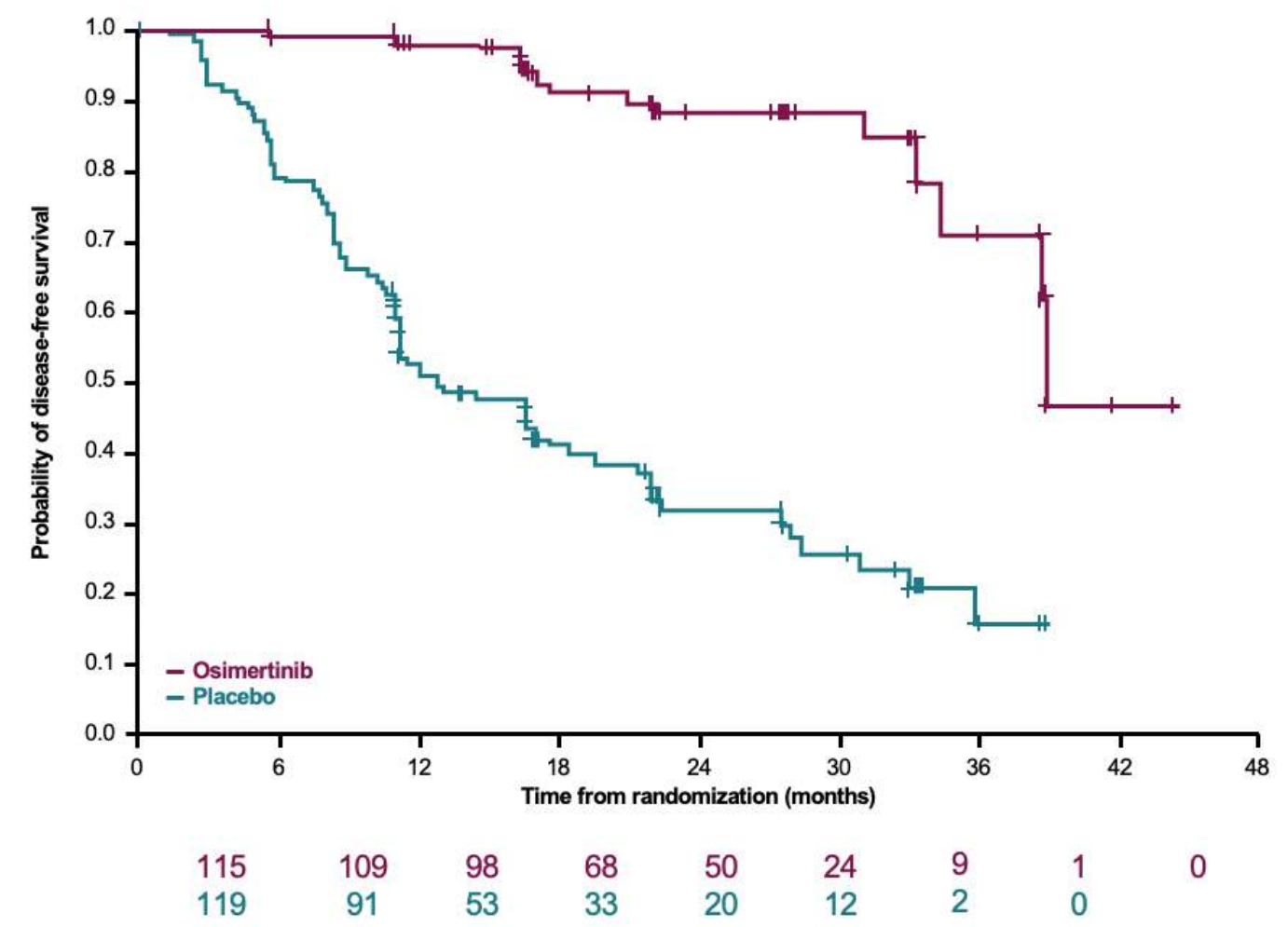
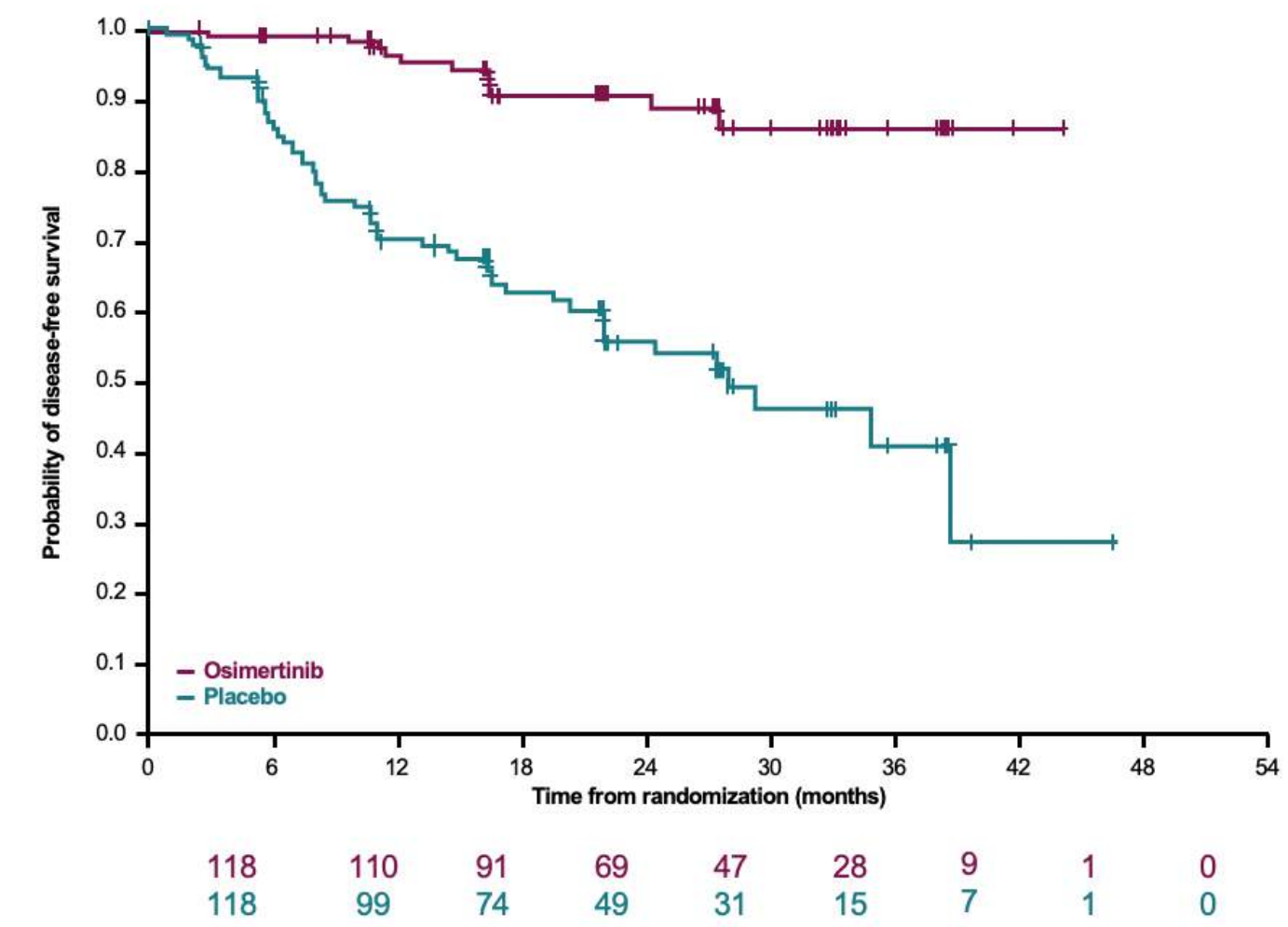
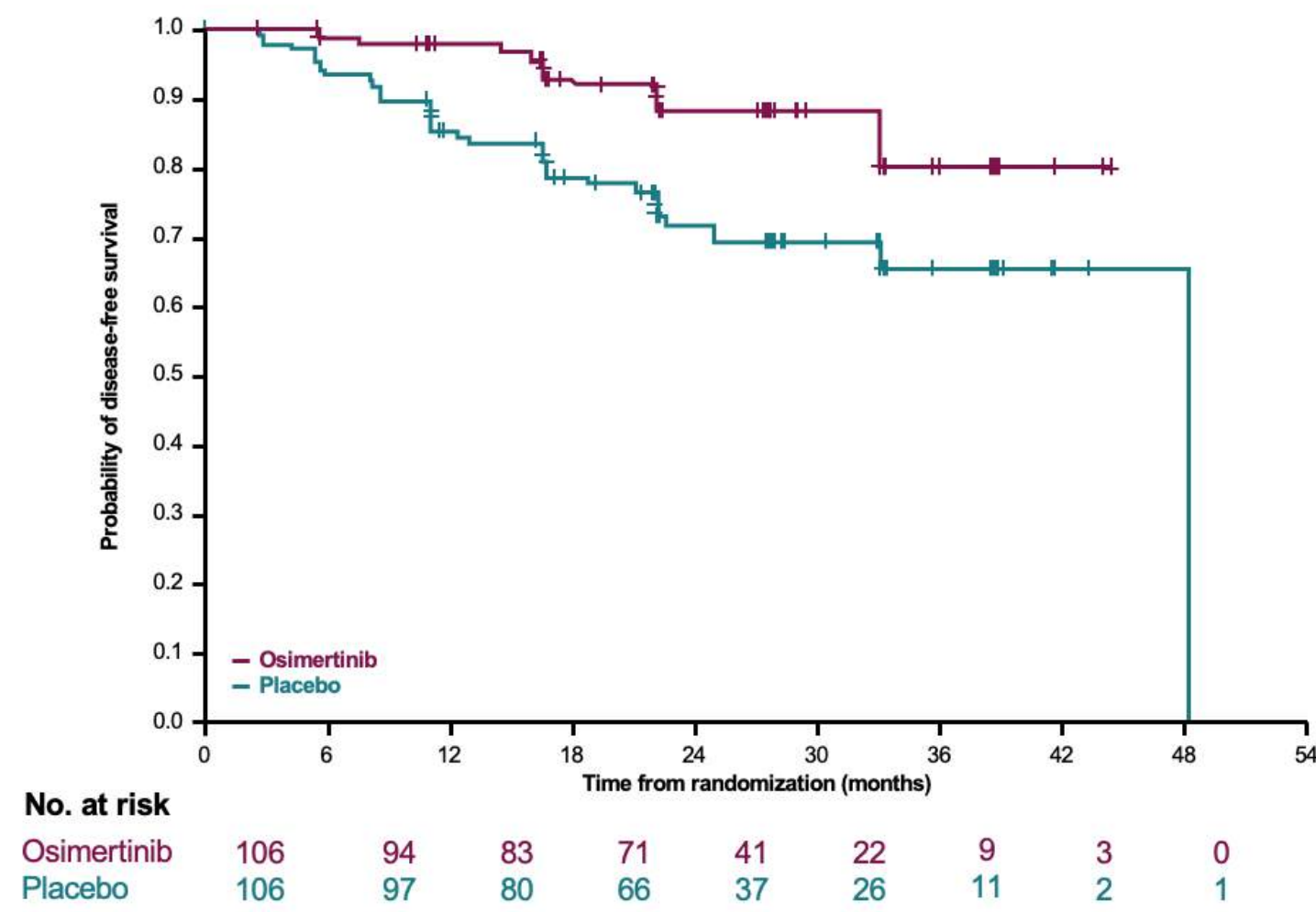
Primary Endpoint: DFS, by investigator assessment, in stage III/IIIA patients^d

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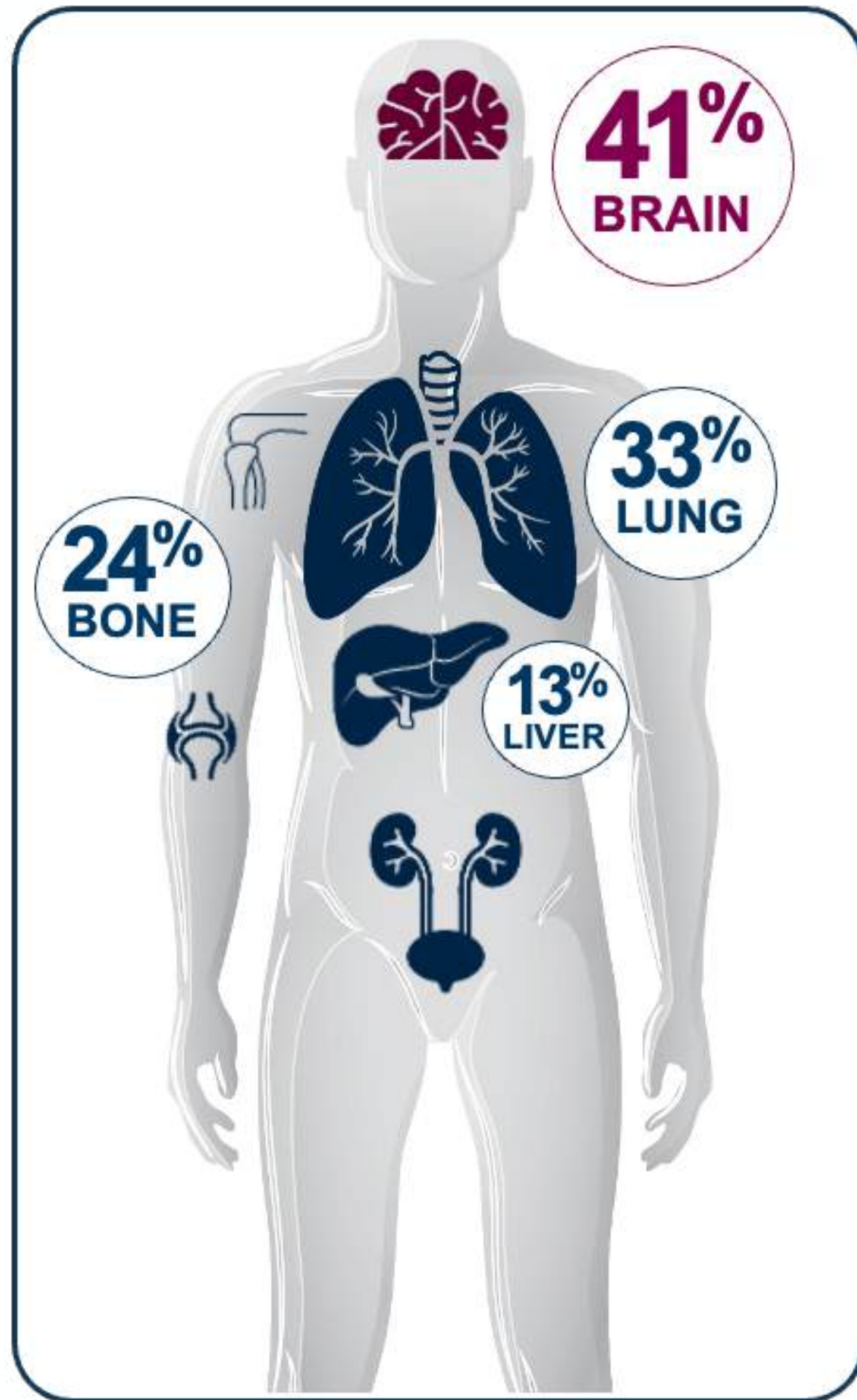
Data cut-off: January 17, 2020. A.J.C.C. = American Joint Committee on Cancer; CNS = central nervous system; CT = computed tomography; DFS = disease-free survival; EGFR = epidermal growth factor receptor mutation positive; ex19del = exon 19 deletion; HR = hazard ratio; IDMC = Independent Data Monitoring Committee; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; OS = overall survival; PS = Performance status; WHO = World Health Organization. ^aAJCC 7th edition, postoperative, pathology-based. ^bPre-, post-, or planned radiotherapy was not allowed. ^cCentrally confirmed in tissue. ^dPatients received a CT scan after resection and within 28 days prior to treatment. ^eDesignated for superiority under the assumed DFS HR of 0.70. Stage IB / II / IIIA. Wu Y-L et al. N Engl J Med 2020; 383:1711-1723.

| | Stage IB | Stage II | Stage IIIA |
|------------------------------------|-------------------------|-------------------------|-------------------------|
| 2 year DFS rate, % (95% CI) | | | |
| – Osimertinib | 88 (78, 94) | 91 (82, 95) | 88 (79, 94) |
| – Placebo | 71 (60, 80) | 56 (45, 65) | 32 (23, 41) |
| Overall HR (95% CI) | 0.39 (0.18-0.76) | 0.17 (0.08-0.31) | 0.12 (0.07-0.20) |



- In the osimertinib arm, 2-year DFS rates were consistent across stages IB, II, and IIIA disease
- Maturity (overall population: stage IB / II / IIIA) 29%: osimertinib events 12%, placebo events 46%

Data cut-off: January 17, 2020.
 CI = confidence interval; DFS = disease-free survival; HR = hazard ratio.
 Wu Y-L et al. *N Engl J Med* 2020; 383:1711-1723



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1:1
 N=682

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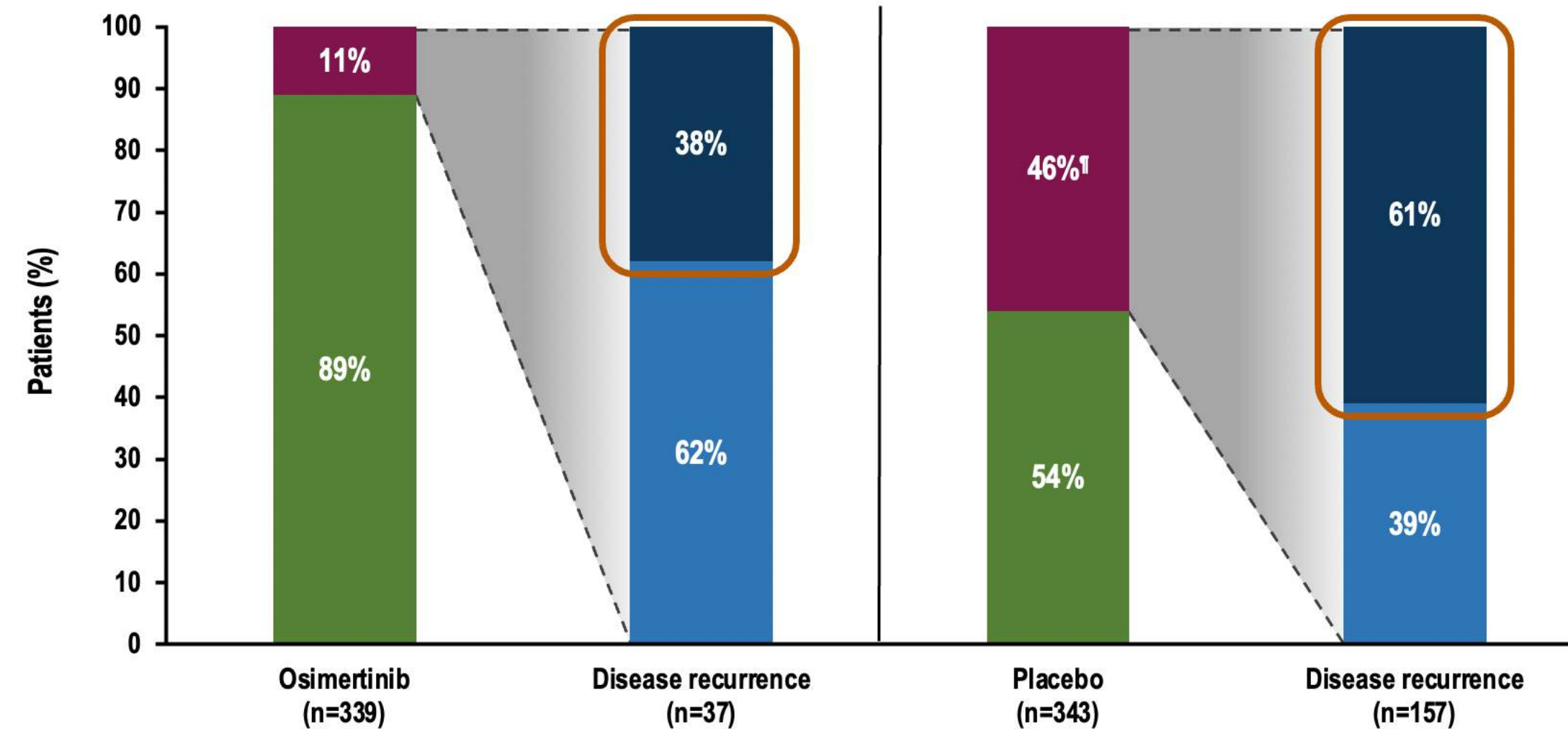
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Data cut-off: January 17, 2020.
 A.J.C.C. = American Joint Committee on Cancer; CNS = central nervous system; CT = computed tomography; DFS = disease-free survival; EGFRm = epidermal growth factor receptor mutation positive; ex19del = exon 19 deletion; HR = hazard ratio; IDMC = Independent Data Monitoring Committee; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; OS = overall survival.
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^aAJCC 7th edition, postoperative, pathology-based. ^bPre-, post-, or planned radiotherapy was not allowed. ^cCentrally confirmed in tissue. ^dPatients received a CT scan after resection and within 28 days prior to treatment. ^eDesigned for superiority under the assumed DFS HR of 0.70. Stage IB / IIIA.
 Wu Y-L et al. *N Engl J Med* 2020; 383:1711-1723.



Patient disposition^a

- DFS event
- No DFS event

Type of disease recurrence

- Distant^b recurrence
- Local/regional^c recurrence only

Data cut-off: January 17, 2020.
 CNS = central nervous system.

^aPatient disposition at time of data cut-off; ^bIncludes patients with distant recurrence only and those with distant and local/regional recurrence. Distant recurrence is defined as spread of disease beyond the area of the tumour bed, hilum or mediastinal lymph nodes (diagnosed by radiological examination and/or histopathological confirmation); ^cDefined as recurrence in the area of the tumour bed, hilum or mediastinal lymph nodes (cytologically/histologically confirmed). There were two incidences of death in the absence of disease recurrence (any site); these patients are excluded from the analysis of site of recurrence.

Wu Y-L et al. *N Engl J Med* 2020; 383:1711-1723 (Supplementary)

ADAURA: CNS DFS in the Overall Population

ADAURA: Study Design

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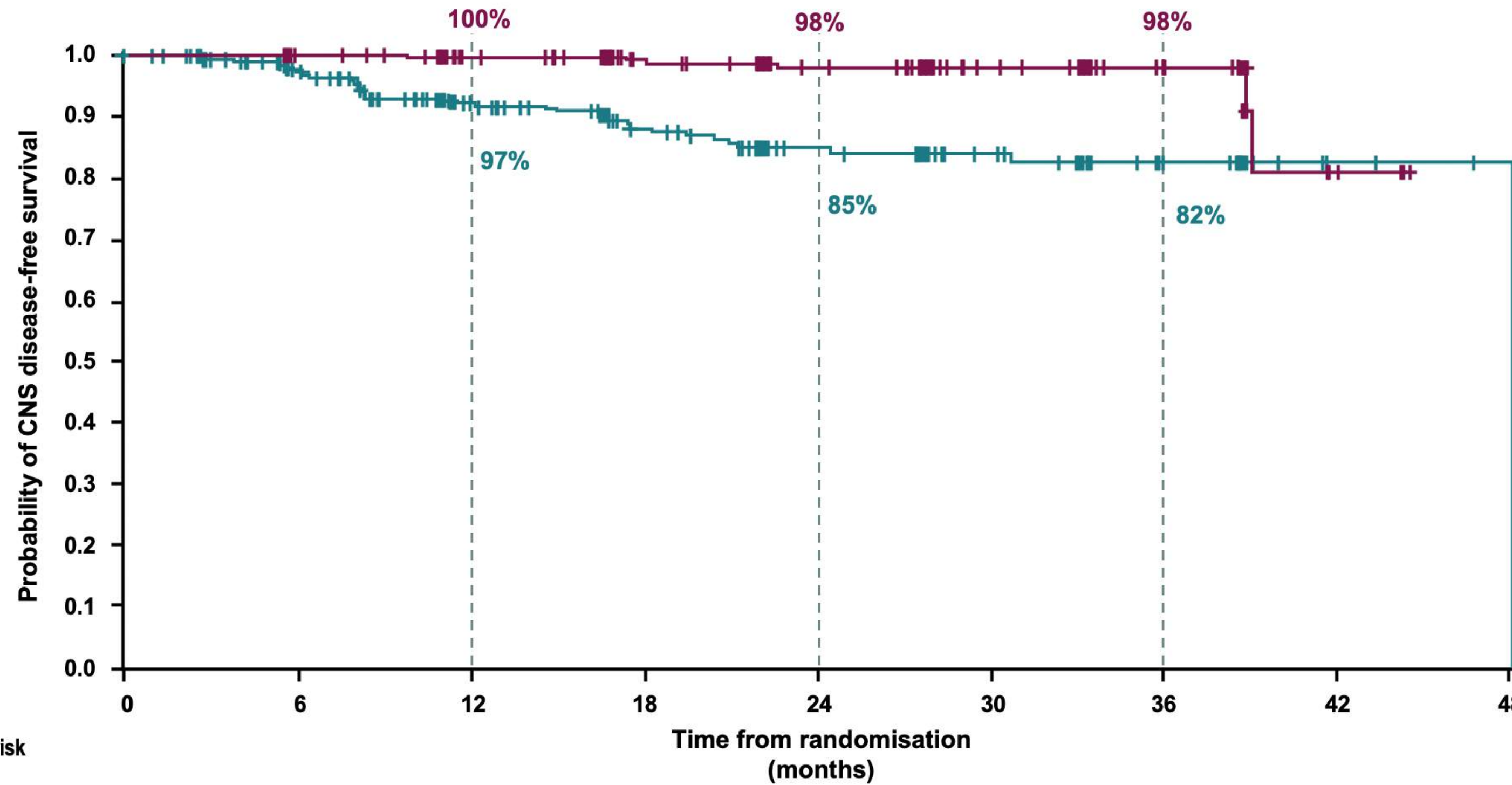
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| Treatment arms | Median DFS, months (95% CI) |
|----------------|-----------------------------|
| Osimertinib | NR (39-NC) |
| Placebo | 48.2 (NC-NC) |

HR (95% CI) 0.18 (0.10, 0.33); p<0.0001

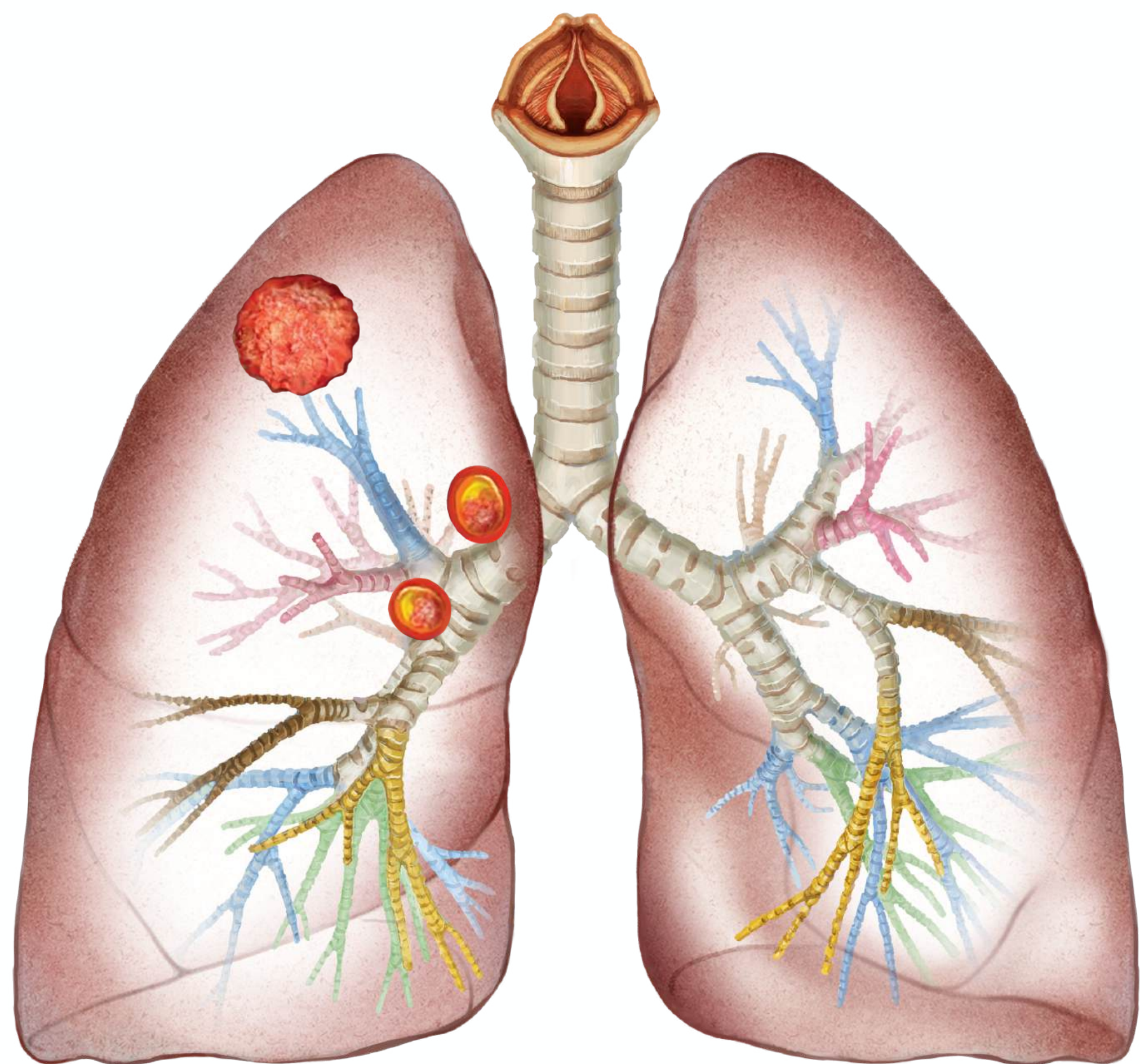
Maturity 7%:
osimertinib 2%, placebo 11%

Data cut-off: January 17, 2020.

CI = confidence interval; CNS = central nervous system; DFS = disease-free survival; HR = hazard ratio; NC = not calculable.

^aMaturity 7%: osimertinib 2%, placebo 11%. ^bDeath in absence of CNS disease recurrence, or death within two visits of baseline where the patient has no evaluable assessments or no baseline data. ^cDefined as the probability of observing a CNS recurrence event, conditional on the patient not experiencing a competing risk event (non-CNS recurrence and death by any cause) by time t.

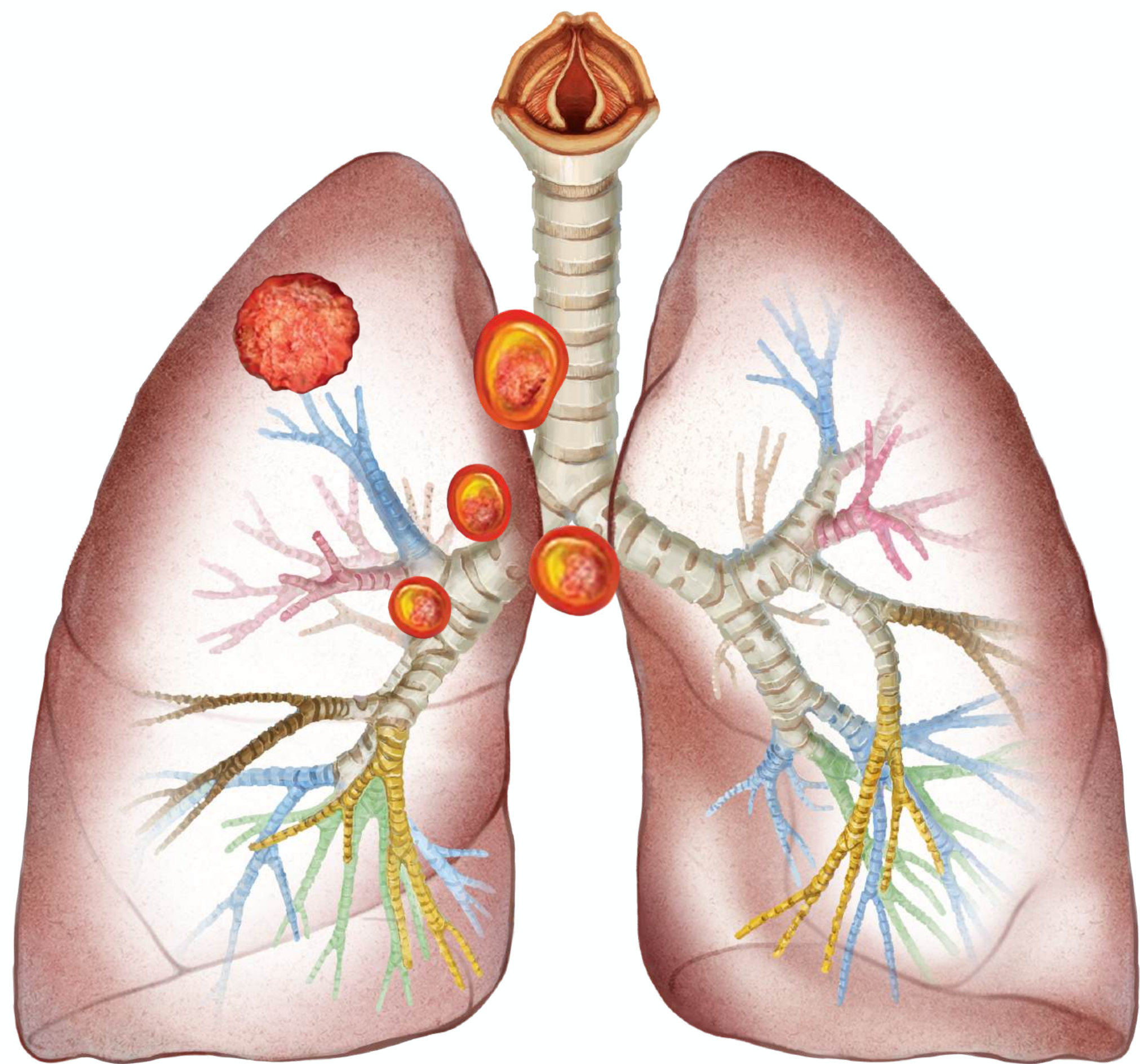
Wu Y-L et al. *N Engl J Med* 2020; 383:1711-1723



Stage II/IIIA

**Surgery + Adjuvant Chemotherapy
EGFR + Tagrisso / ALK + Alectinib**

**Neoadjuvant Chemotherapy +
Surgery**



Stage IIIA

Neoadjuvant Concurrent Chemoradiation?

Or

Definitive Concurrent Chemoradiation?

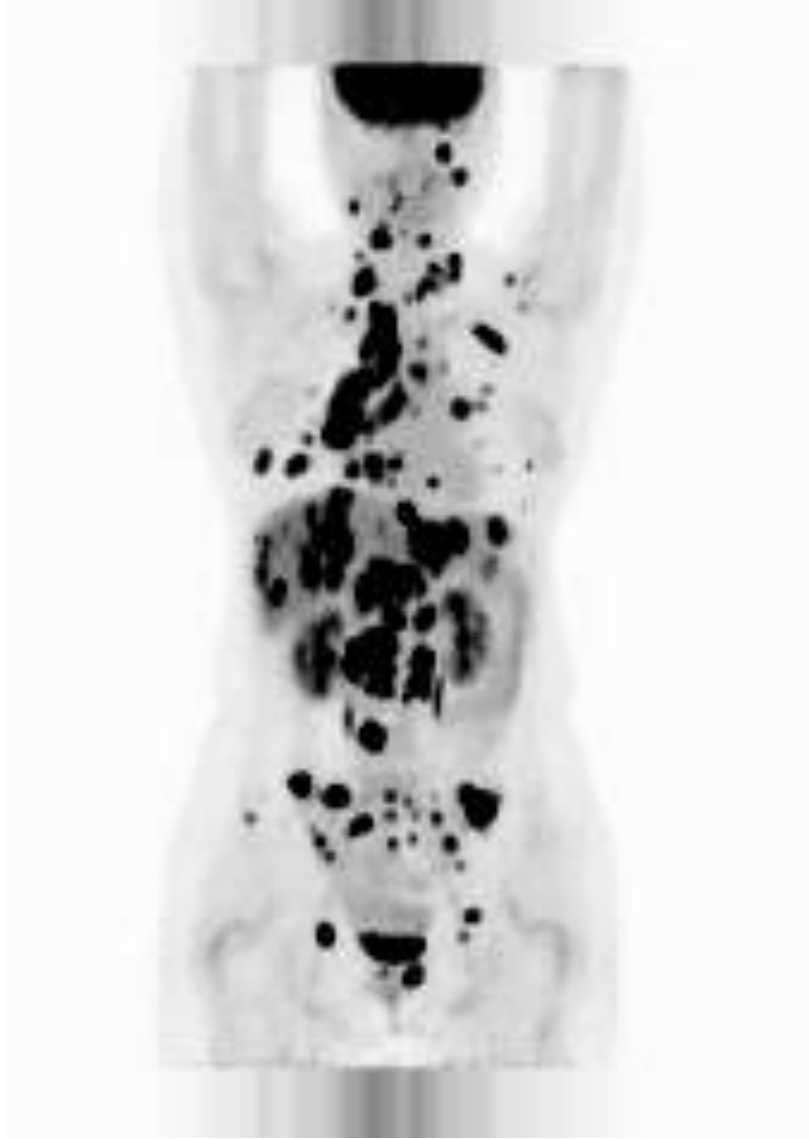
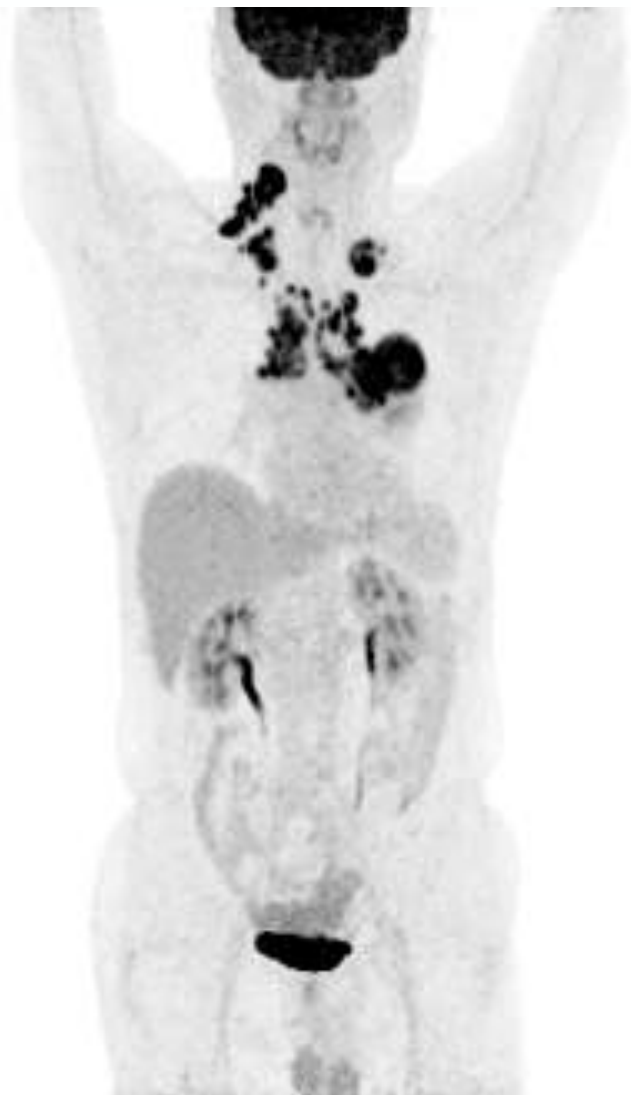
Or

Neoadjuvant Chemotherapy?

Localized disease

Occult Systemic disease

Systemic disease



Stage I

Stage II

Stage IIIA

Stage IIIB

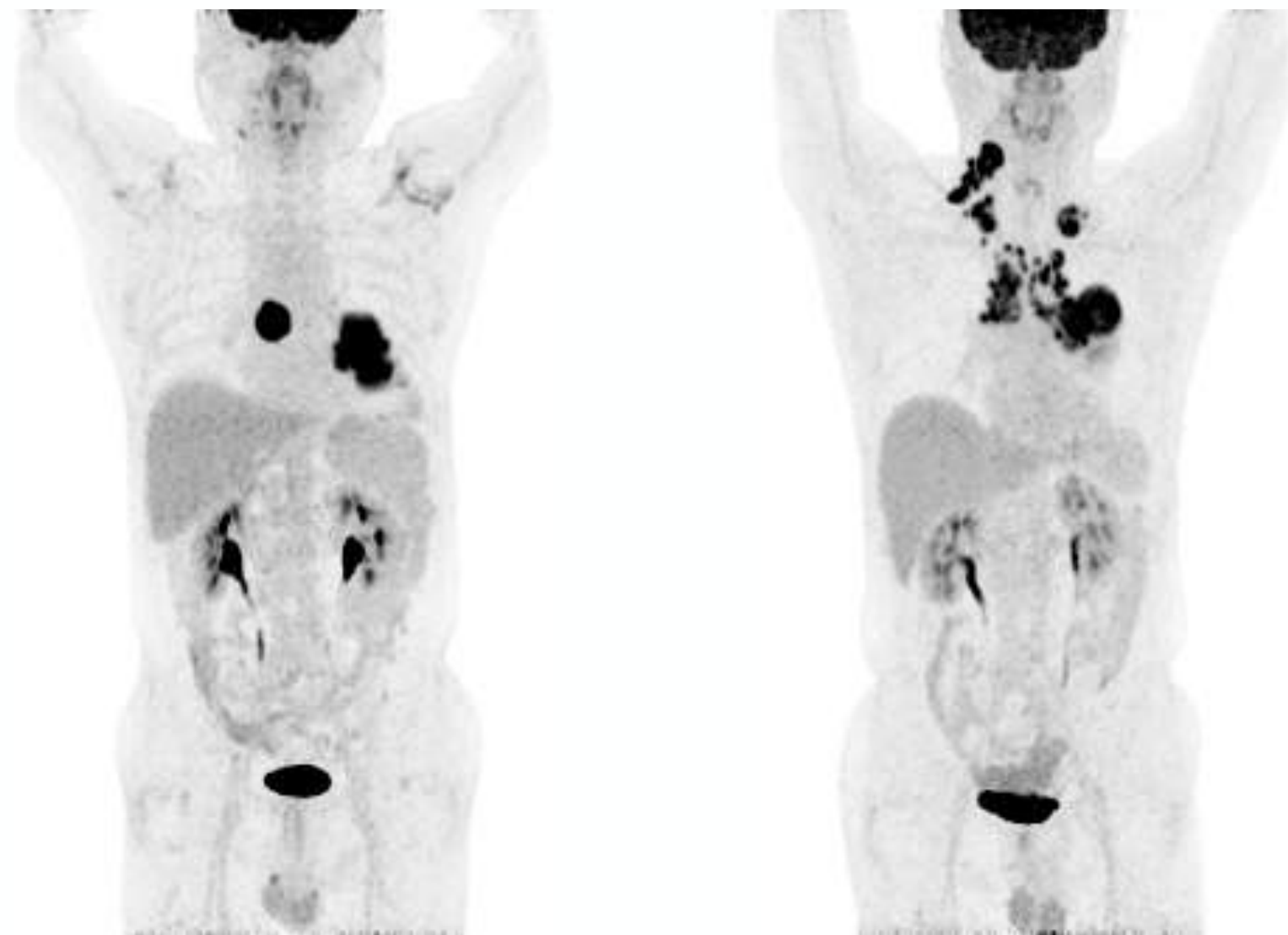
Stage IV

Early

Locally Advanced

Advanced

Ocult Systemic disease



Stage IIIA

Stage IIIB

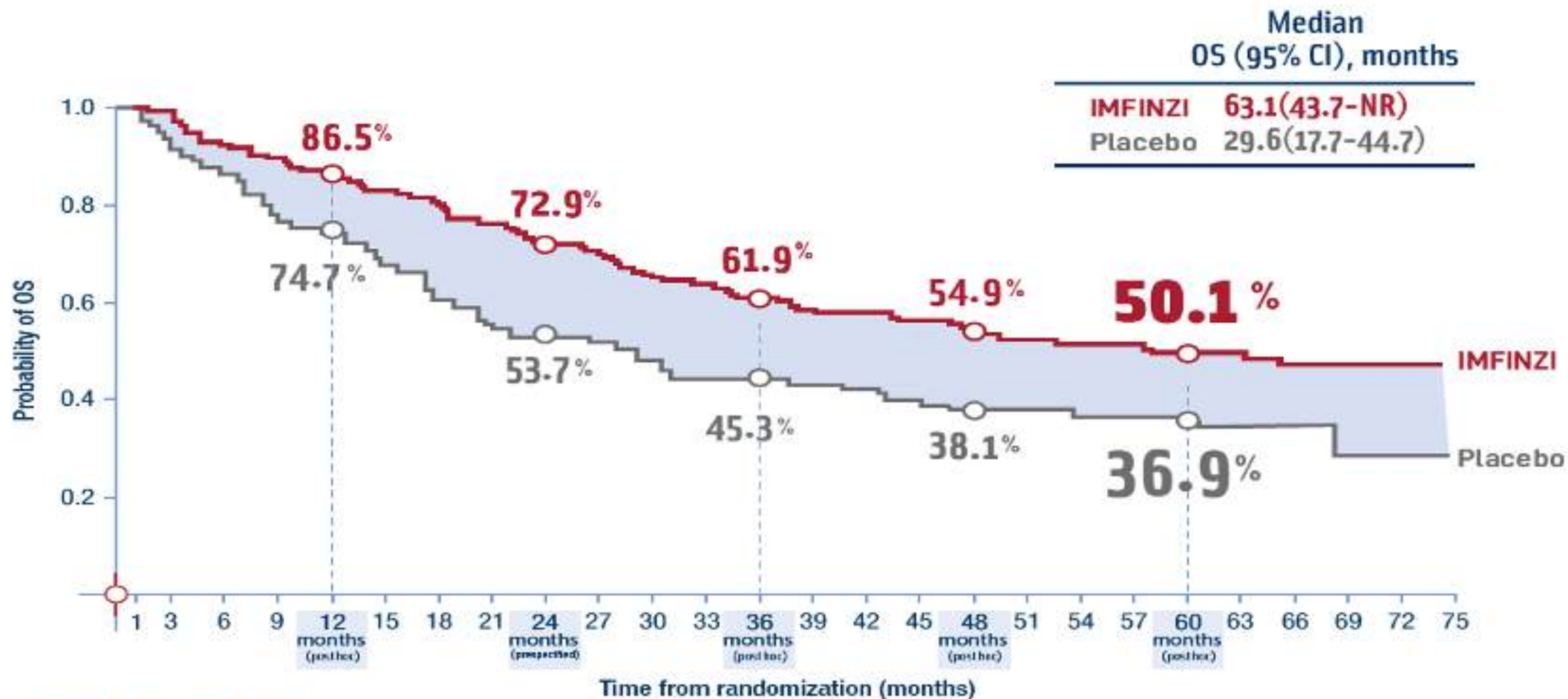
Locally Advanced

The prognosis after **surgery alone** remains **poor**

∴ **Systemic therapy** is required despite **locally advanced** disease

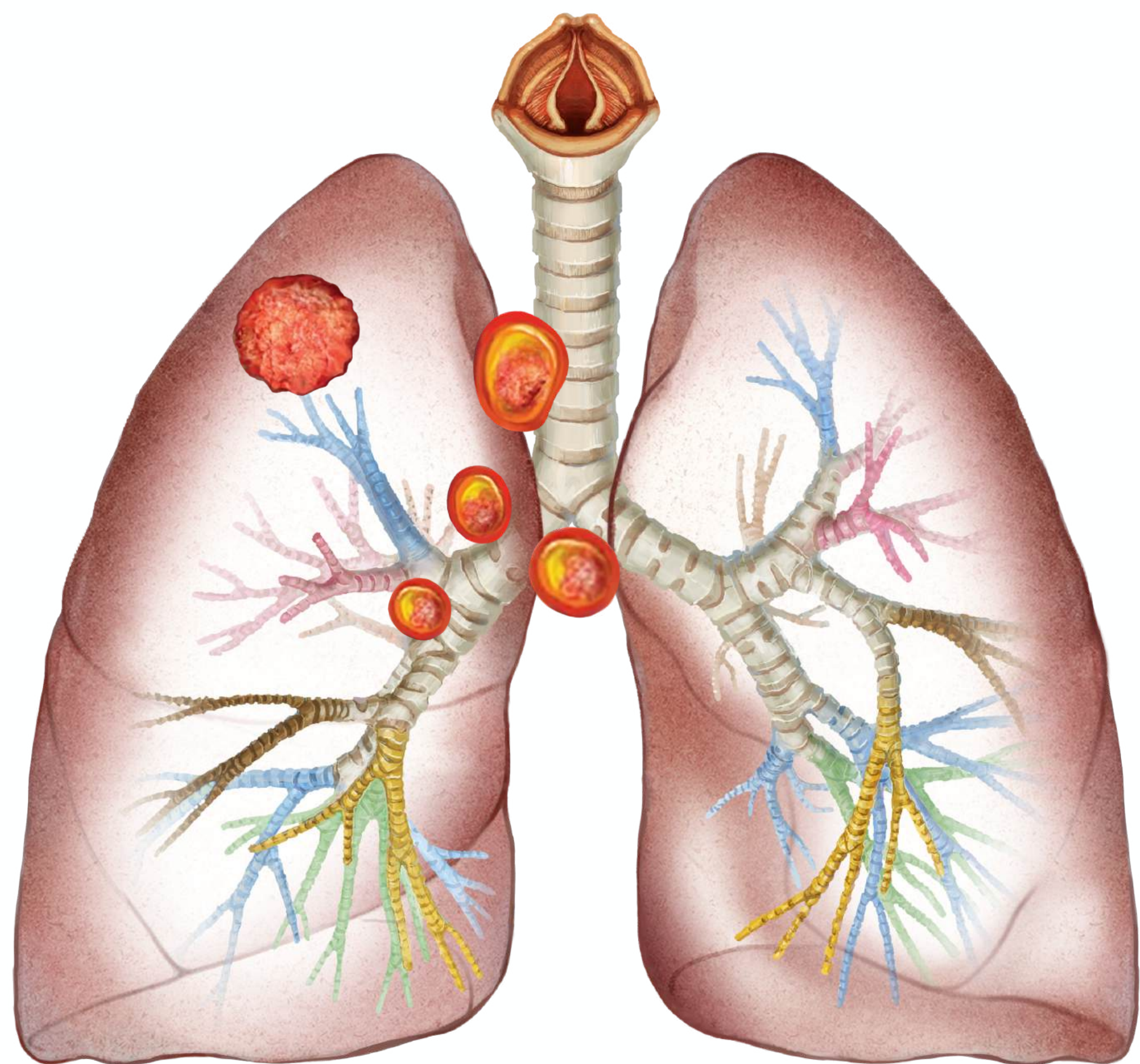
Definitive CCRT+Durvalumab

OS IN PATIENTS WITH PD-L1 $\geq 1\%$ ³



Number of patients at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|---|---|
| IMFINZI | 212 | 208 | 193 | 186 | 178 | 171 | 165 | 156 | 146 | 141 | 132 | 129 | 124 | 118 | 117 | 114 | 109 | 105 | 103 | 98 | 74 | 52 | 29 | 14 | 1 | 0 |
| Placebo | 91 | 81 | 75 | 67 | 64 | 58 | 52 | 47 | 45 | 44 | 41 | 38 | 38 | 37 | 36 | 33 | 31 | 31 | 30 | 29 | 24 | 14 | 8 | 5 | 2 | 0 |



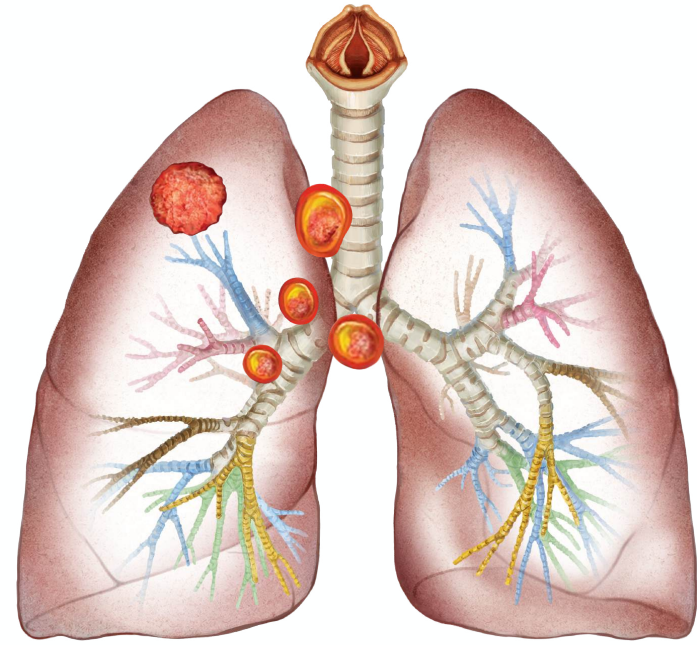
Stage IIIA

**EGFR Mutation Positive
PD-L1 Negative**

Neoadjuvant Concurrent Chemoradiation?

Or

Definitive Concurrent Chemoradiation?



ADAURA: Study Design

Phase III, double-blind, randomized, placebo-controlled, multicenter study

Patients with completely resected Stage^a IB, II, IIIA NSCLC, with or without adjuvant chemotherapy^b

Key inclusion criteria:

- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R^c
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins^d
- Maximum interval between surgery and randomization:
 - 10 weeks without adjuvant chemotherapy
 - 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFR^m (Ex19del vs L858R)
Race (Asian vs non-Asian)

R 1:1
N=682

Osimertinib
 80 mg, once daily

Placebo
 once daily

Planned treatment duration: 3 years

Treatment continues until:

- Disease recurrence, treatment completed, or discontinuation criterion met

Follow up:

- Until recurrence: week 12 and 24, then every 24 weeks to 5 years, then yearly after recurrence: every 24 weeks for 5 years, then yearly

Upon early unblinding cross-over was allowed after confirmed disease recurrence

Primary Endpoint:

- DFS, by investigator assessment, in stage II/IIIA patients^e

Secondary Endpoints:

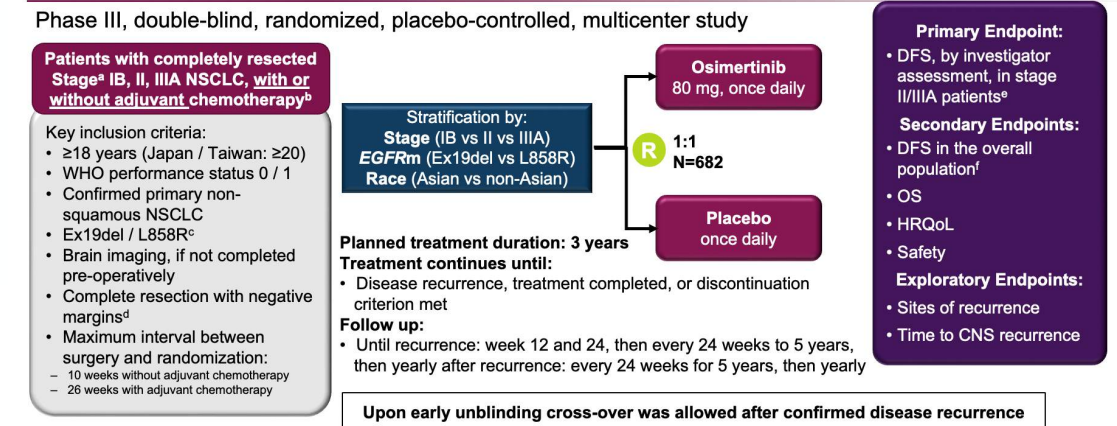
- DFS in the overall population^f
- OS
- HRQoL
- Safety

Exploratory Endpoints:

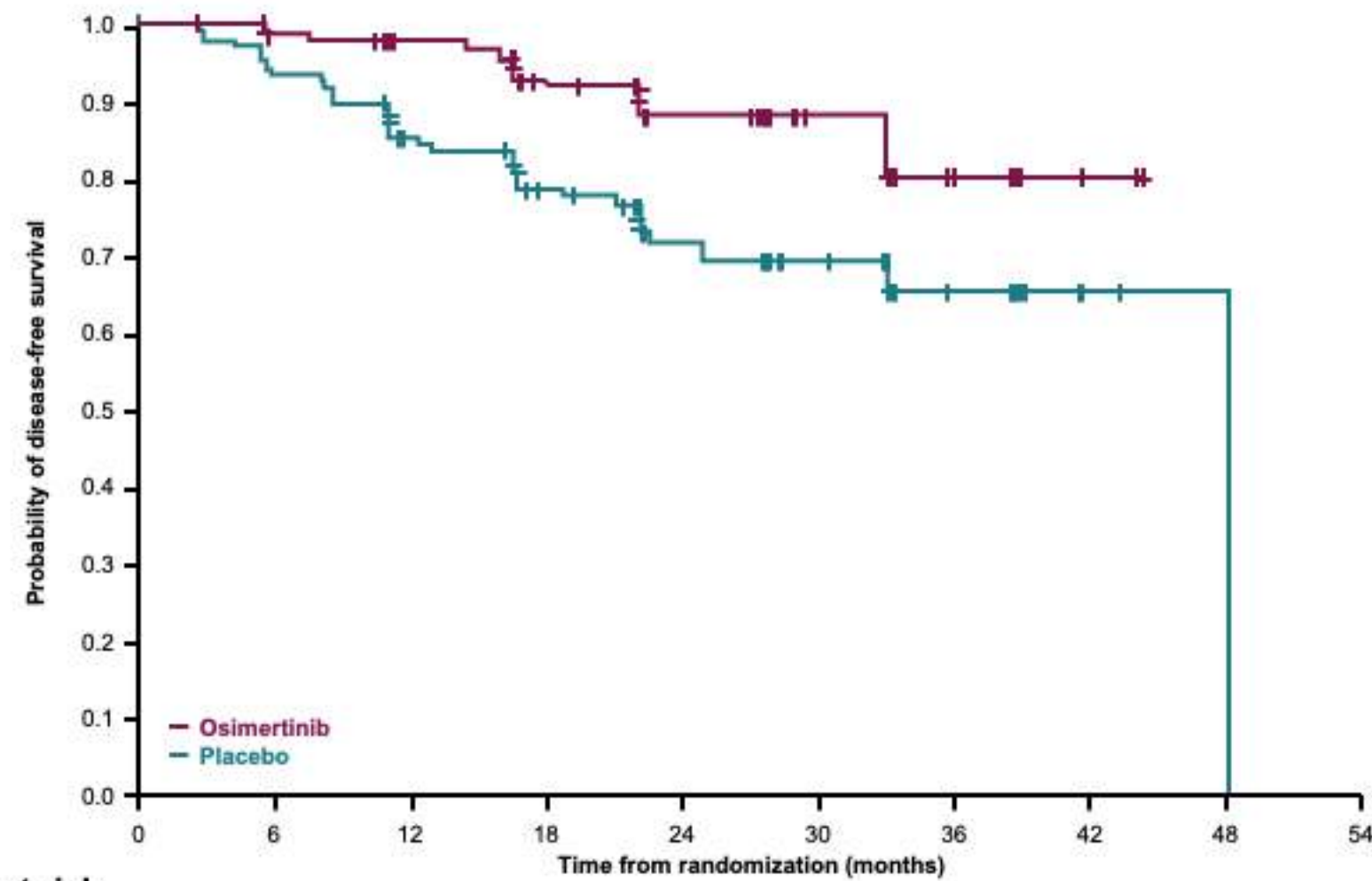
- Sites of recurrence
- Time to CNS recurrence

ADAURA: DFS by Stage

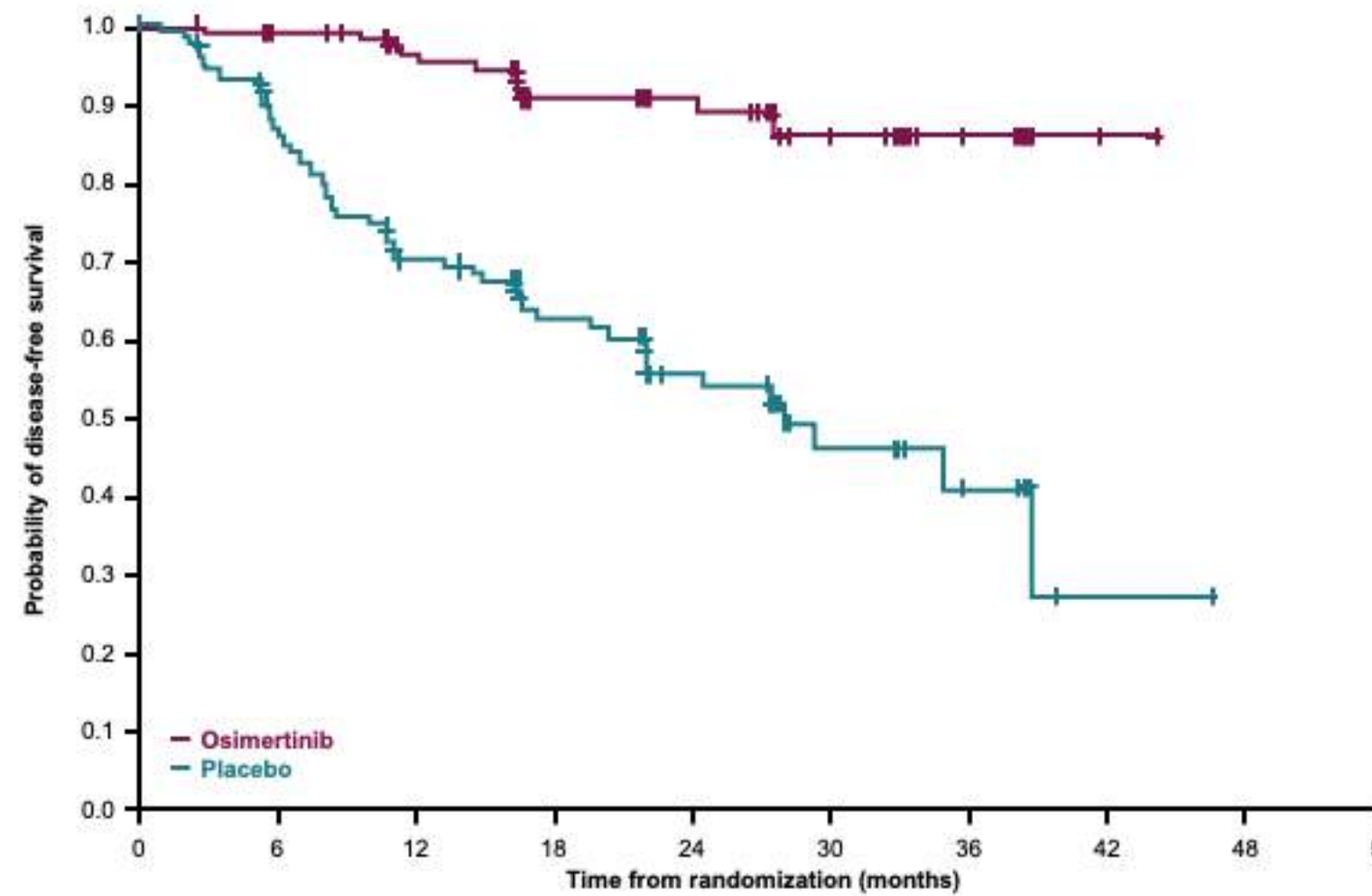
ADAURA: Study Design



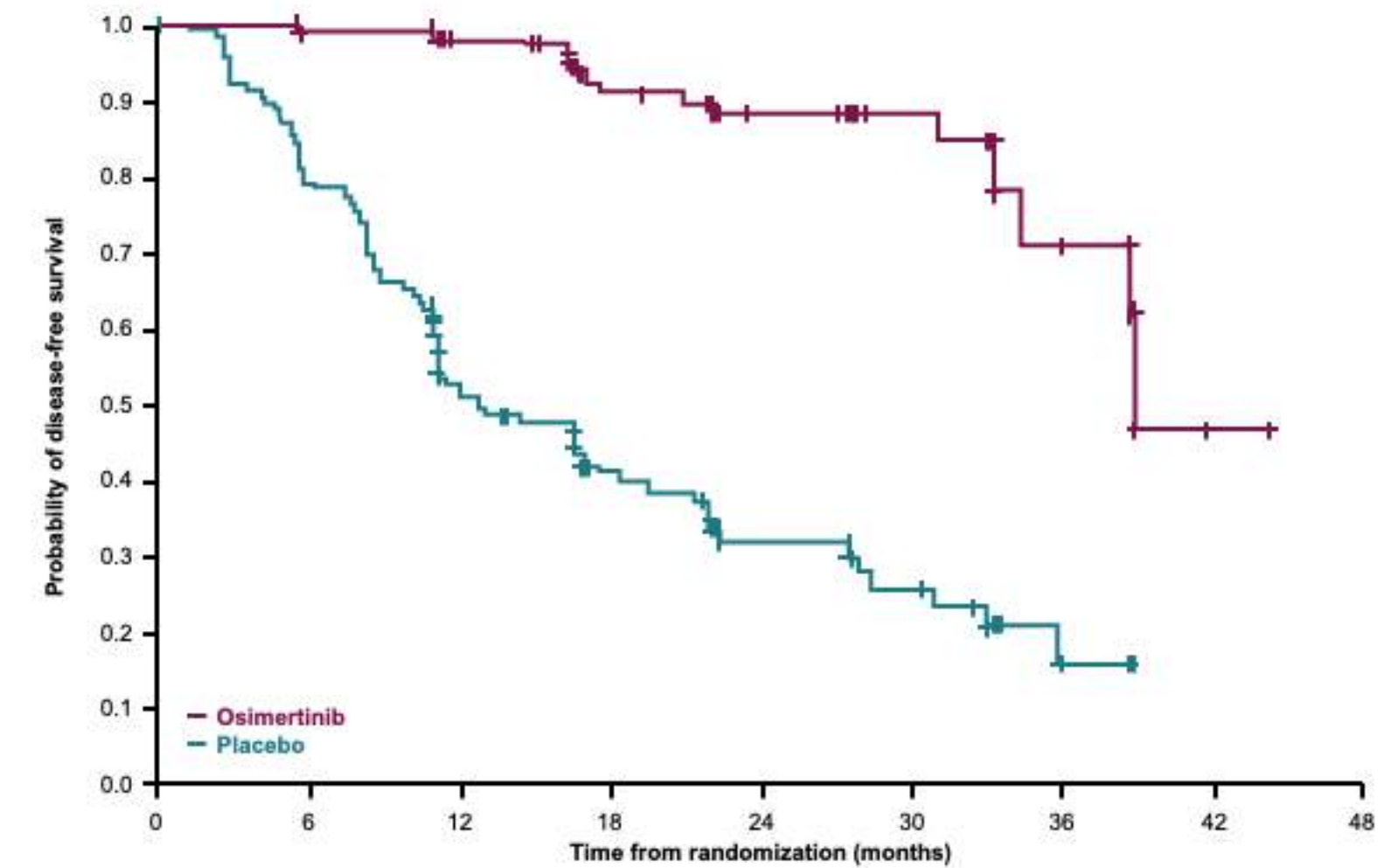
| | Stage IB | Stage II | Stage IIIA |
|------------------------------------|-------------------------|-------------------------|-------------------------|
| 2 year DFS rate, % (95% CI) | | | |
| – Osimertinib | 88 (78, 94) | 91 (82, 95) | 88 (79, 94) |
| – Placebo | 71 (60, 80) | 56 (45, 65) | 32 (23, 41) |
| Overall HR (95% CI) | 0.39 (0.18-0.76) | 0.17 (0.08-0.31) | 0.12 (0.07-0.20) |



| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|-------------|-----|----|----|----|----|----|----|----|----|
| Osimertinib | 106 | 94 | 83 | 71 | 41 | 22 | 9 | 3 | 0 |
| Placebo | 106 | 97 | 80 | 66 | 37 | 26 | 11 | 2 | 1 |



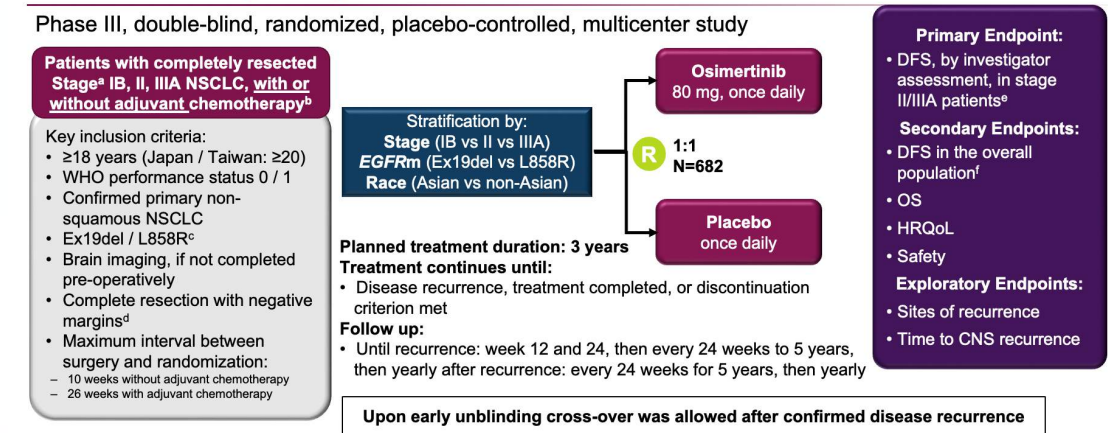
| | | | | | | | | | |
|-------------|-----|-----|----|----|----|----|---|---|---|
| Osimertinib | 118 | 110 | 91 | 69 | 47 | 28 | 9 | 1 | 0 |
| Placebo | 118 | 99 | 74 | 49 | 31 | 15 | 7 | 1 | 0 |



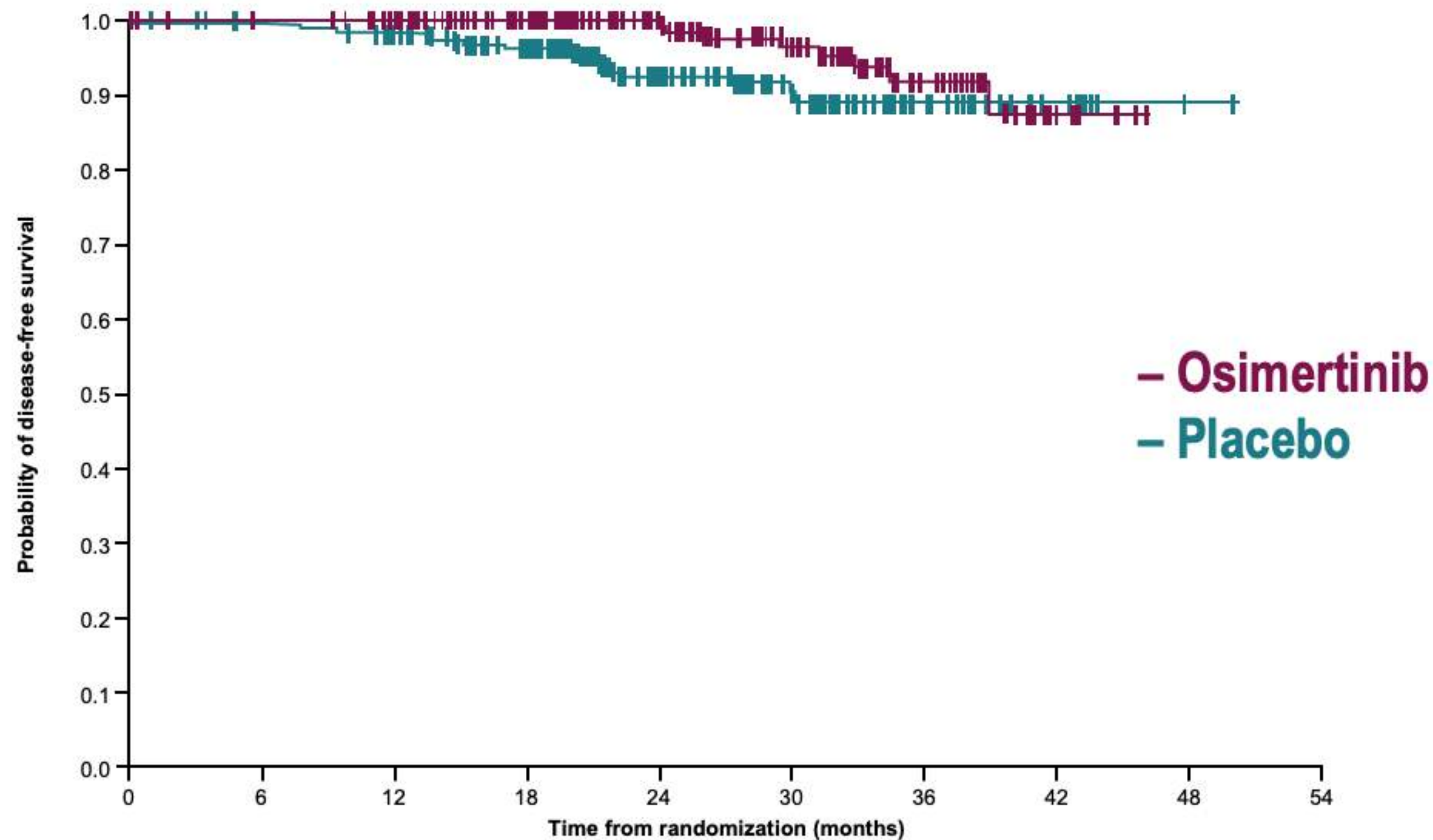
| | | | | | | | | | |
|-------------|-----|-----|----|----|----|----|---|---|---|
| Osimertinib | 115 | 109 | 98 | 68 | 50 | 24 | 9 | 1 | 0 |
| Placebo | 119 | 91 | 53 | 33 | 20 | 12 | 2 | 0 | 0 |

ADAURA: Overall Survival in Stage II/IIIA Patients

ADAURA: Study Design



- Median follow-up: osimertinib 26.1 months, placebo 24.6 months
- OS was immature; 9 patients died in the osimertinib arm and 20 patients died in the placebo arm



| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|-------------|-----|-----|-----|-----|-----|----|----|----|----|----|
| Osimertinib | 233 | 229 | 221 | 192 | 137 | 82 | 39 | 10 | 0 | |
| Placebo | 237 | 231 | 222 | 190 | 127 | 68 | 31 | 11 | 1 | 0 |

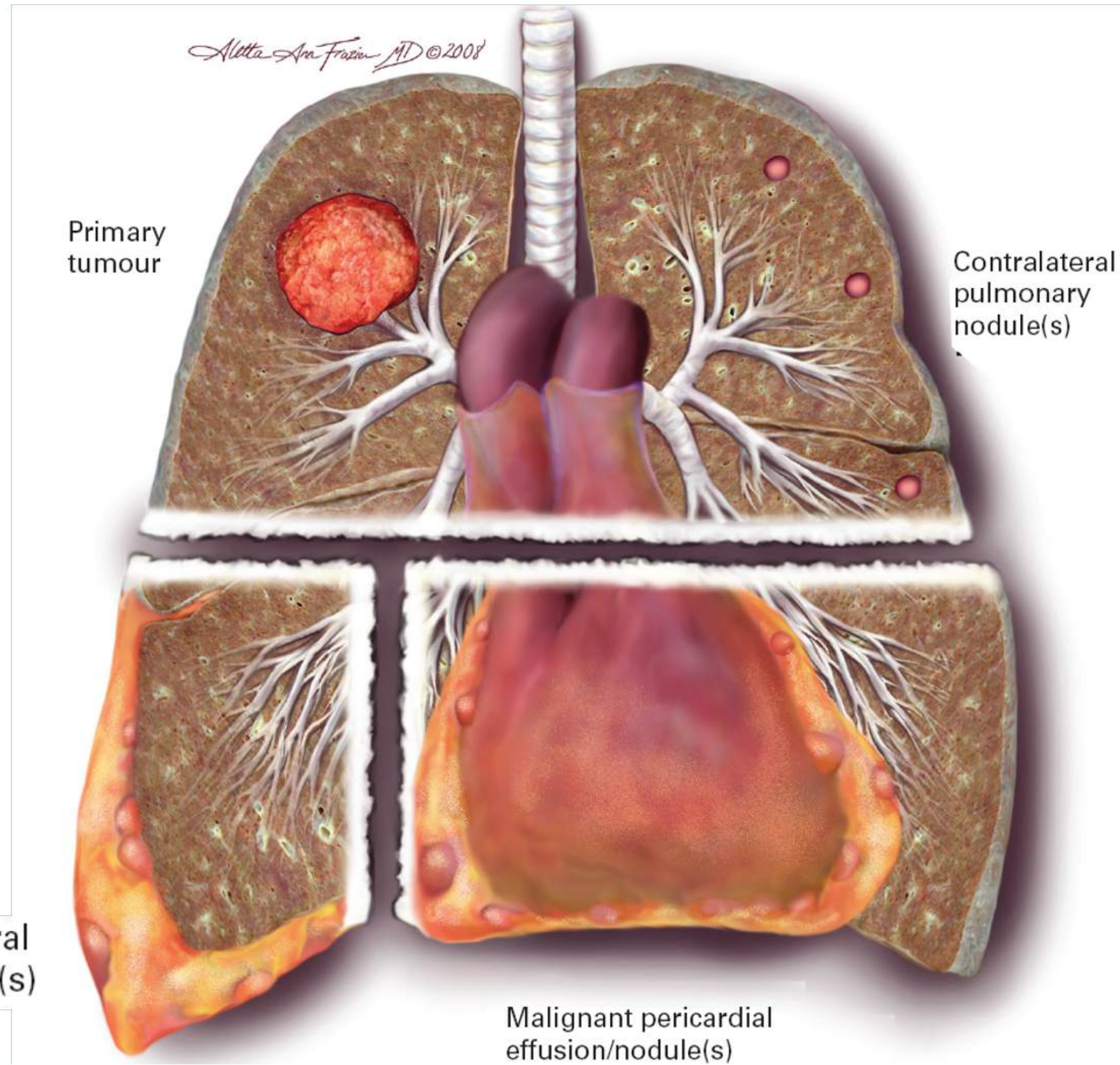
| Treatment arms | Median DFS, months (95% CI) |
|----------------|-----------------------------|
| Osimertinib | NR (NC-NC) |
| Placebo | NR (NC-NC) |

HR 0.40 (99.98% CI, 0.09-1.83)
Maturity 5%

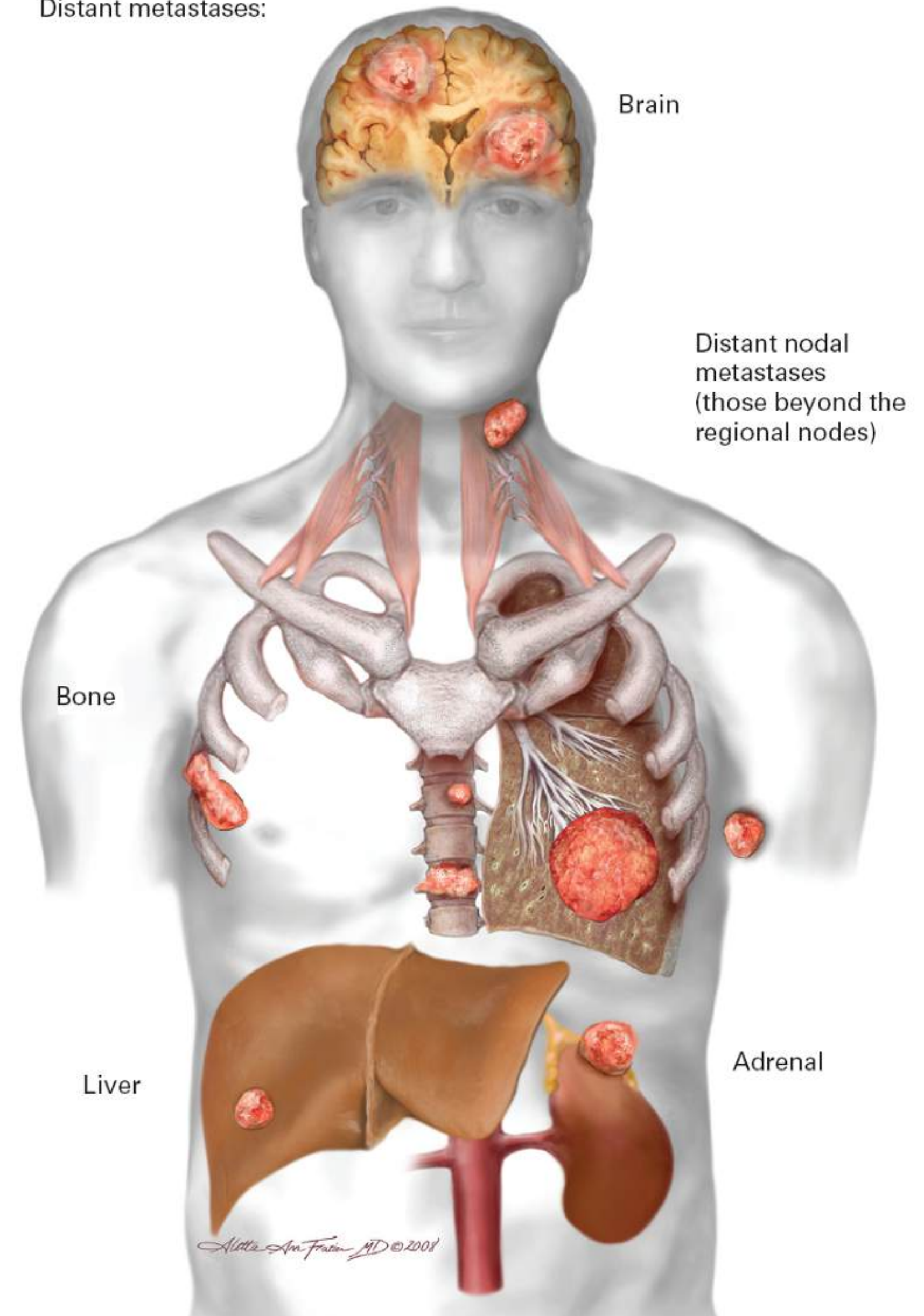
**There were a small number of deaths in stage IB patients:²
osimertinib 1 death,
placebo 2 deaths**

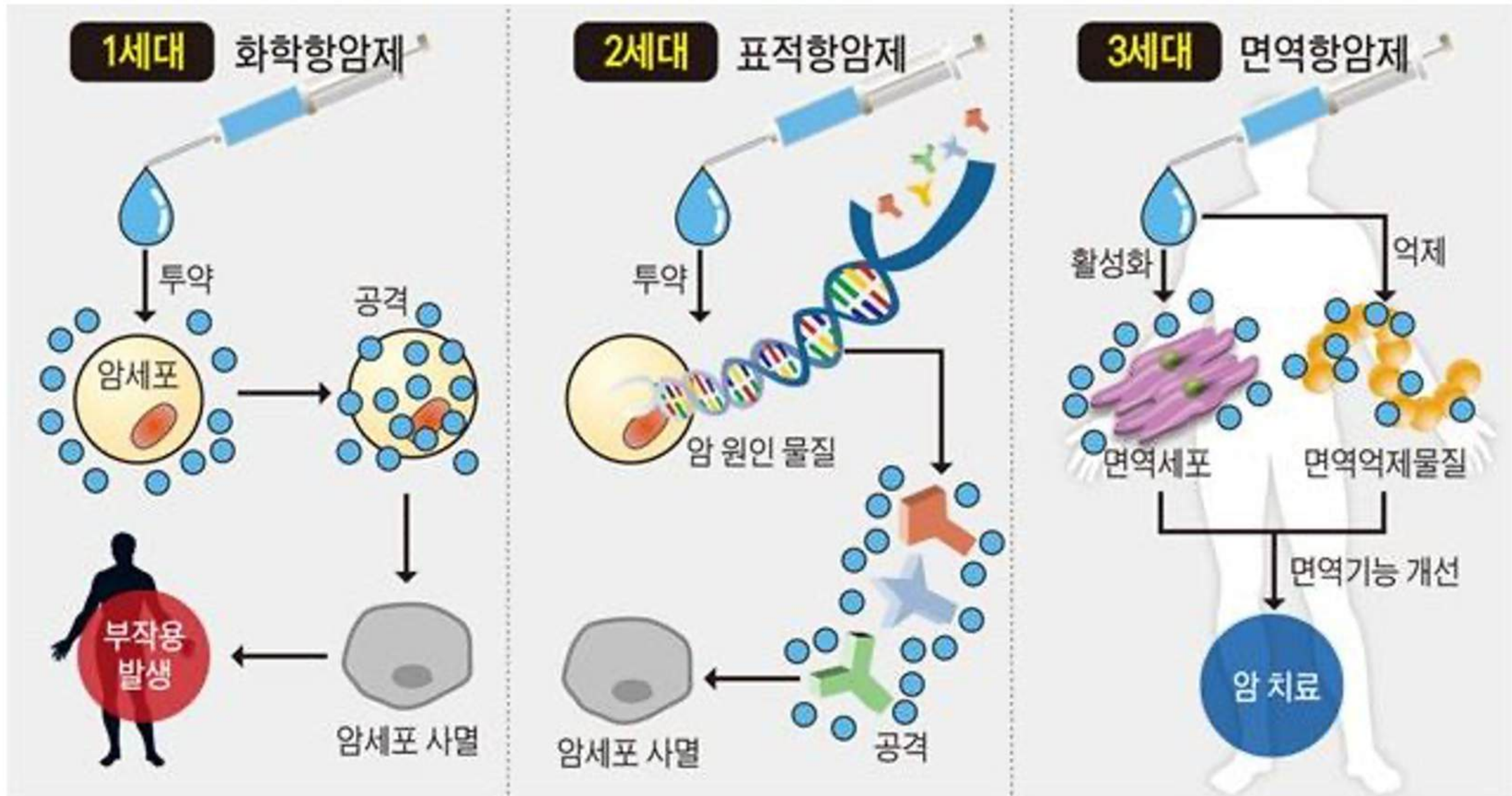
Stage IV of Lung Cancer

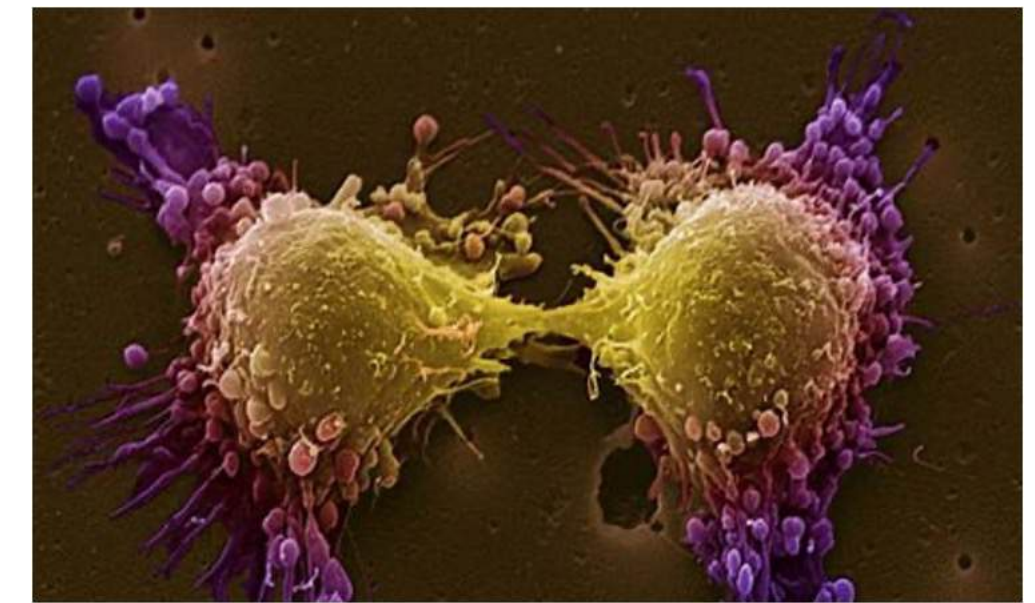
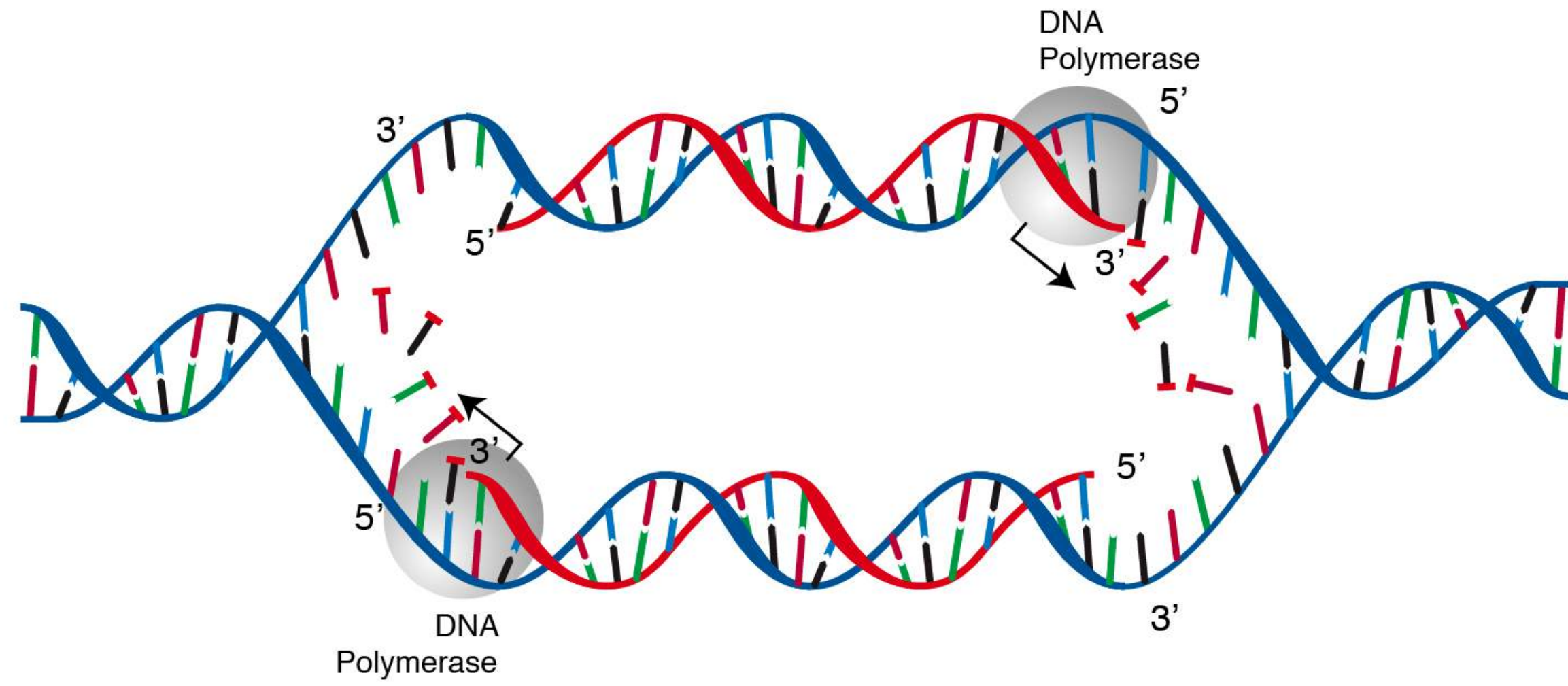
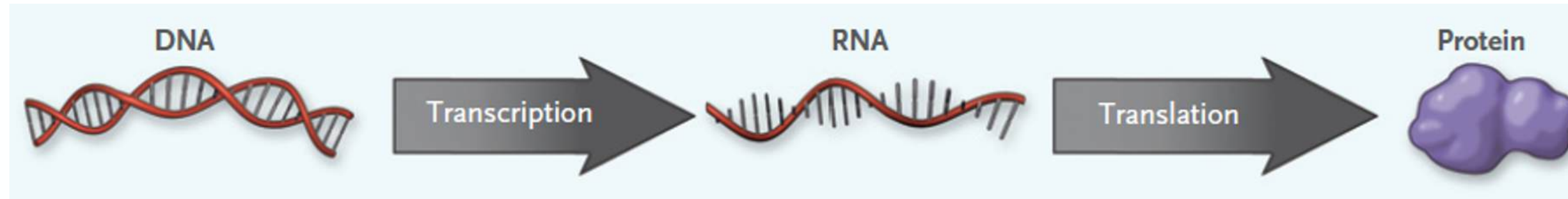
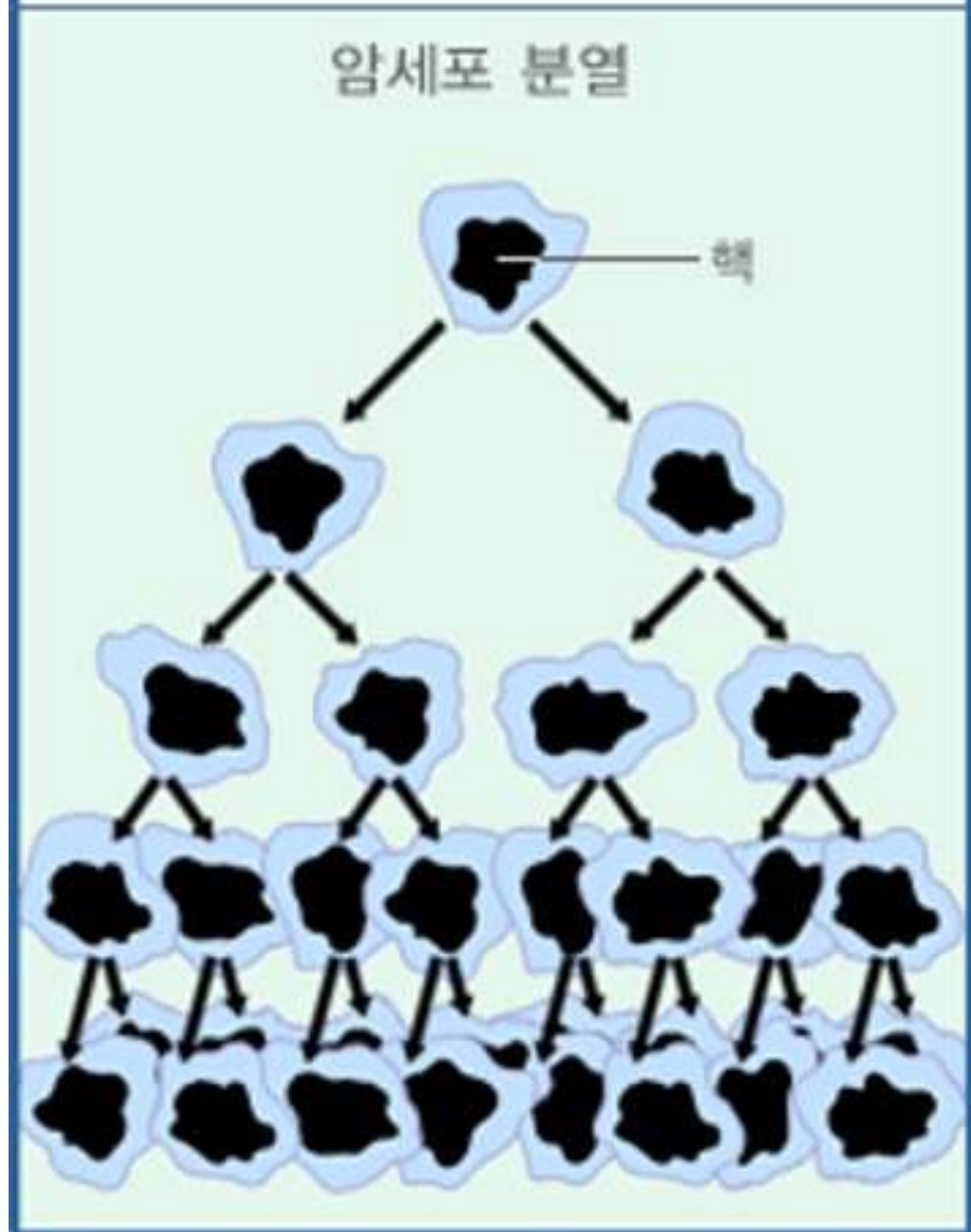
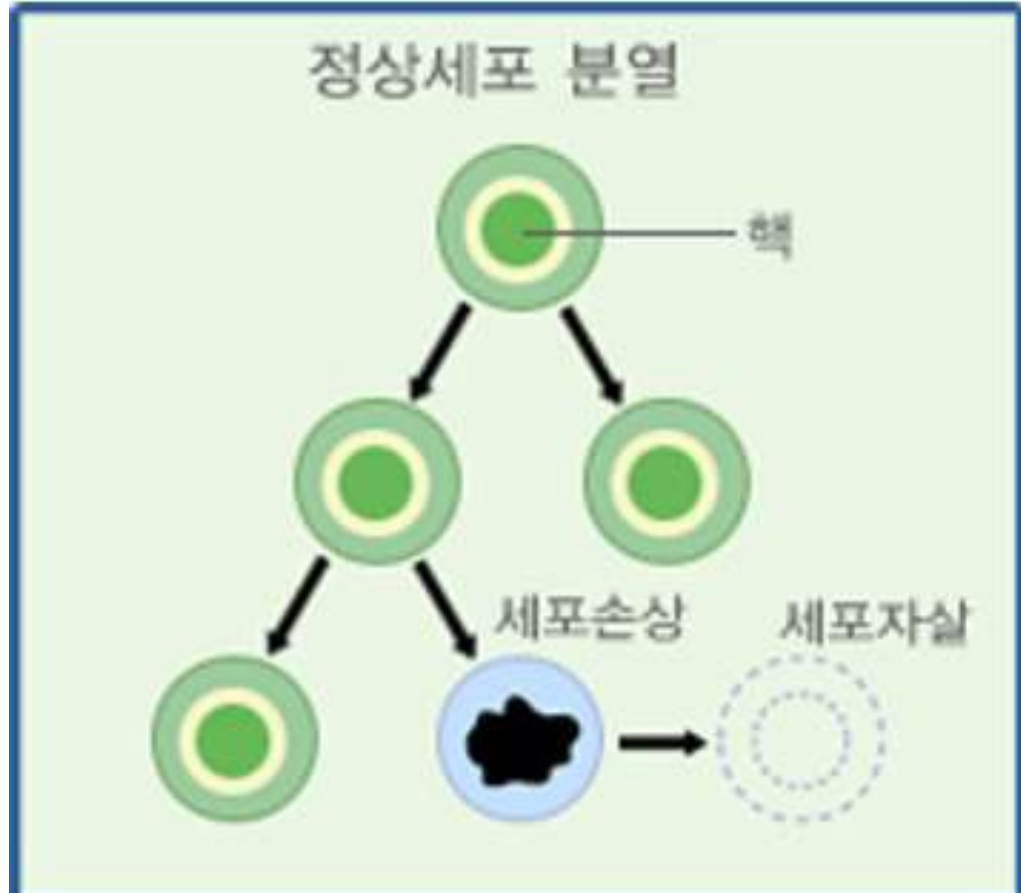
M1a




Distant metastases:







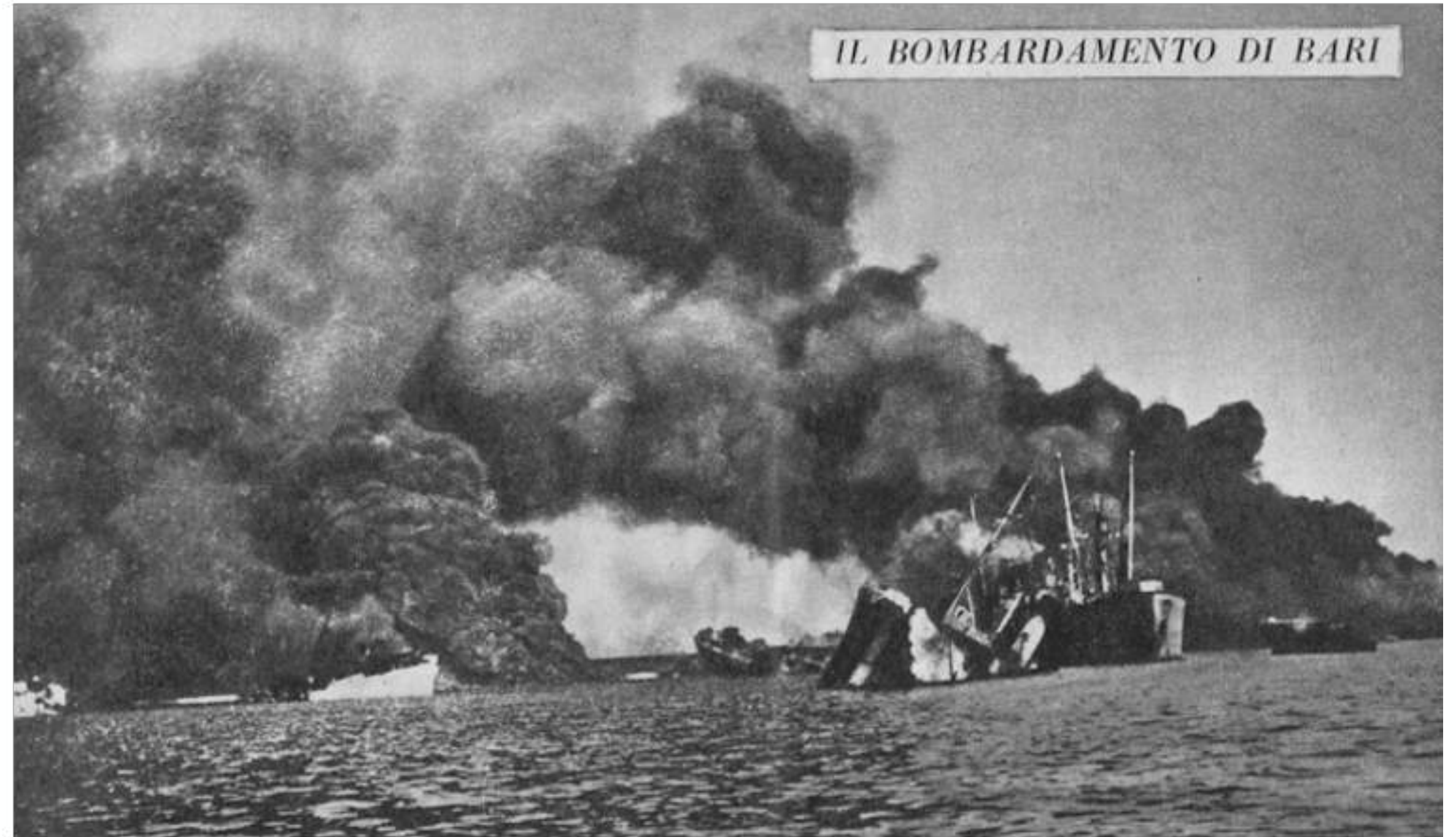
MUSTARD GAS



Smells like
GARLIC ...

HORSERADISH · MUSTARD
STRONG VESICANT

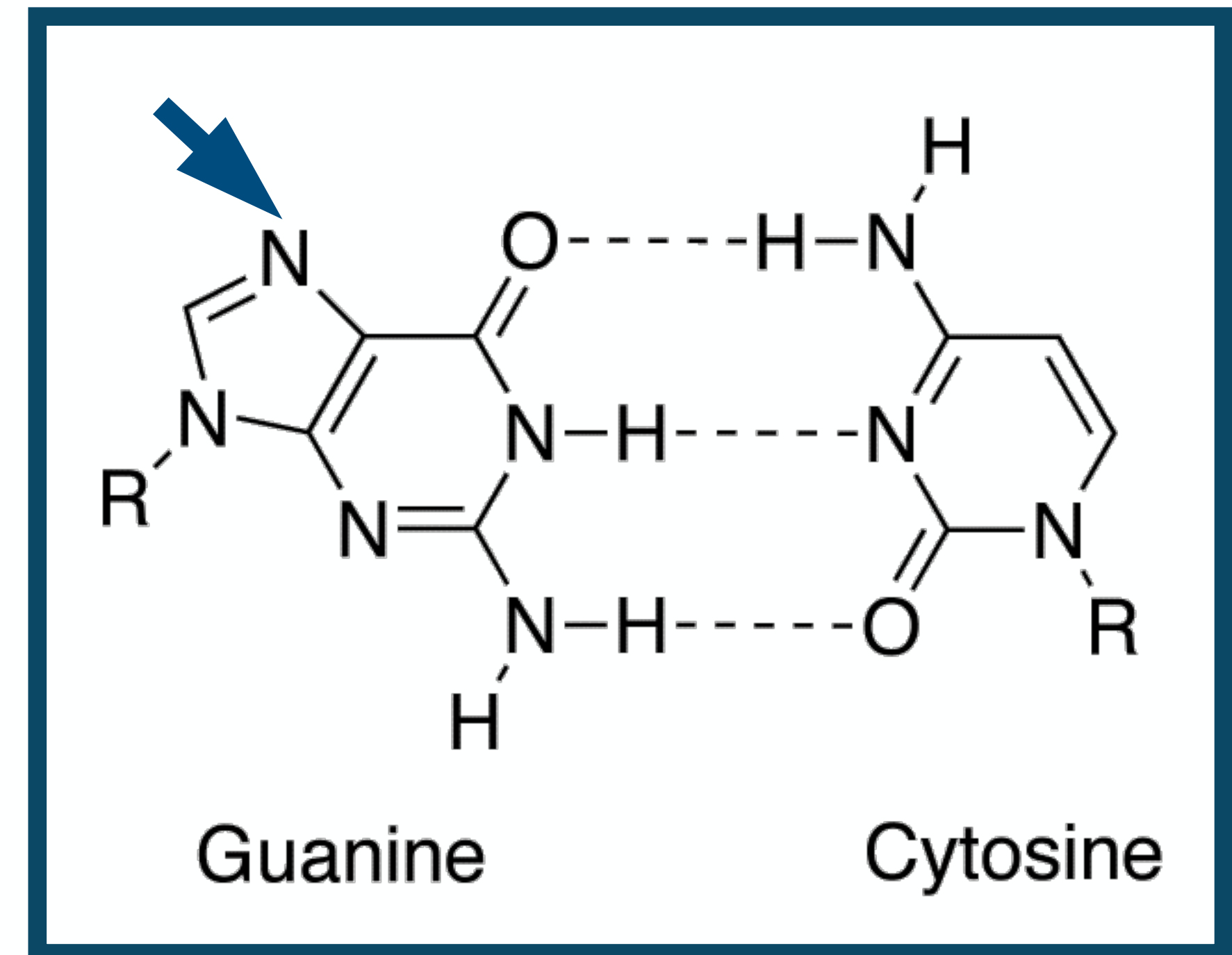
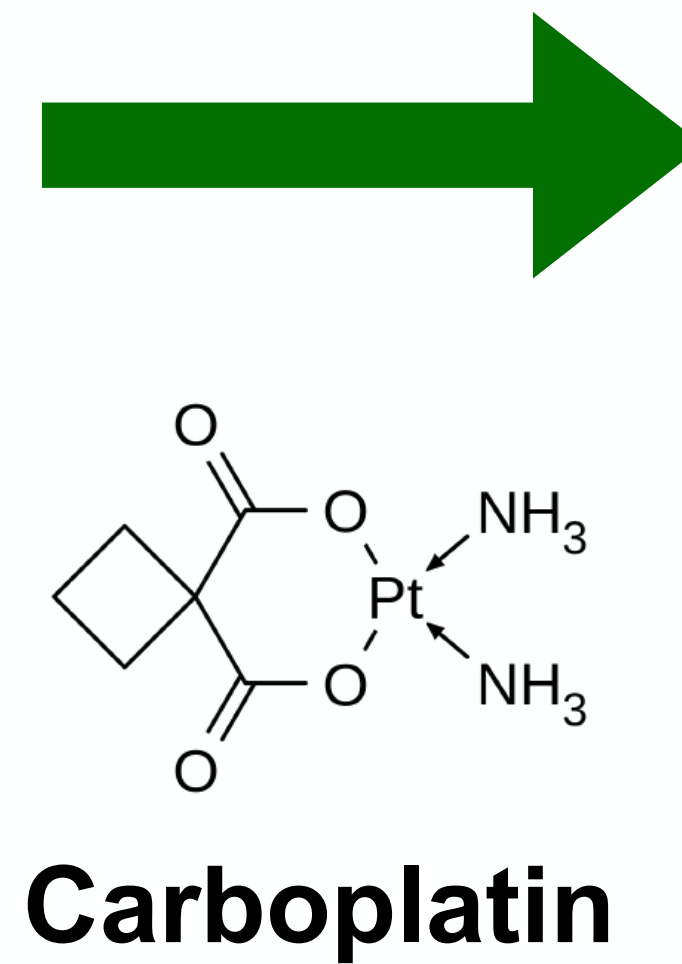
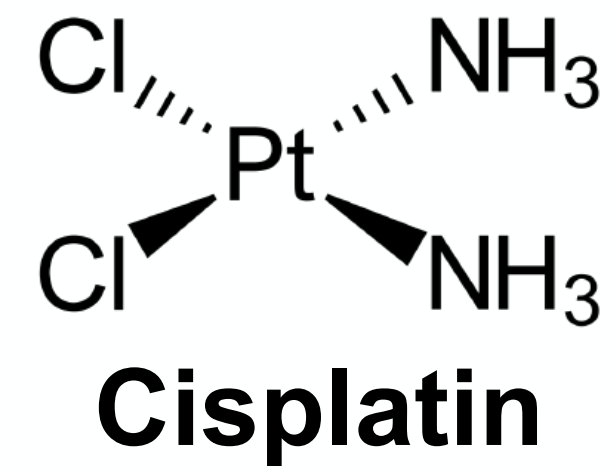
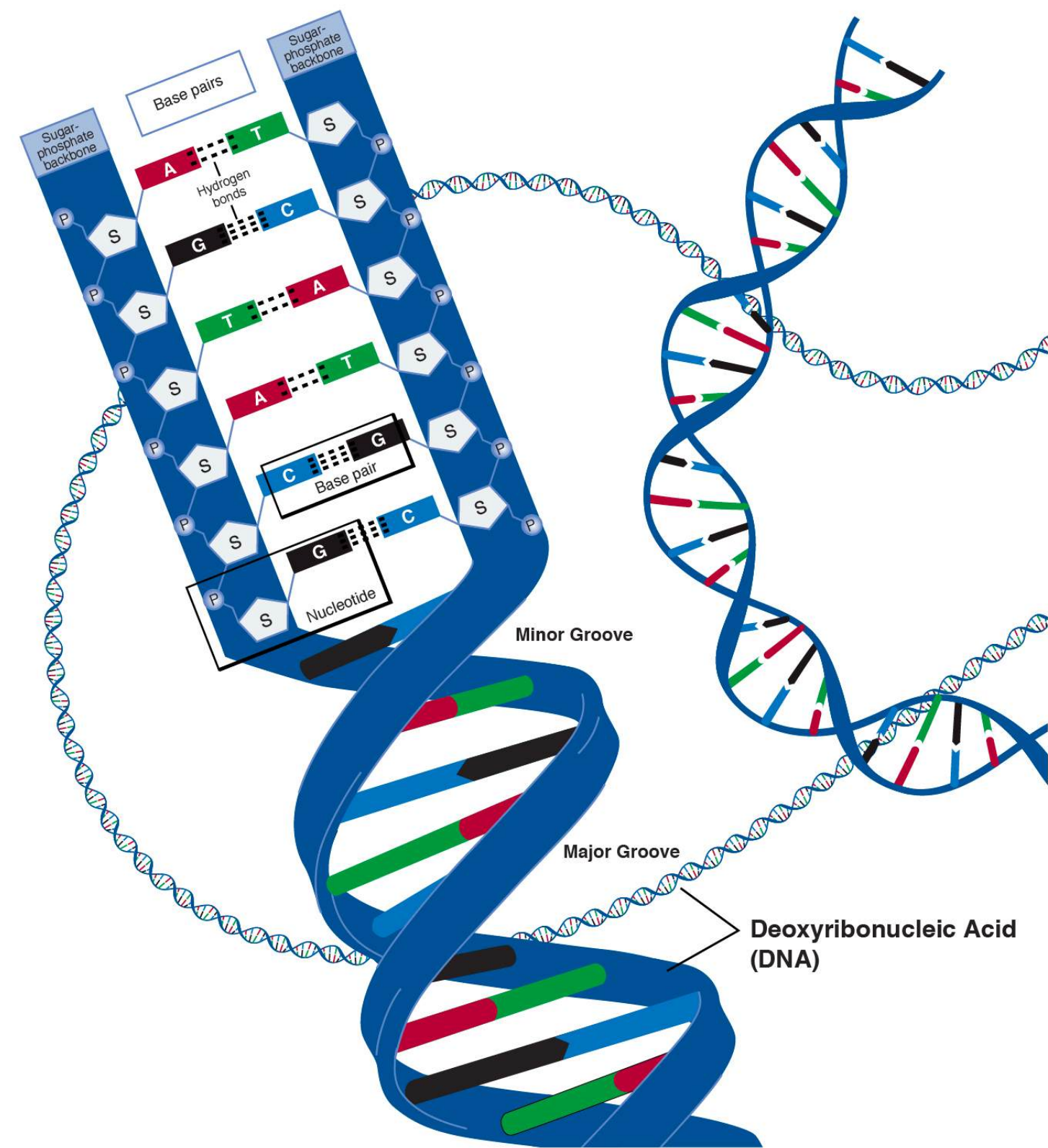
MUSTARD GAS
BY THE
MUSTARD
GAS





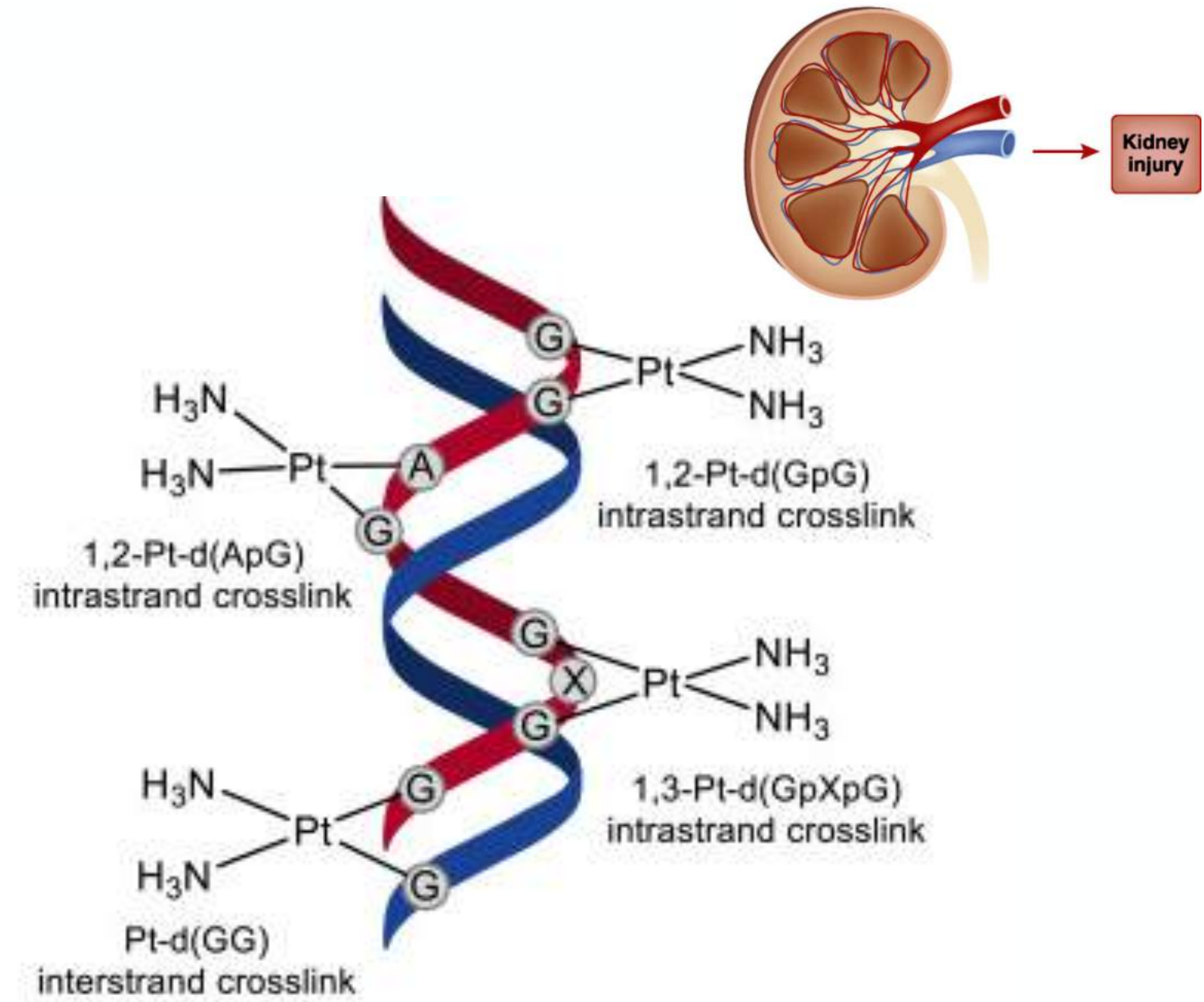
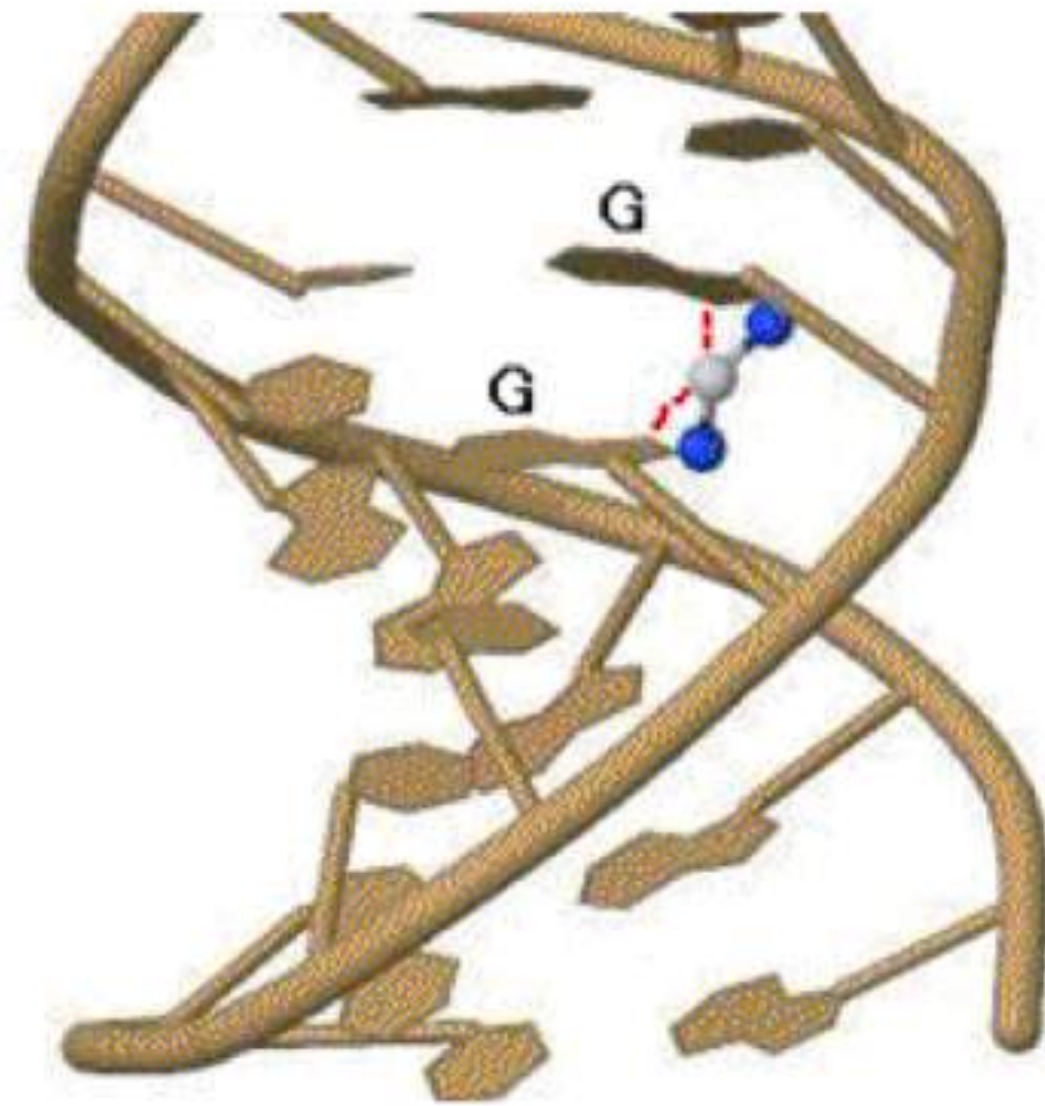
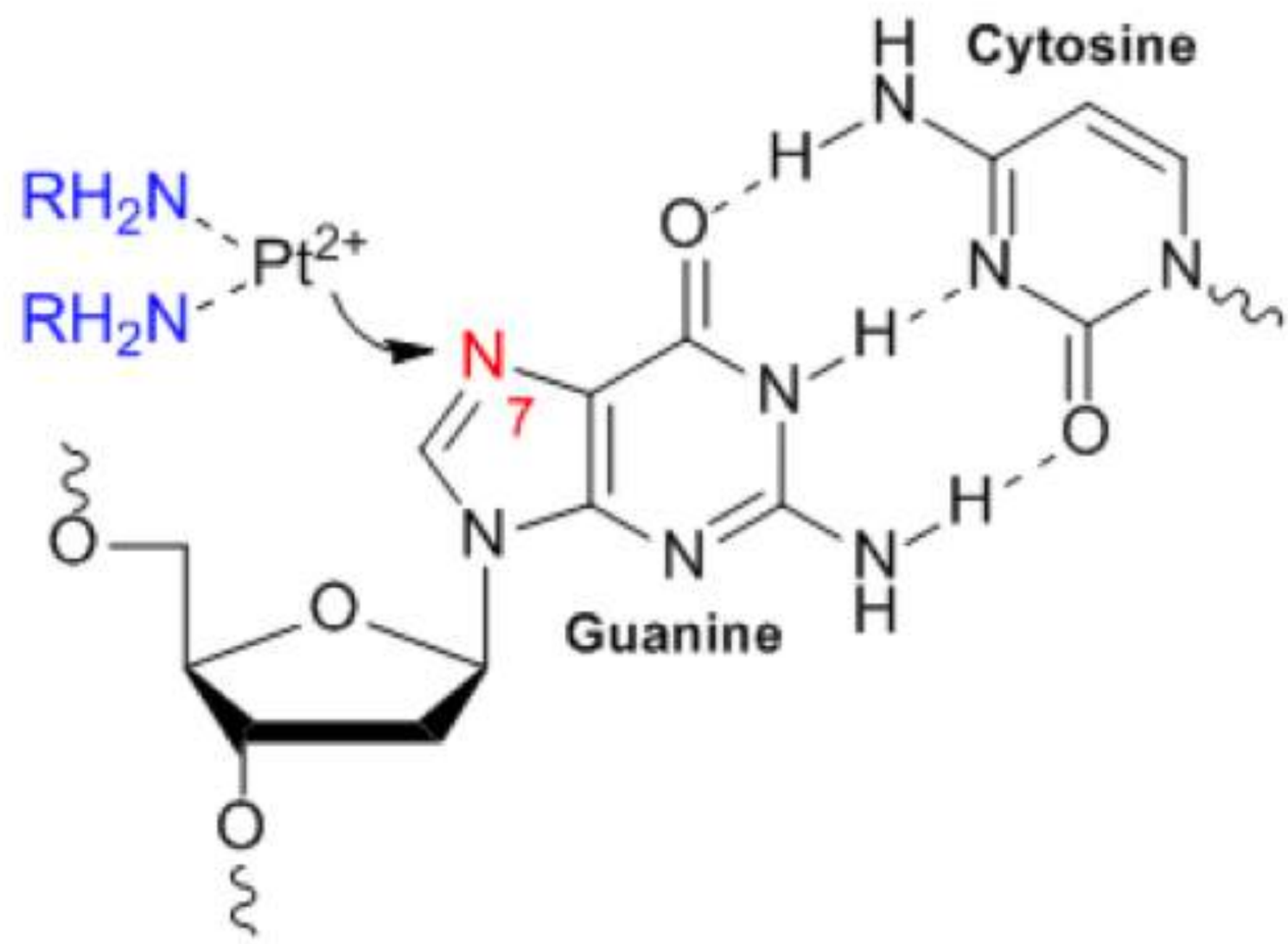
Alkylating Agents

Year 1978



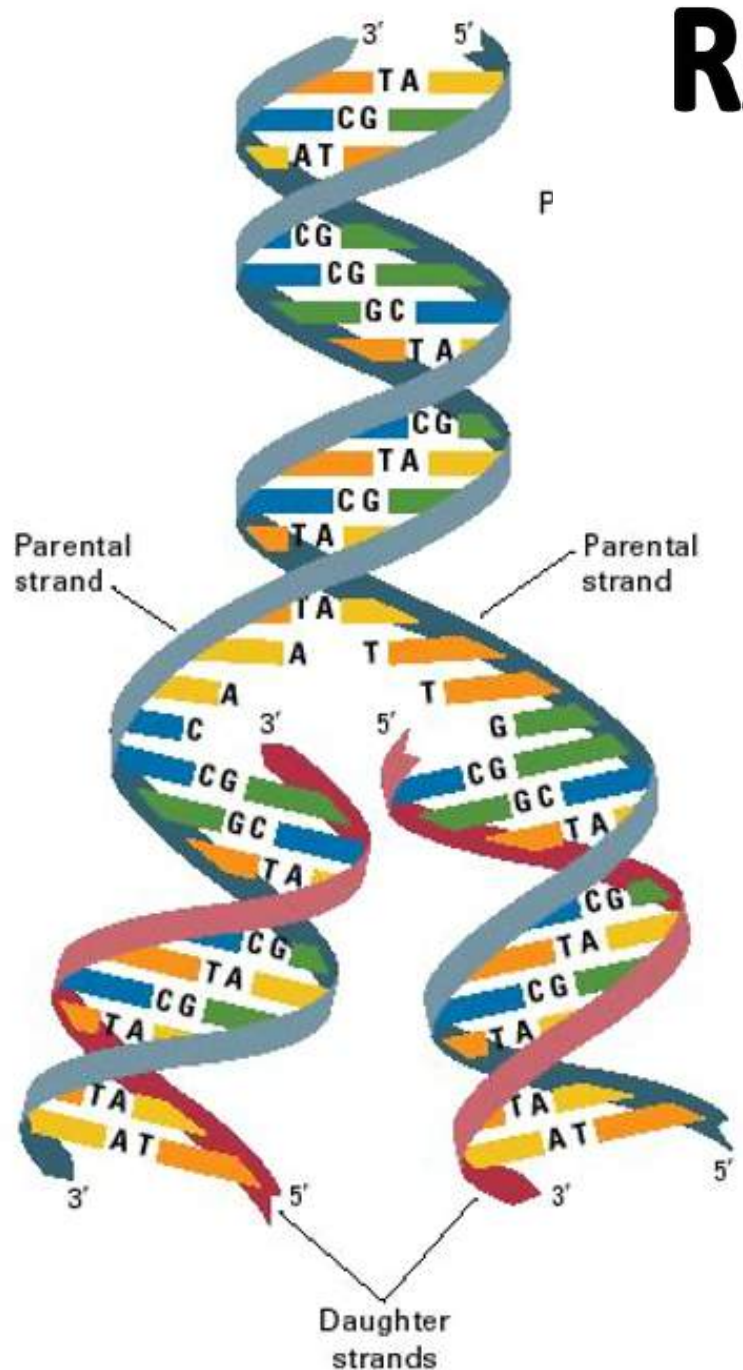
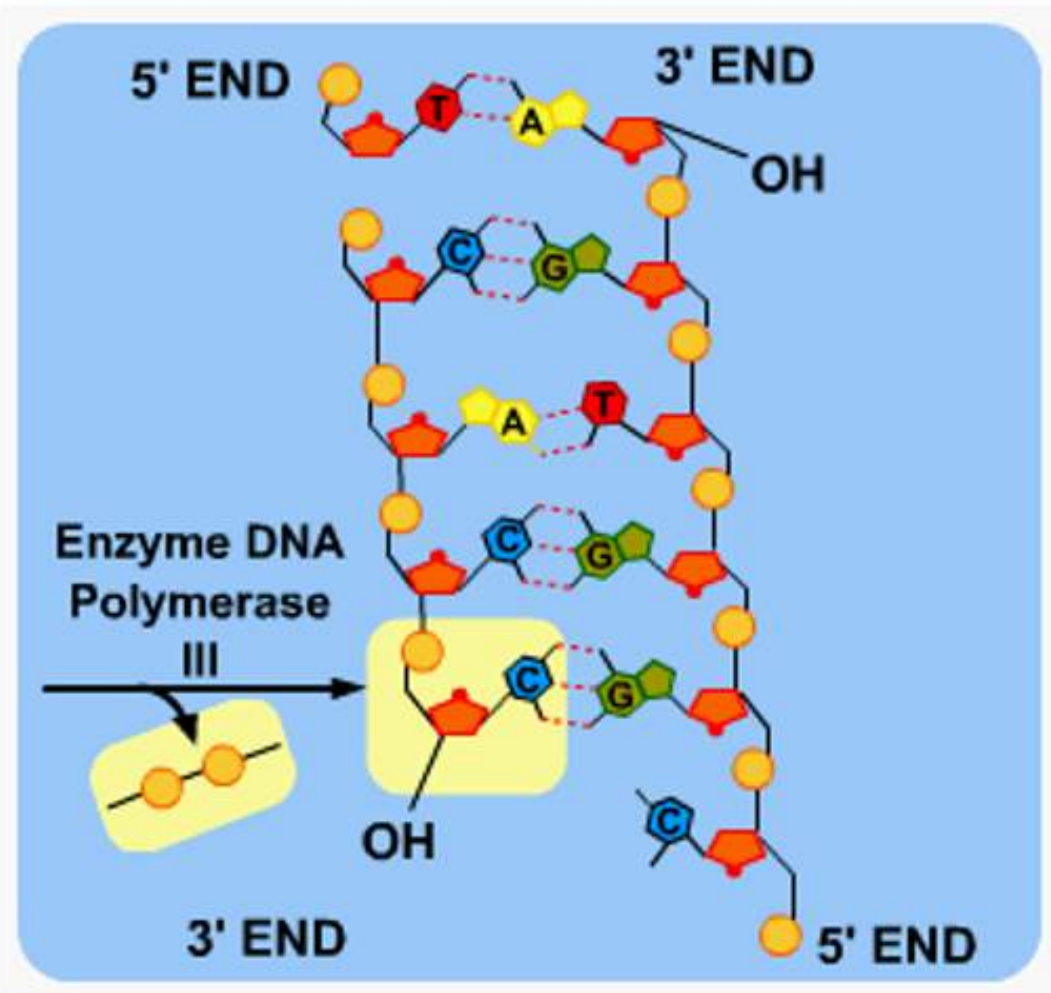
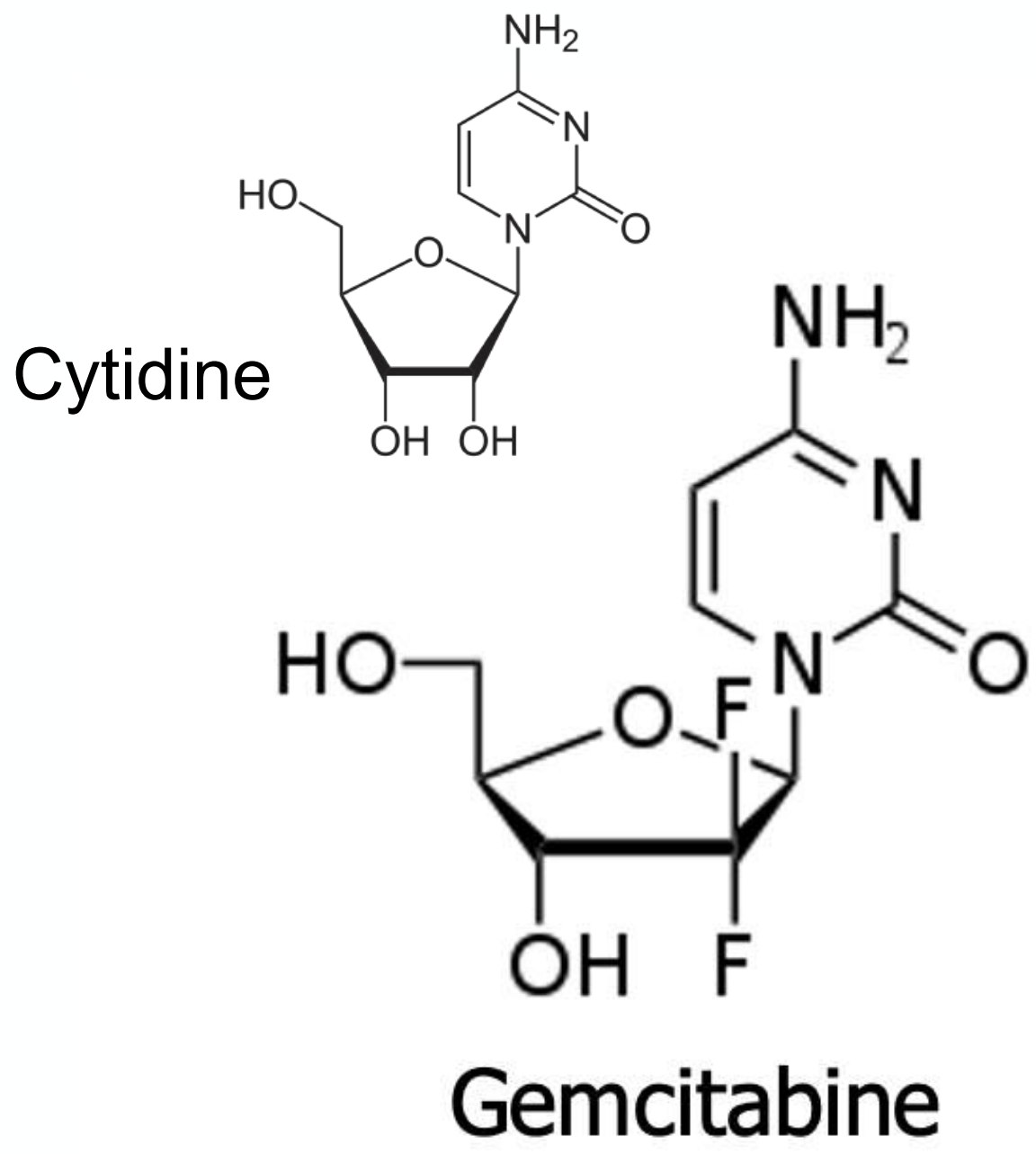
Alkylating Agents

Year 1978



Nucleoside Analog

Year 1989



RADIATION!



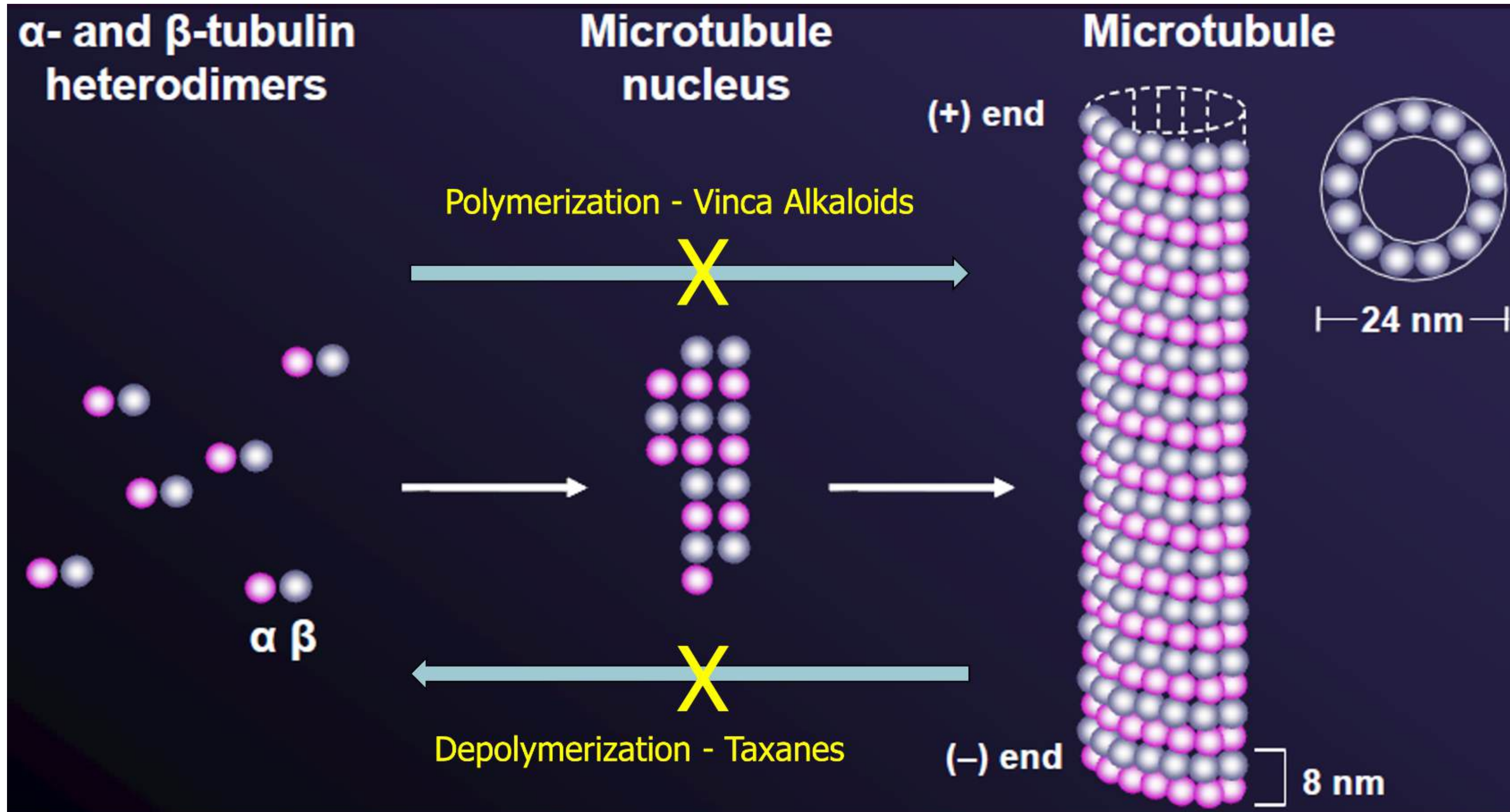
Reduced incorporation of deoxycytidine nucleotide

DNA POLYMERASES Allow incorporation of deoxynucleotides during DNA replication

Increased incorporation of gemcitabine nucleotide

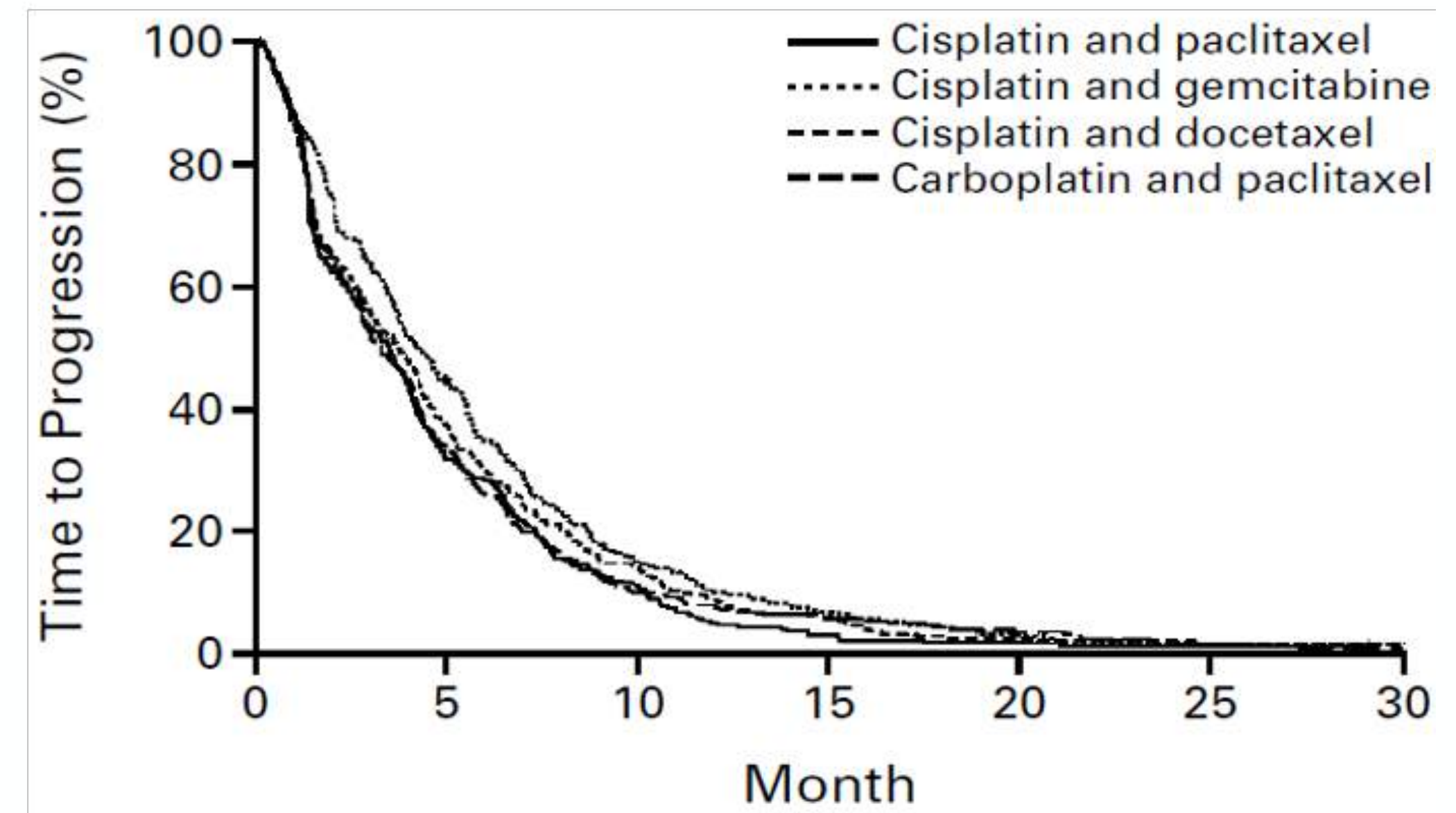
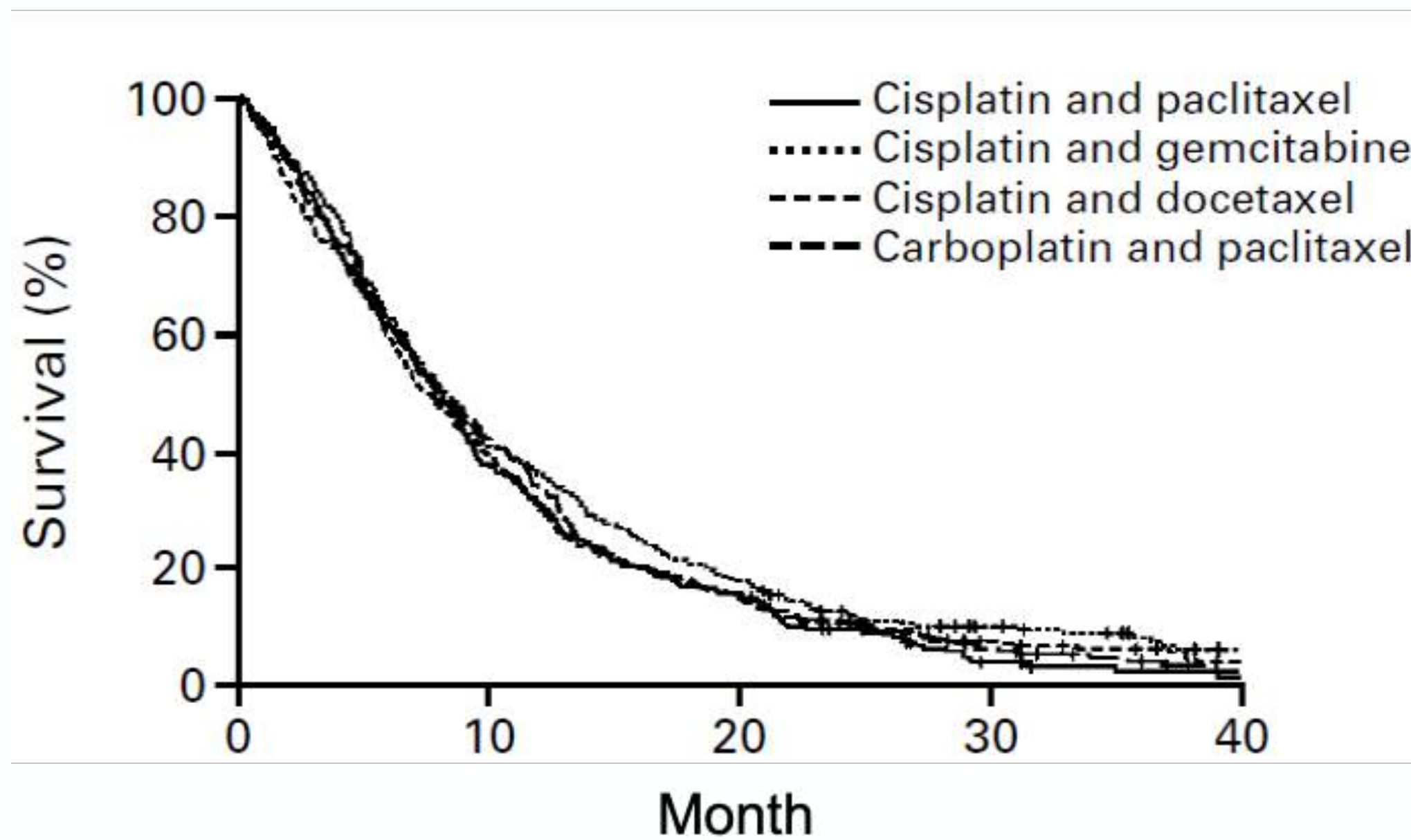
Microtubules - Antimitotic Drugs

Year 1999



Comparison of Chemotherapy Regimens

Year 2002

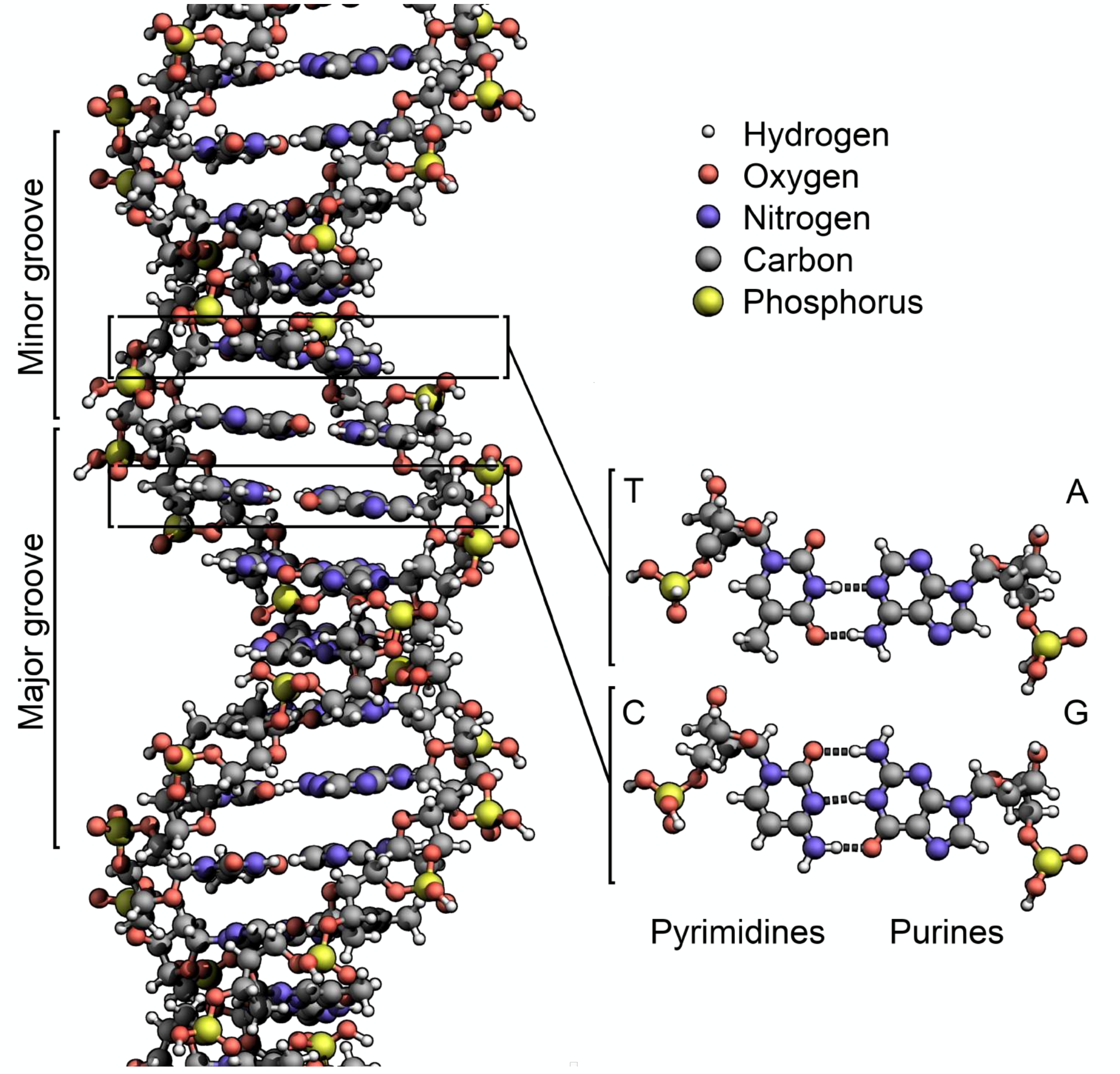
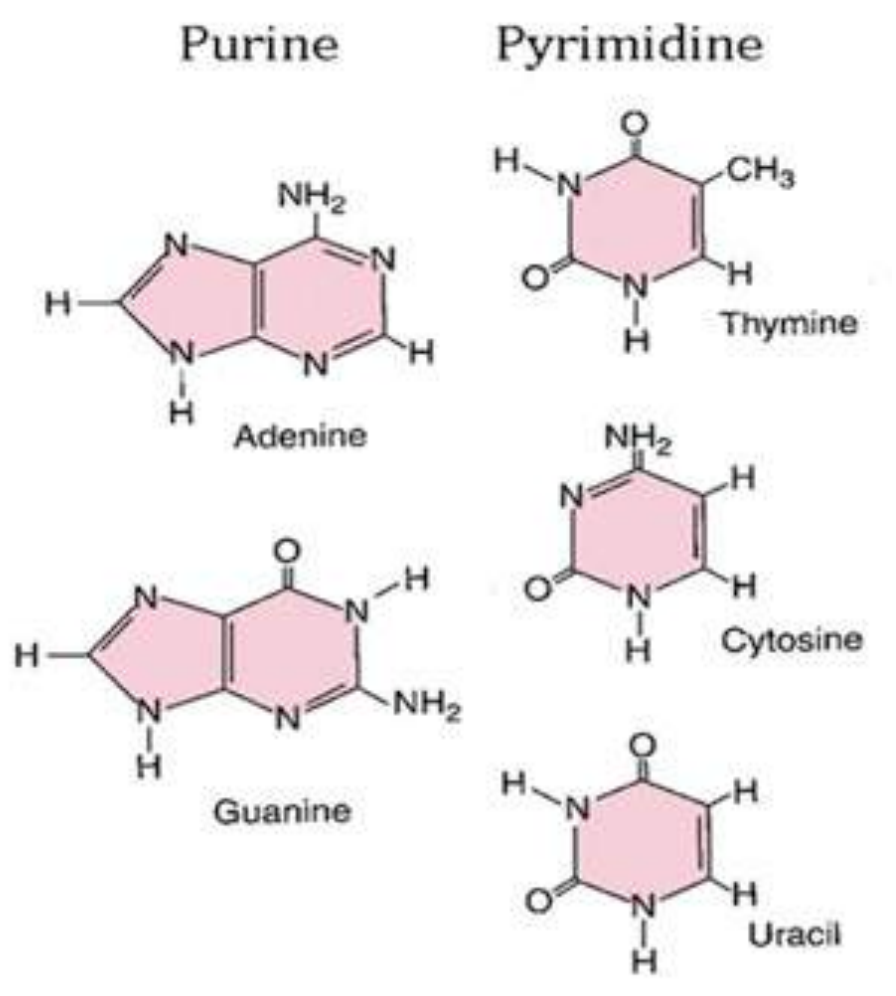
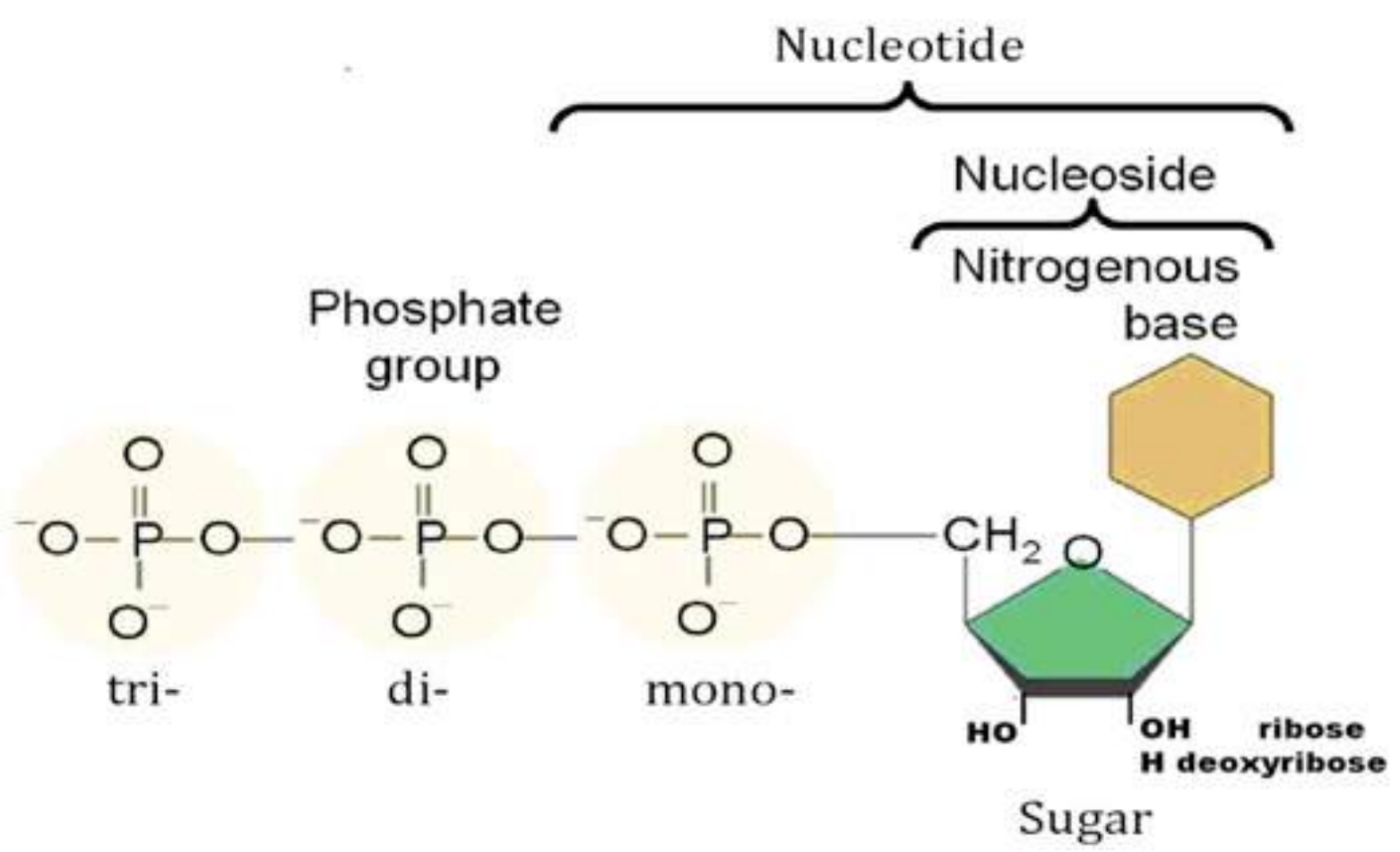
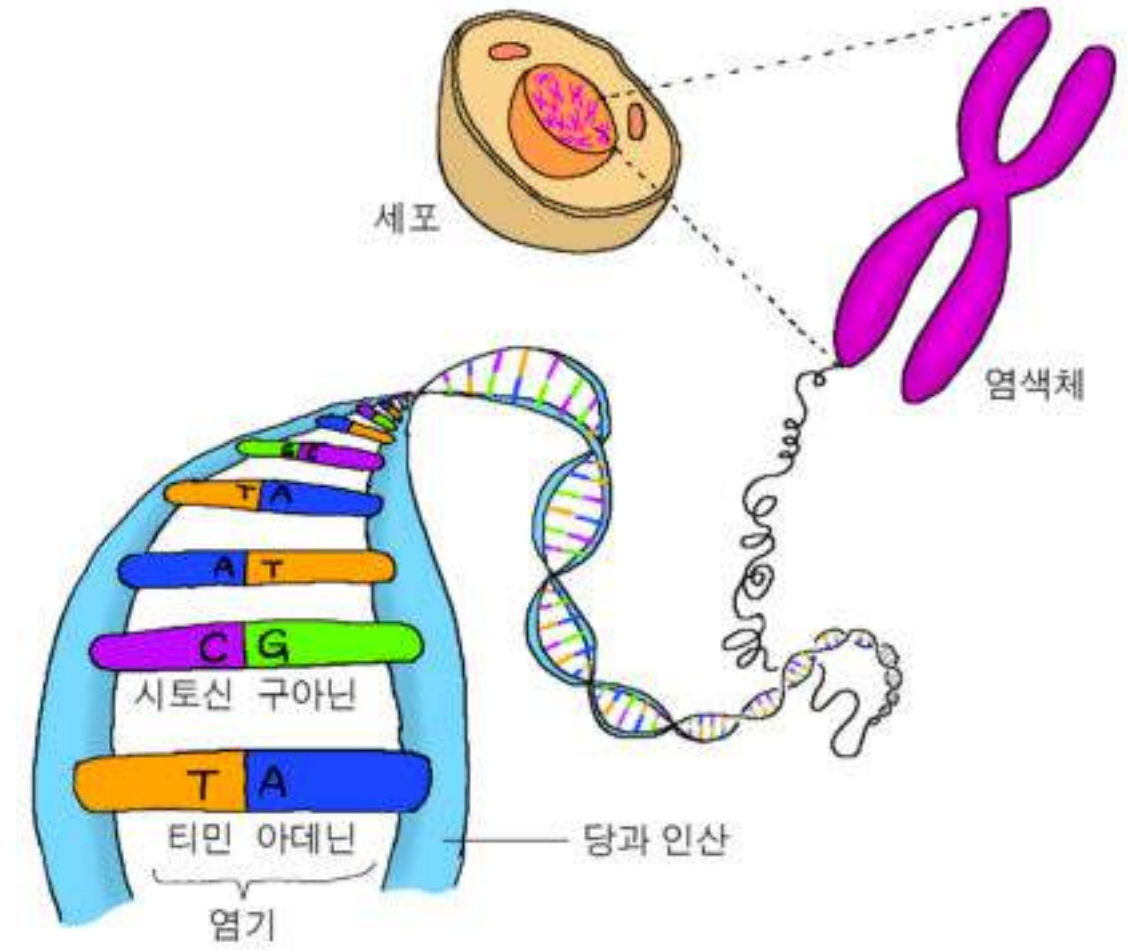


Schiller JH et al. N Eng J Med. 2002;346:92-8

Median Survival Time ~ 8 months

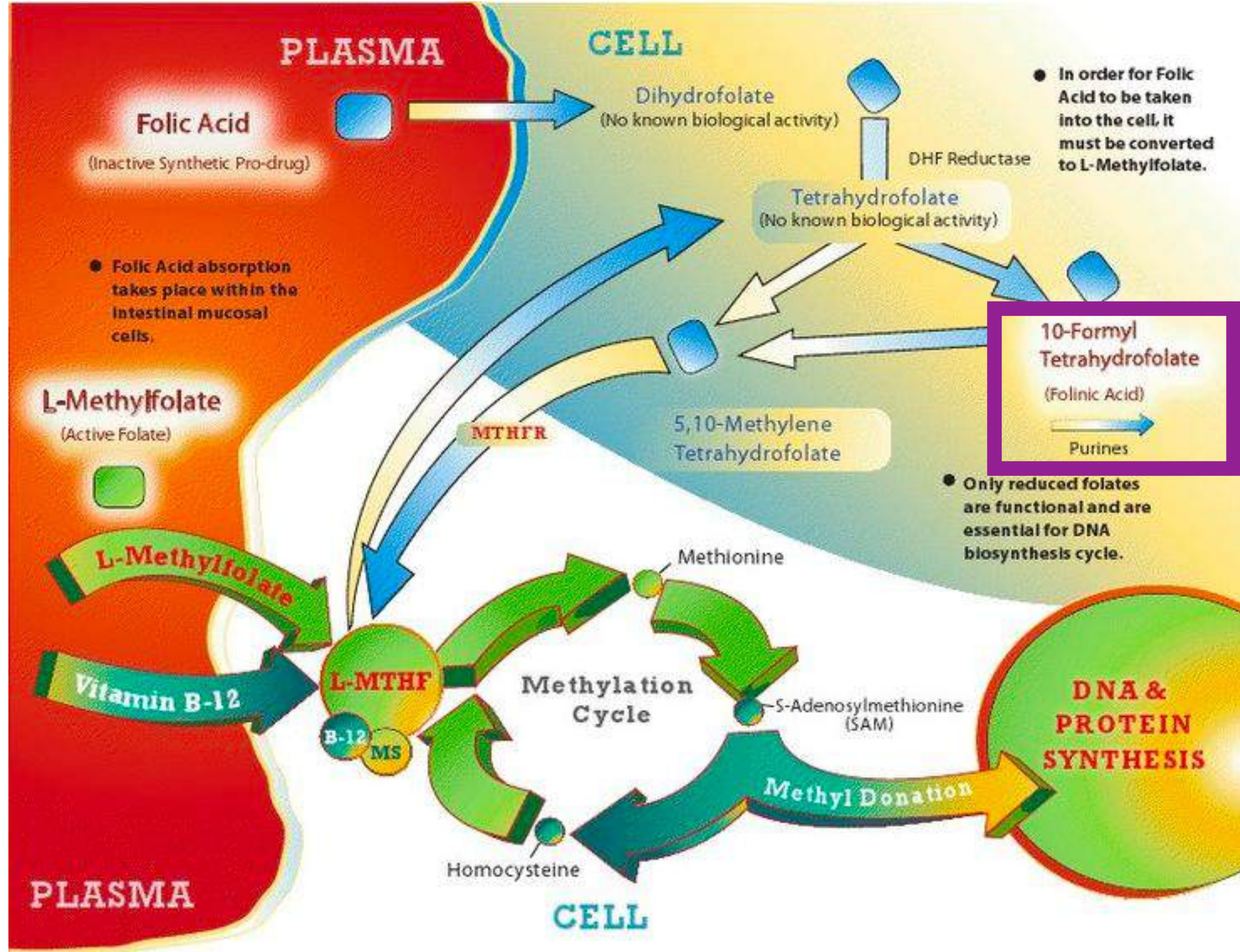
Antifolates - Pemetrexed

Year 2004



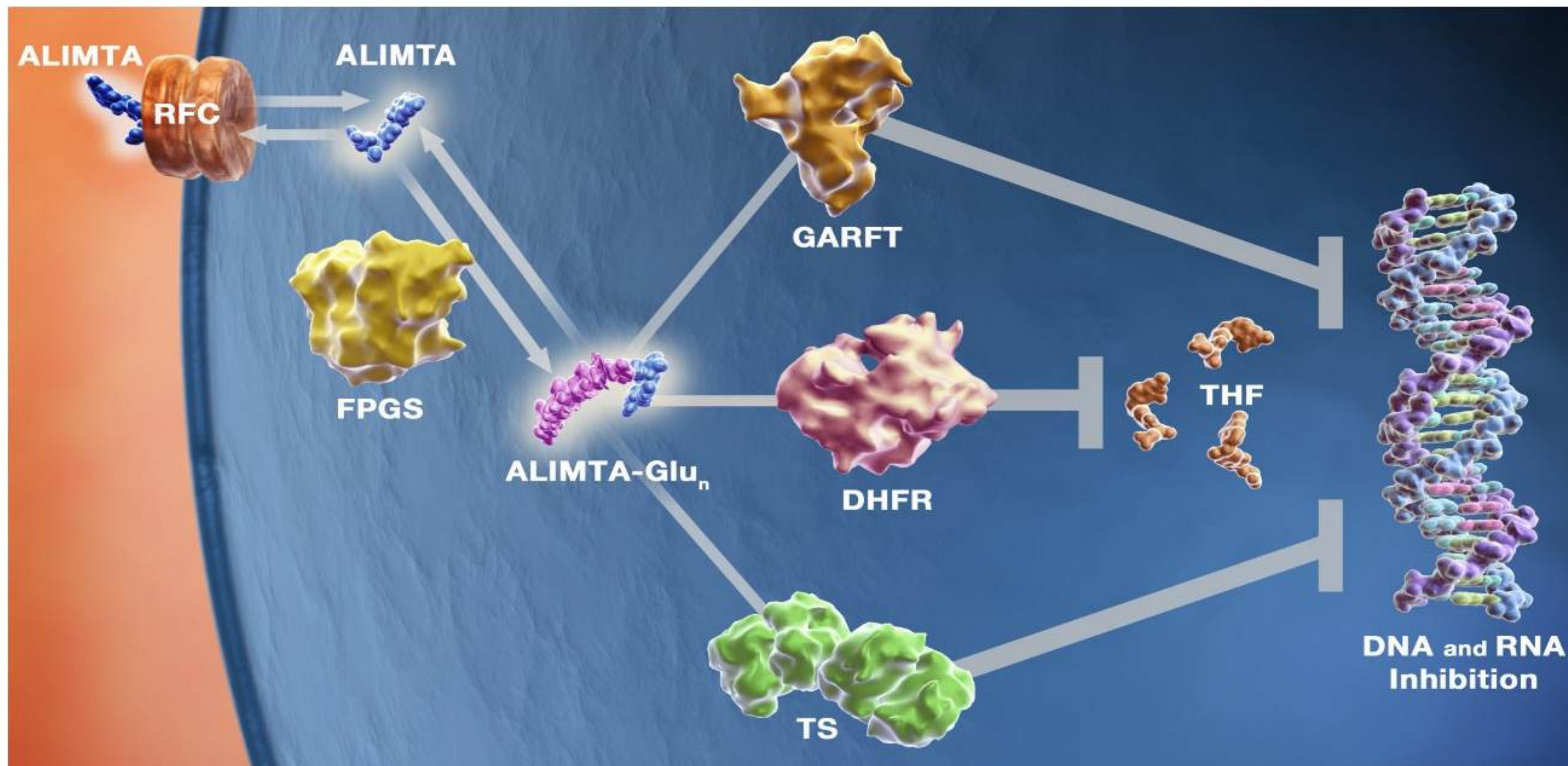
Antifolates - Pemetrexed

Year 2004



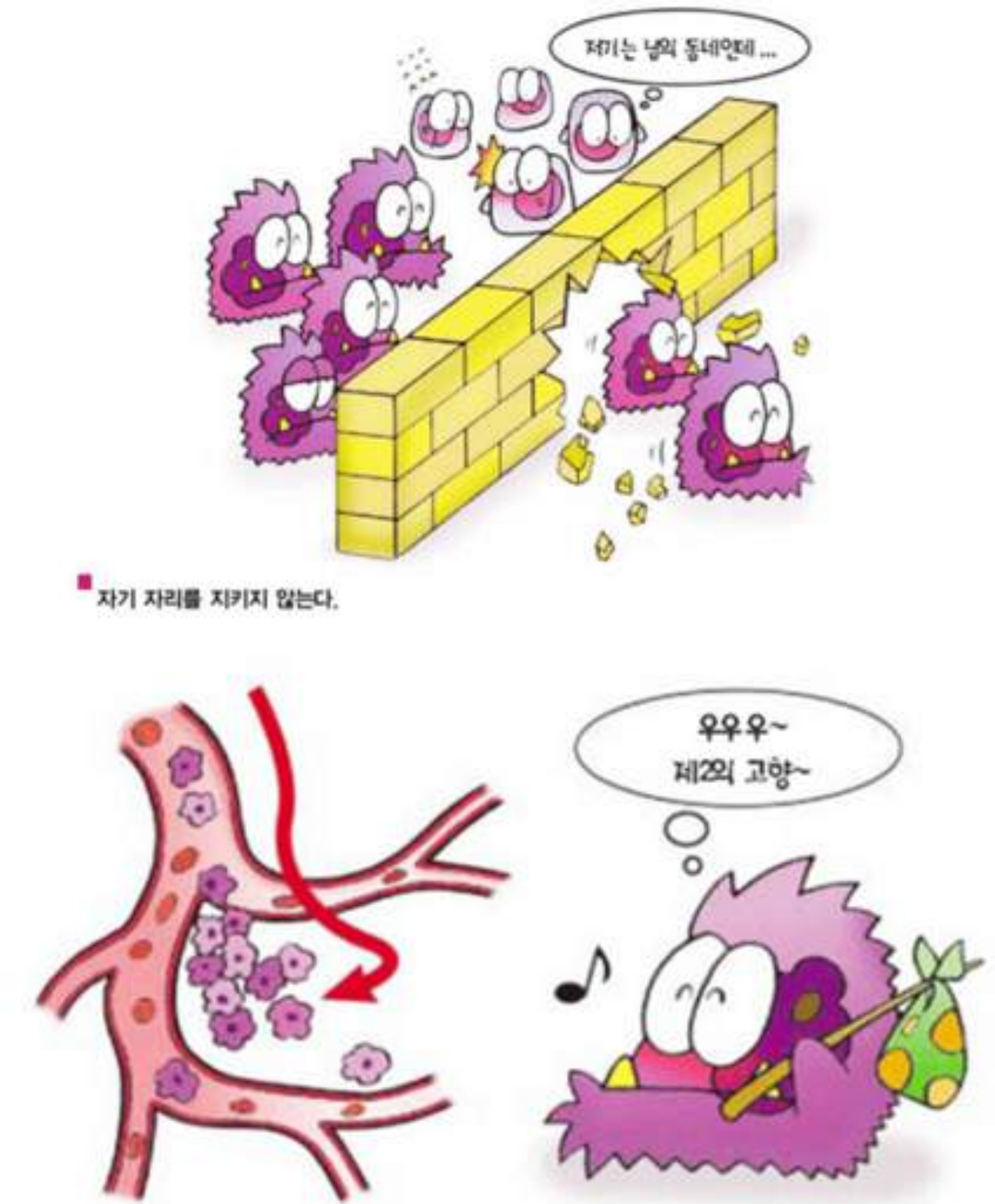
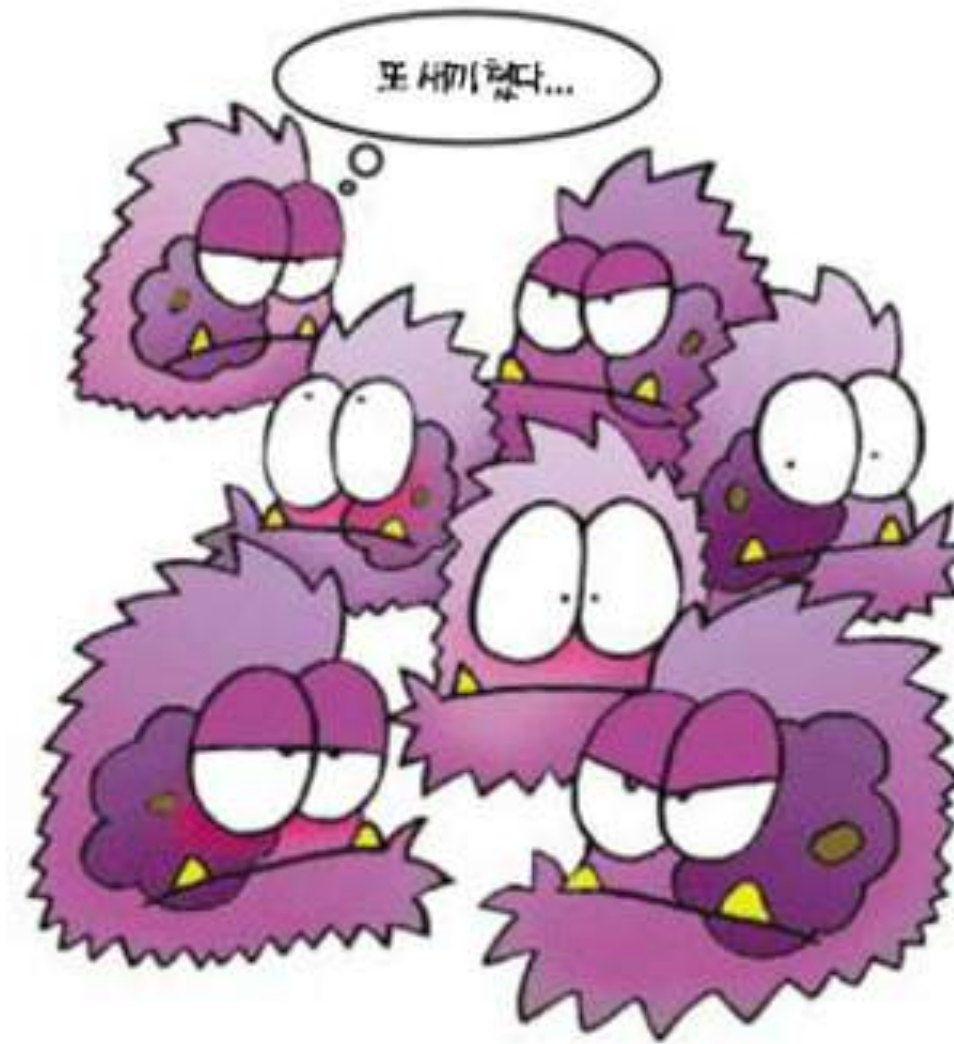
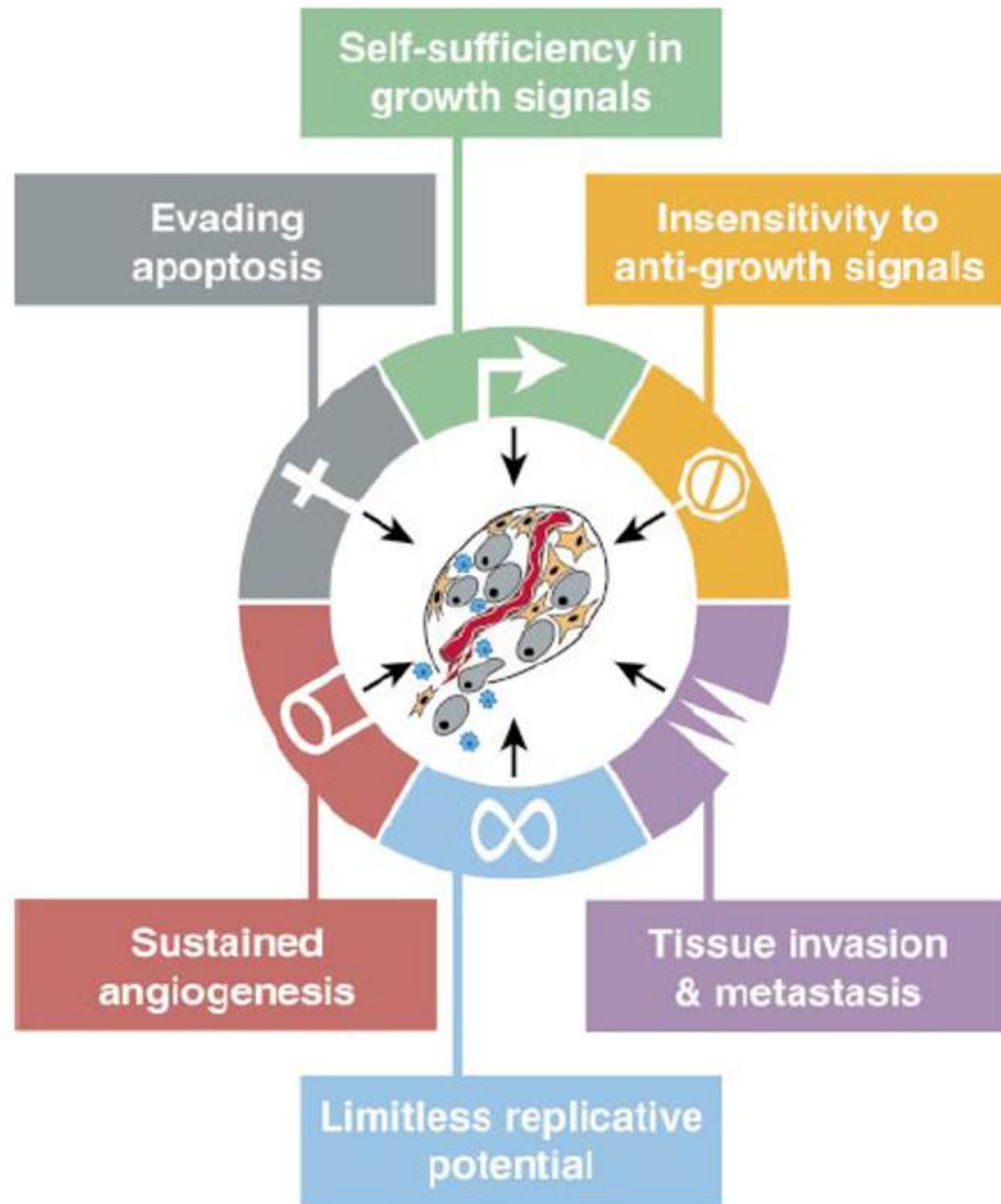
2004

Antifolates - Pemetrexed



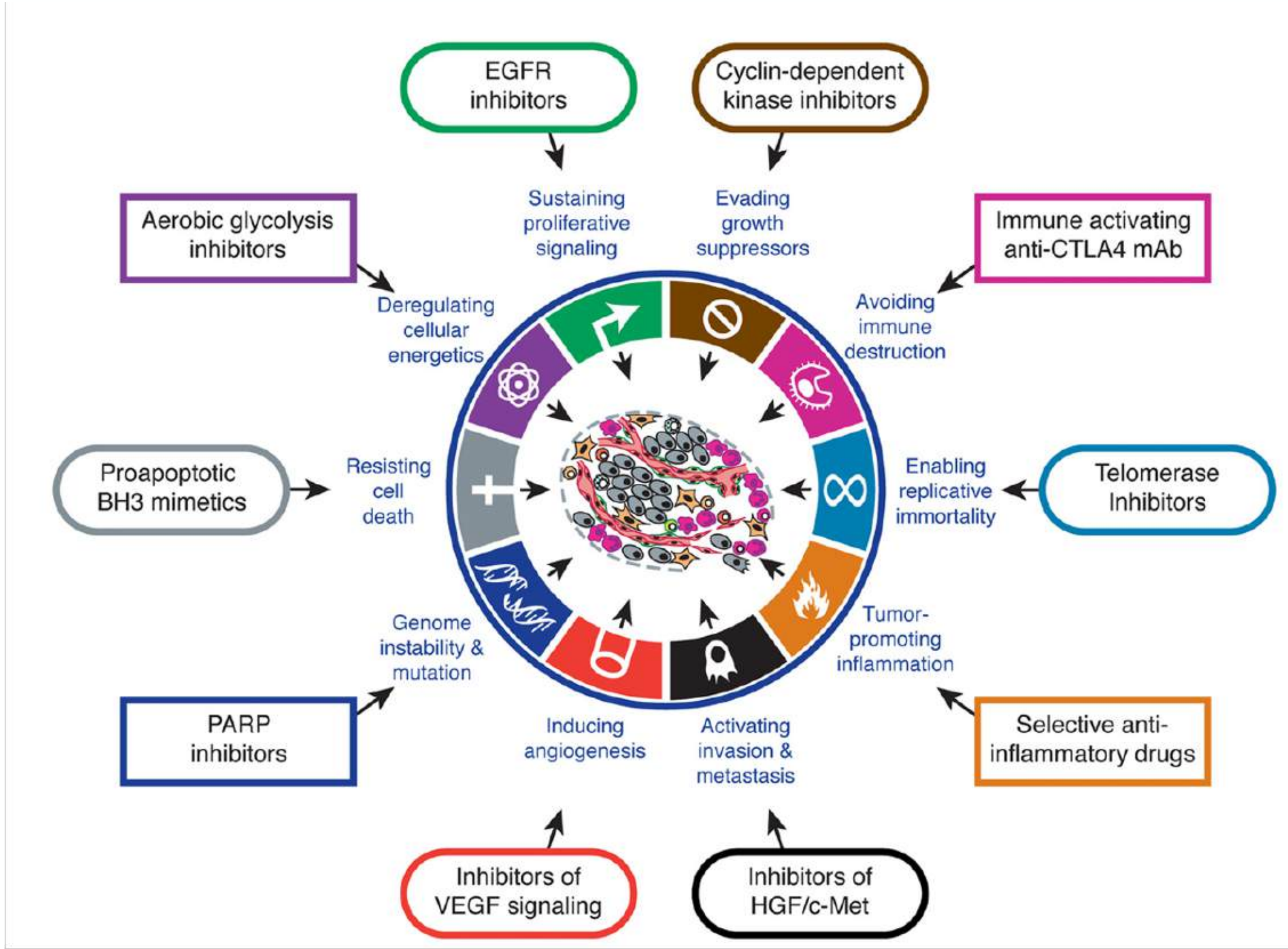
Hallmarks of Cancer

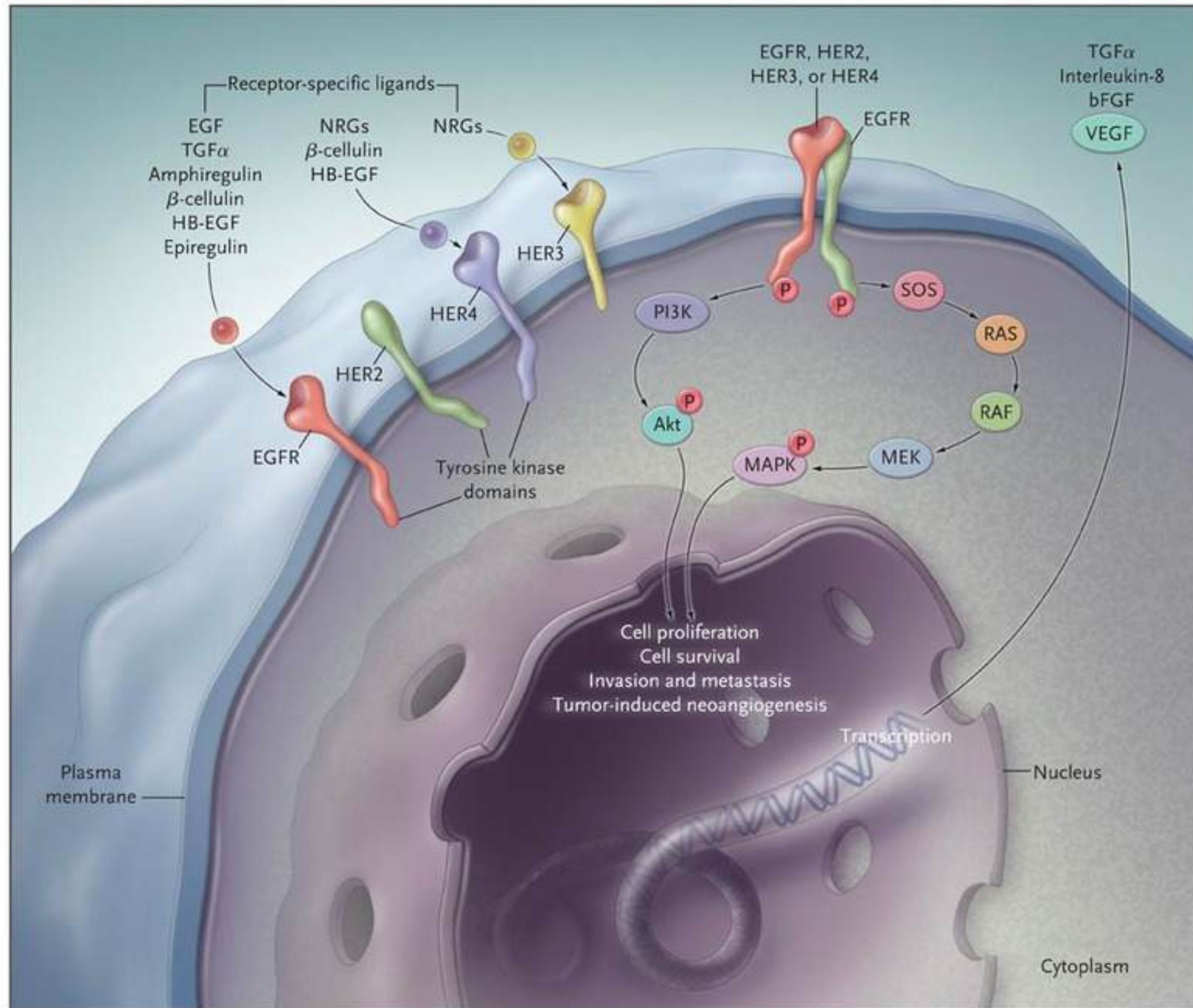
Year 2000

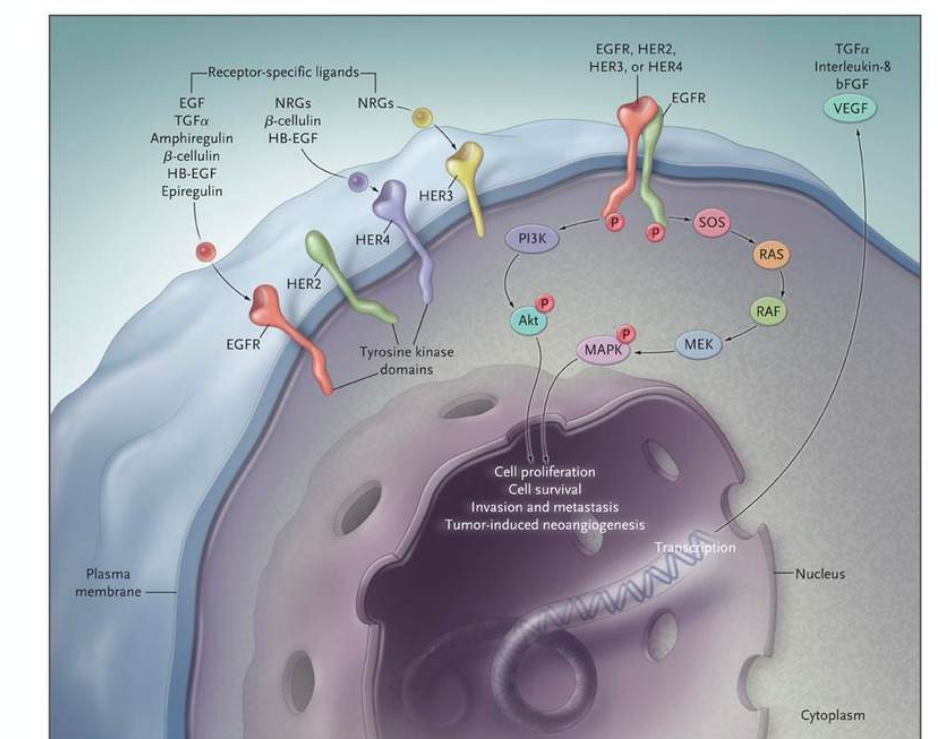
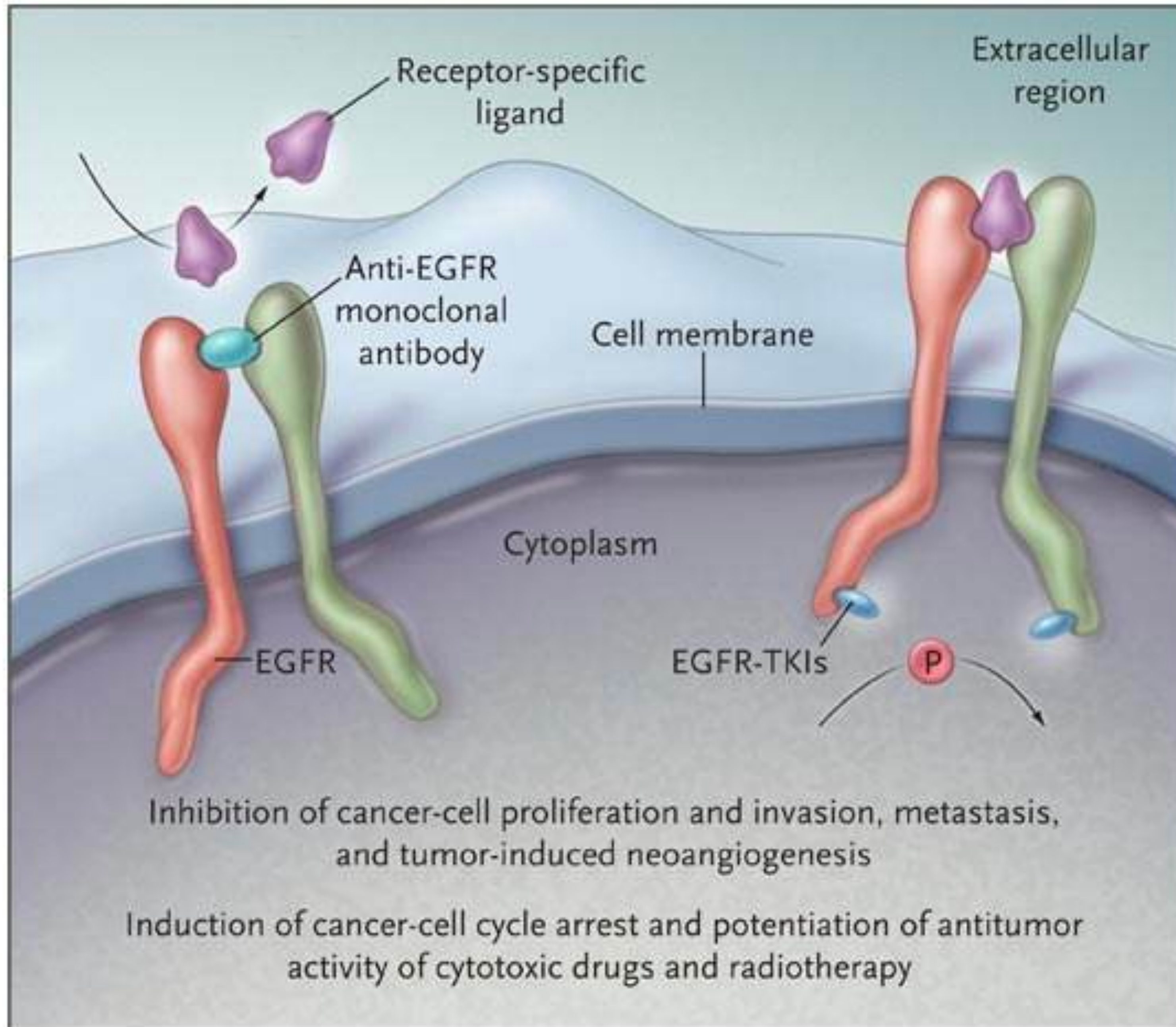


Hallmarks of Cancer

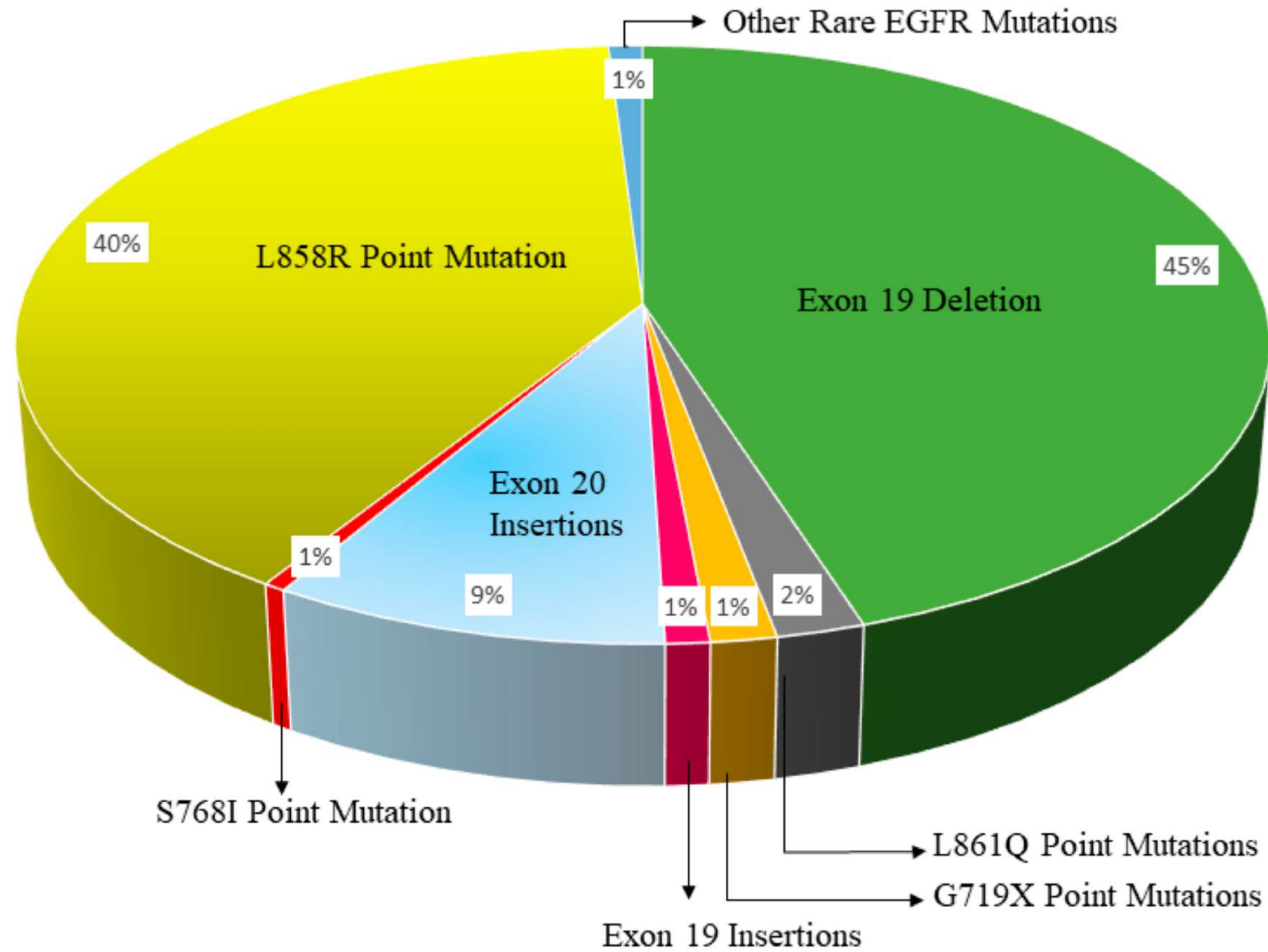
Year 2010



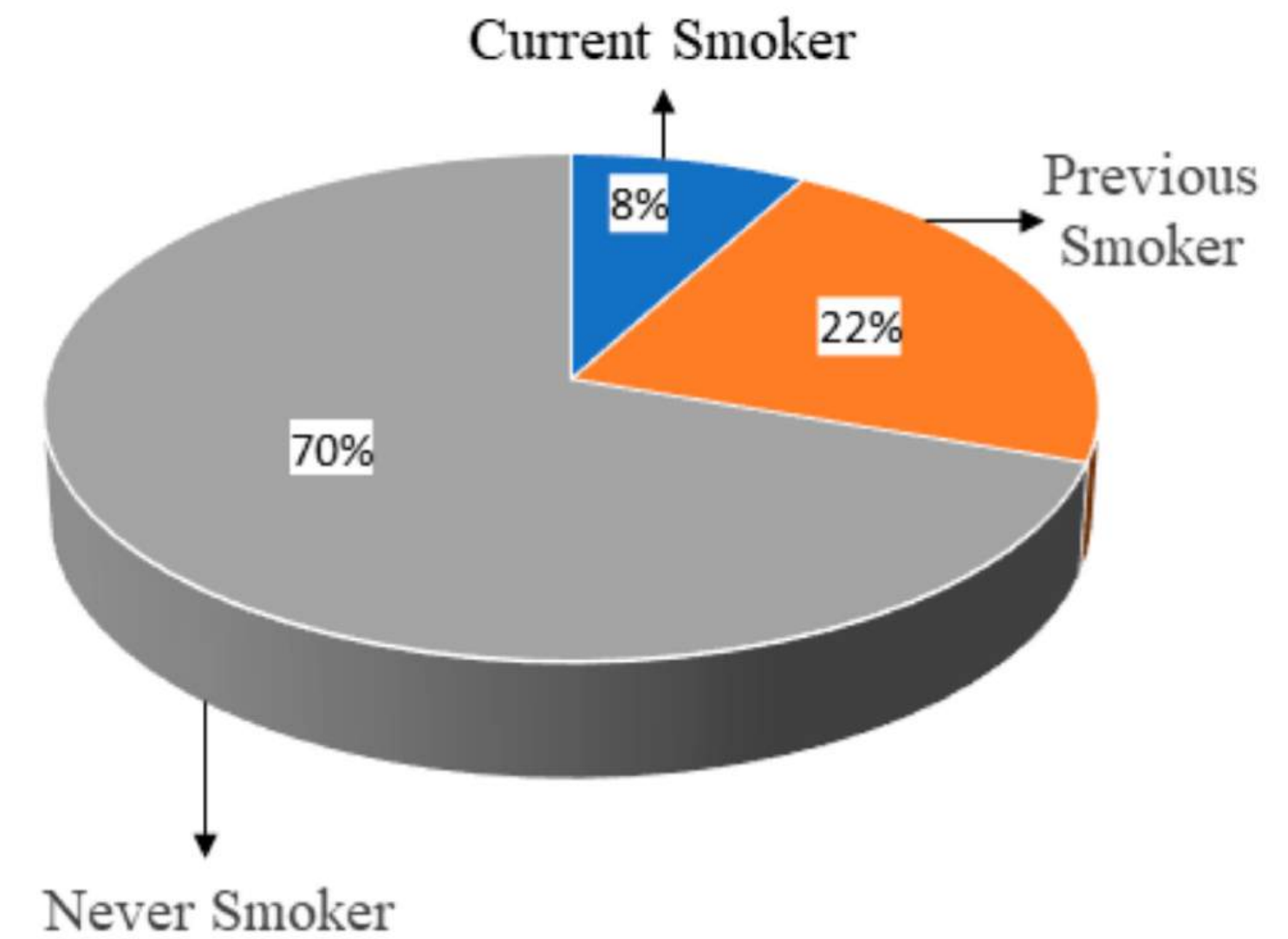


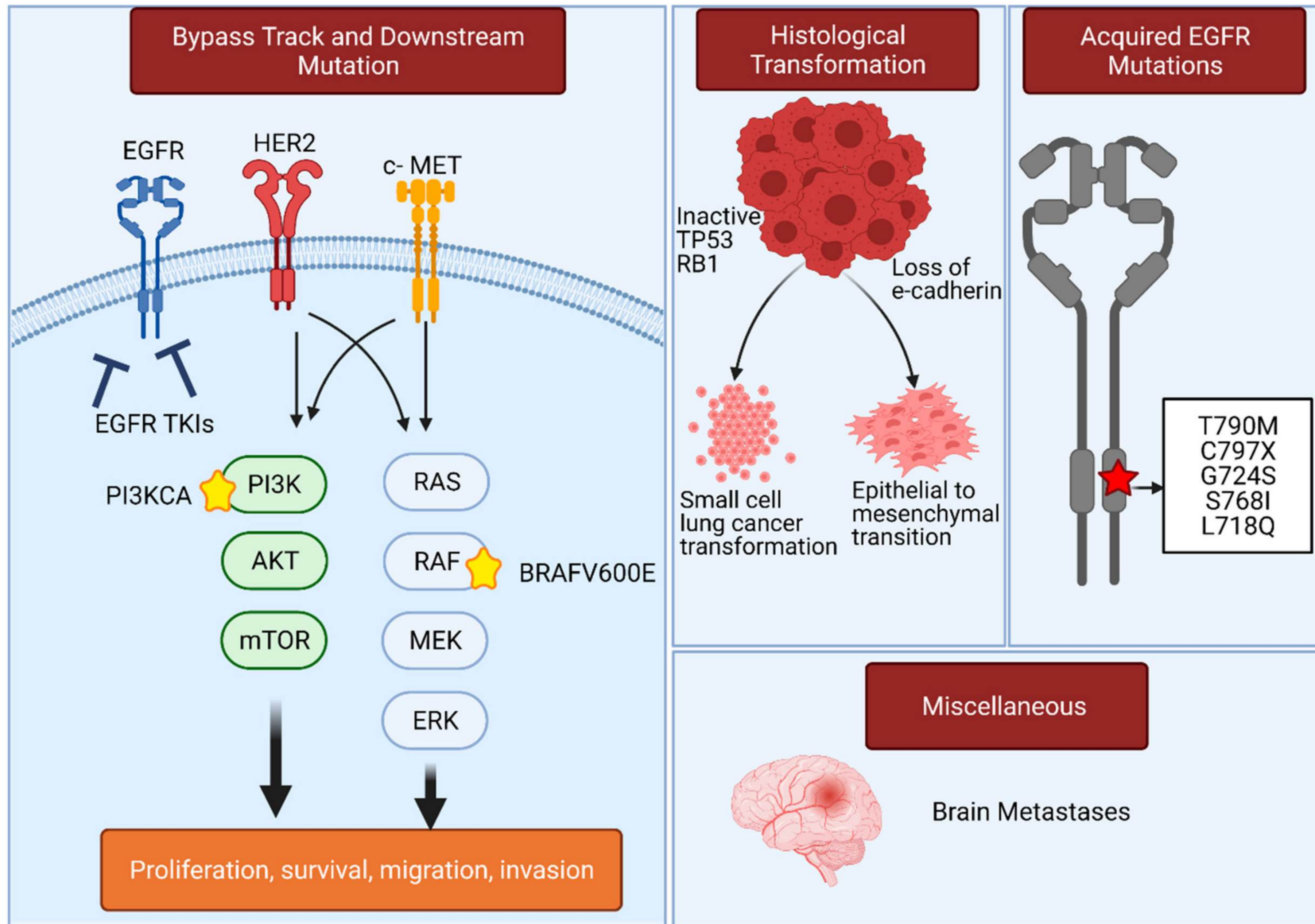


(A) Frequency of EGFR Specific Mutations in Lung Adenocarcinoma

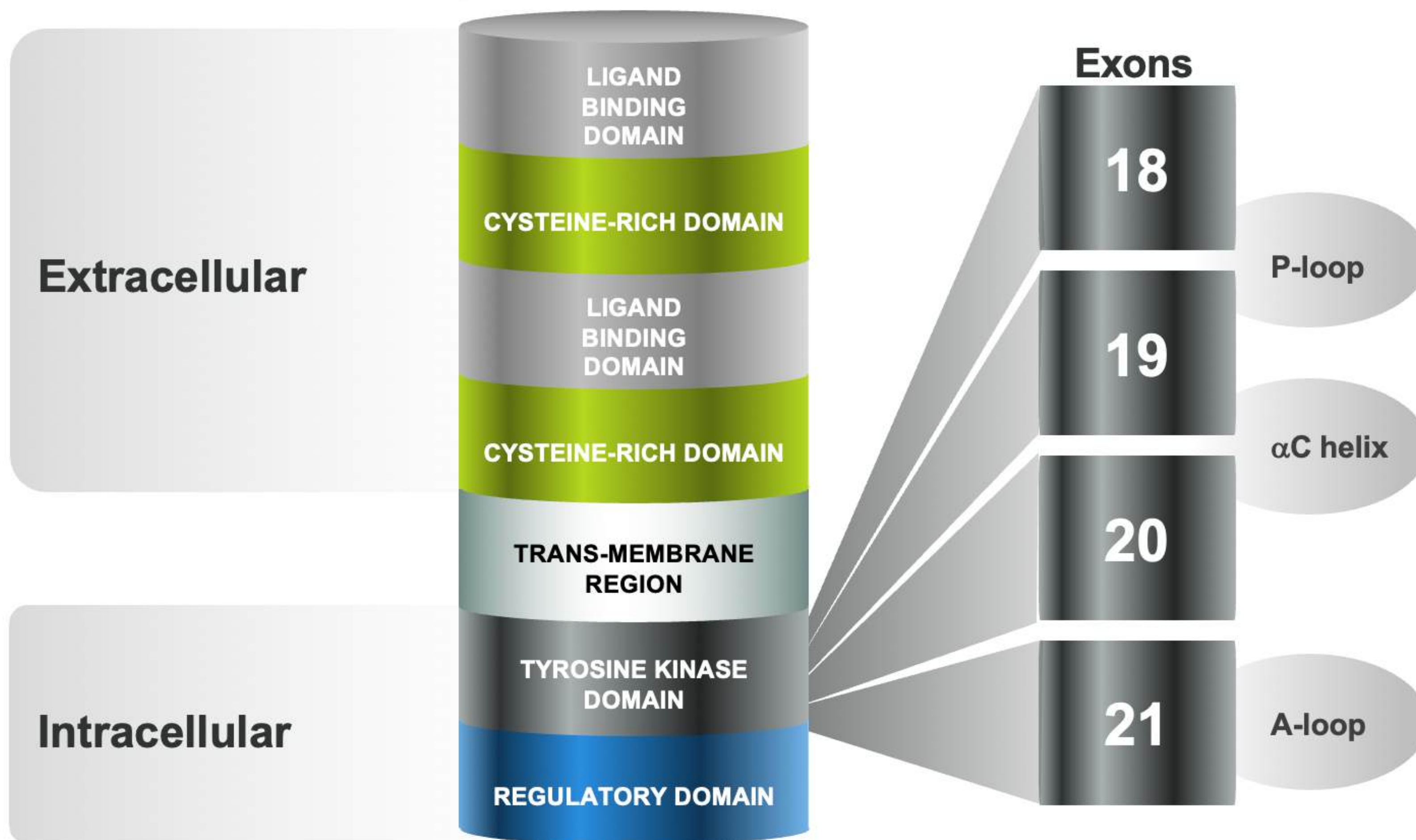


(B) Frequency of EGFR Mutations by Smoking Status





EGFR gene¹⁻⁴



Distribution of mutation types^{4,a,b}

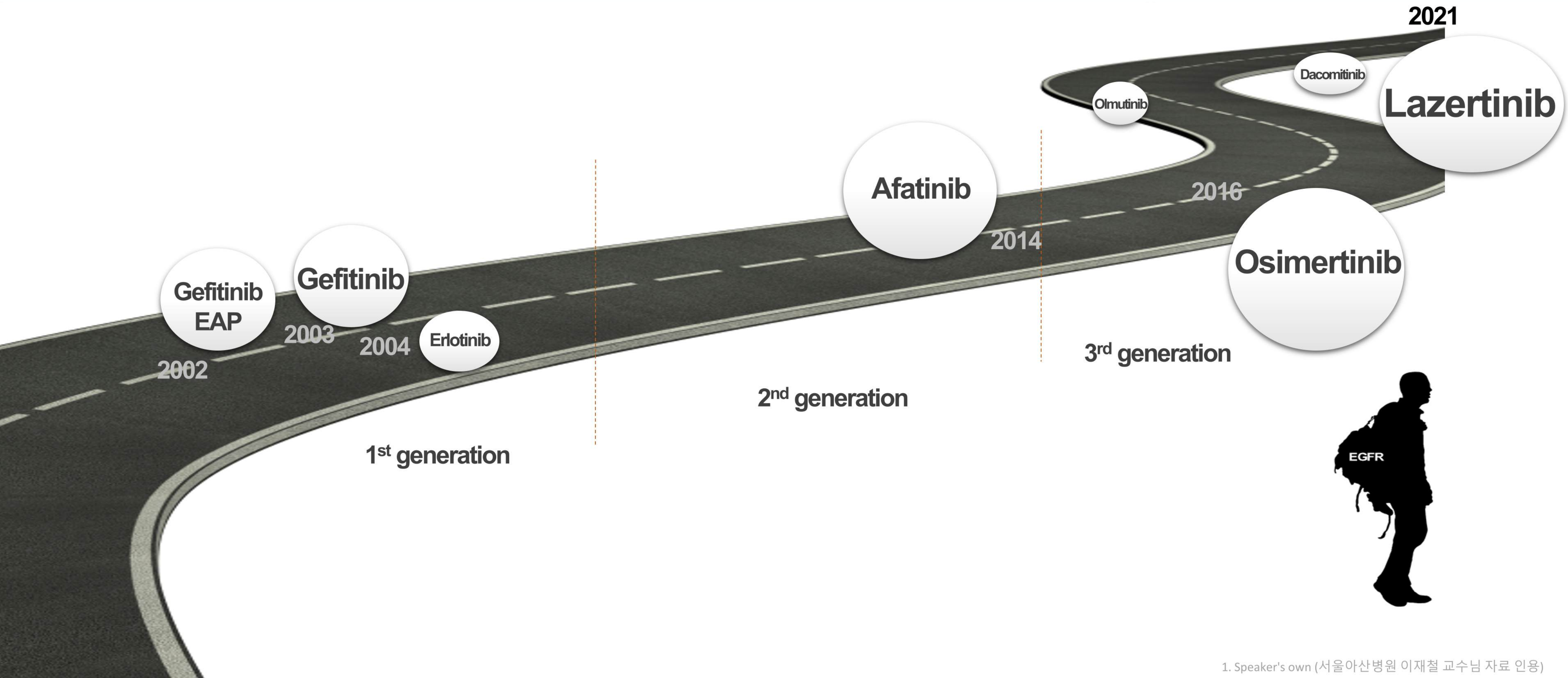
| Mutation type | Percent |
|--|----------------|
| Exon 18 G719A/S/C | 1.5% |
| Exon 19 deletion | 46% |
| Exon 20 T790M ^b Other exon 20 mutations | 4.1% 2.0% |
| Exon 21 point mutation L858R L861Q | 37.5% 1.12% |

EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.

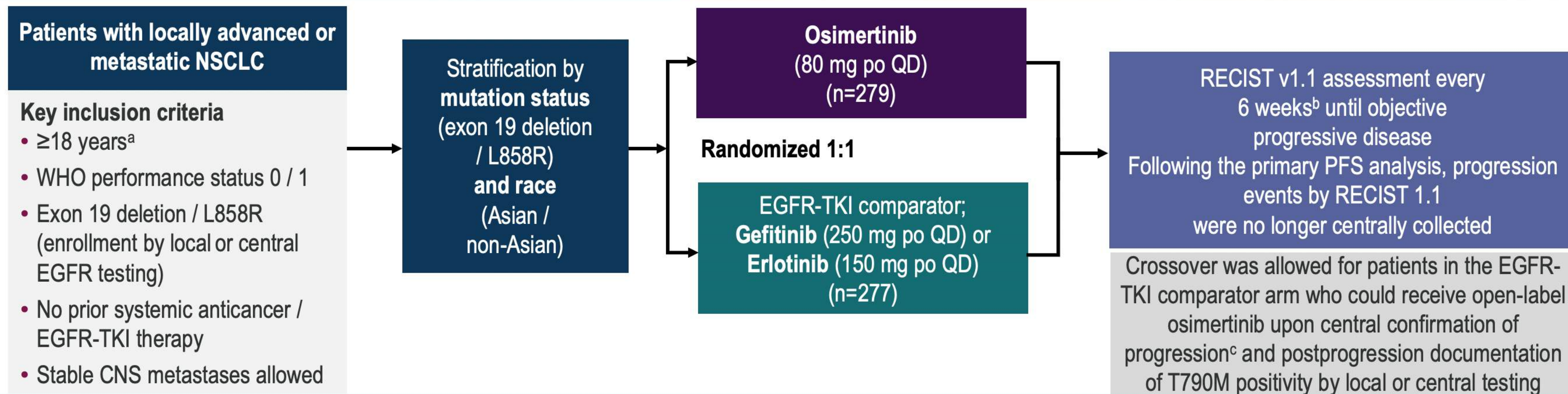
^aLiterature review as reported in COSMIC (Catalogue of Somatic Mutations in Cancer) database; may vary depending on study and population factors; ^bThe percentage of rarer mutation including T790M may be underrepresented as methodologies for mutation detected differed across studies. In addition, the rate of T790M also represents a mixture of primary mutations and those acquired as resistance mutations after TKI therapy.

1. Shigematsu H et al. *J Natl Cancer Inst.* 2005;97:339-346. 2. Lynch TJ et al. *N Engl J Med.* 2004;350:2129-2139. 3. Paez JG et al. *Science.* 2004;304:1497-1500. 4. Siegelin MD et al. *Lab Invest.* 2014;94:129-137.

EGFR TKI



FLAURA double-blind study design^{1,2}



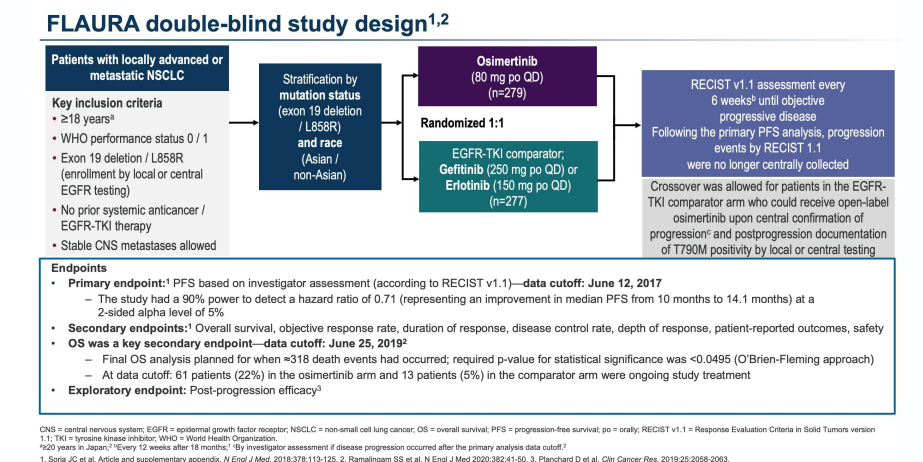
Endpoints

- **Primary endpoint:**¹ PFS based on investigator assessment (according to RECIST v1.1)—**data cutoff: June 12, 2017**
 - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a 2-sided alpha level of 5%
- **Secondary endpoints:**¹ Overall survival, objective response rate, duration of response, disease control rate, depth of response, patient-reported outcomes, safety
- **OS was a key secondary endpoint—data cutoff: June 25, 2019²**
 - Final OS analysis planned for when ≈318 death events had occurred; required p-value for statistical significance was <0.0495 (O’Brien-Fleming approach)
 - At data cutoff: 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment
- **Exploratory endpoint:** Post-progression efficacy³

CNS = central nervous system; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; po = orally; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

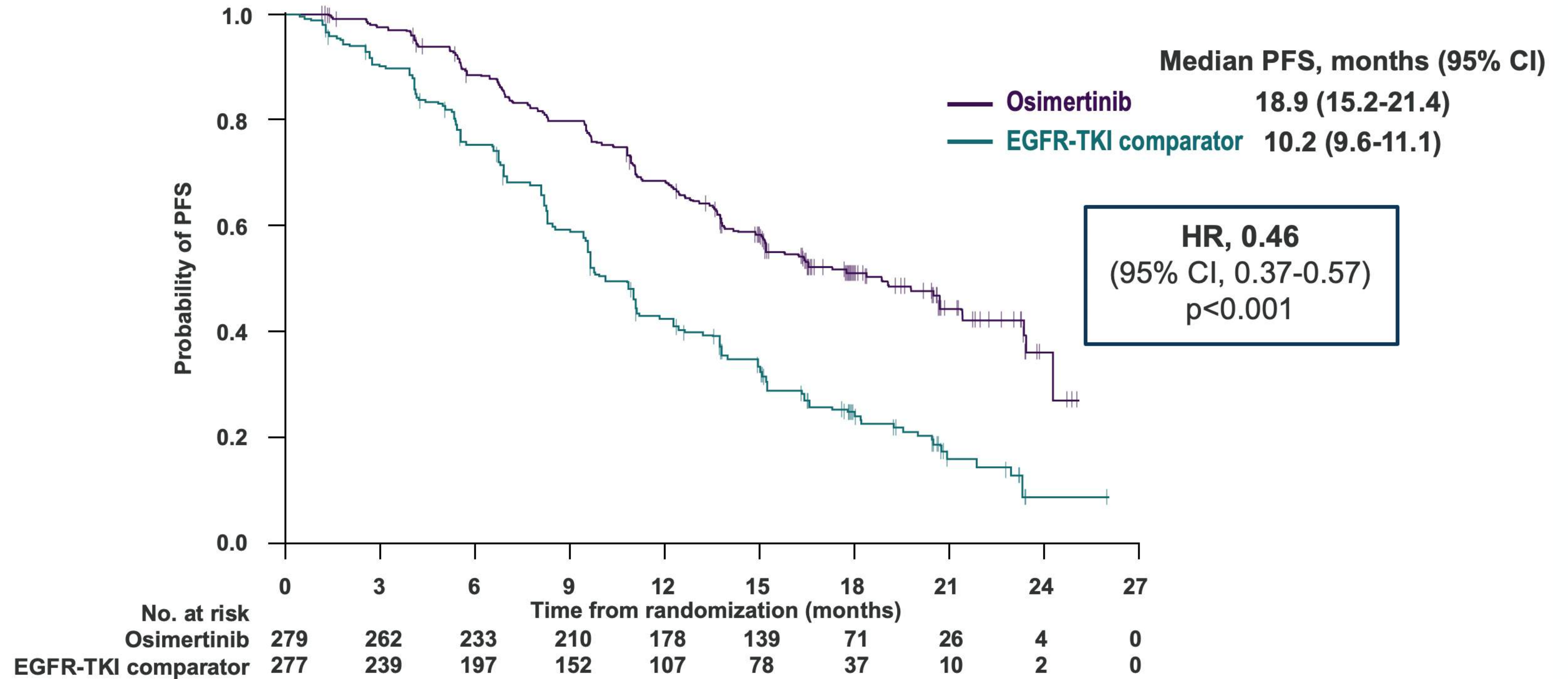
^a≥20 years in Japan; ^bEvery 12 weeks after 18 months; ¹By investigator assessment if disease progression occurred after the primary analysis data cutoff.²

1. Soria JC et al. Article and supplementary appendix. *N Engl J Med.* 2018;378:113-125. 2. Ramalingam SS et al. *N Engl J Med* 2020;382:41-50. 3. Planchard D et al. *Clin Cancer Res.* 2019;25:2058-2063.



FLAURA primary endpoint: PFS by investigator assessment (DCO: June 12, 2017)^{1,2}

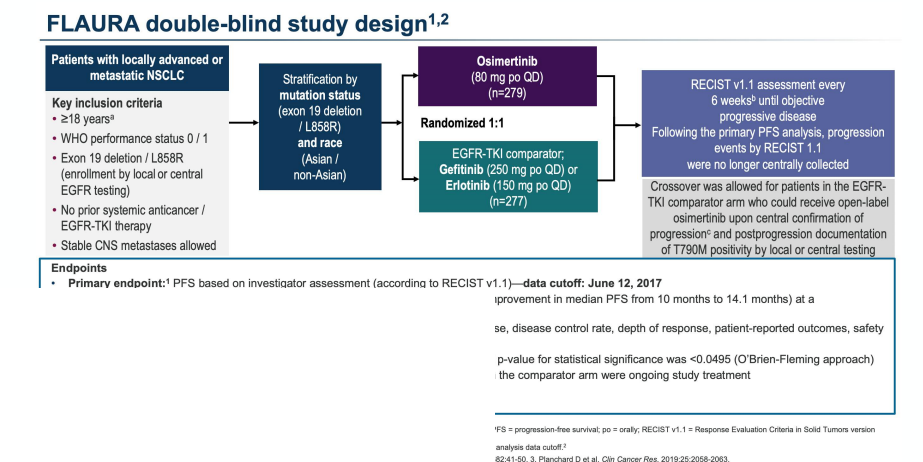
342 events in 556 patients at data cutoff: 62% maturity; osimertinib: 136 events (49%), EGFR-TKI comparator: 206 events (74%)



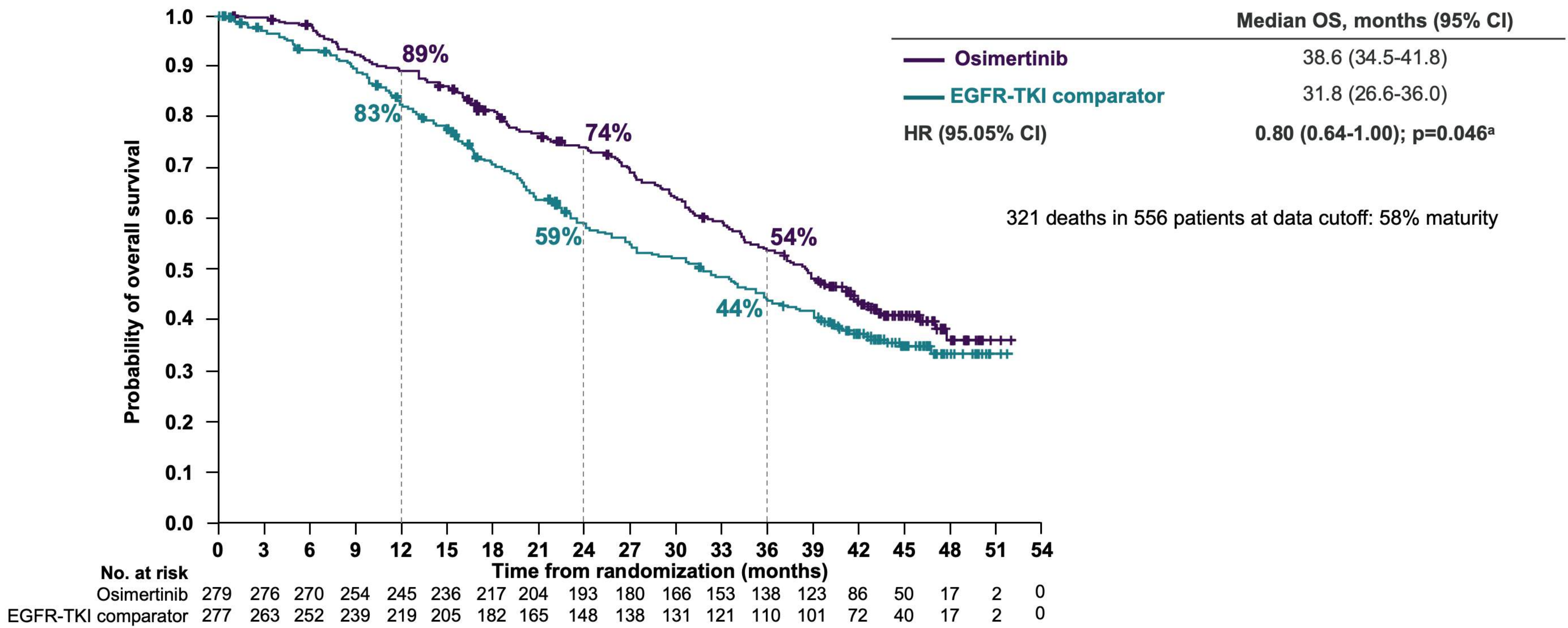
DCO = data cutoff; EGFR = epidermal growth factor receptor; HR = hazard ratio; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

Tick marks indicate censored data.

1. Soria JC et al. *N Engl J Med*. 2018;378:113-125. 2. Ramalingam SS et al. *N Engl J Med* 2020;382:41-50.



FLAURA: Final overall survival analysis (DCO: June 25, 2019)



DCO = data cut off; EGFR = epidermal growth factor receptor; HR = hazard ratio; OS = overall survival; TKI = tyrosine kinase inhibitor. Censored data are indicated by tick marks. Data from patients who had not died at the time of the analysis were censored on the basis of the last recorded date on which the patient was known to be alive. ^aFor statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required. Ramalingam SS et al. N Engl J Med 2020;382:41-50.

TEAEs Occurring \geq 10% of All Patients

| Patients with TEAEs, n (%) | 240 mg (n=78) | | Overall (N=181) | |
|----------------------------|---------------|----------------|-----------------|----------------|
| | All grade | Grade \geq 3 | All grade | Grade \geq 3 |
| Rash | 29 (37) | 1 (1) | 54 (30) | 1 (1) |
| Pruritus | 27 (35) | 0 | 52 (29) | 0 |
| Constipation | 15 (19) | 0 | 43 (24) | 0 |
| Paraesthesia | 26 (33) | 2 (3) | 40 (22) | 2 (1) |
| Decreased appetite | 20 (26) | 0 | 38 (21) | 0 |
| Diarrhoea | 21 (27) | 1 (1) | 38 (21) | 1 (1) |
| Headache | 22 (28) | 0 | 34 (19) | 0 |
| Cough | 16 (21) | 0 | 29 (16) | 0 |
| Muscle spasms | 22 (28) | 0 | 28 (16) | 0 |
| Nausea | 13 (17) | 0 | 27 (15) | 2 (1) |
| Paronychia | 16 (21) | 1 (1) | 26 (14) | 1 (1) |
| Fatigue | 12 (15) | 0 | 22 (12) | 0 |
| Dyspepsia | 9 (12) | 0 | 21 (12) | 0 |
| Vomiting | 8 (10) | 1 (1) | 20 (11) | 2 (1) |
| Dizziness | 10 (13) | 0 | 19 (11) | 0 |

LASER301 AEs Occurring > 10% and of Interest

| Preferred term, n(%) | Lazertinib (N=196) | | | Gefitinib (N=197) | | |
|--------------------------------|---------------------------------|---------|-----------|-------------------------------|---------|-----------|
| | Any grade | Grade 3 | > Grade 4 | Any grade | Grade 3 | > Grade 4 |
| Median duration of exposure | 15.1 months (range 0.2 to 29.0) | | | 11 months (range 0.1 to 27.7) | | |
| Rash | 71 (36) | 2 (1) | 0 | 72 (37) | 5 (3) | 0 |
| Diarrhoea | 51 (26) | 5 (3) | 0 | 77 (39) | 1 (1) | 0 |
| Paraesthesia | 77 (39) | 5 (3) | 0 | 13 (7) | 0 | 0 |
| ALT increased | 30 (15) | 2 (1) | 0 | 59 (30) | 18 (9) | 0 |
| Pruritus | 52 (27) | 1 (1) | 0 | 36 (18) | 0 | 0 |
| AST increased | 22 (11) | 1 (1) | 0 | 52 (26) | 13 (7) | 0 |
| Paronychia | 35 (18) | 1 (1) | 0 | 34 (17) | 1 (1) | 0 |
| Decreased appetite | 33 (17) | 3 (2) | 0 | 31 (16) | 1 (1) | 0 |
| Anaemia | 36 (18) | 7 (4) | 0 | 23 (12) | 7 (4) | 0 |
| Dry skin | 29 (15) | 0 | 0 | 23 (12) | 0 | 0 |
| Constipation | 28 (14) | 0 | 0 | 20 (10) | 0 | 0 |
| Nausea | 30 (15) | 0 | 0 | 18 (9) | 0 | 0 |
| Dermatitis acneiform | 21 (11) | 2 (1) | 0 | 27 (14) | 1 (1) | 0 |
| Stomatitis | 31 (16) | 0 | 0 | 16 (8) | 1 (1) | 0 |
| Interstitial lung disease * | 5 (3) | 2 (1) | 1 (1) | 3 (2) | 2 (1) | 0 |
| Electrocardiogram QT prolonged | 7 (4) | 2 (1) | 0 | 3 (2) | 2 (1) | 0 |

N=number of patients in the analysis population; n=number of patients in the specified category.
 Patients with two or more adverse events with the same AE term is counted only once for that AE term. *ILD and Pneumonitis.
 Data cut off date: 29 Jul 2022

LASER301 AEs Occurring > 10% and of Interest

| Preferred term, n(%) | Lazertinib (N=196) | | | Gefitinib (N=197) | | |
|--------------------------------|---------------------------------|---------|-----------|-------------------------------|---------|-----------|
| | Any grade | Grade 3 | > Grade 4 | Any grade | Grade 3 | > Grade 4 |
| Median duration of exposure | 15.1 months (range 0.2 to 29.0) | | | 11 months (range 0.1 to 27.7) | | |
| Rash | 71 (36) | 2 (1) | 0 | 72 (37) | 5 (3) | 0 |
| Diarrhoea | 51 (26) | 5 (3) | 0 | 77 (39) | 1 (1) | 0 |
| Paraesthesia | 77 (39) | 5 (3) | 0 | 13 (7) | 0 | 0 |
| ALT increased | 30 (15) | 2 (1) | 0 | 59 (30) | 18 (9) | 0 |
| Pruritus | 52 (27) | 1 (1) | 0 | 36 (18) | 0 | 0 |
| AST increased | 22 (11) | 1 (1) | 0 | 52 (26) | 13 (7) | 0 |
| Paronychia | 35 (18) | 1 (1) | 0 | 34 (17) | 1 (1) | 0 |
| Decreased appetite | 33 (17) | 3 (2) | 0 | 31 (16) | 1 (1) | 0 |
| Anaemia | 36 (18) | 7 (4) | 0 | 23 (12) | 7 (4) | 0 |
| Dry skin | 29 (15) | 0 | 0 | 23 (12) | 0 | 0 |
| Constipation | 28 (14) | 0 | 0 | 20 (10) | 0 | 0 |
| Nausea | 30 (15) | 0 | 0 | 18 (9) | 0 | 0 |
| Dermatitis acneiform | 21 (11) | 2 (1) | 0 | 27 (14) | 1 (1) | 0 |
| Stomatitis | 31 (16) | 0 | 0 | 16 (8) | 1 (1) | 0 |
| Interstitial lung disease | 5 (3) | 2 (1) | 1 (1) | 3 (2) | 2 (1) | 0 |
| Electrocardiogram QT prolonged | 7 (4) | 2 (1) | 0 | 3 (2) | 2 (1) | 0 |

N=number of patients in the analysis population; n=number of patients in the specified category.
 Patients with two or more adverse events with the same AE term is counted only once for that AE term. *ILD and Pneumonitis.
 Data cut off date: 29 Jul 2022

Adverse Events of EGFR TKIs : Paresthesia

- 미국 국립암연구소 (NCI) 이상반응 표준 용어 기준 (CTCAE) 버전 5.0에서는 감각 이상 (paresthesia)를 "감각 뉴런의 기능적인 장애로 인해 저림, 무감각, 압력, 냉감, 그리고/또는 비정상적인 피부 감각을 유발하는 장애"로 정의하고 있으며, 중증도는 아래와 같습니다

| Grade | Management |
|---|--|
| 1 (mild symptoms) | <ul style="list-style-type: none"> General safety measures are recommended Nutraceutical/non-pharmacologic interventions may be considered Topical therapy (capsaicin, lidocaine) may be considered (if available) |
| 2 (moderate symptoms, limiting instrumental ADL*) | <ul style="list-style-type: none"> General safety measures are recommended Duloxetine, pregabalin, or gabapentin is recommended, if symptom continues Neurologic consultation may be considered, if the symptom persists on medication Adding tricyclic antidepressants may be considered |
| 3 (severe symptoms, limiting self care ADL*) or intolerable 2 | <ul style="list-style-type: none"> General safety measures are recommended Duloxetine, pregabalin, or gabapentin is recommended (if not started yet) Neurologic consultation is recommended (if not done yet) Adding Tricyclic antidepressants may be considered (if not started yet) Opioids (tramadol or strong opioids) may be considered |

*ADL: activities of daily living

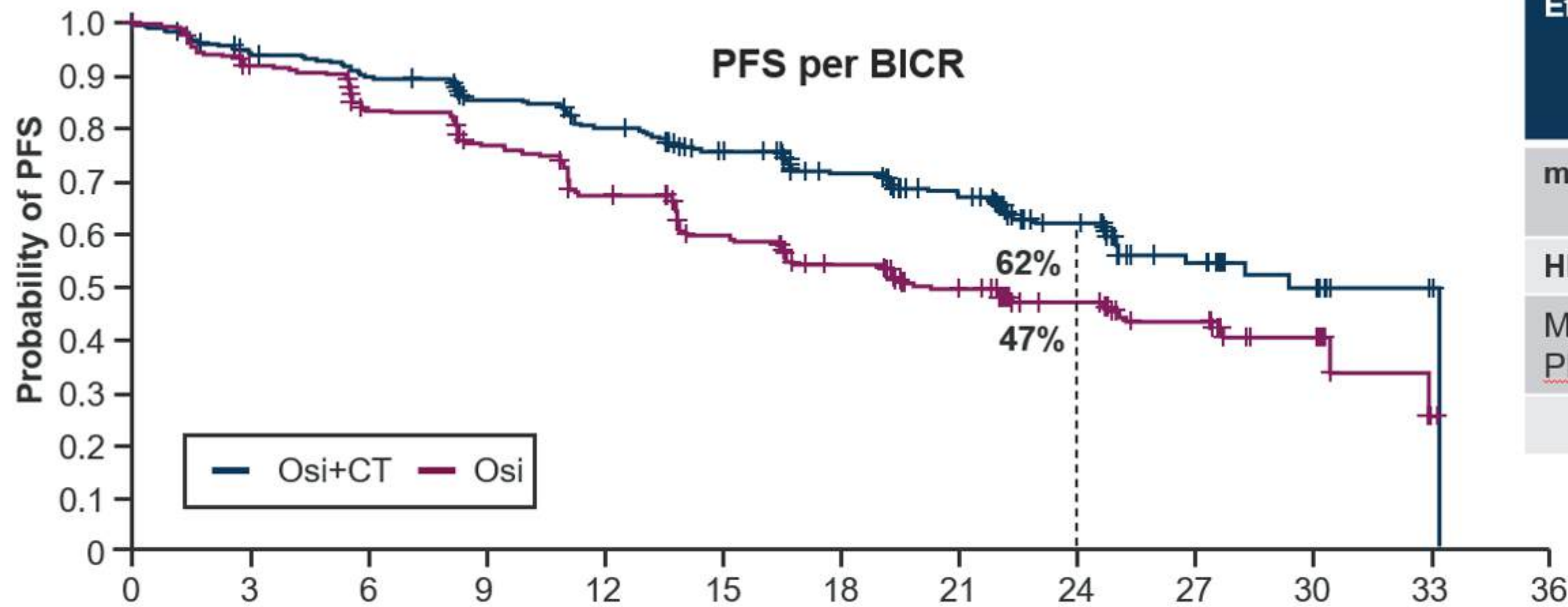
The screenshot shows a table with columns for adverse events (AEs) and their occurrence rates. The table lists various AEs such as Paresthesia, Fatigue, and Nausea, along with their respective percentages and other clinical data points. The table is partially obscured by a redacted area.

Pharmacological Management of Paresthesia

| Selective Serotonin Reuptake Inhibitors (SSRI) | |
|---|--|
| Duloxetine | 30 mg/day for 1 week, then 60 mg/day |
| Venlafaxine | 50 mg/day initially, followed by 37.5 mg twice daily |
| Anticonvulsants | |
| Gabapentin | Targeted dose: 2700 mg/day |
| Pregabalin | Targeted dose: 300 mg twice daily |
| Lamotrigine | Starting dose: 25 mg/day, Targeted dose: 300 mg/day |
| Tricyclic Antidepressants | |
| Amitriptyline | Starting dose: 10 or 25 mg/day, Targeted dose: 50 mg/day |
| Nortriptyline | Target maximum dose: 100 mg/day |
| Opioids | |
| Tramadol | 200-400 mg in two or three doses |
| Strong Opioids | Smallest effective dose |

FLAURA2: 1L Osimertinib + Platinum-Pemetrexed Significantly Improved PFS by 9.5 Months vs. Osimertinib Monotherapy in *EGFRm* Advanced NSCLC (per BICR)

- At DCO, osimertinib + platinum-pemetrexed demonstrated a statistically significant and clinically meaningful improvement in BICR assessed PFS (29.4 months) vs. osimertinib monotherapy (19.9 months).
- PFS rate was higher in the osimertinib + platinum-pemetrexed arm vs. osimertinib arm at 24 months.



| Efficacy | Osimertinib + platinum-pemetrexed (n=279) | Osimertinib (n=278) |
|--|---|---------------------|
| mPFS months (95% CI) | 29.4 (25.1-NC) | 19.9 (16.6-25.3) |
| HR (95% CI) | 0.62 (0.48-0.80); p=0.0002 | |
| Median follow up for PFS ^a , months (range) | 19.4 (0-33.2) | 14.6 (0-33.2) |
| Overall maturity: 43% | | |

| No. at risk: | Time from randomization (months) | | | | | | | | | | | | |
|--------------|----------------------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|
| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 |
| Osi+CT 279 | 279 | 255 | 242 | 223 | 207 | 184 | 158 | 128 | 81 | 39 | 20 | 3 | 0 |
| Osi 278 | 278 | 247 | 218 | 195 | 169 | 139 | 116 | 88 | 59 | 42 | 18 | 2 | 0 |

DCO: April 03, 2023. **Note:** CT includes cisplatin or carboplatin with pemetrexed. ^aIn all patients.

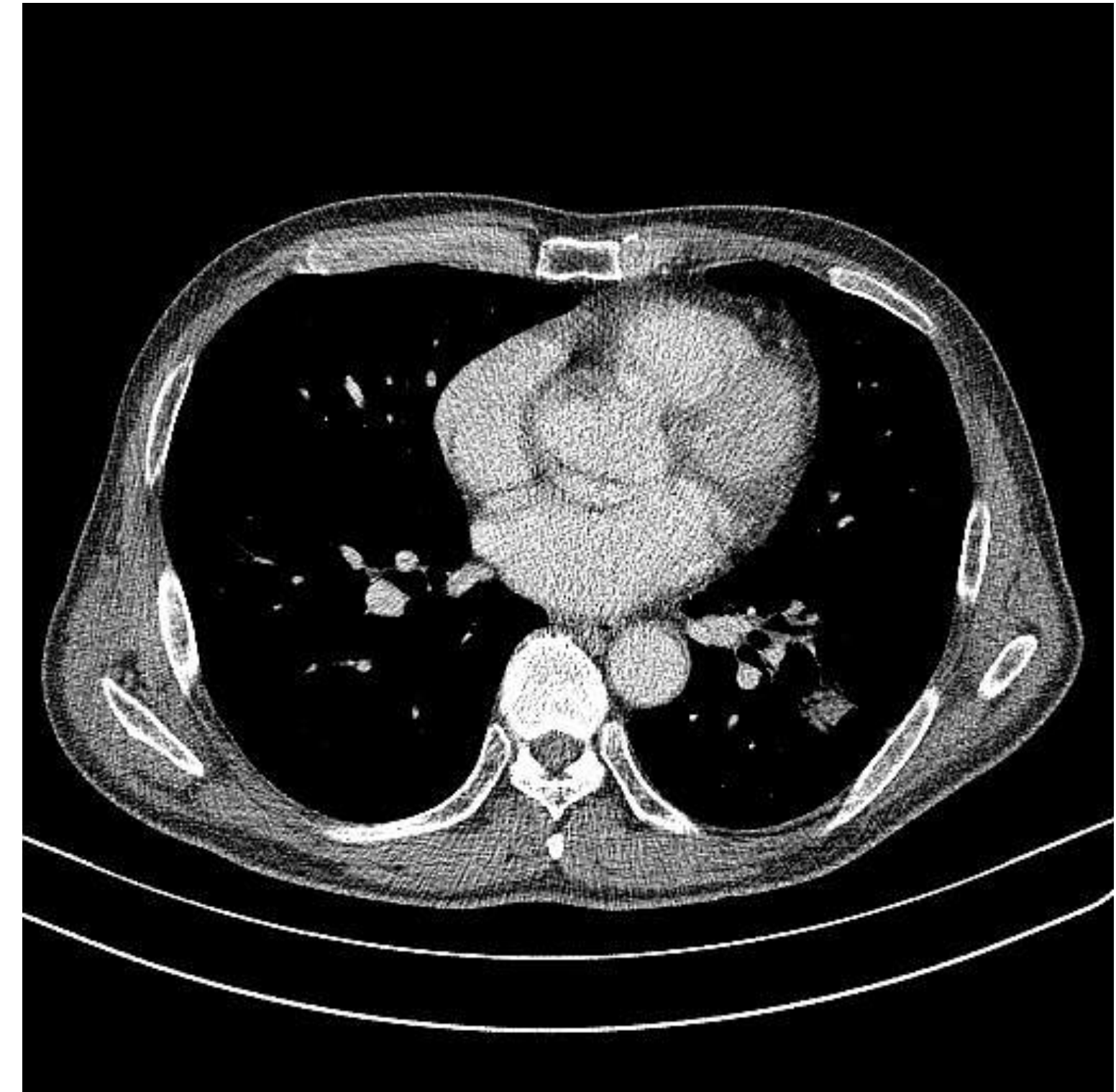
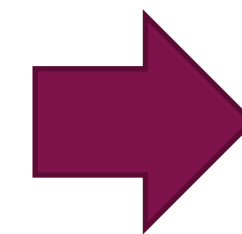
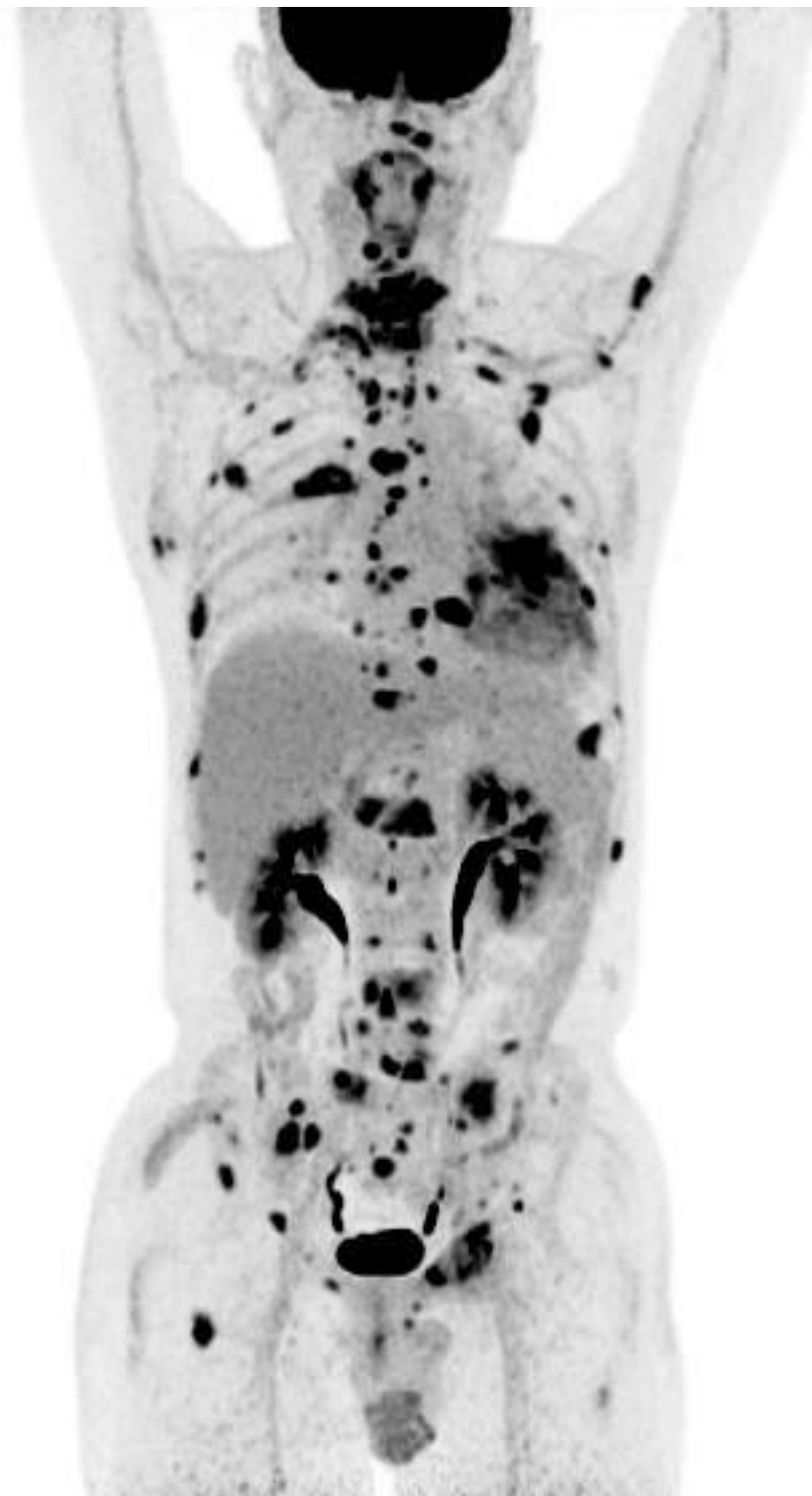
BICR = Blinded Independent Central Review; CI = confidence interval; CT = chemotherapy; DCO = data cut-off; *EGFRm* = epidermal growth factor receptor mutation-positive; HR = hazard ratio; mPFS = median progression-free survival; NC = not calculable; NSCLC = non-small cell lung cancer; PFS = progression-free survival.

Case #4 61 years old Male

- NSCLC Adenocarcinoma T4N3M1c Bone
- EGFR 19Del, NGS TP53, TERT amp, NKX2-1 amp
- Tagrisso+PC



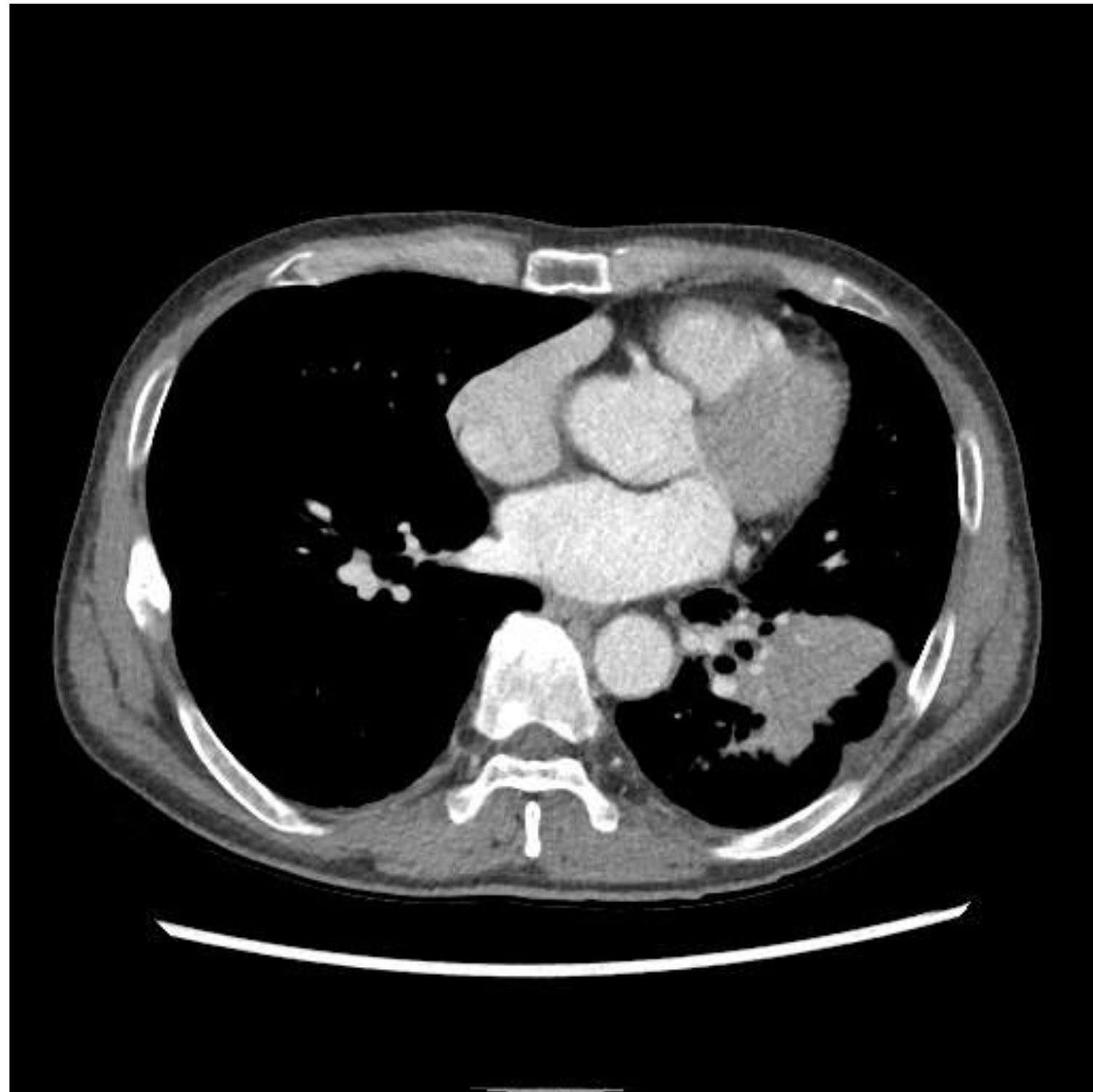
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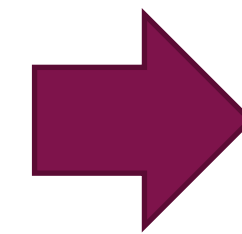
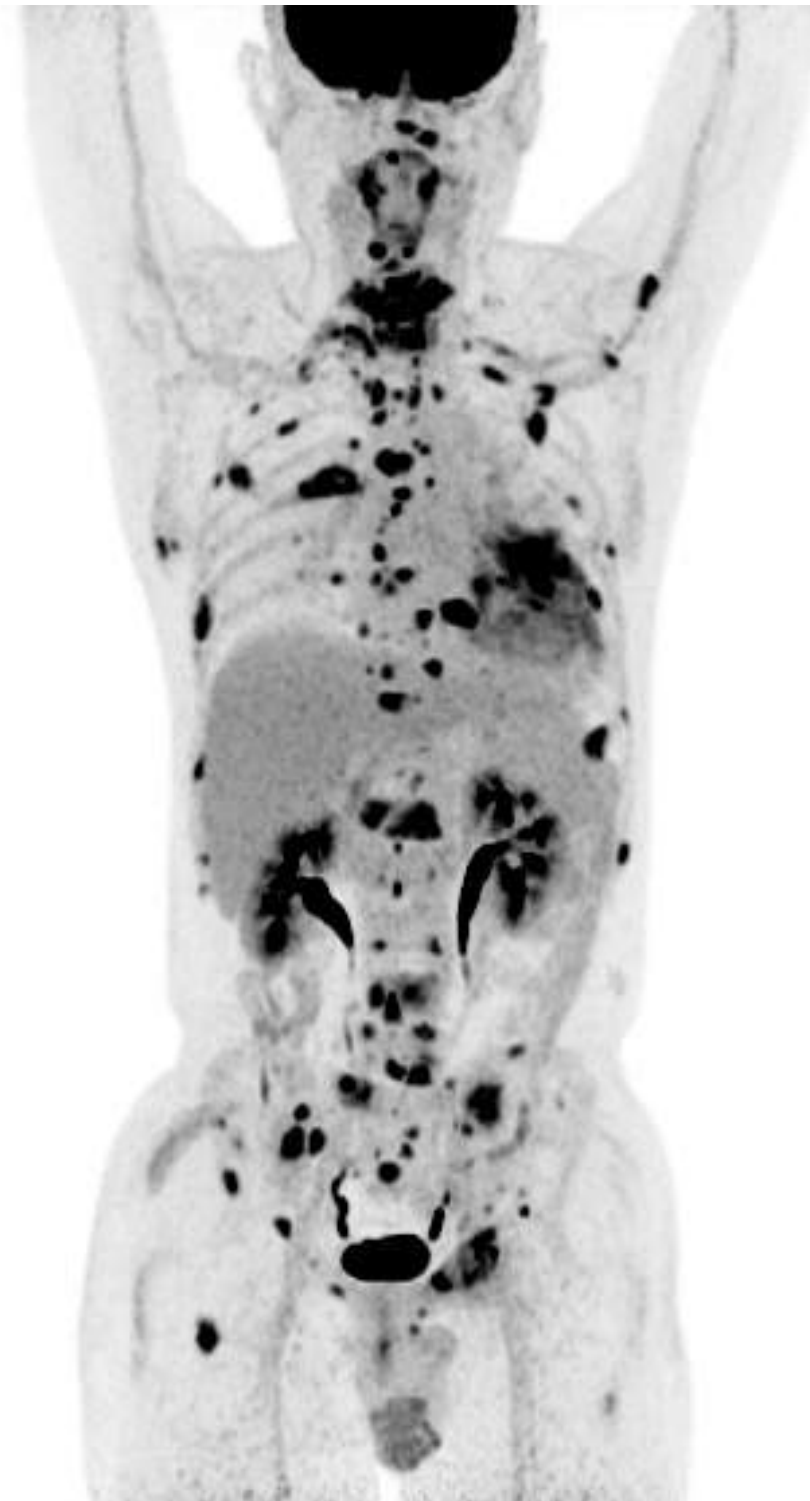
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Case #4 61 years old Male

- NSCLC Adenocarcinoma T4N3M1c Bone
- EGFR 19Del, NGS TP53, TERT amp, NKX2-1 amp
- Tagrisso+PC



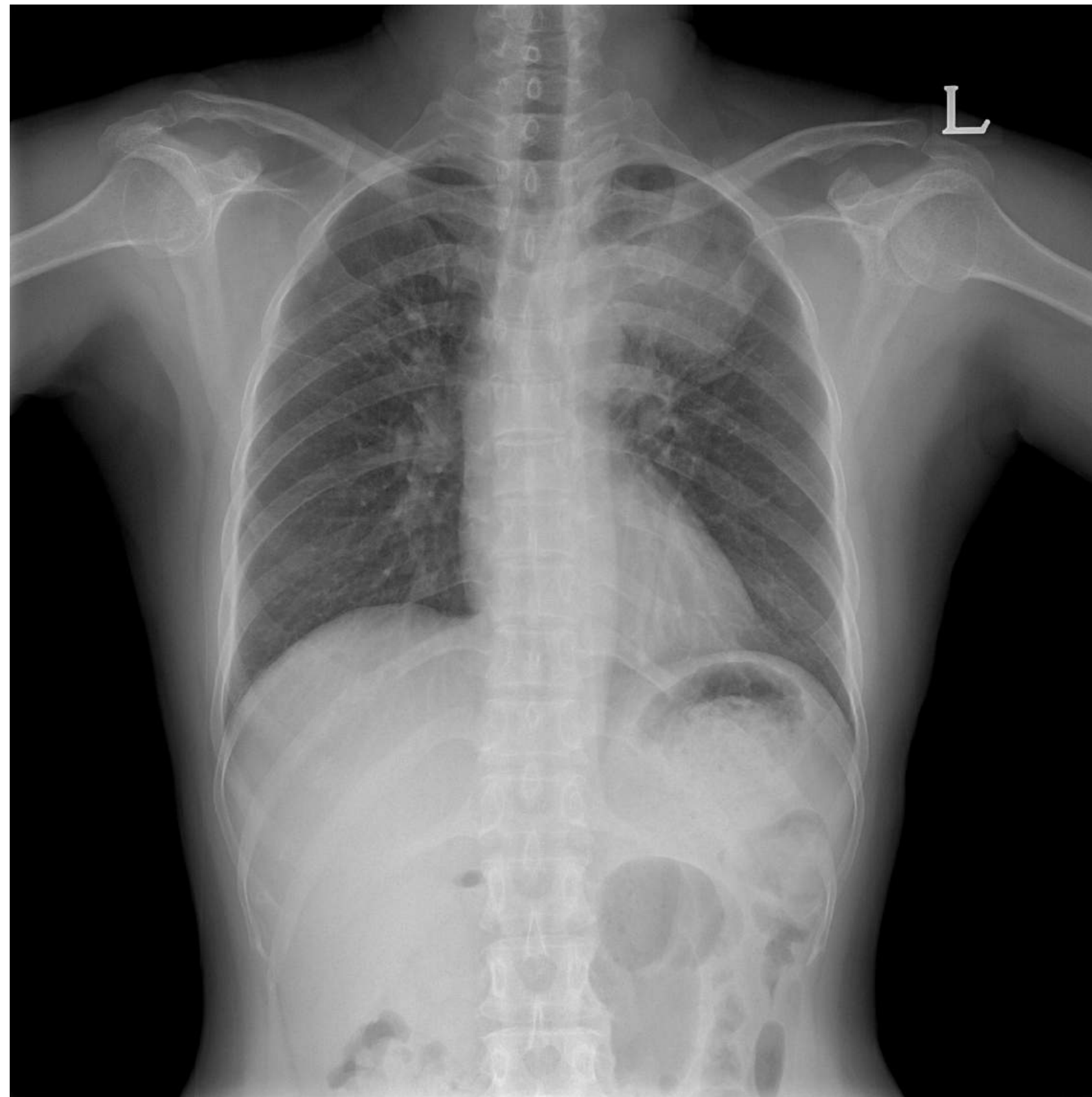
2025.6



2026.3

Case #1 51 years old Female

- NSCLC Adenocarcinoma cT3N3M1c Bone, Brain
- EGFR L858R



2025.9

Case #1 51 years old Female

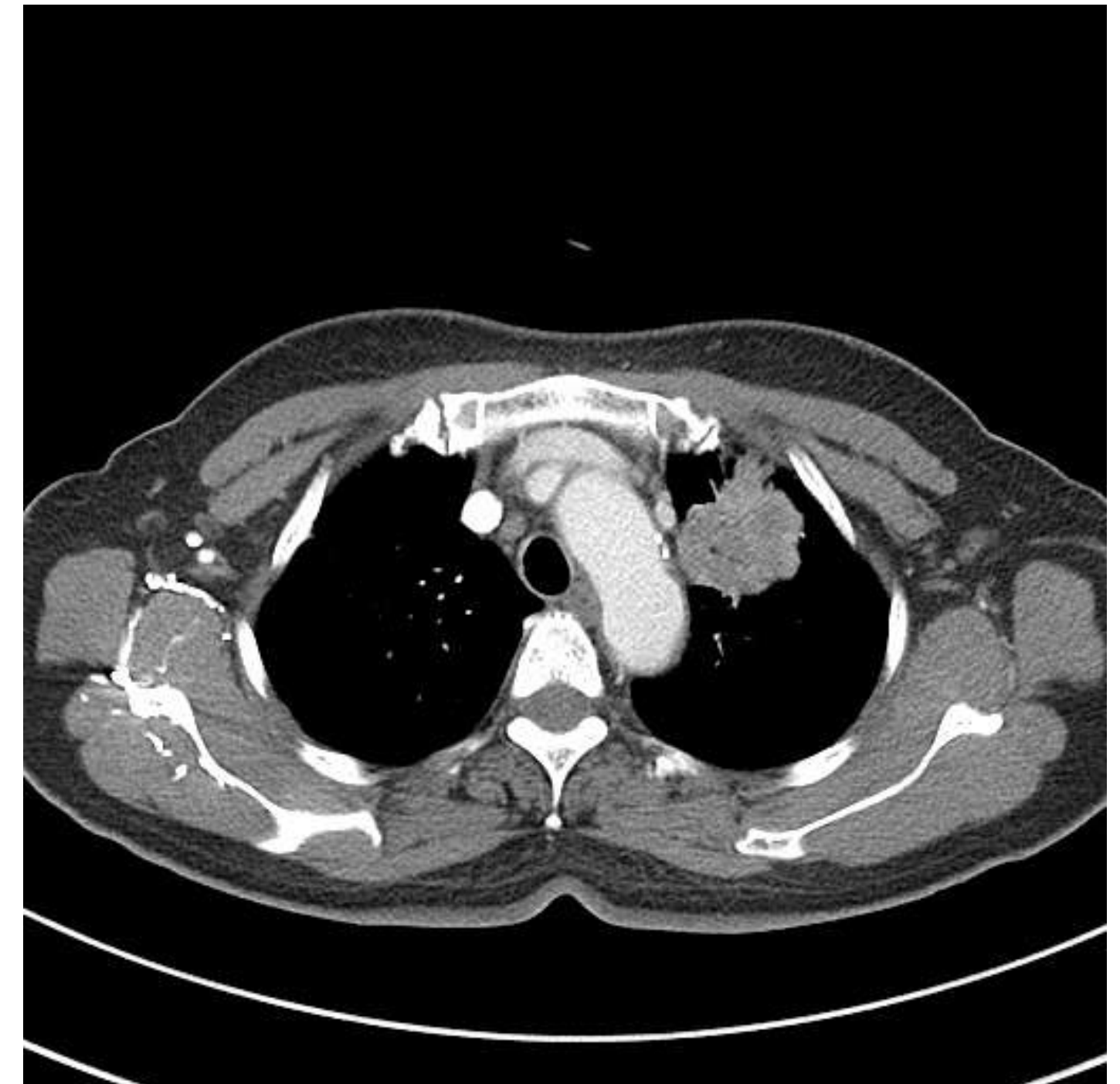
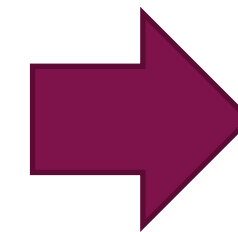
- NSCLC Adenocarcinoma cT3N3M1c Bone, Brain
- EGFR L858R – Tagrisso start



2025.9



2025.9



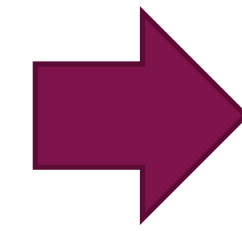
2026.1

Case #1 51 years old Female

- NSCLC Adenocarcinoma cT3N3M1c Bone (C-spine), Brain
- EGFR L858R – Tagrisso start



2025.9



Patient Name: AHN MISOOK, F51
Study Name: Bone Scan (Whole body bone scan)
99mTc-DPD Whole Body Bone Scan

Patient ID: 71551168
Study Date: 2026-04-02

Oncoflash

Post I.V 3 hrs 12 min



ANTERIOR
1666K Counts



POSTERIOR
1585K Counts



ANTERIOR
1666K Counts



POSTERIOR
1585K Counts

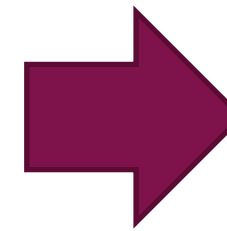
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Case #1 51 years old Female

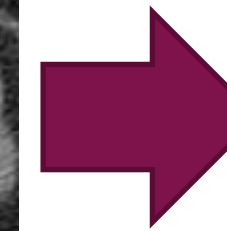
- NSCLC Adenocarcinoma cT3N3M1c Bone, Brain
- EGFR L858R – Tagrisso – Early PD



2025.9



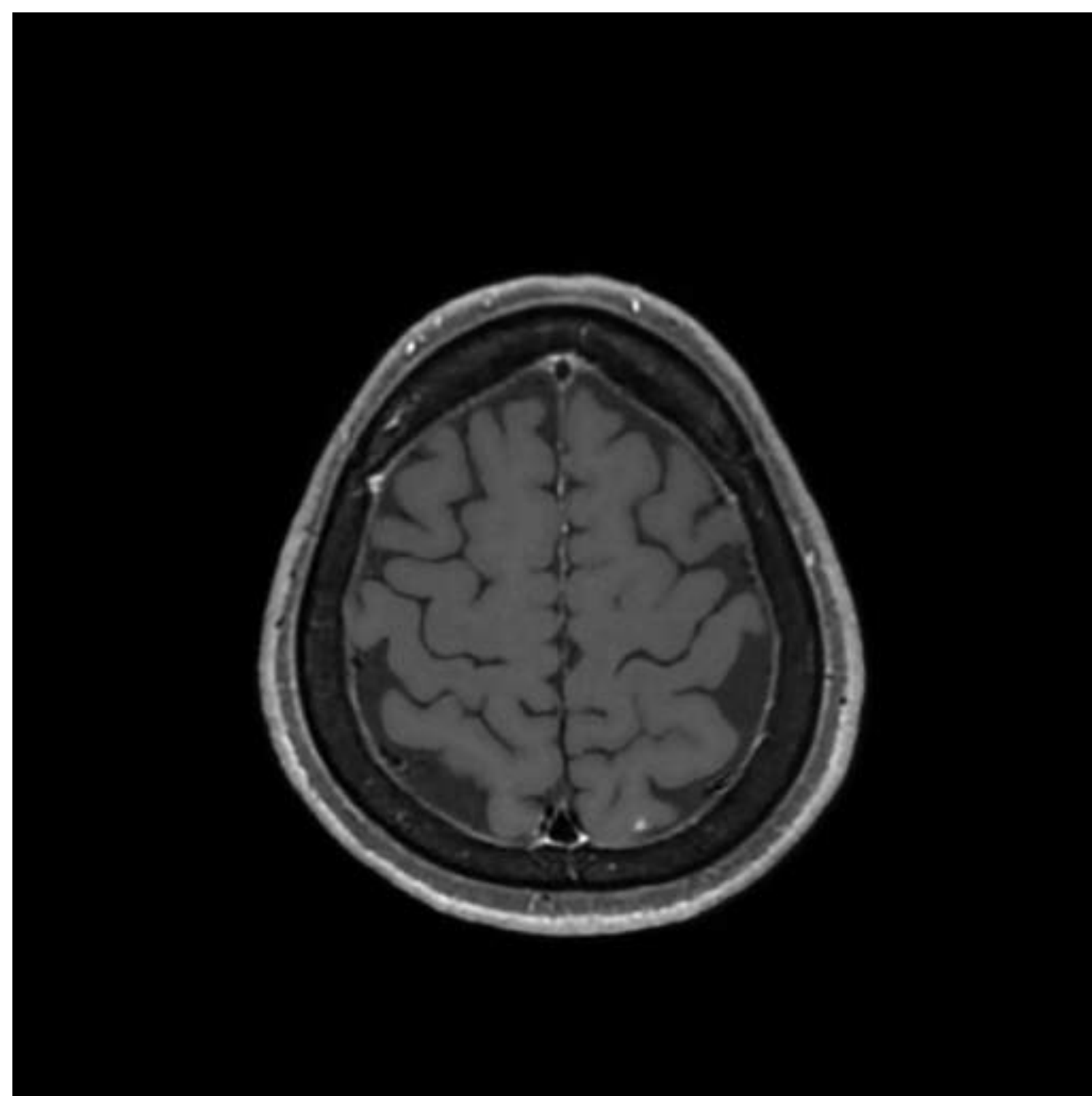
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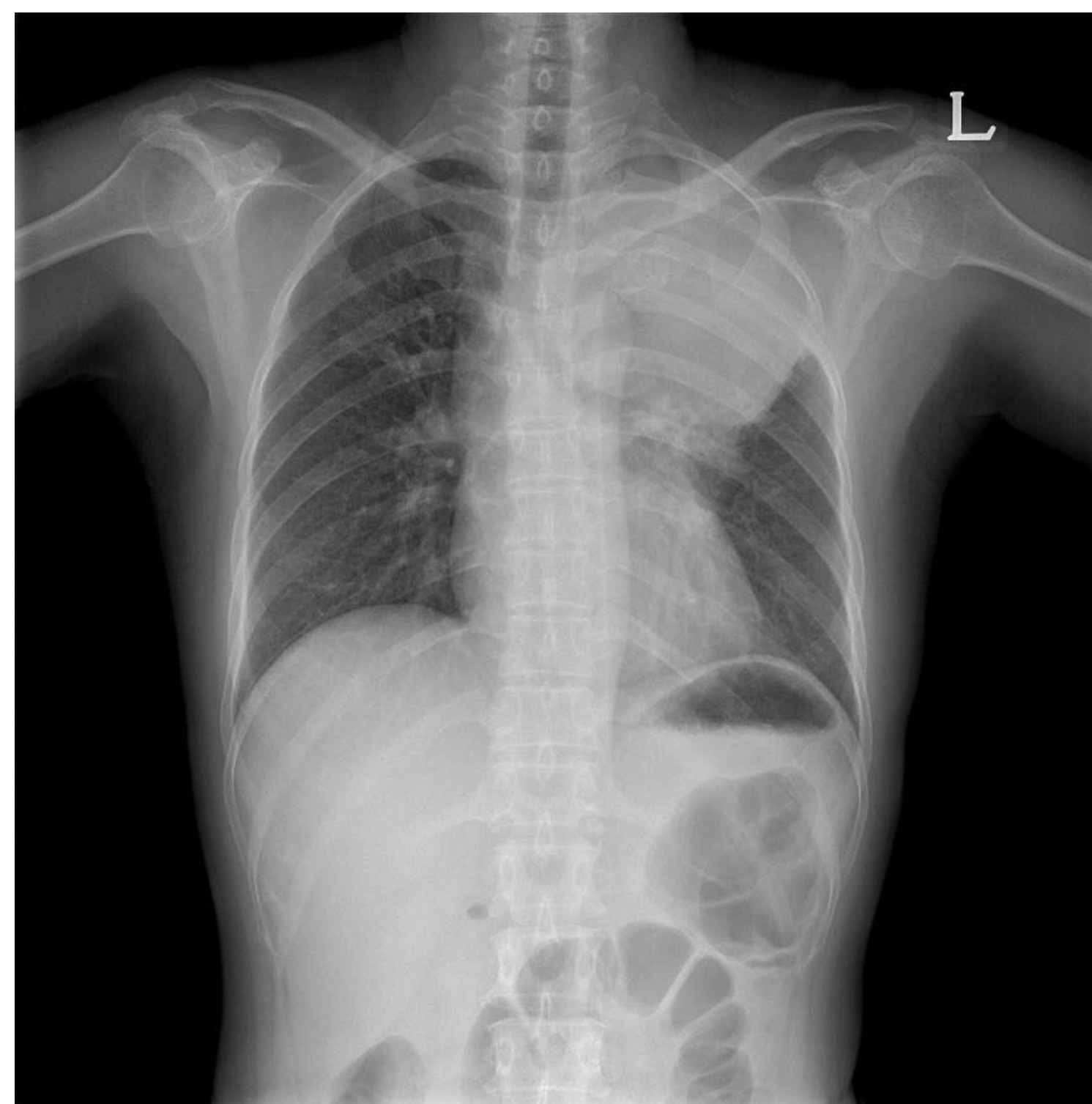
2026.3

Case #1 51 years old Female

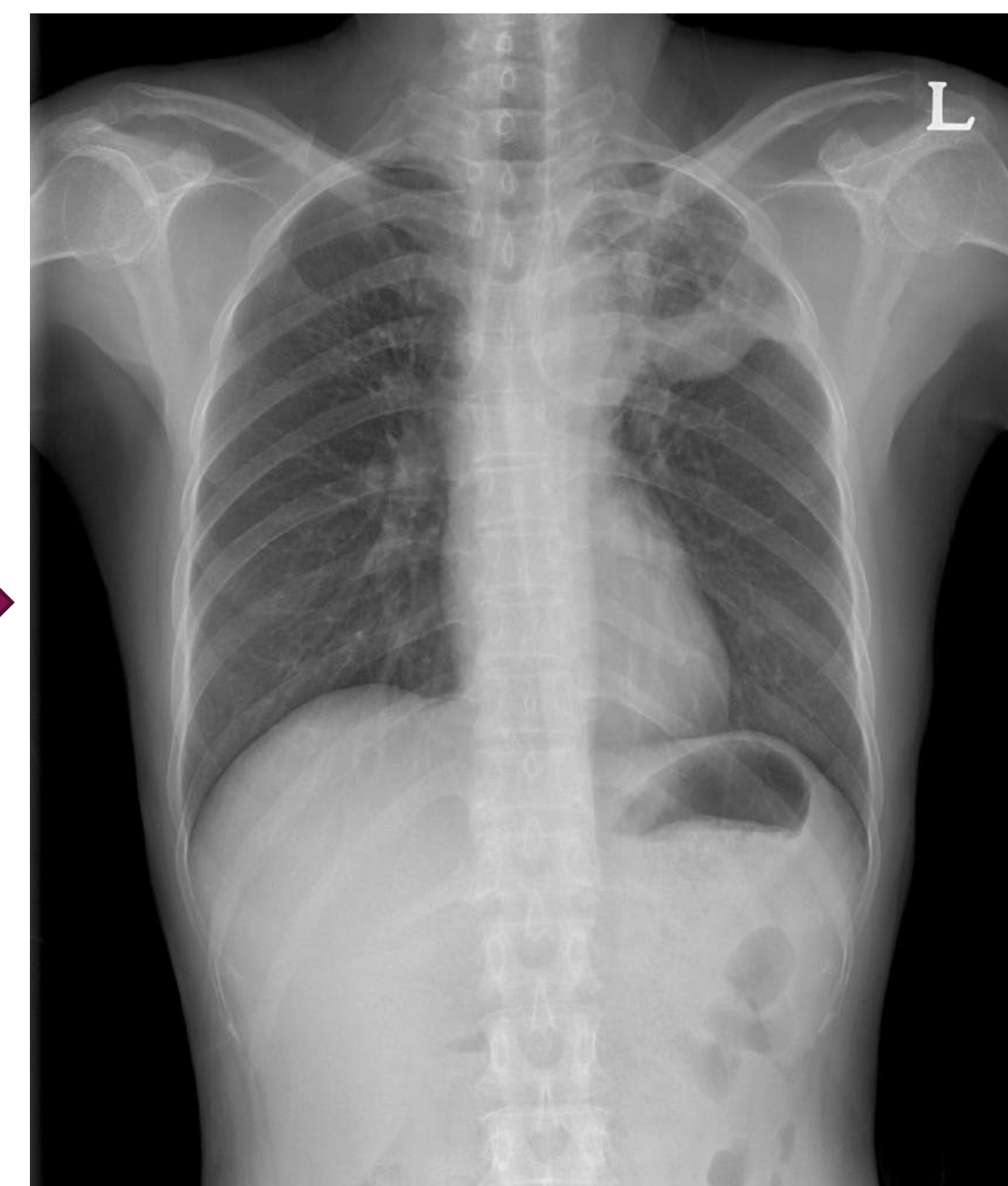
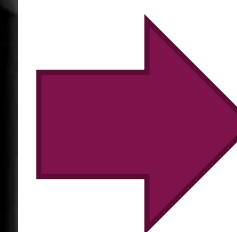
- NSCLC Adenocarcinoma cT3N3M1c Bone, Brain
- EGFR L858R, NGS L858R, TP53
- Tagrisso – Early PD, Rebiopsy – NSCLC Amivantamab + PC



2026.3



2026.3



2026.4

Status in Korea

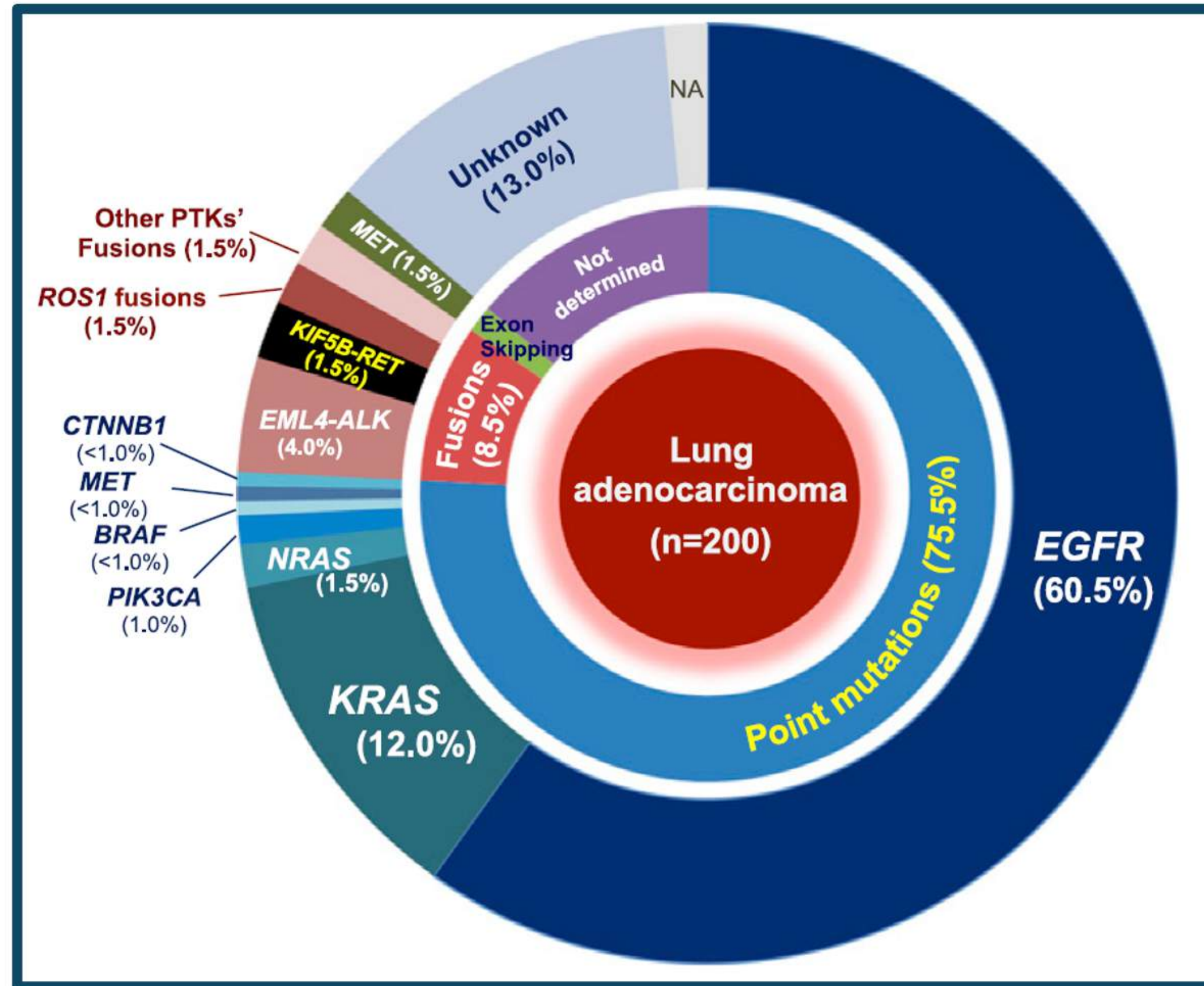


Fig. Mutational profiles of the 200 lung adenocarcinomas in Korean patients

Seo, et al., *Genome Res.* 2012;22:2109-2119

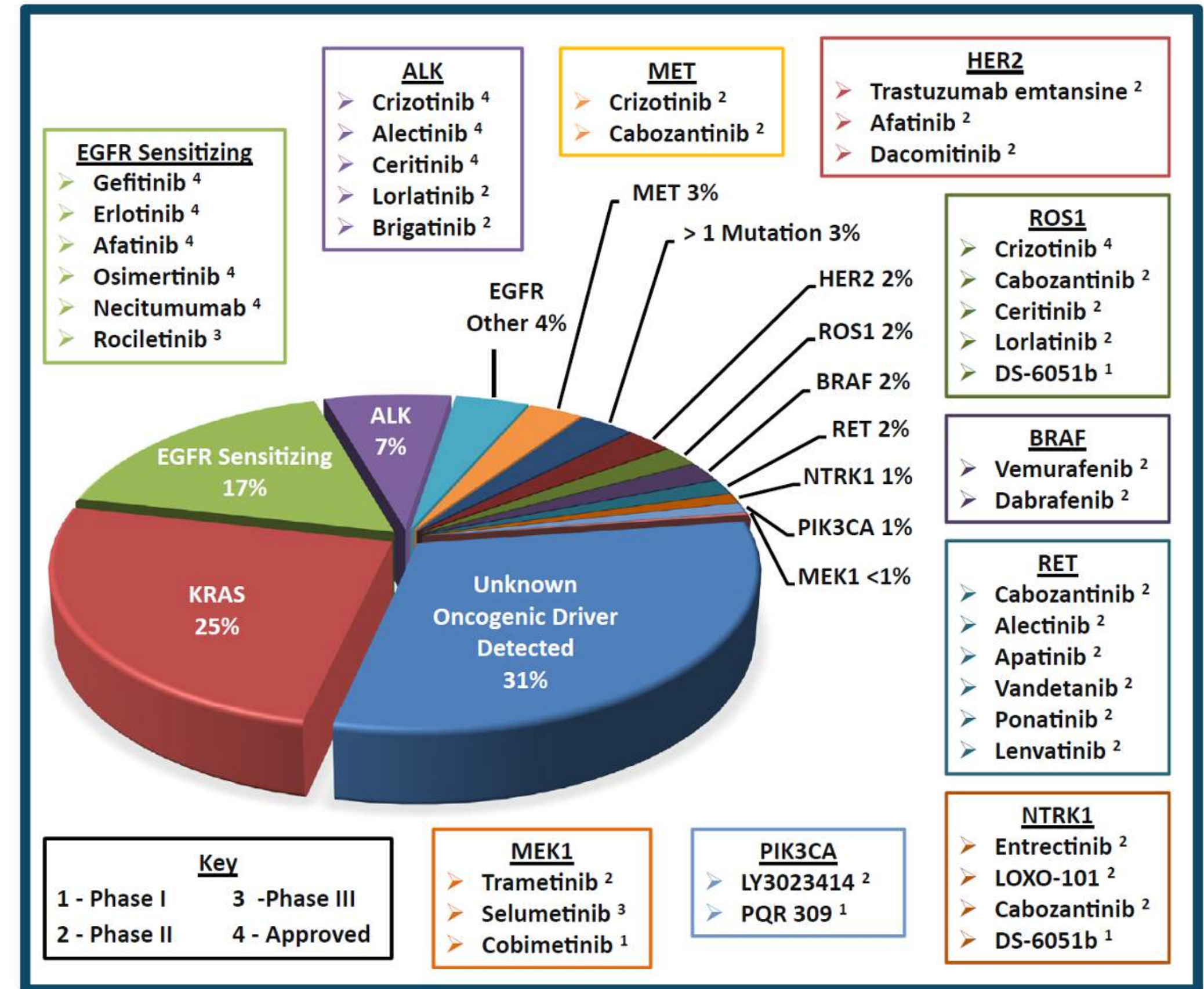
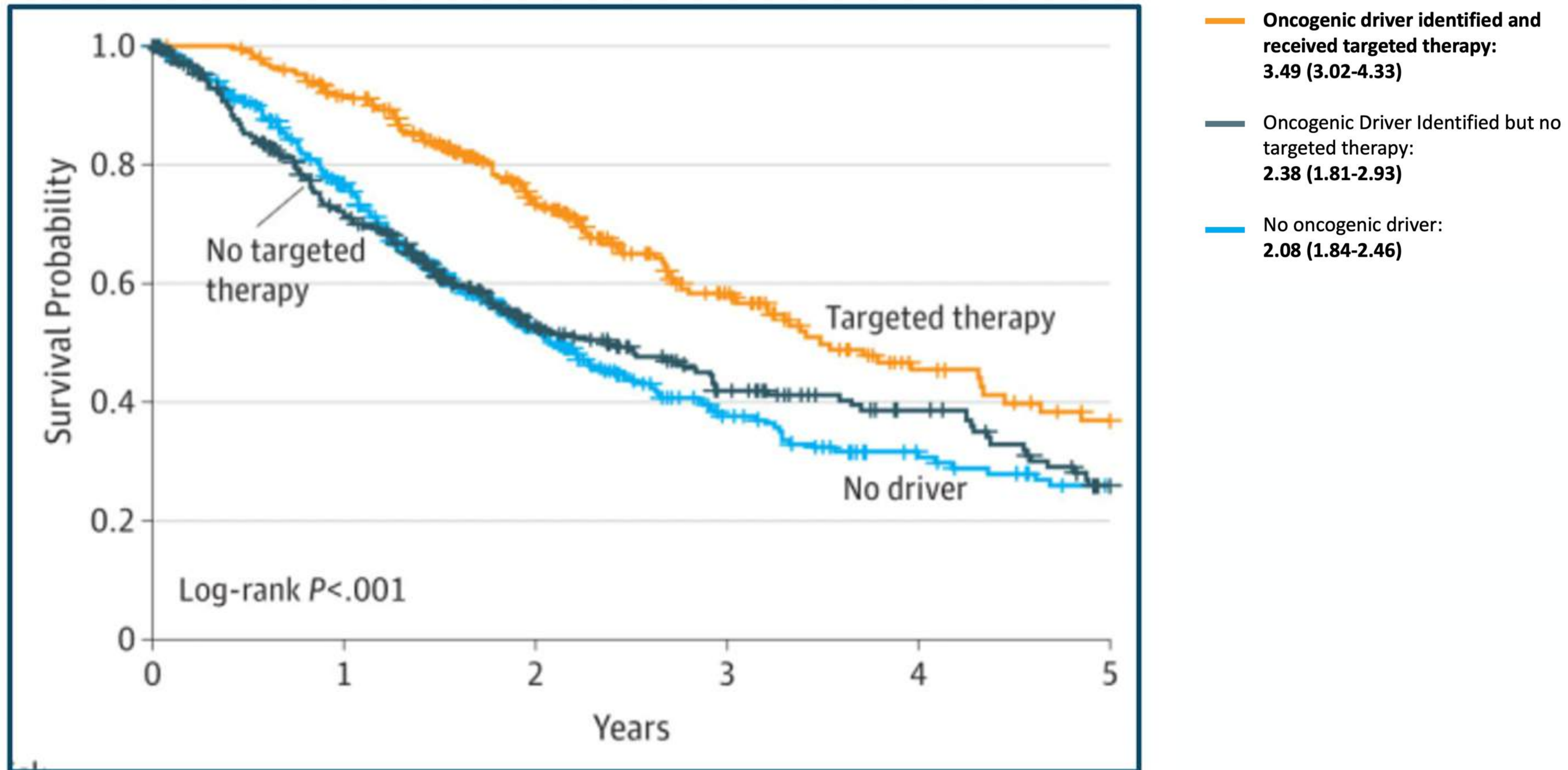


Fig. Frequency of molecular aberrations in various driver oncogenes in lung adenocarcinomas and current available drugs against these oncogenic proteins

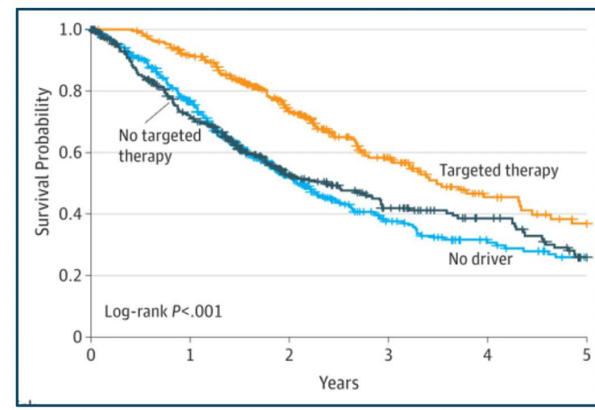
Tsao AS, et al. *J Thorac Oncol.* 2016; 11(5): 613-38

Actionable Genetic Alteration



Study design : From 2009 through 2012, 14 sites in the United States enrolled patients with metastatic lung adenocarcinomas and a performance status of 0 through 2 and tested their tumors for 10 drivers to determine the frequency of oncogenic drivers in patients with lung adenocarcinomas and to use the data to select treatments targeting the identified driver(s) and measure survival.

Kris et al. JAMA. 2014 May 21;311(19):1998-2006.



**— Oncogenic driver identified and received targeted therapy:
3.49 (3.02-4.33)**

Medial Survival Time - 42months

**— Oncogenic Driver Identified but no targeted therapy:
2.38 (1.81-2.93)**

**— No oncogenic driver:
2.08 (1.84-2.46)**



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 5.2026 — March 13, 2026

[NCCN Guidelines for Patients®](#)



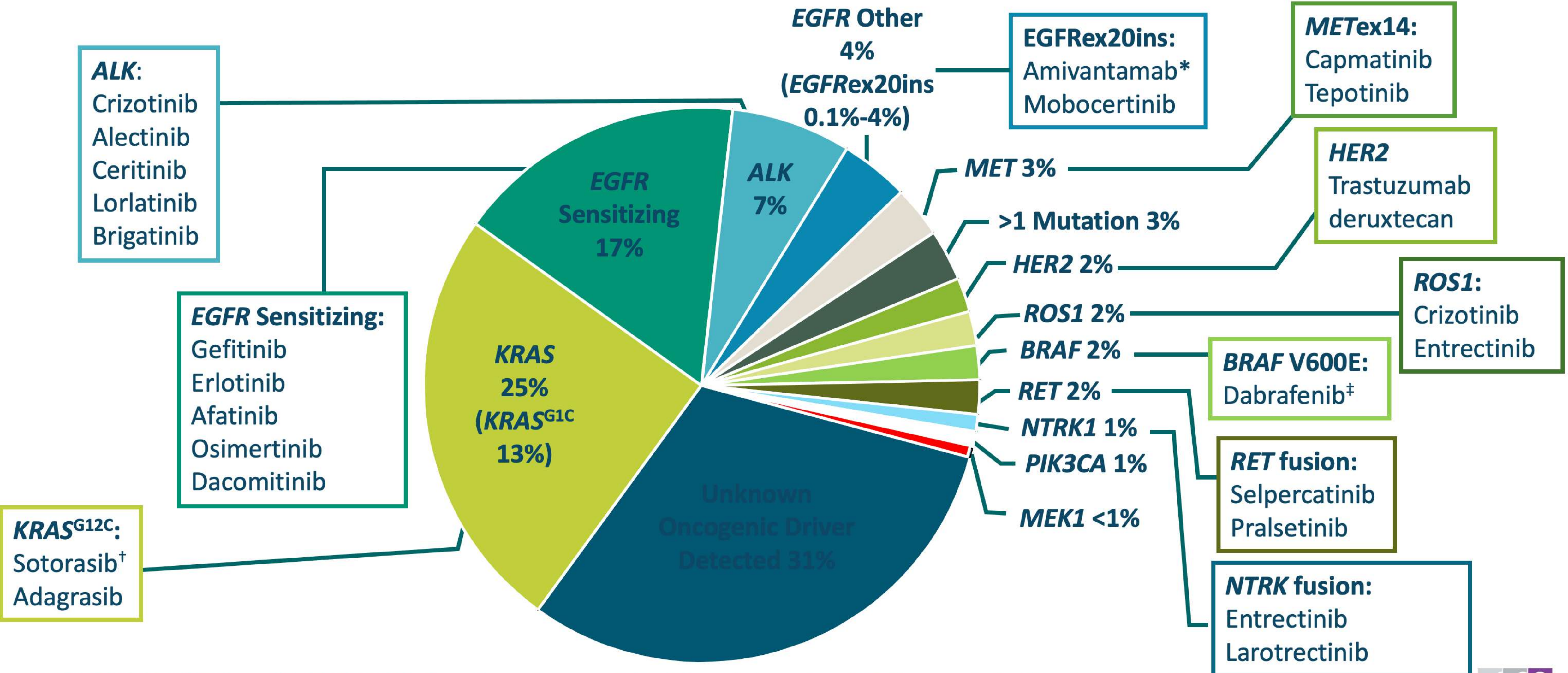
NCCN Guidelines Version 5.2026

Non-Small Cell Lung Cancer

TESTING RESULTS^{qq,rr}

| | |
|--|-------------------------|
| <i>EGFR</i> exon 19 deletion or L858R mutation positive | NSCL-21 |
| <i>EGFR</i> S768I, L861Q, and/or G719X mutation positive | NSCL-24 |
| <i>EGFR</i> exon 20 insertion mutation positive | NSCL-25 |
| <i>KRAS</i> G12C mutation positive | NSCL-26 |
| <i>ALK</i> gene fusion positive | NSCL-27 |
| <i>ROS1</i> gene fusion positive | NSCL-30 |
| <i>BRAF</i> V600E mutation positive | NSCL-32 |
| <i>NTRK1/2/3</i> gene fusion positive | NSCL-33 |
| <i>MET</i> exon 14 skipping mutation positive | NSCL-34 |
| <i>RET</i> gene fusion positive | NSCL-35 |
| <i>ERBB2 (HER2)</i> mutation positive | NSCL-36 |
| <i>NRG1</i> gene fusion positive | NSCL-37 |
| PD-L1 ≥1% and negative for actionable biomarkers above | NSCL-38 |
| PD-L1 <1% and negative for actionable biomarkers above | NSCL-39 |

FDA Approved or Clinical Trial in 2020



Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613. Burnett. *Approved after PD on platinum-based CT. †Approved after ≥1 prior systemic therapy. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.‡Approved in combination with trametinib (MEK inhibitor) for BRAF V600E mutation. Slide credit: clinicaloptions.com

Summary of drugs used for oncogene addicted metastatic NSCLC

EGFR exon-19 deletion or exon-12 L858R mutation

- 1 Osimertinib
- 2 (Nonsquamous)
Osimertinib + pemetrexed + (cisplatin or carboplatin)
- 3 or erlotinib
- 4 or afatinib
- 5 or gefitinib
- 6 or dacomitinib
- 7 or Erlotinib + ramucirumab
- 8 or Erlotinib + bevacizumab

Second line

- 1 Surgery or stereotactic ablative radiotherapy
- 2 or amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)

EGFR S768I, L861Q, and/or G719X mutations

- 1 Afatinib
- 2 or osimertinib
- 3 or erlotinib
- 4 or dacomitinib

EGFR exon-20 insertion mutations

Platinum-based doublet chemotherapy

Second line

Amivantamab-vmjw + carboplatin/pemetrexed (nonsquamous)

ALK rearrangement

- 1 Alectinib
- 2 or brigatinib
- 3 or lorlatinib
- 4 or ceritinib
- 5 or crizotinib

Second line

- 1 Consider local therapy, e.g., surgery or stereotactic ablative radiotherapy
- 2 or continue first-line drugs

BRAF V600E mutation

- 1 Dabrafenib + trametinib
- 2 or encorafenib + binimetinib

Second line

- 1 Dabrafenib
- 2 or vemurafenib

ROS1 rearrangement

- 1 Crizotinib
- 2 or entrectinib
- 3 or repotrectinib

Second line

- 1 Ceritinib for crizotinib resistant tumors
- 2 Consider local therapy, e.g., surgery or stereotactic ablative radiotherapy
- 3 or continue first-line drugs

RET rearrangement

- 1 Selpercatinib
- 2 or Pralsetinib
- 3 or cabozantinib

NTRK gene fusion

- 1 Larotrectinib
- 2 or entrectinib

MET exon-14 skipping mutations

- 1 Capmatinib
- 2 or tepotinib
- 3 or crizotinib

KRAS G12C mutation

- 1 Platinum-based chemotherapy
- 2 or PD1 or PDL1 immunotherapy
- 3 or surgery
- 4 or radiation
- 5 or a combination

Second line

- 1 Sotorasib
- 2 or adagrasib

ERBB2 (HER2) mutations

- 1 Platinum-based chemotherapy
- 2 or PD1 or PDL1 immunotherapy
- 3 or surgery
- 4 or radiation
- 5 or a combination

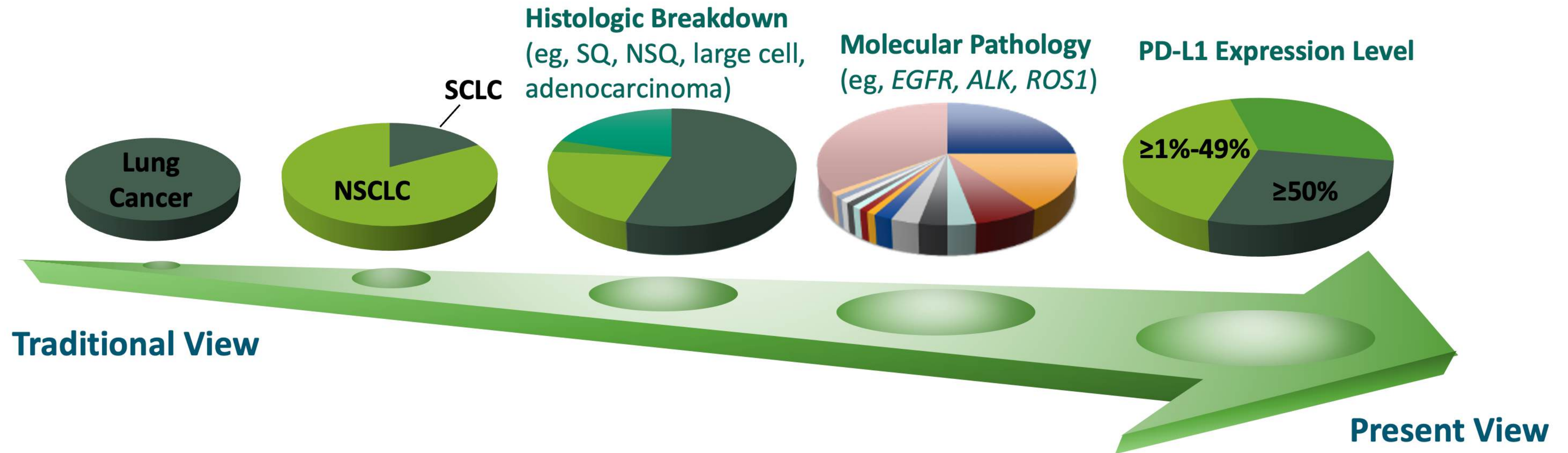
Second line

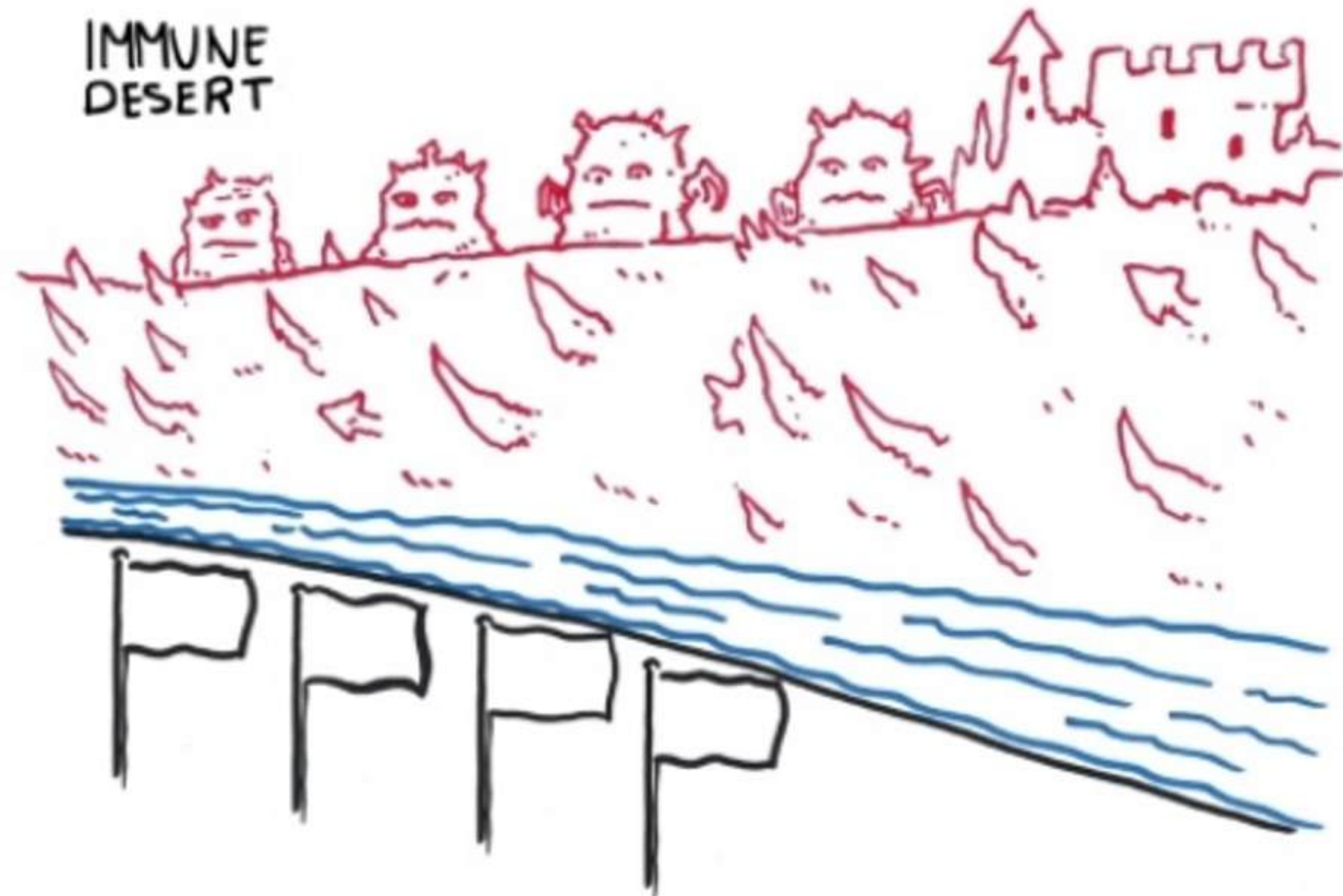
- 1 Fam-trastuzumab deruxtecan-nxki
- 2 or ado-trastuzumab emtansine

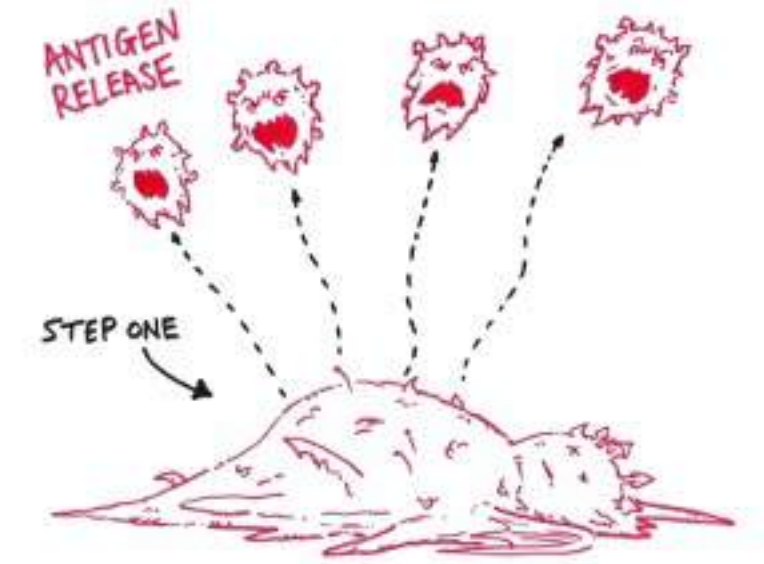
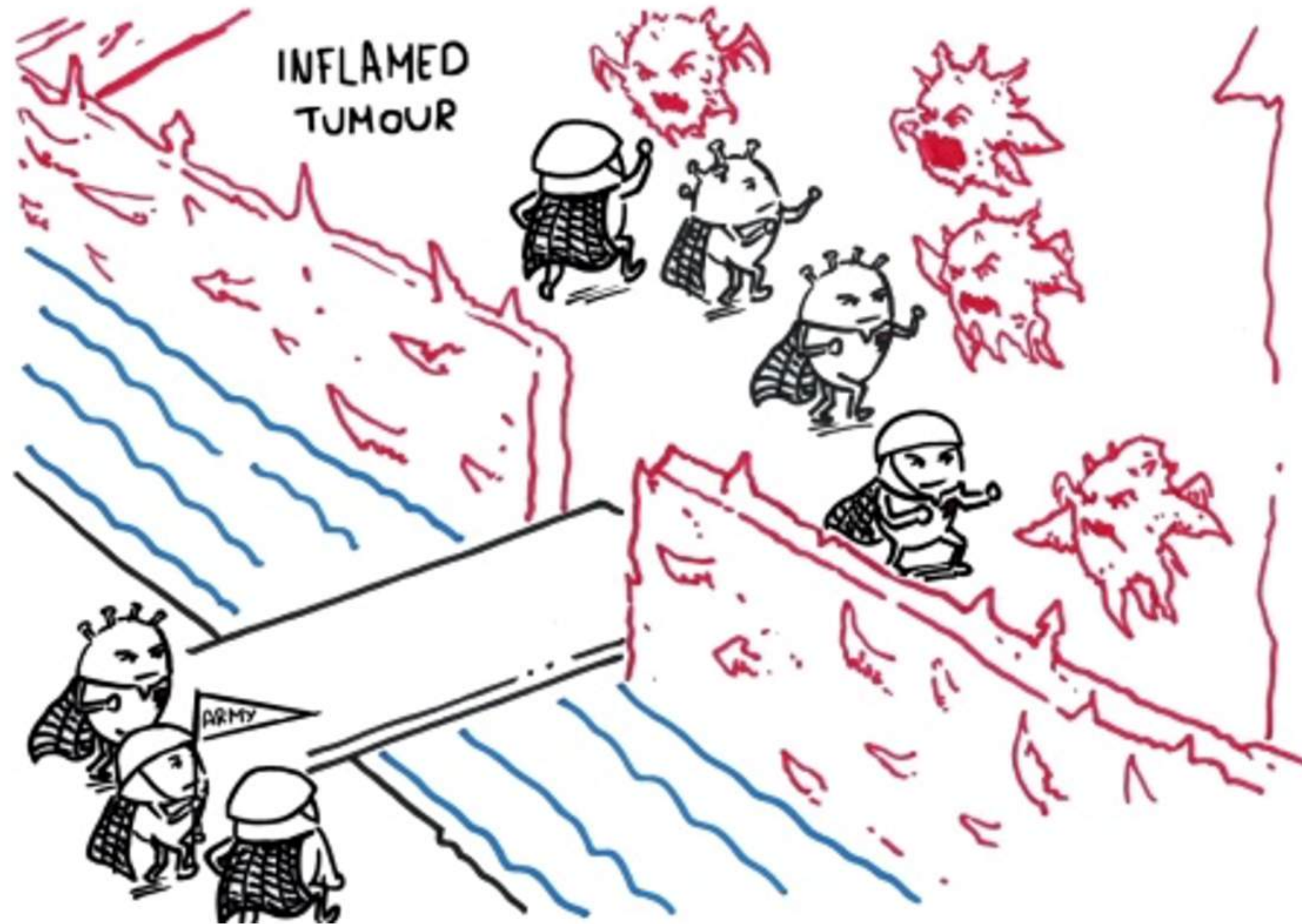


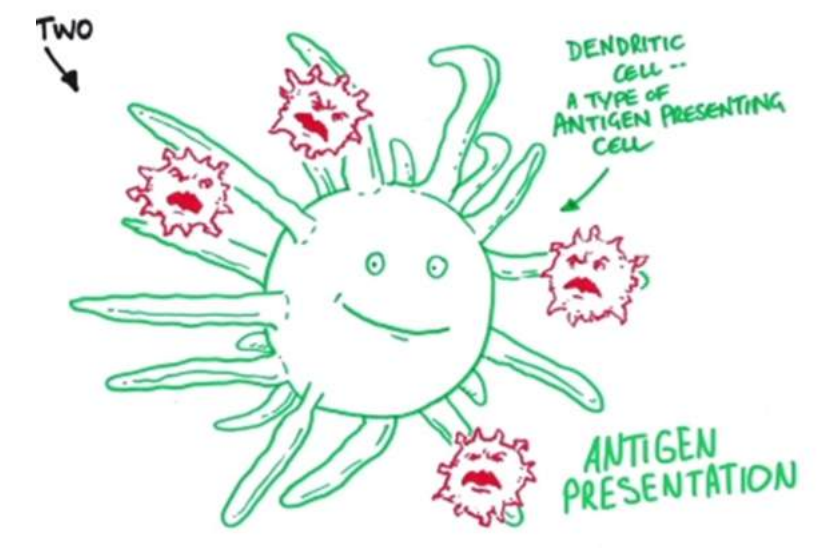
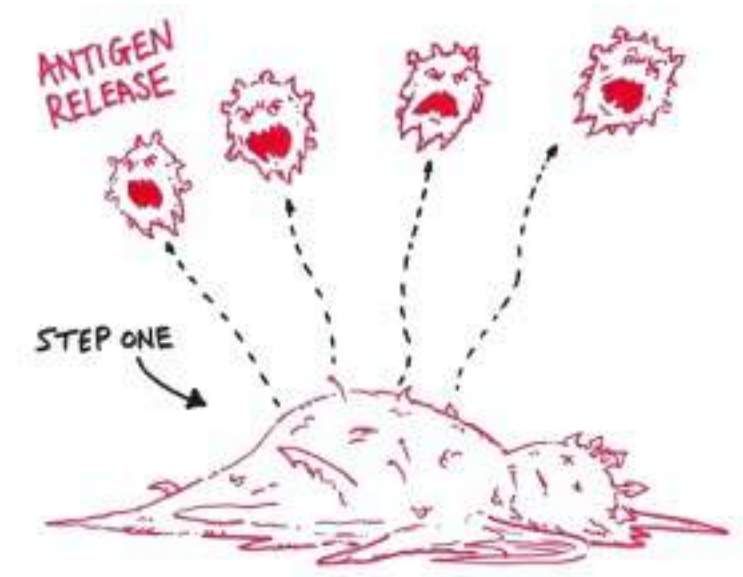
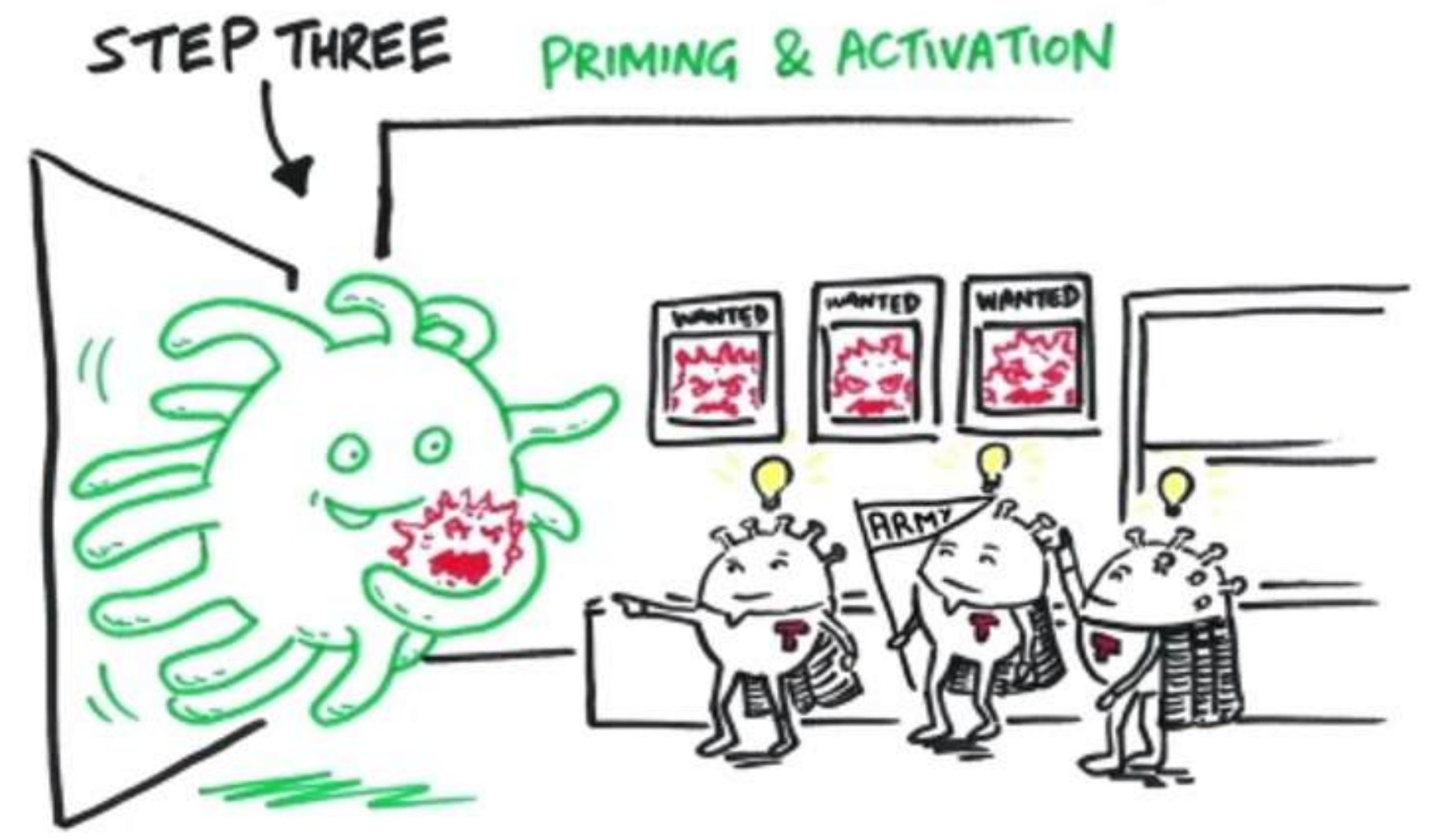
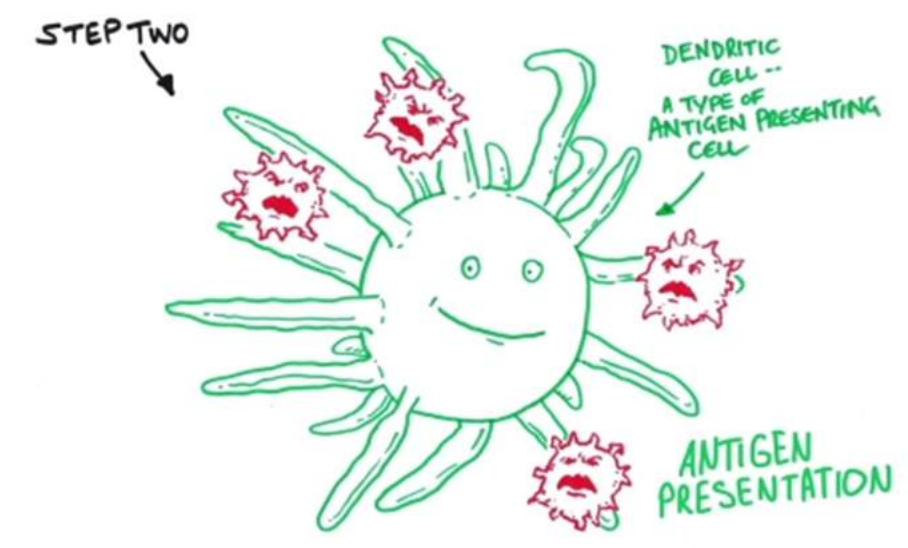
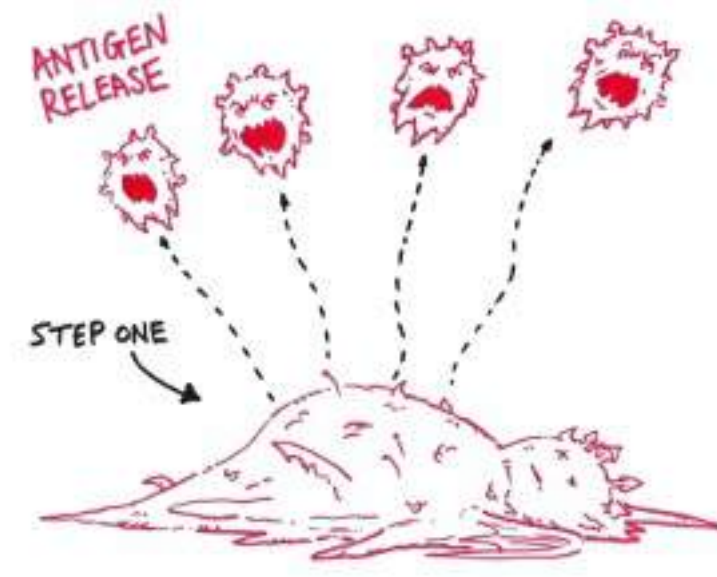
Evolution of Therapy in Lung Cancer

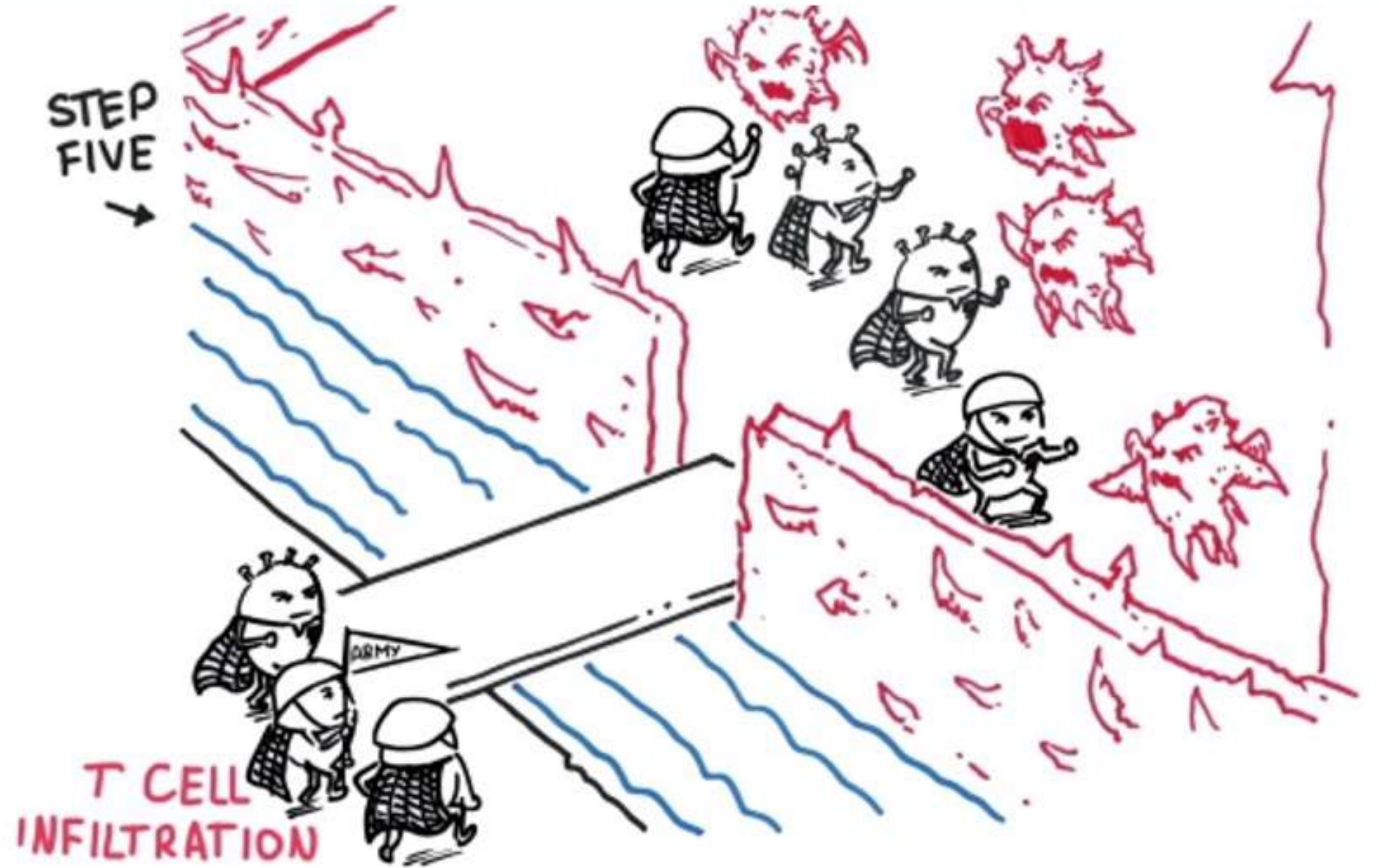
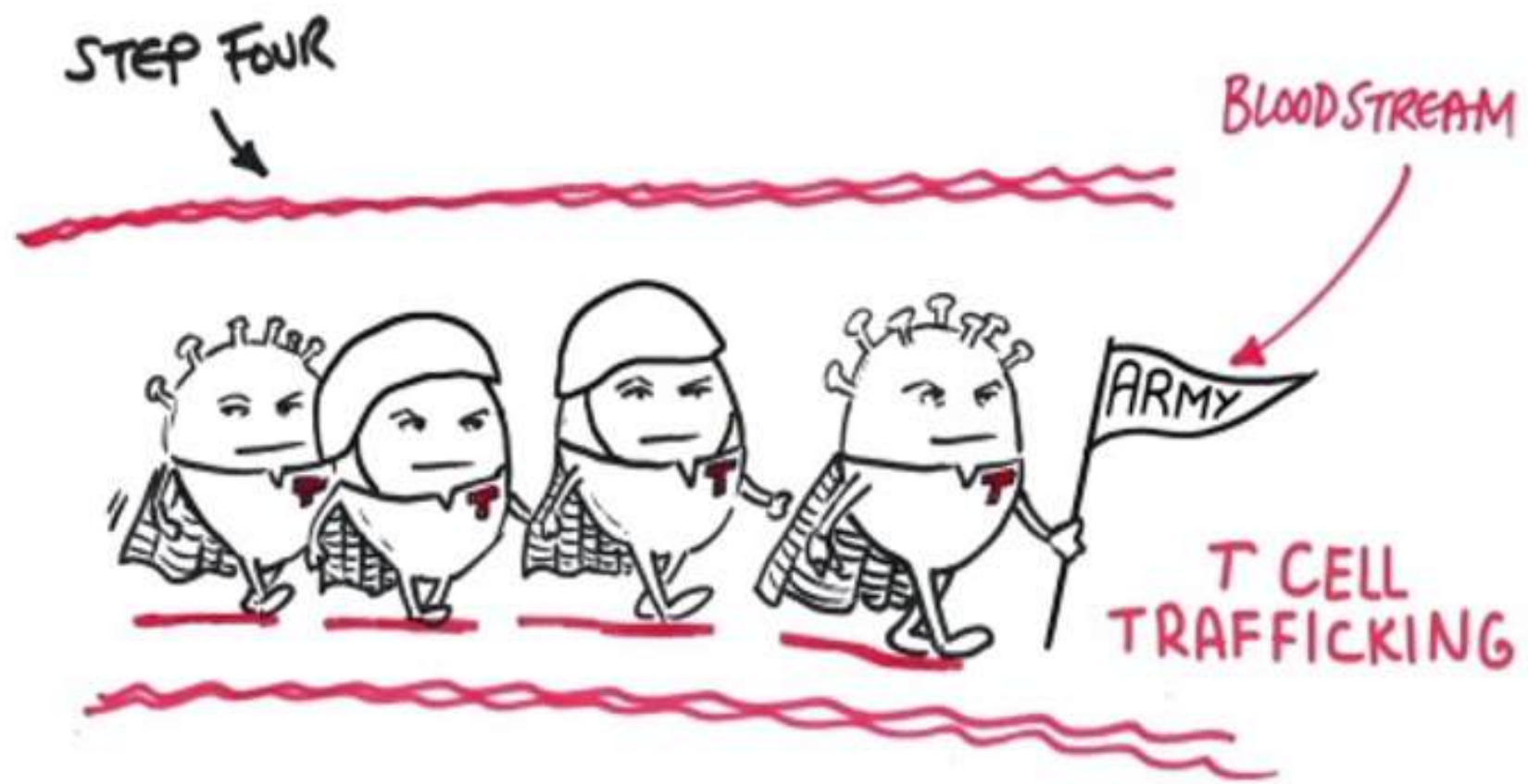
Not 1 disease, but many

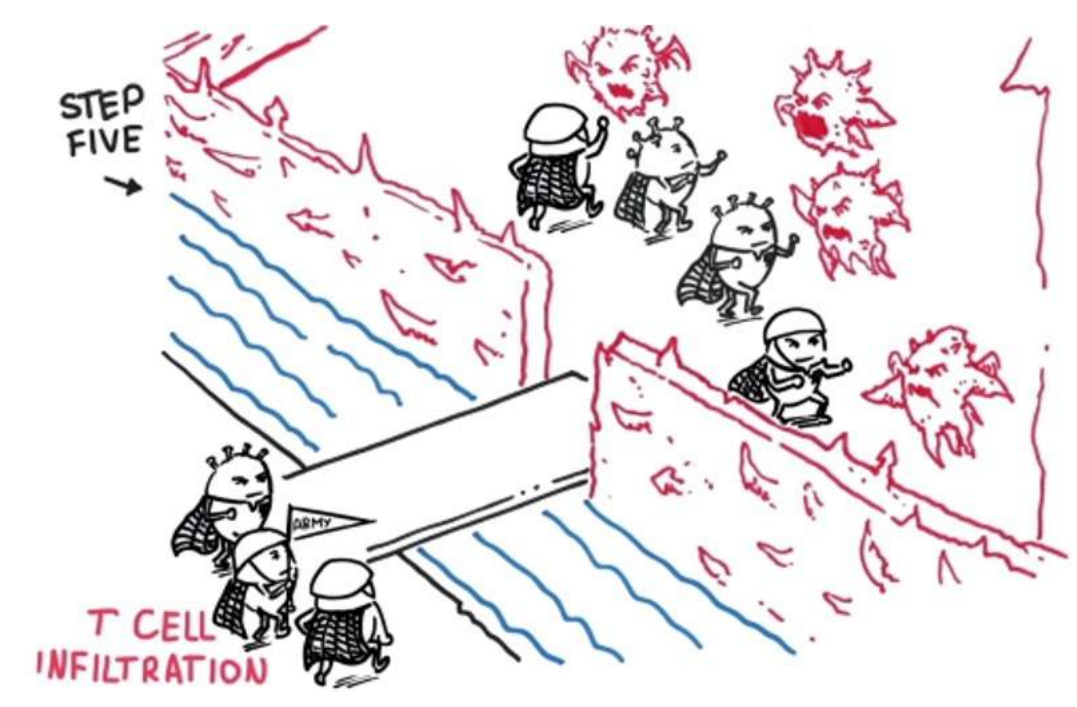
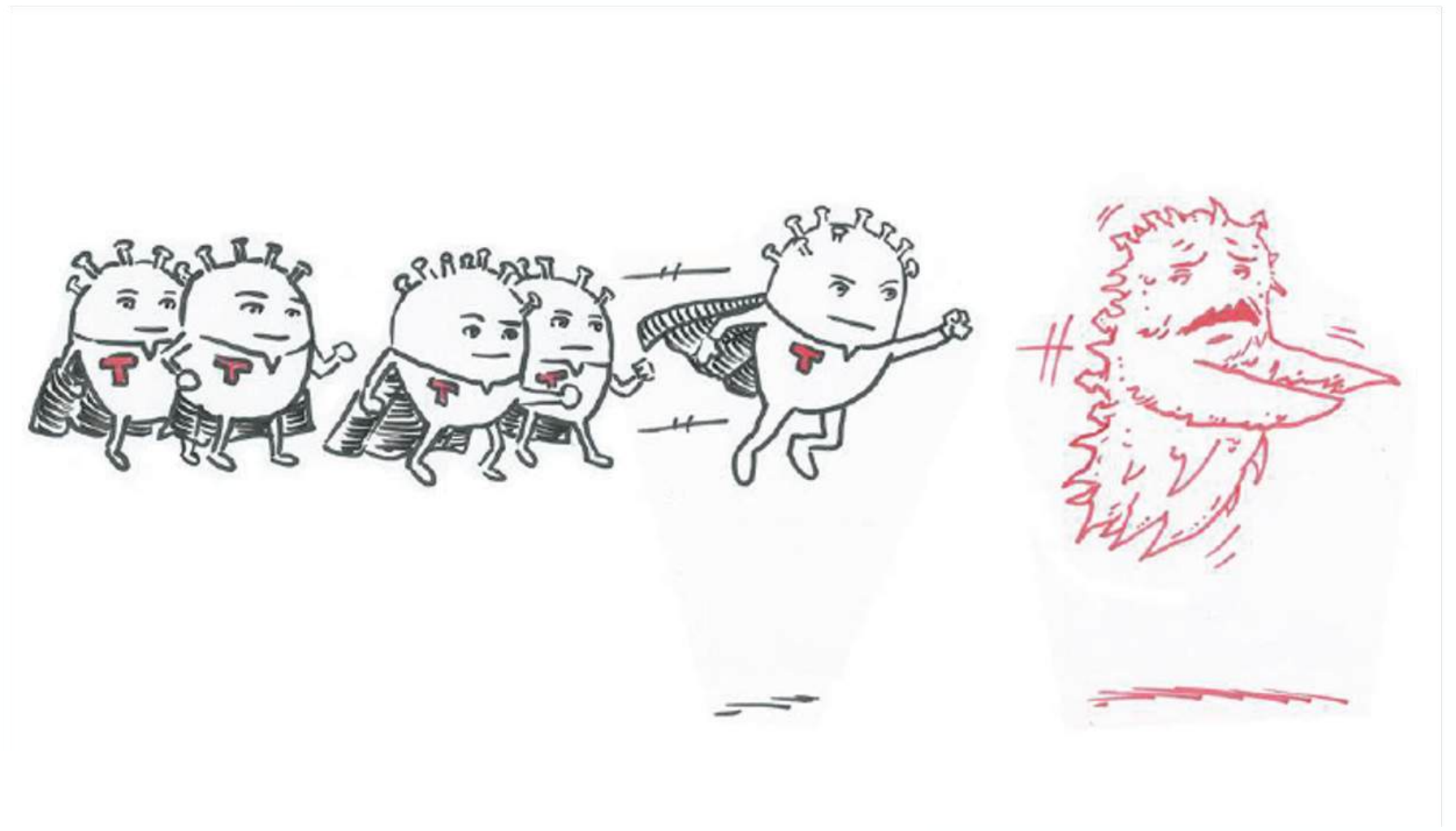
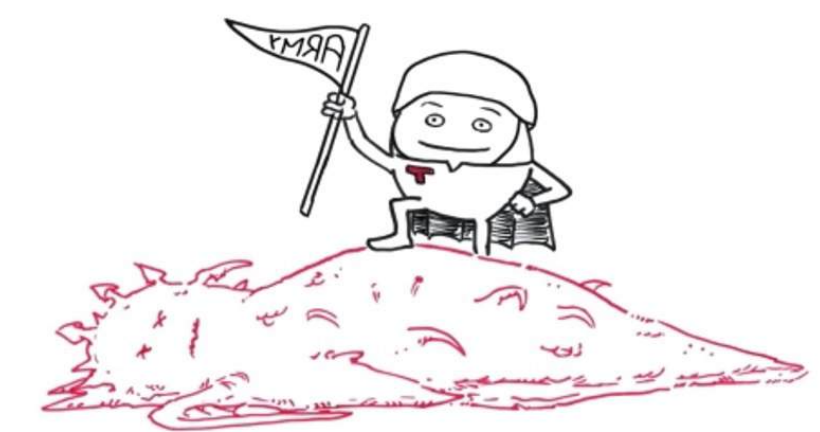
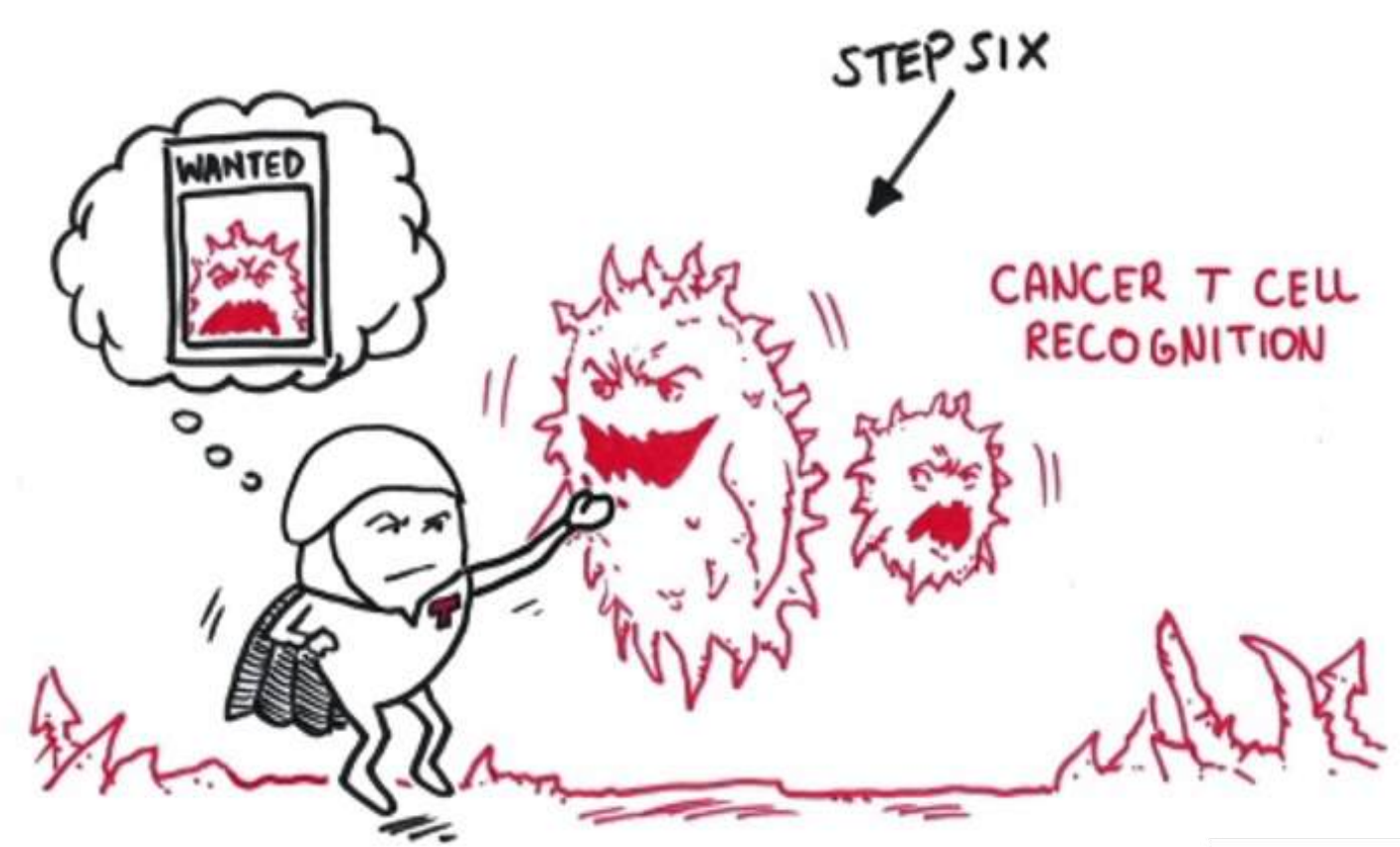


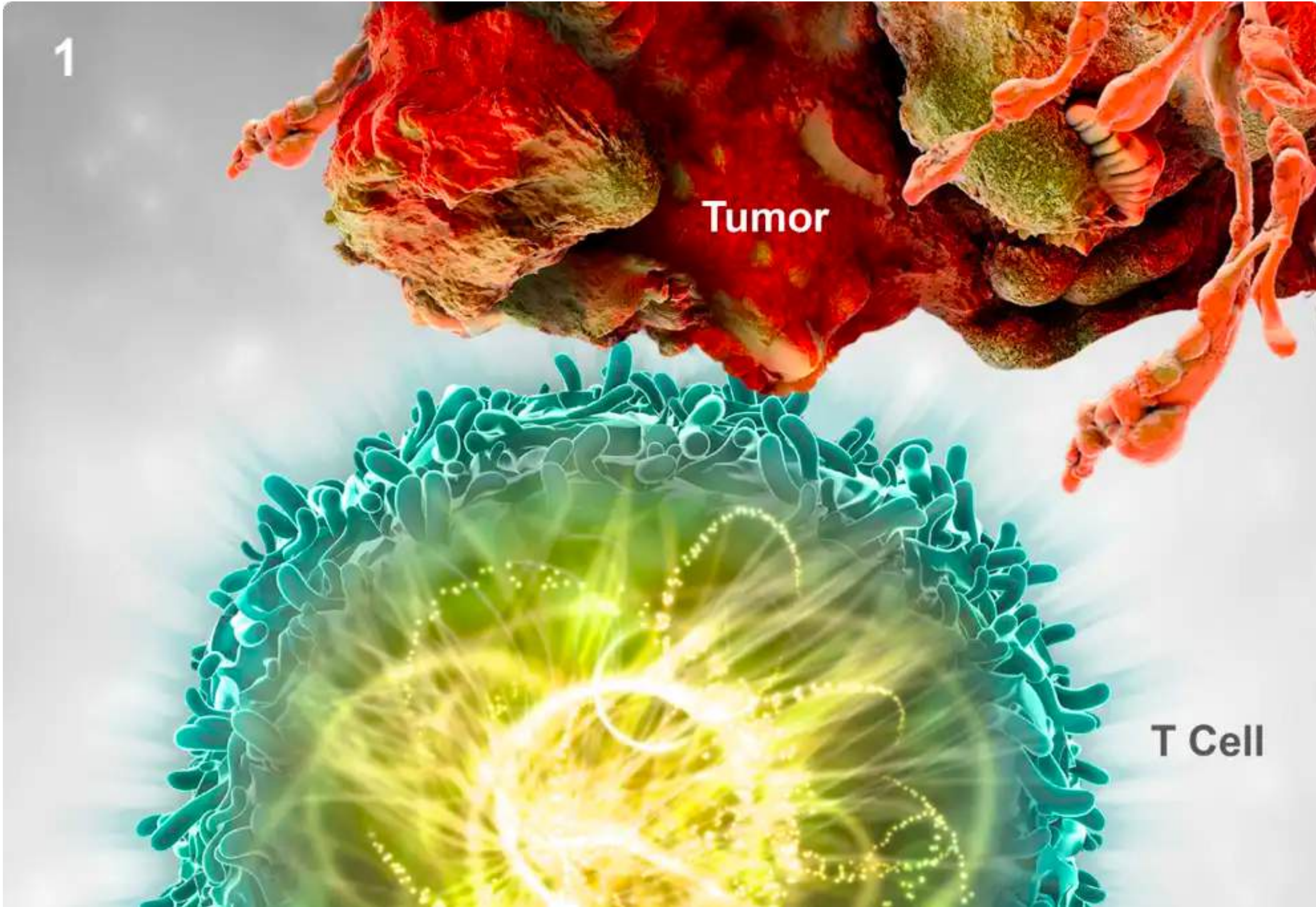


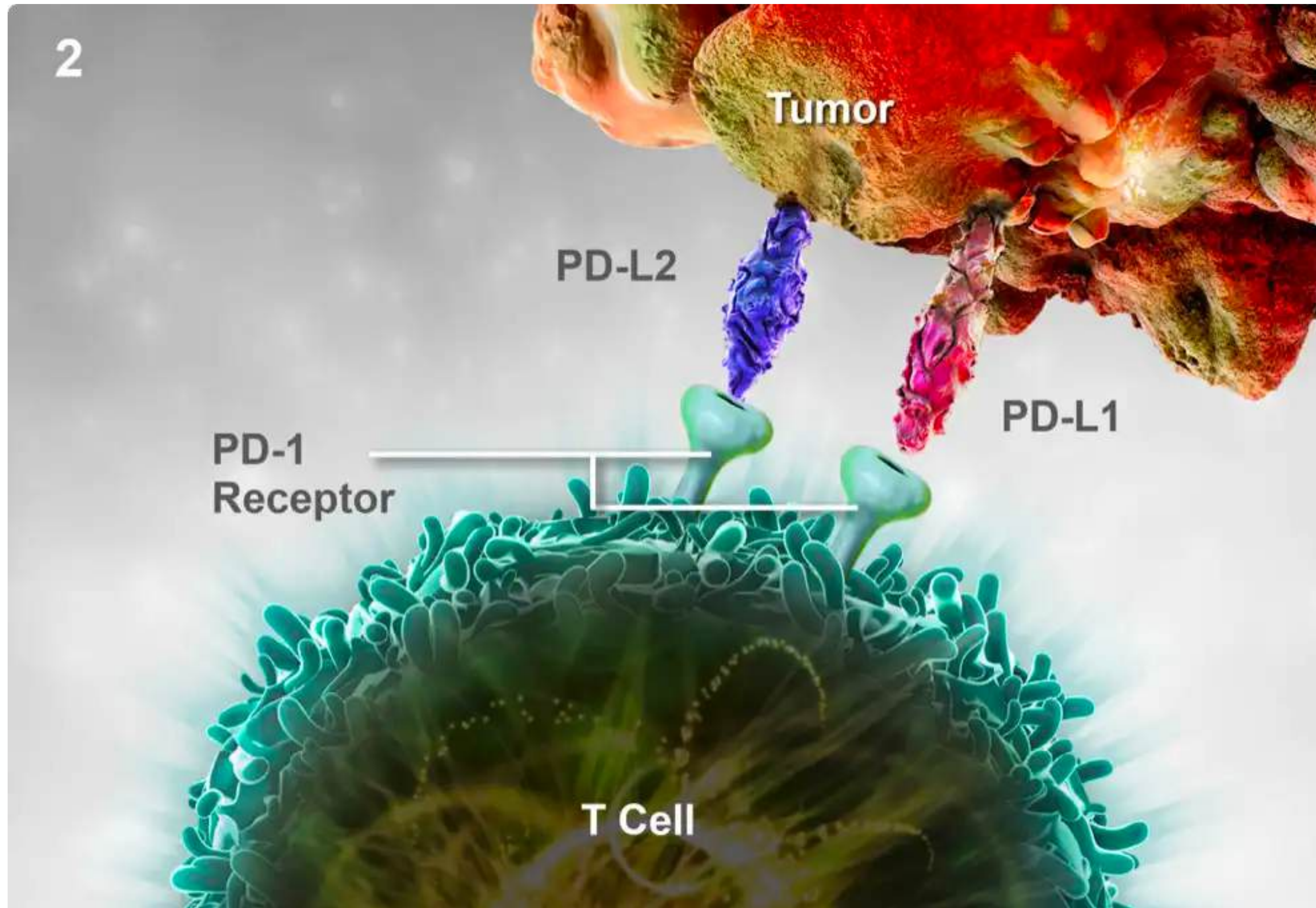
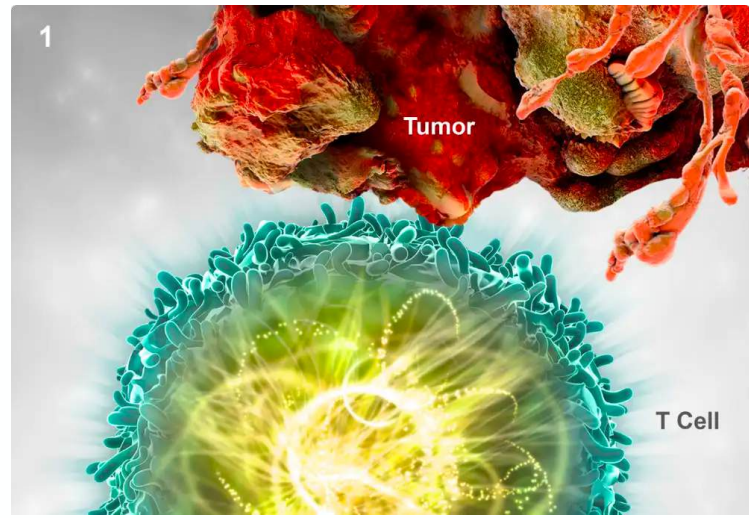


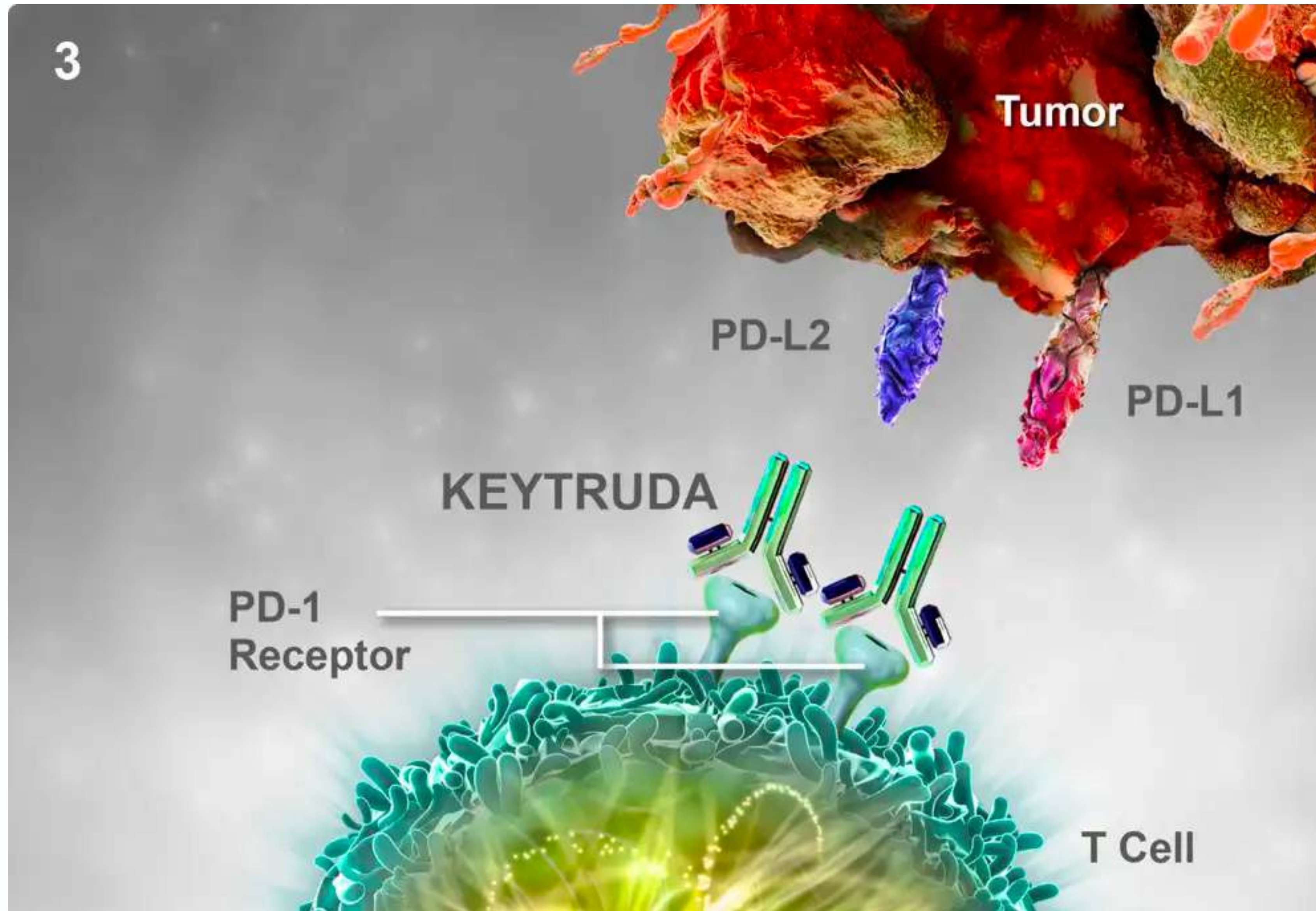
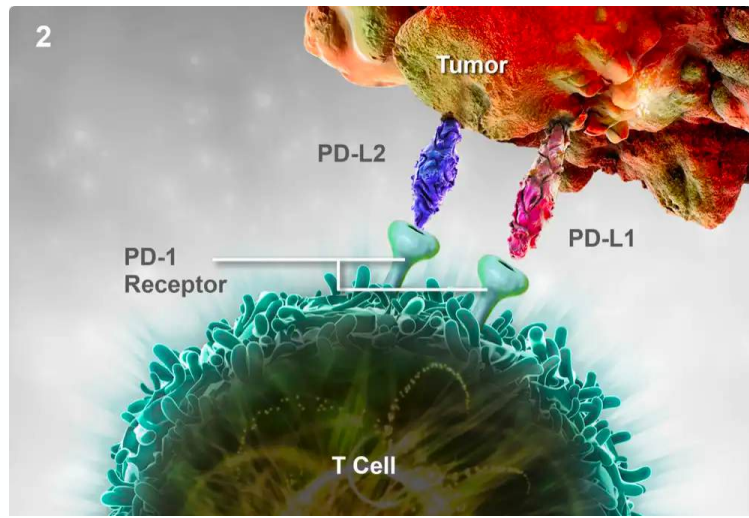
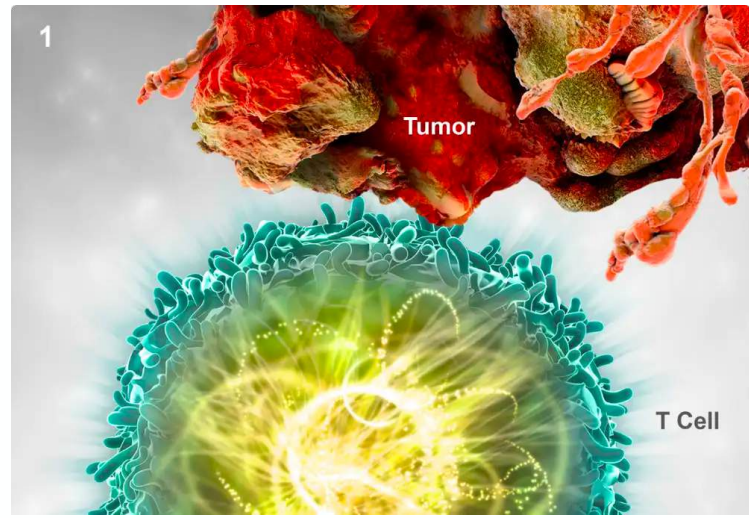


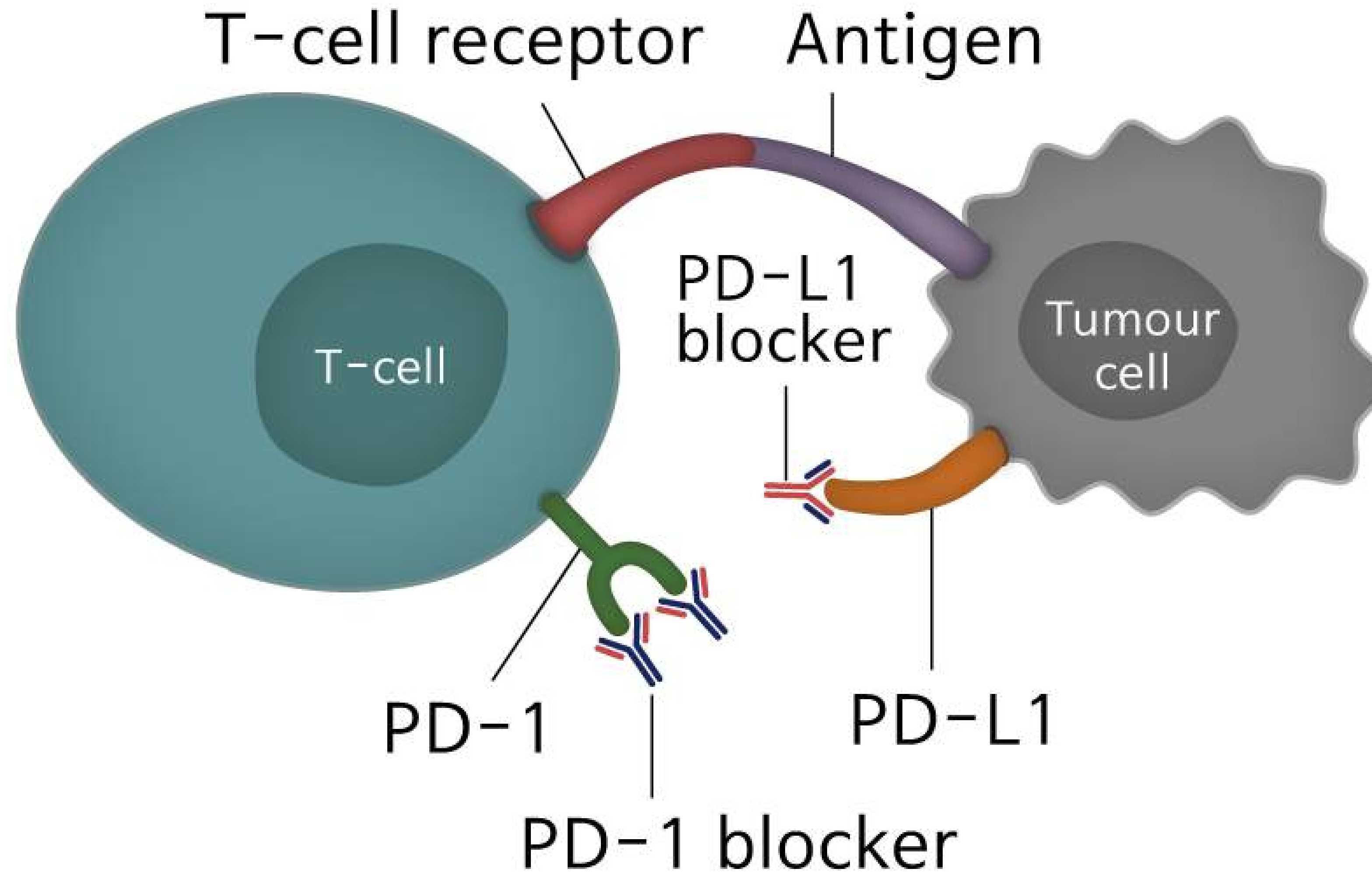












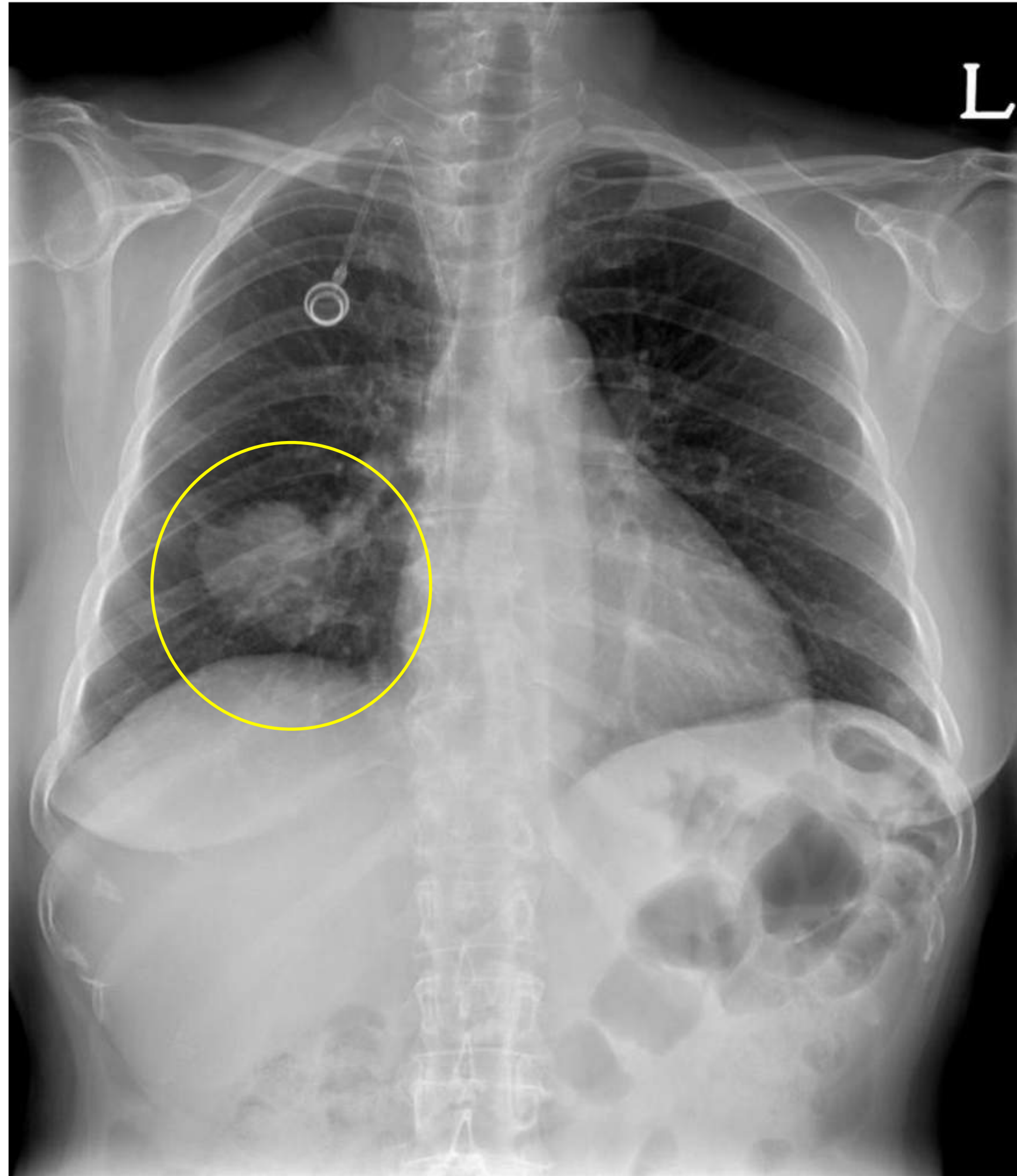
OPDIVO
 (nivolumab)
 INJECTION FOR INTRAVENOUS USE 10 mg/mL

KEYTRUDA
 (pembrolizumab) for Injection 50 mg

TECENTRIQ
 atezolizumab INJECTION FOR INTRAVENOUS USE 1200 mg

IMFINZI
 durvalumab
 Injection for Intravenous Use 50 mg/mL

Immunotherapy - 5 weeks Later



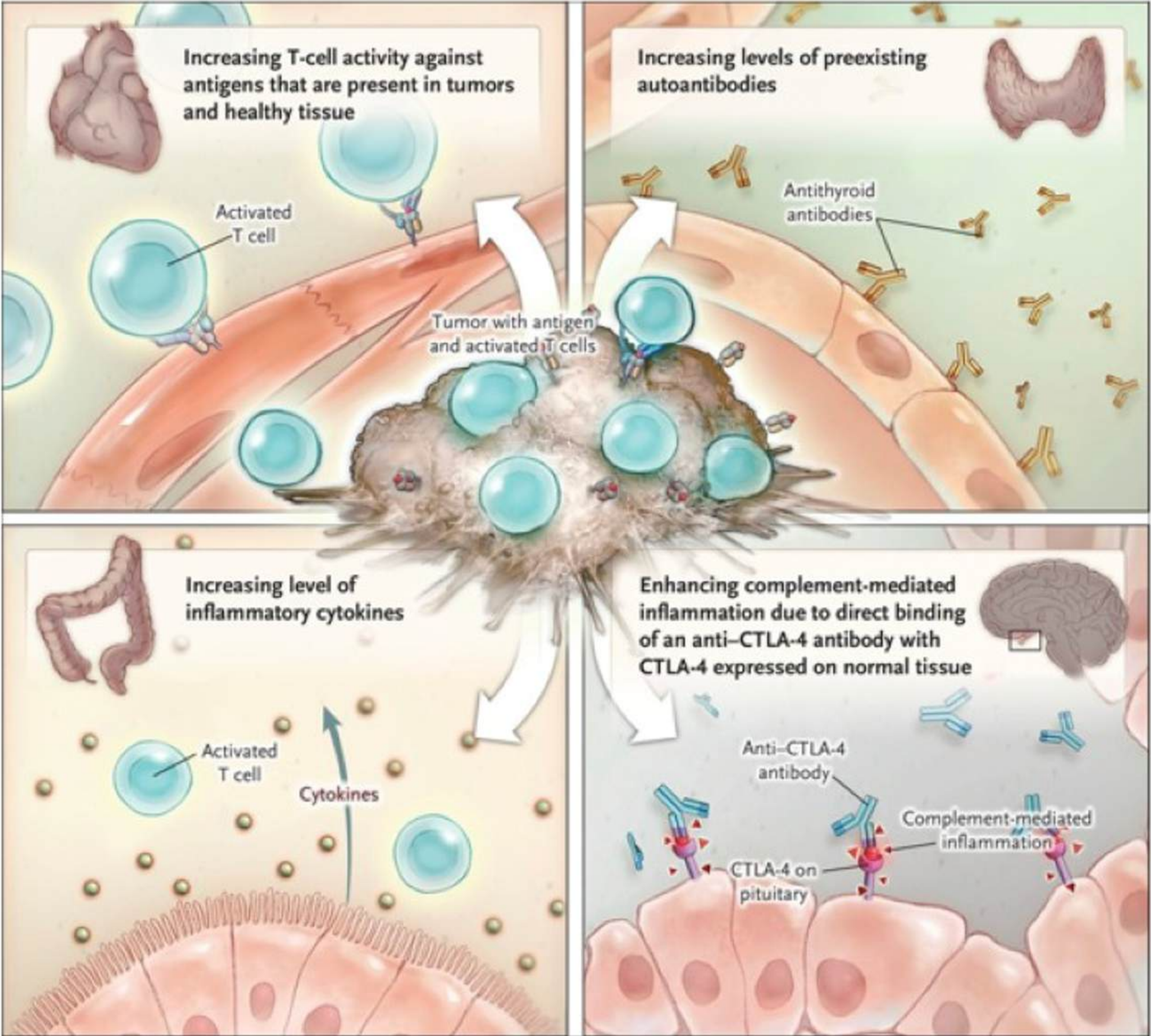
Immunotherapy Result in Inflammation

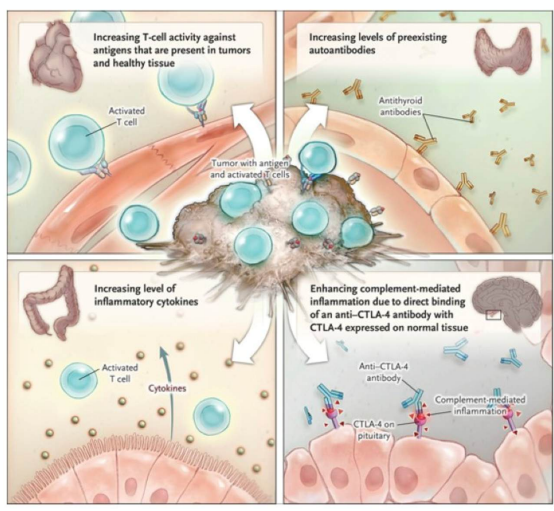
T cell Activity

Autoantibody

Cytokine

Direct Binding





Dermatologic

- Rash
- Pruritis
- Mucositis
- Xerostomia
- Vitiligo*
- Bullous pemphigoid
- Drug reaction with eosinophilia and systemic symptoms
- Steven-Johnson syndrome
- Acute generalized exanthematous pustulosis
- Dermatomyositis

Pulmonary

- Pneumonitis
- Sarcoidosis
- Pleural effusion
- Reactive airway disease

Cardiovascular

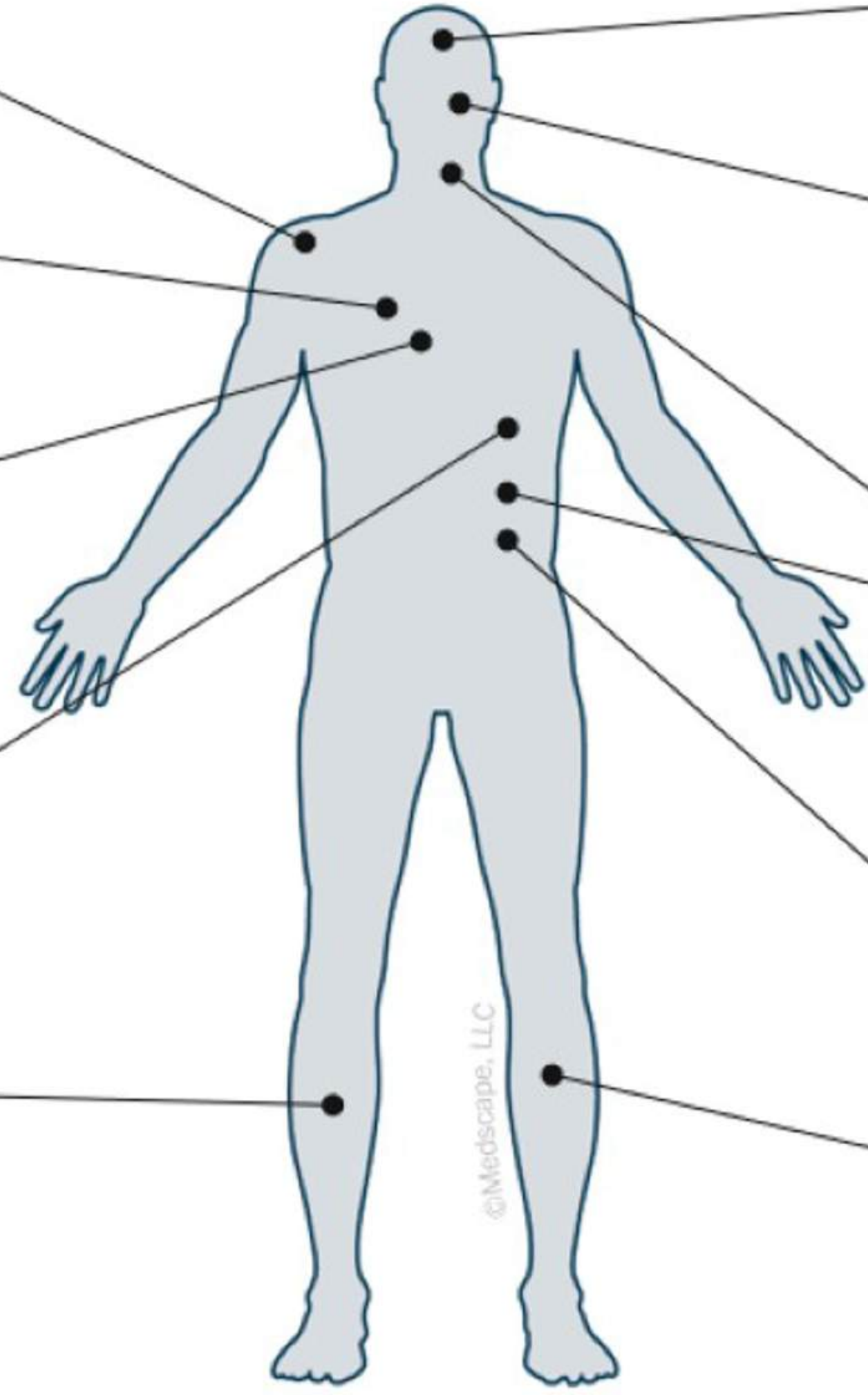
- Myocarditis
- Pericarditis
- Arrhythmia
- Heart failure
- Accelerated atherosclerosis

Gastrointestinal

- Diarrhea
- Colitis
- Hepatitis
- Gastritis
- Enteritis
- Pancreatitis

Marrow

- Thrombocytopenia
- Hemolytic anemia
- Neutropenia
- Aplastic anemia
- Pure red cell aplasia
- Hemophagocytic lymphohistiocytosis



Neurotoxicity

- Encephalitis
- Aseptic meningitis
- Posterior reversible Encephalopathy syndrome
- Demyelinating diseases
- Cranial nerve syndromes
- Polyneuropathies
- Sensory/ small fiber/ autonomic neuropathies
- Guillain-Barre syndrome
- Not otherwise specified (ataxia, movement disorders)



Ocular

- Uveitis
- Scleritis
- Retinitis
- Conjunctivitis
- Keratoconjunctivitis sicca
- Blepharitis



Endocrine

- Hypothyroidism
- Hyperthyroidism
- Hypophysitis
- Hypoparathyroidism
- Type 1 diabetes
- Adrenal insufficiency



Renal

- Nephritis



Musculoskeletal

- Arthralgias
- Myalgias
- Arthritis
- Myositis
- Vasculitis

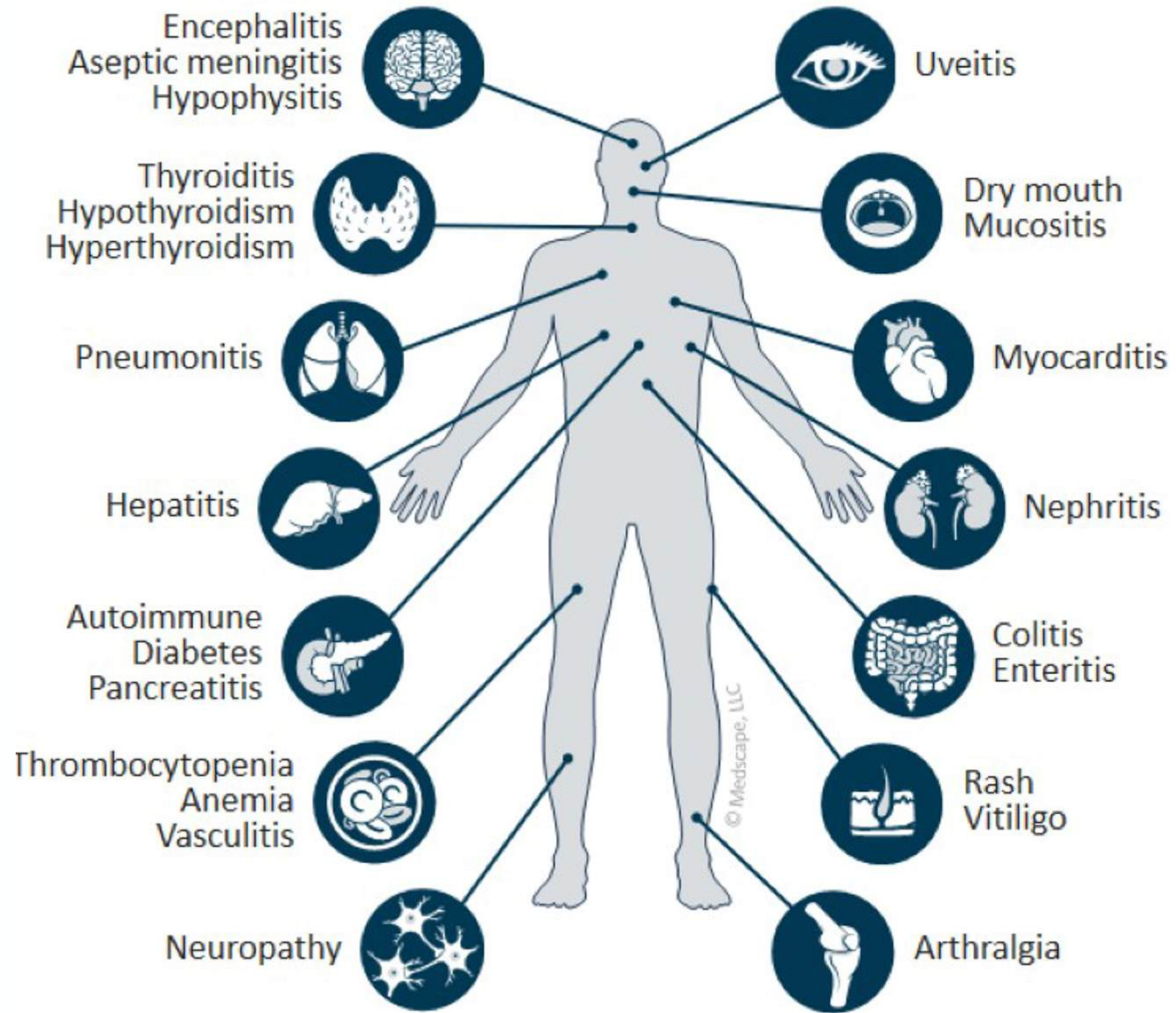
- ≥ 10% incidence
- ≥ 1 and < 10% incidence
- < 10% incidence

* ≥ 10% in melanoma

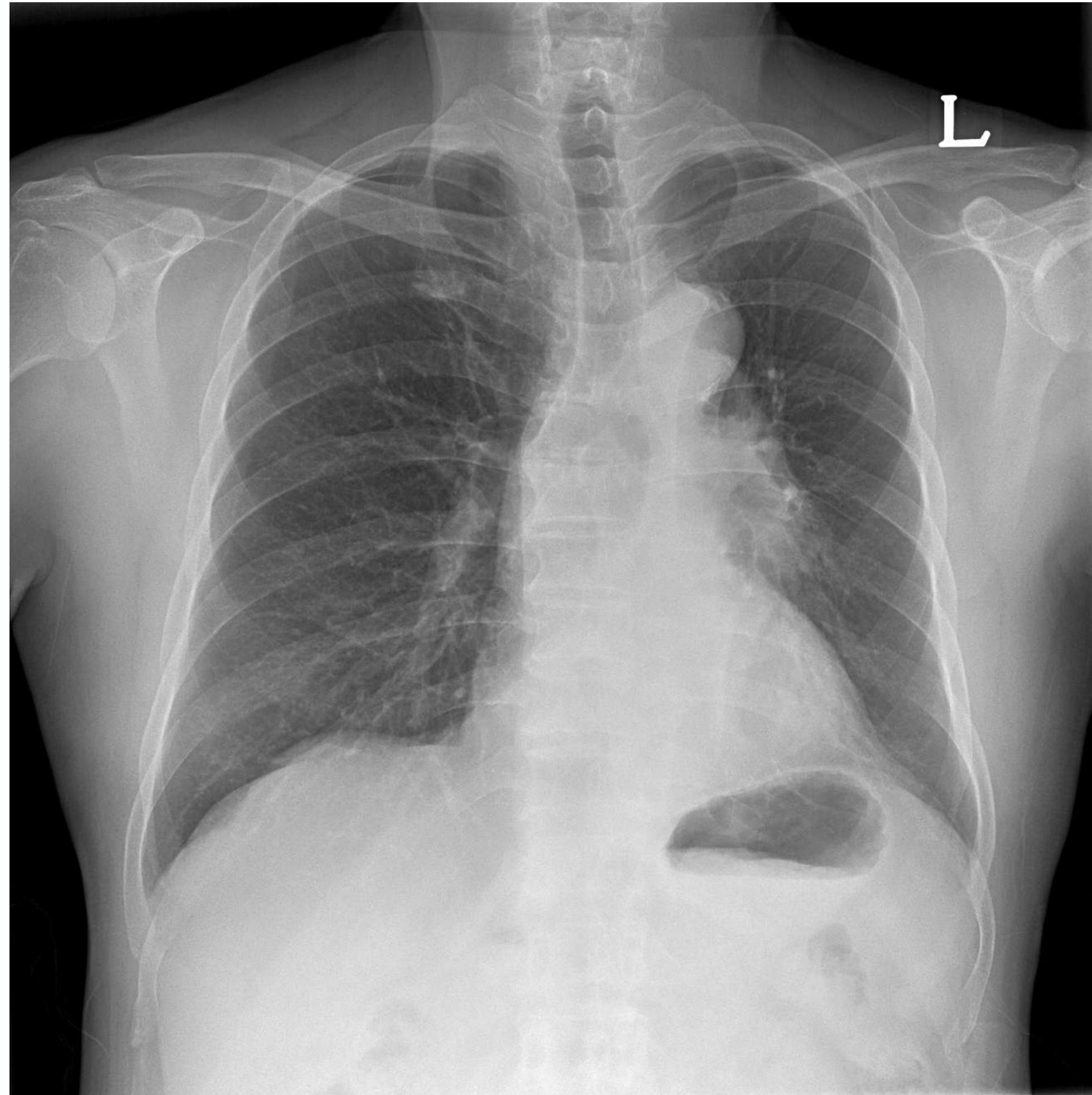
Immune checkpoint inhibitors

- Ipilimumab
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab
- Durvalumab
- Cemiplimab
- Dostarlimab

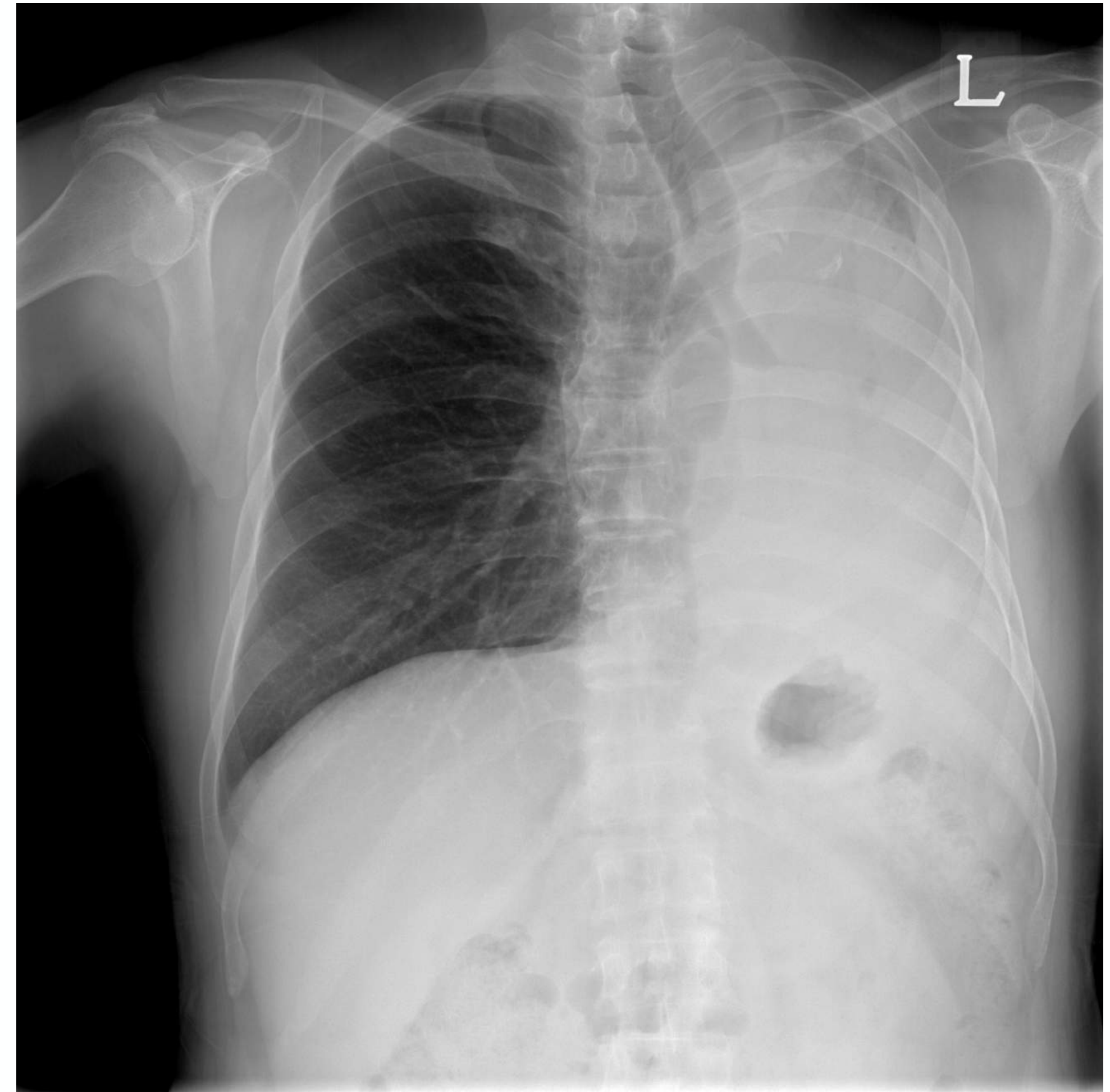
irAE, immune-related adverse event.
Darnell EP, et al. Curr Oncol Rep. 2020;22:3.9.



Immunotherapy - Hyperprogression

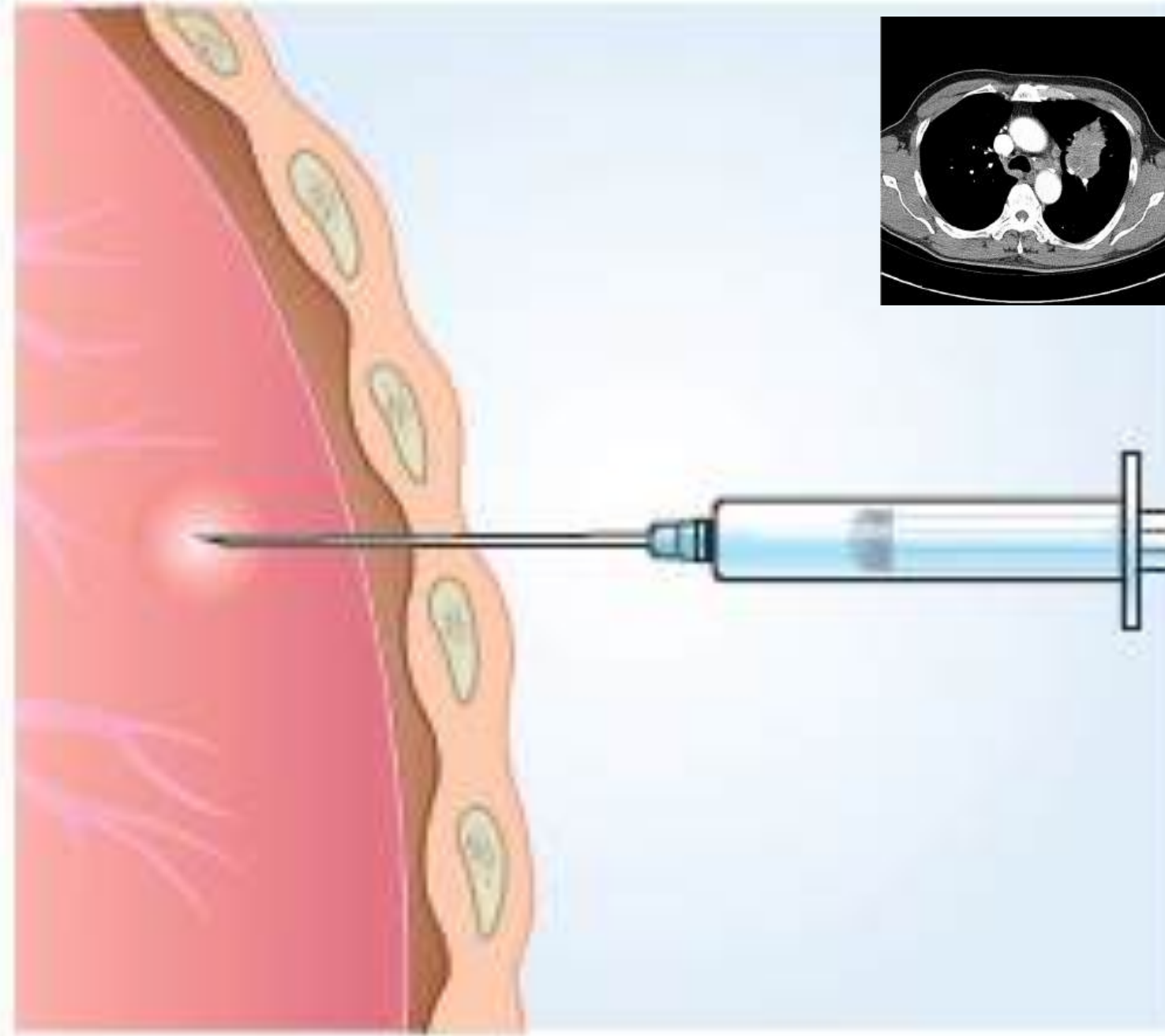



3 weeks

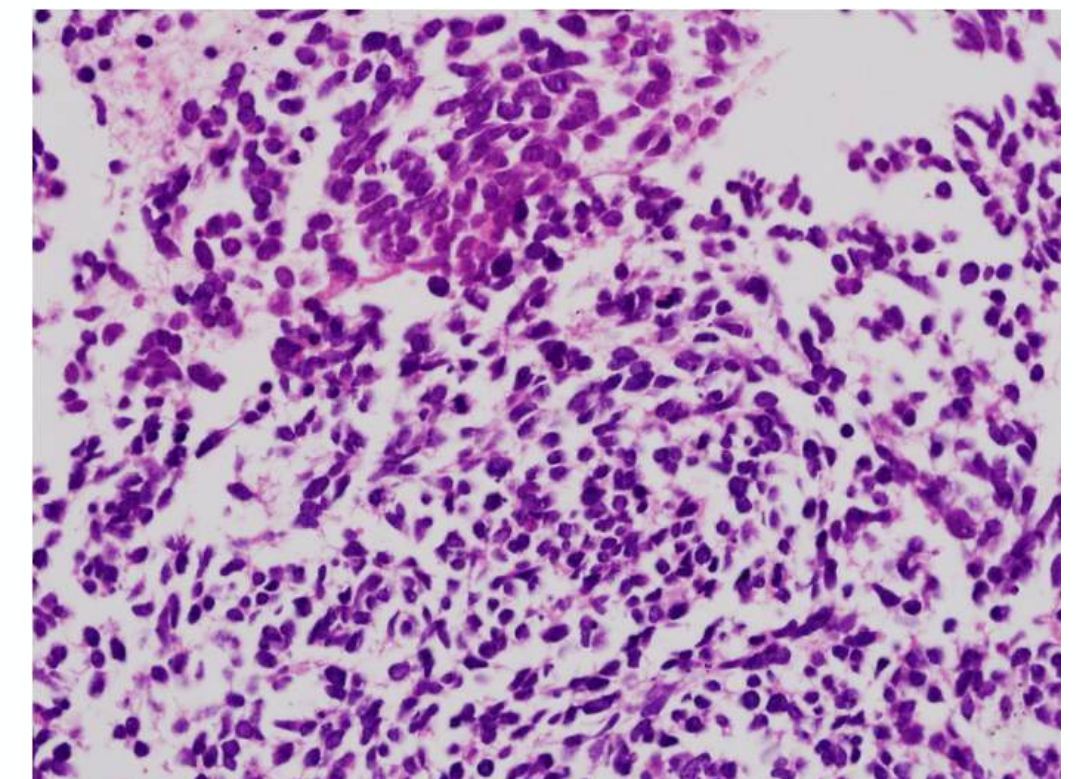
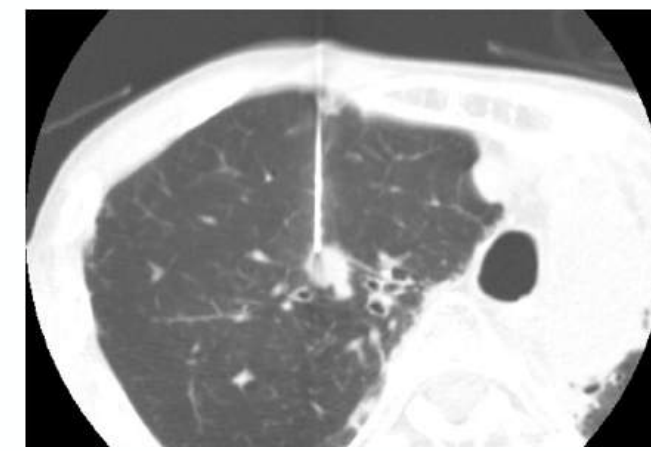
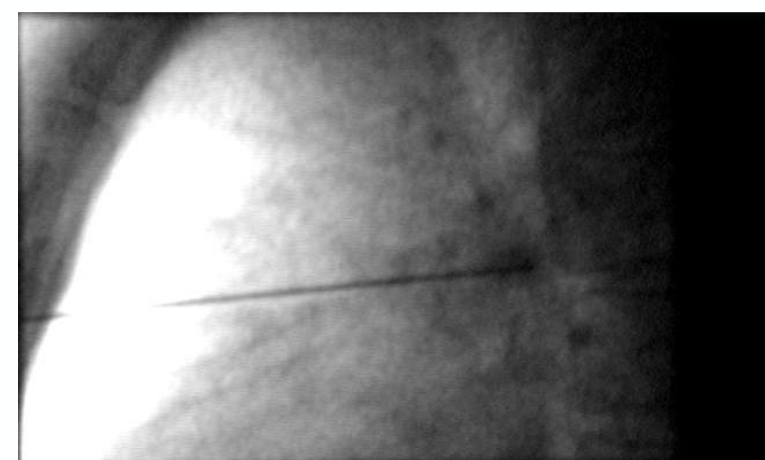
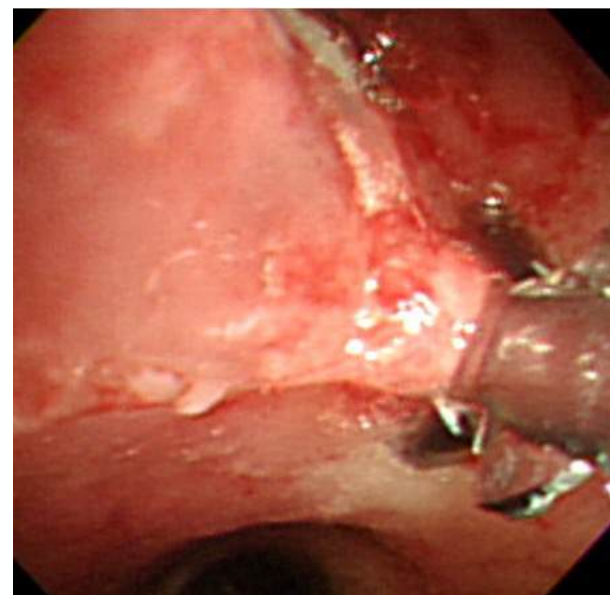
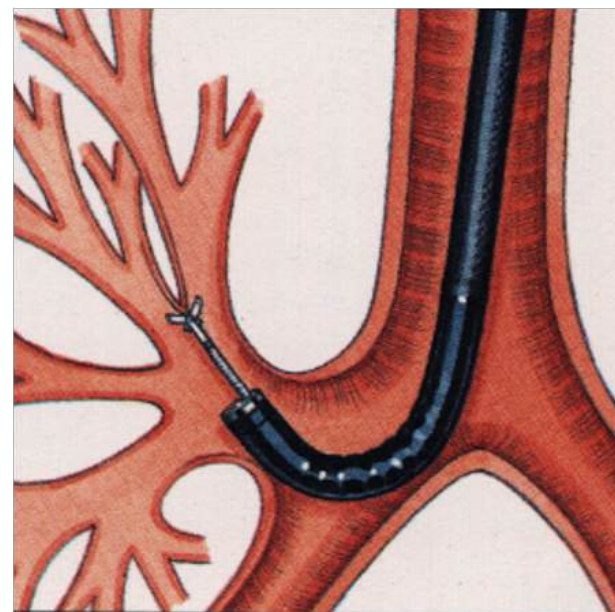
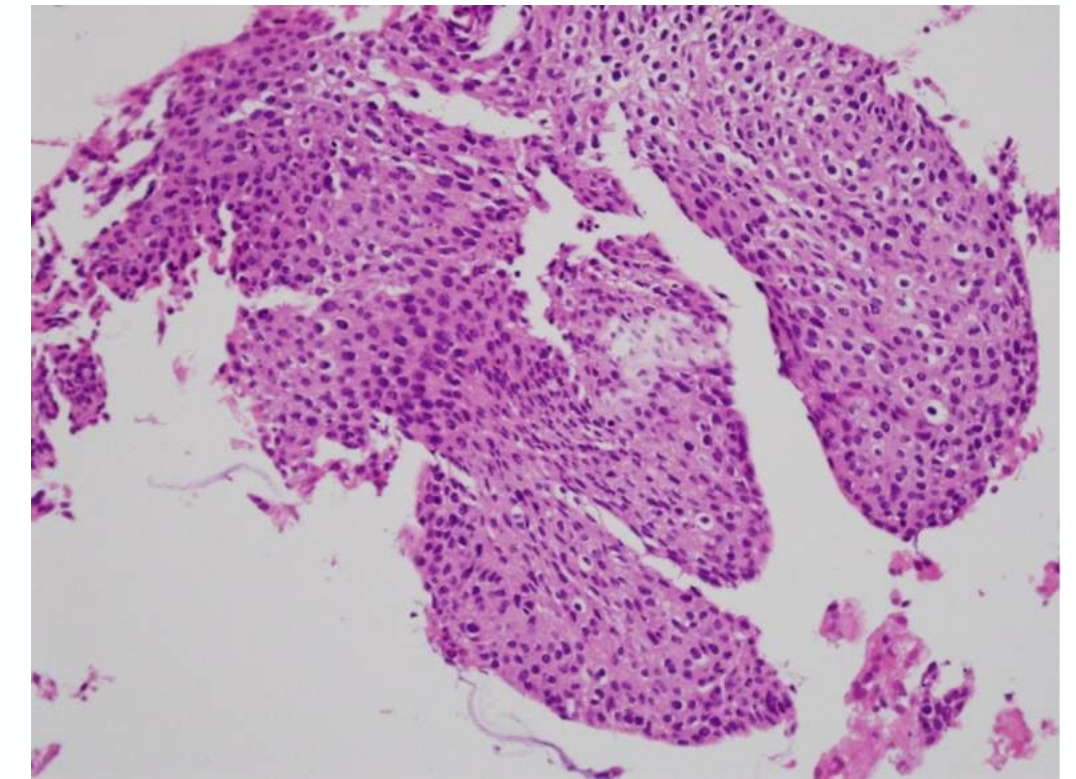
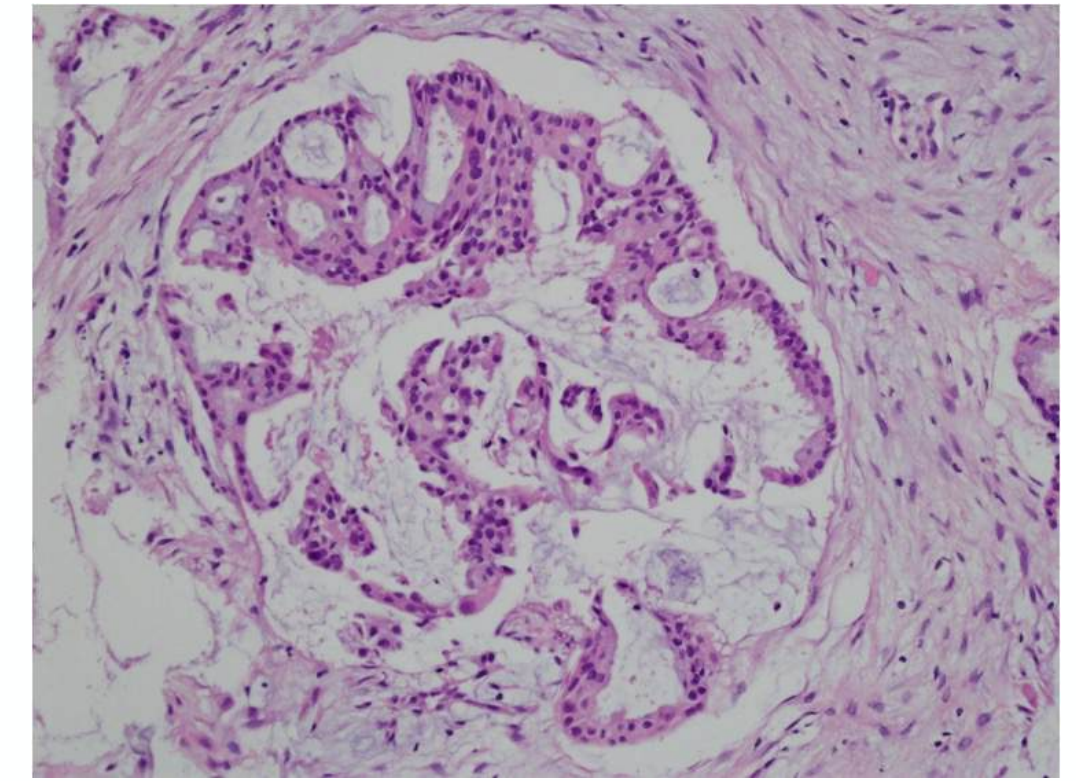




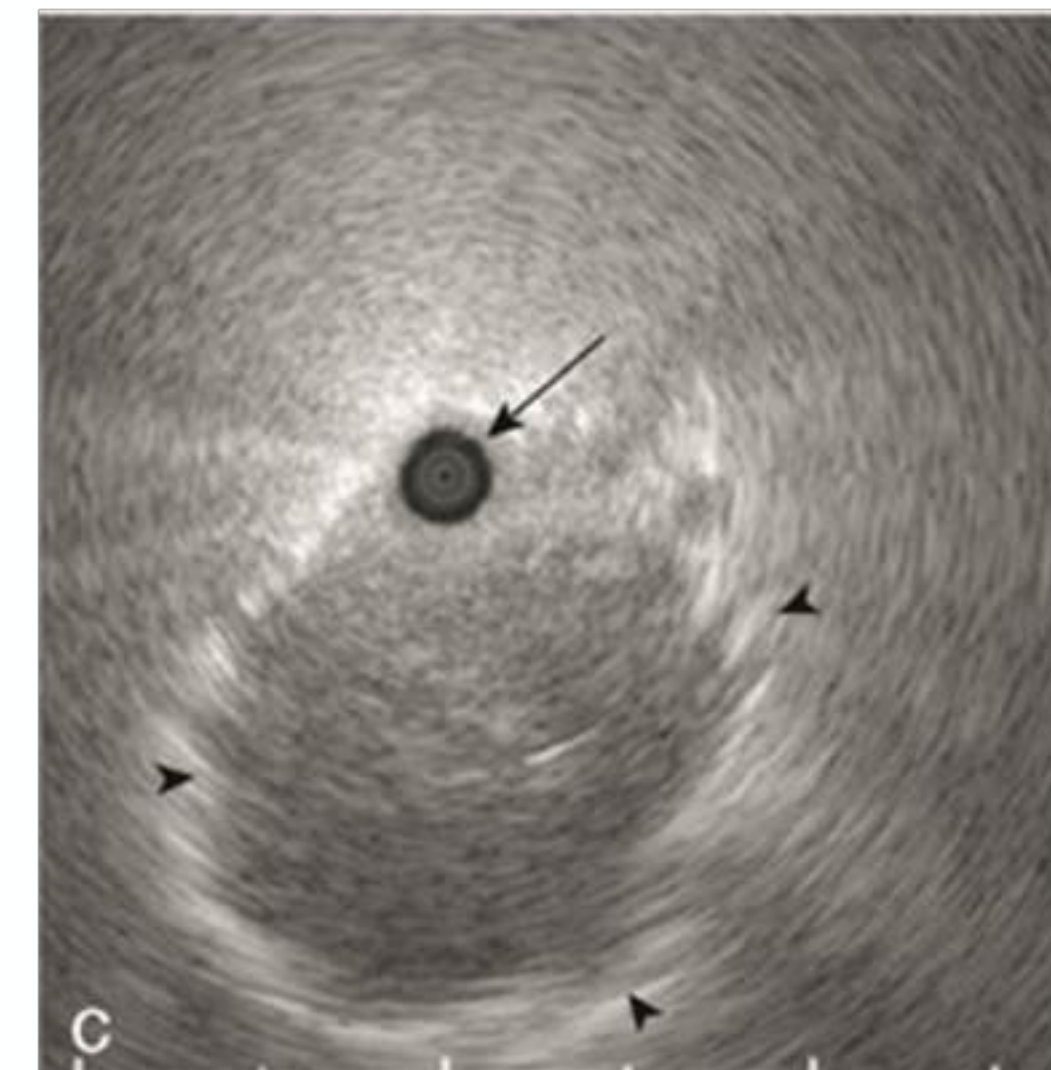
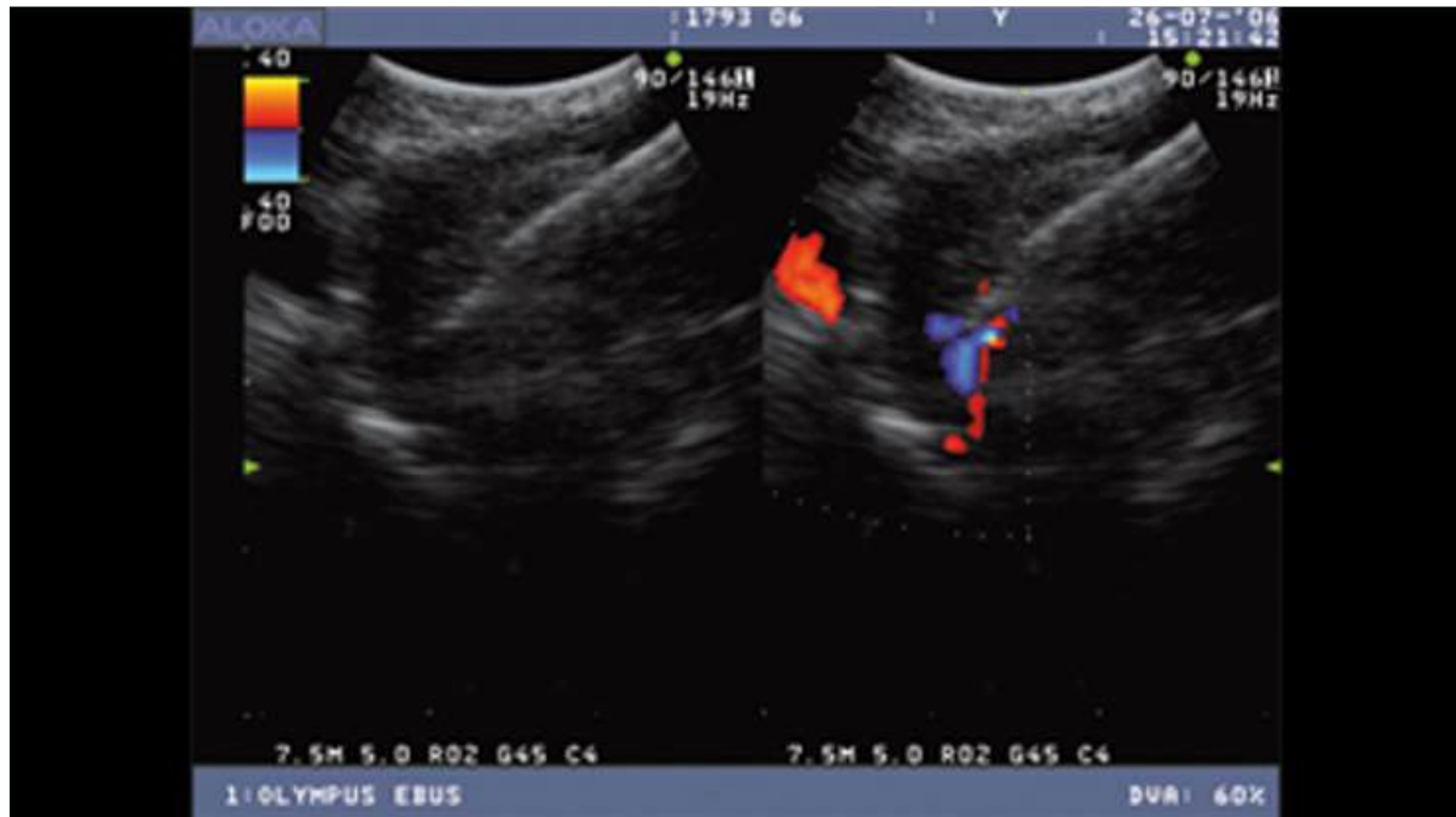
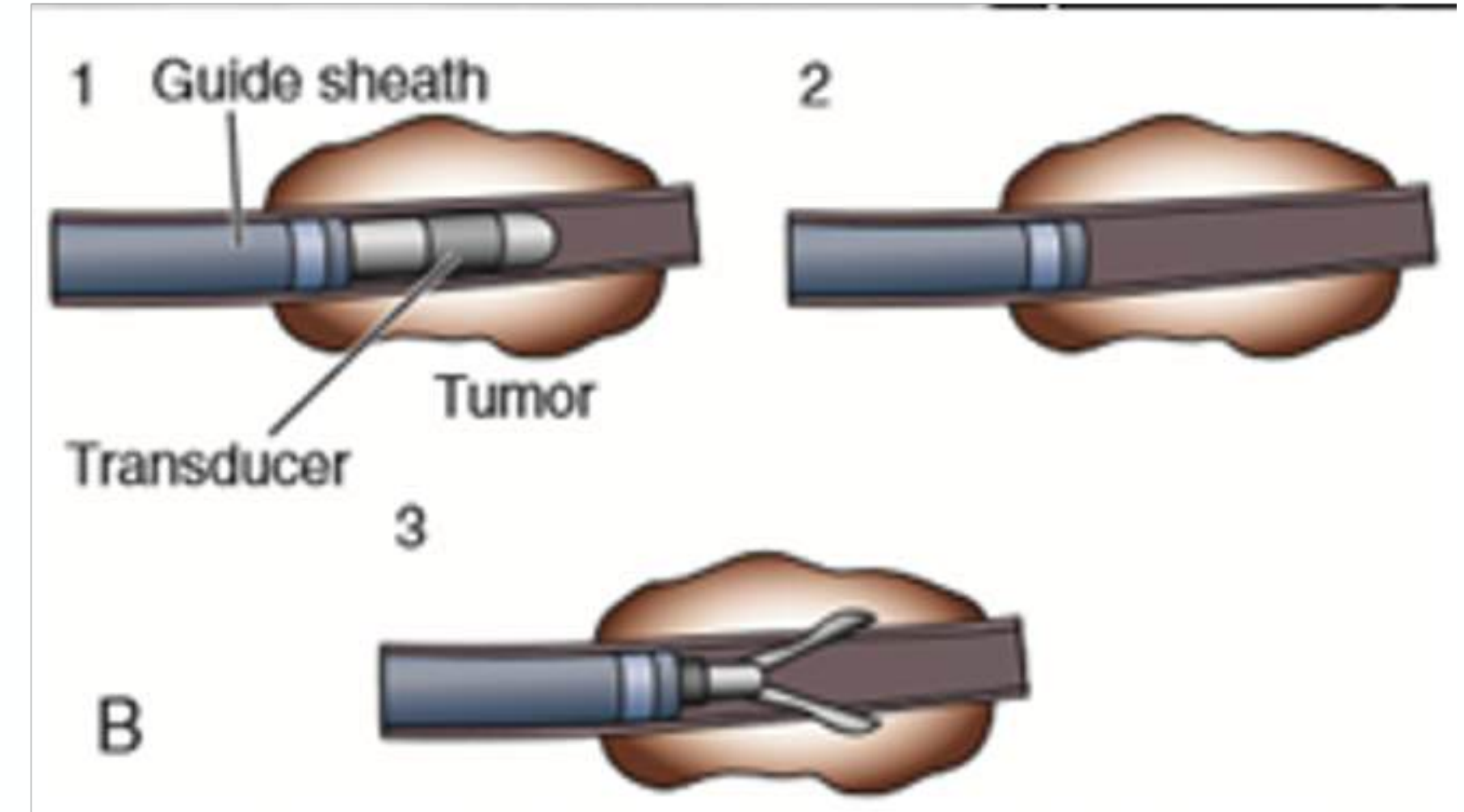
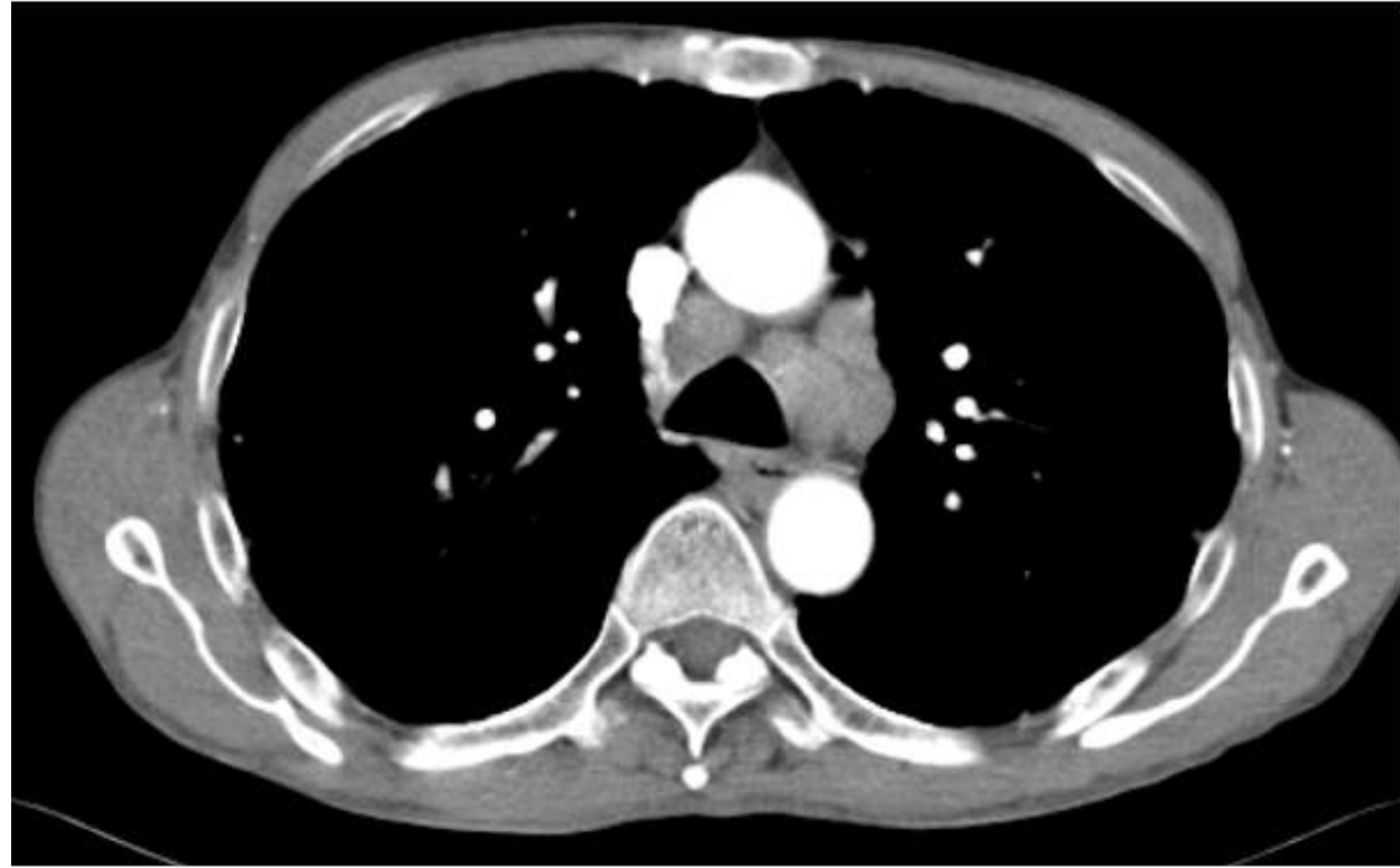
기관지내시경검사



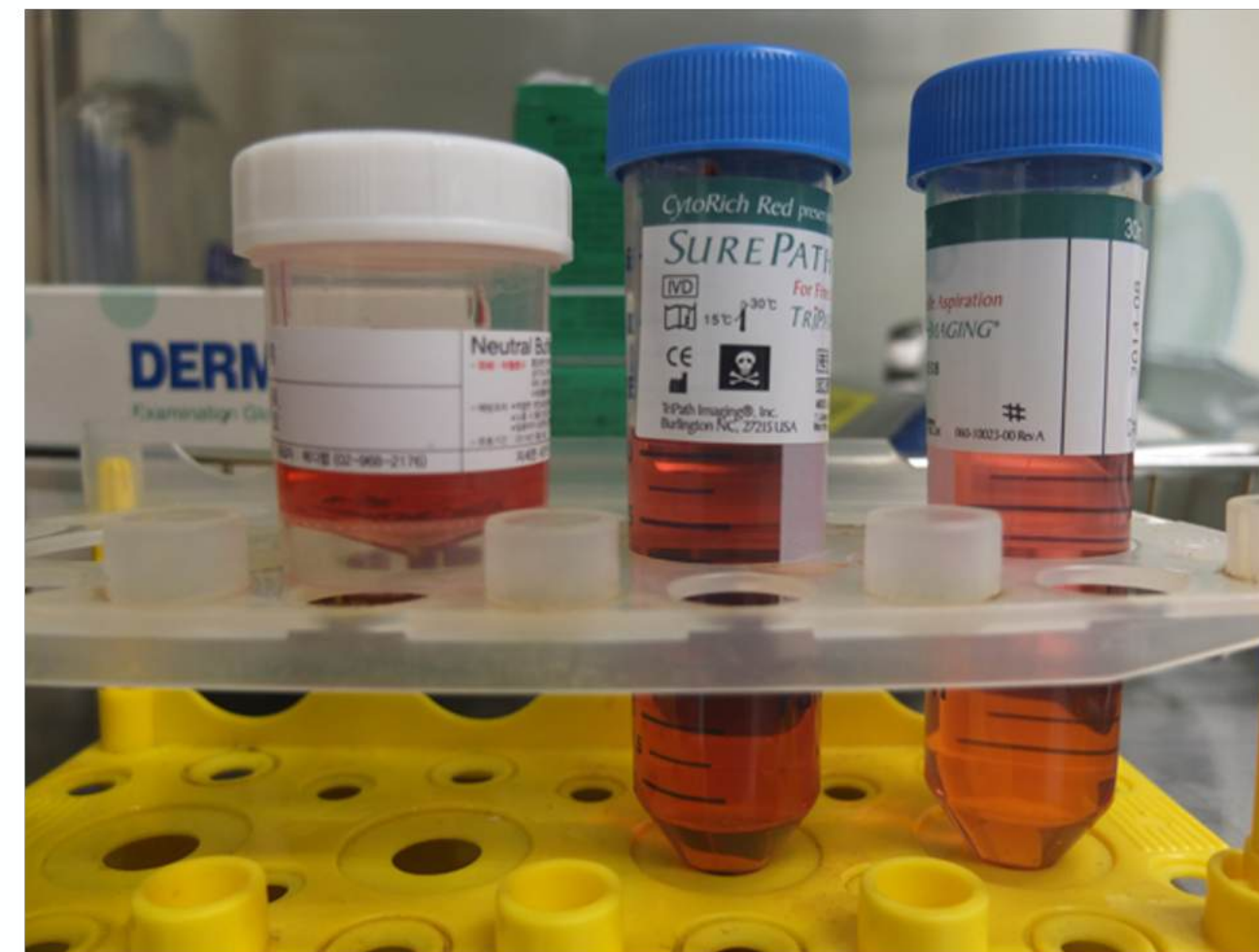
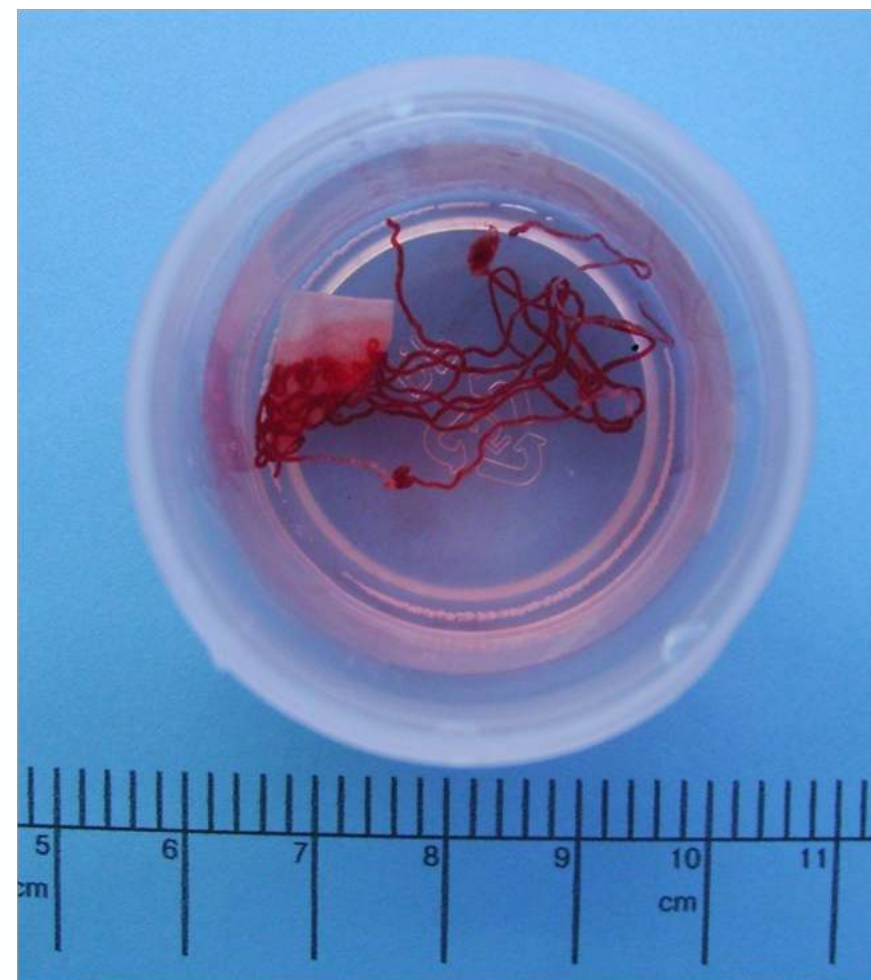
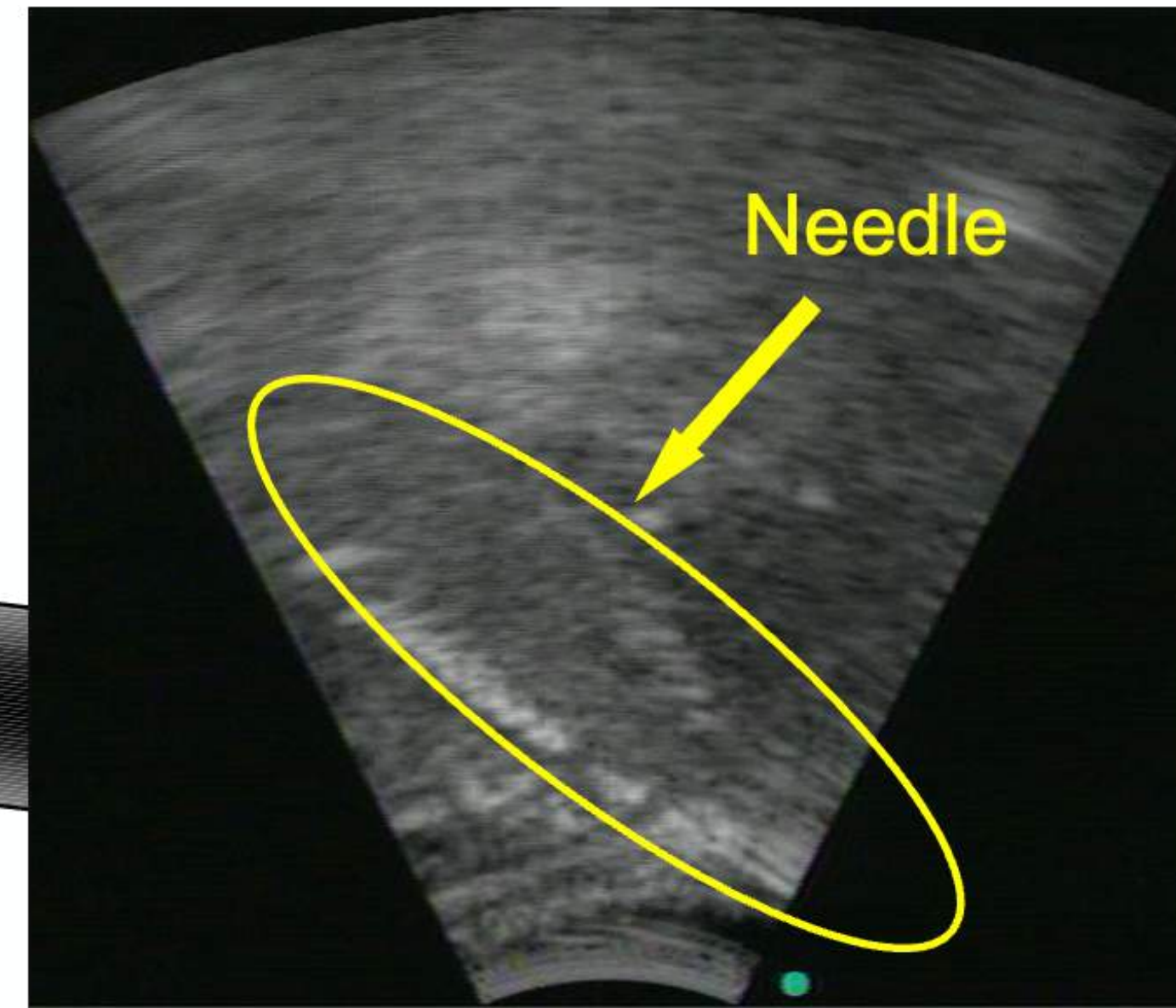
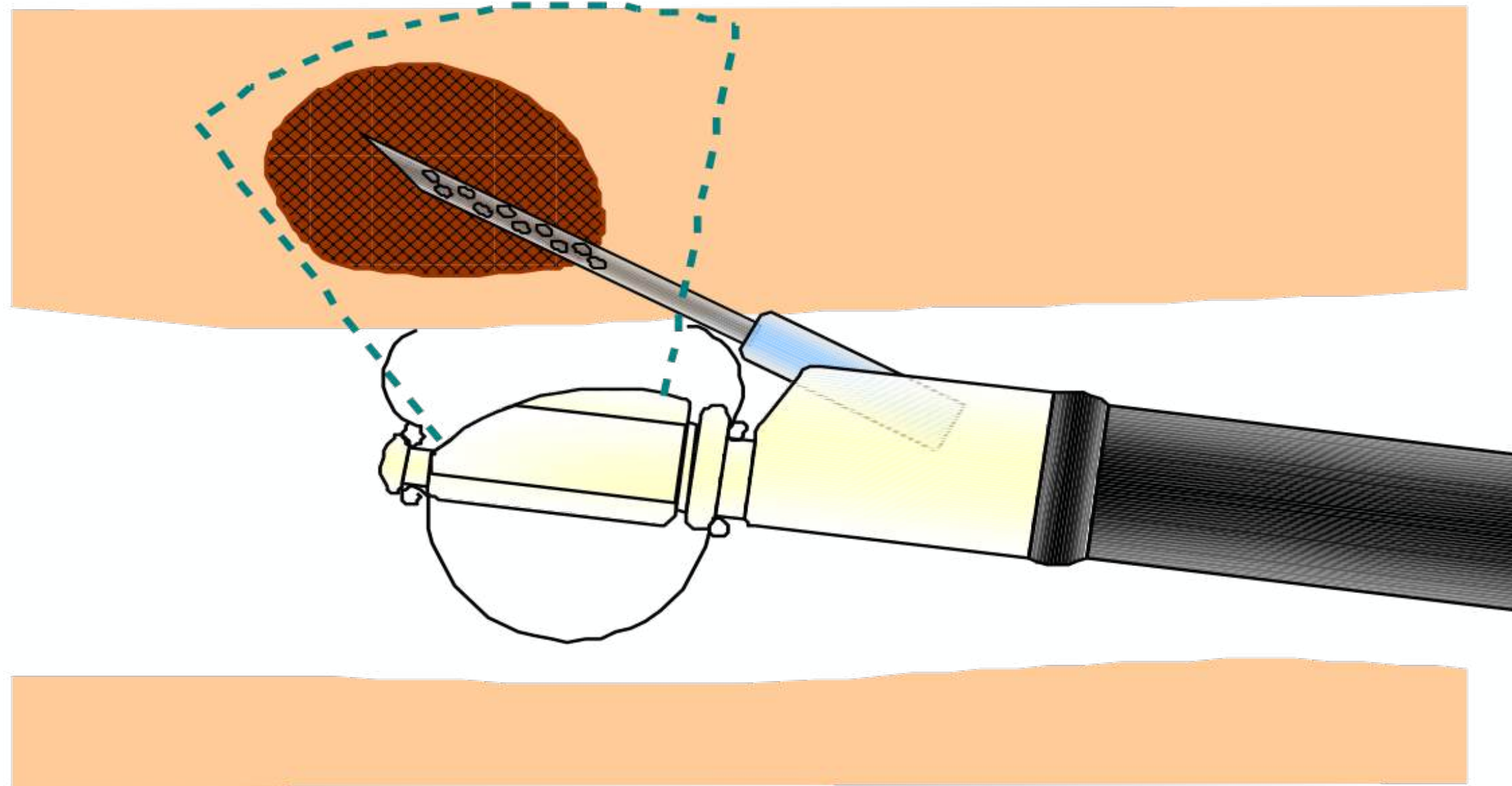
경피 바늘 조직검사

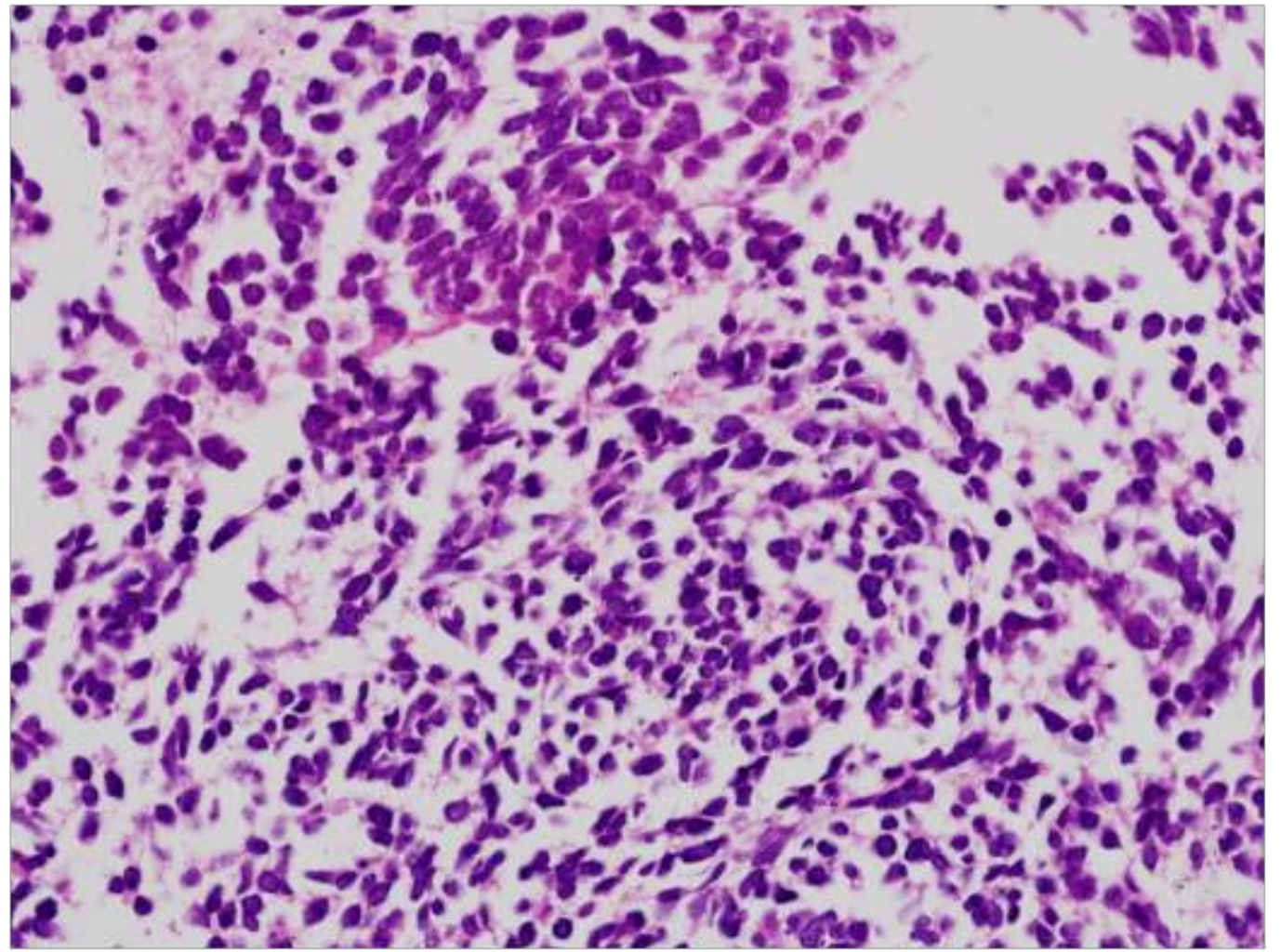
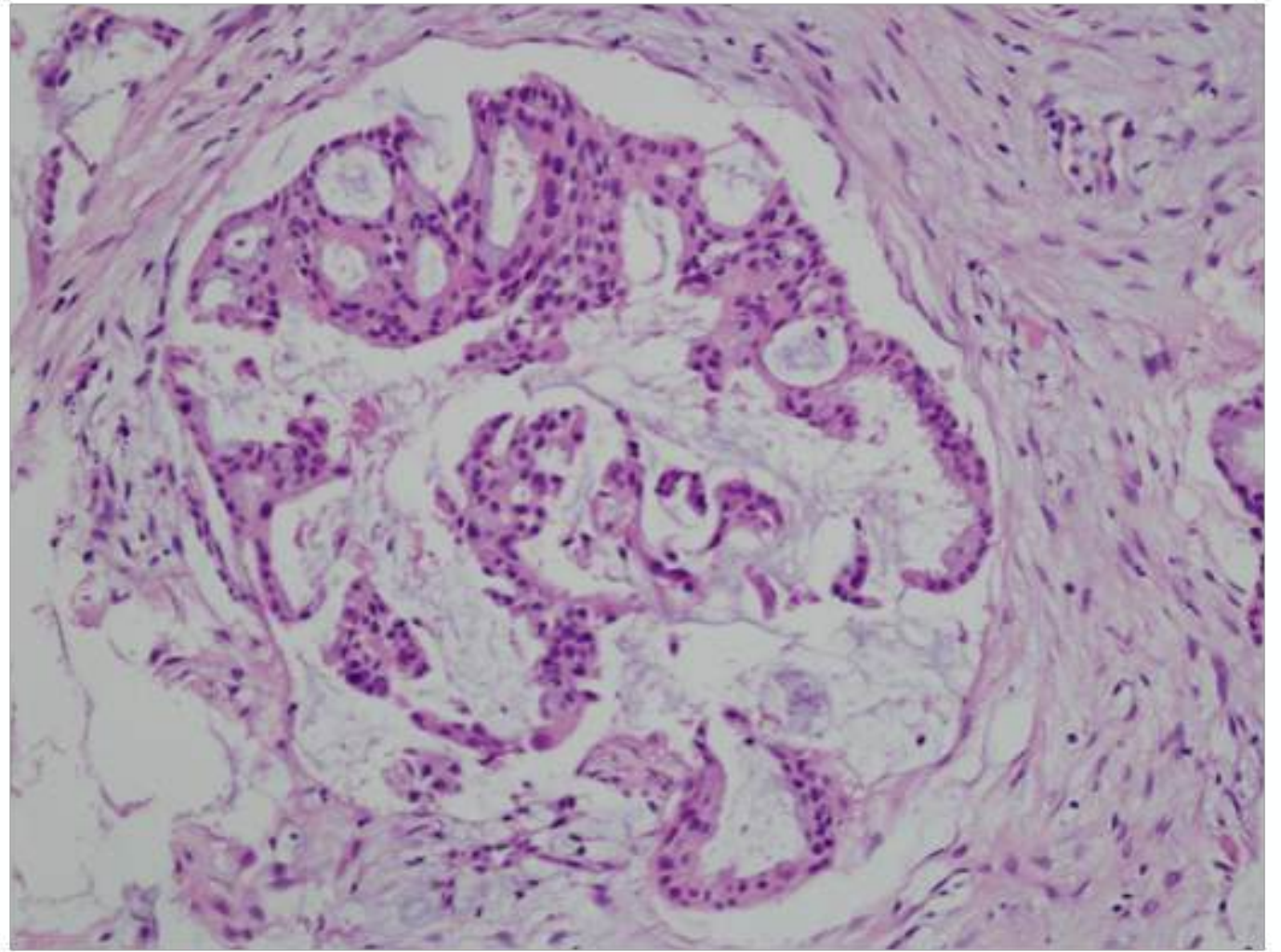
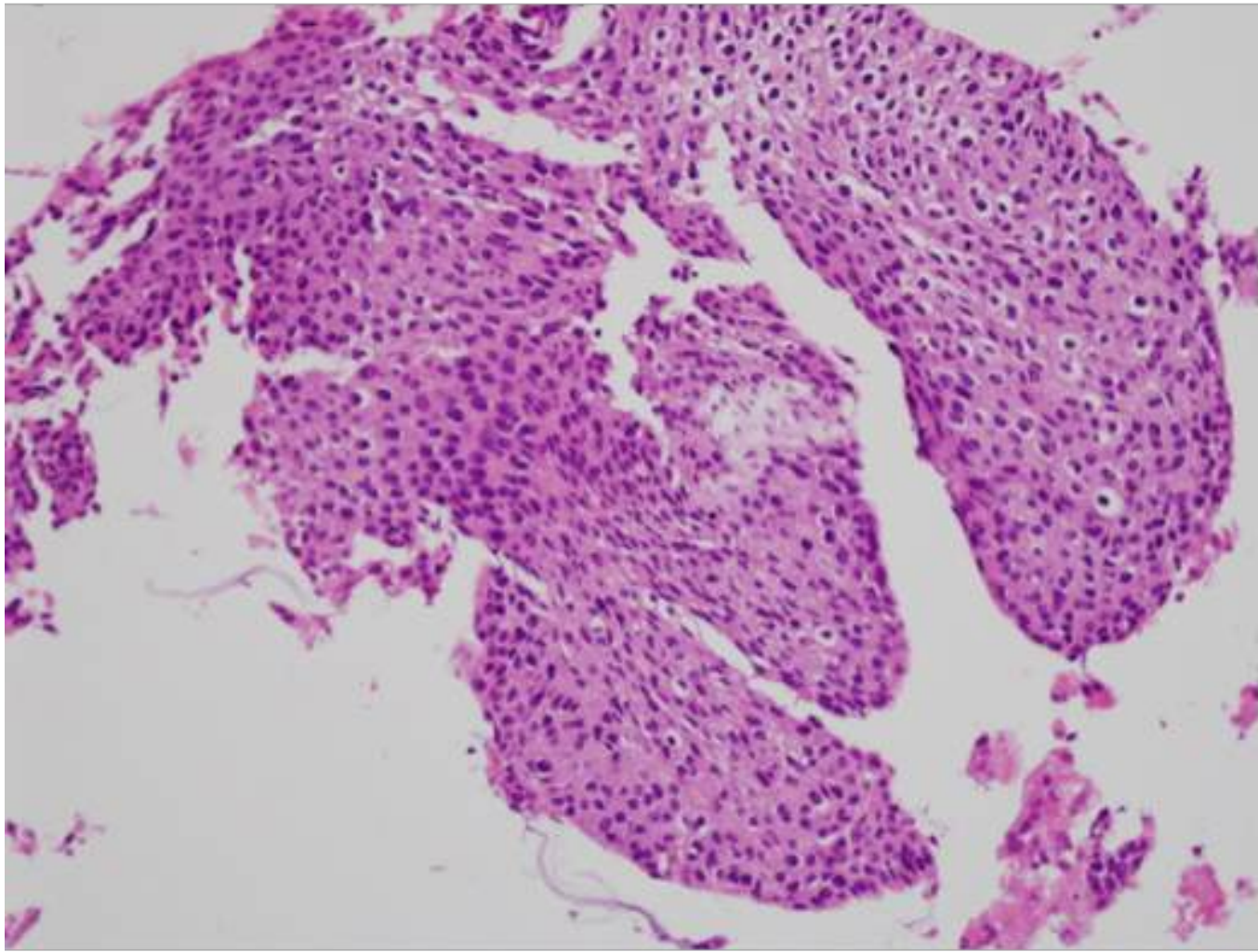
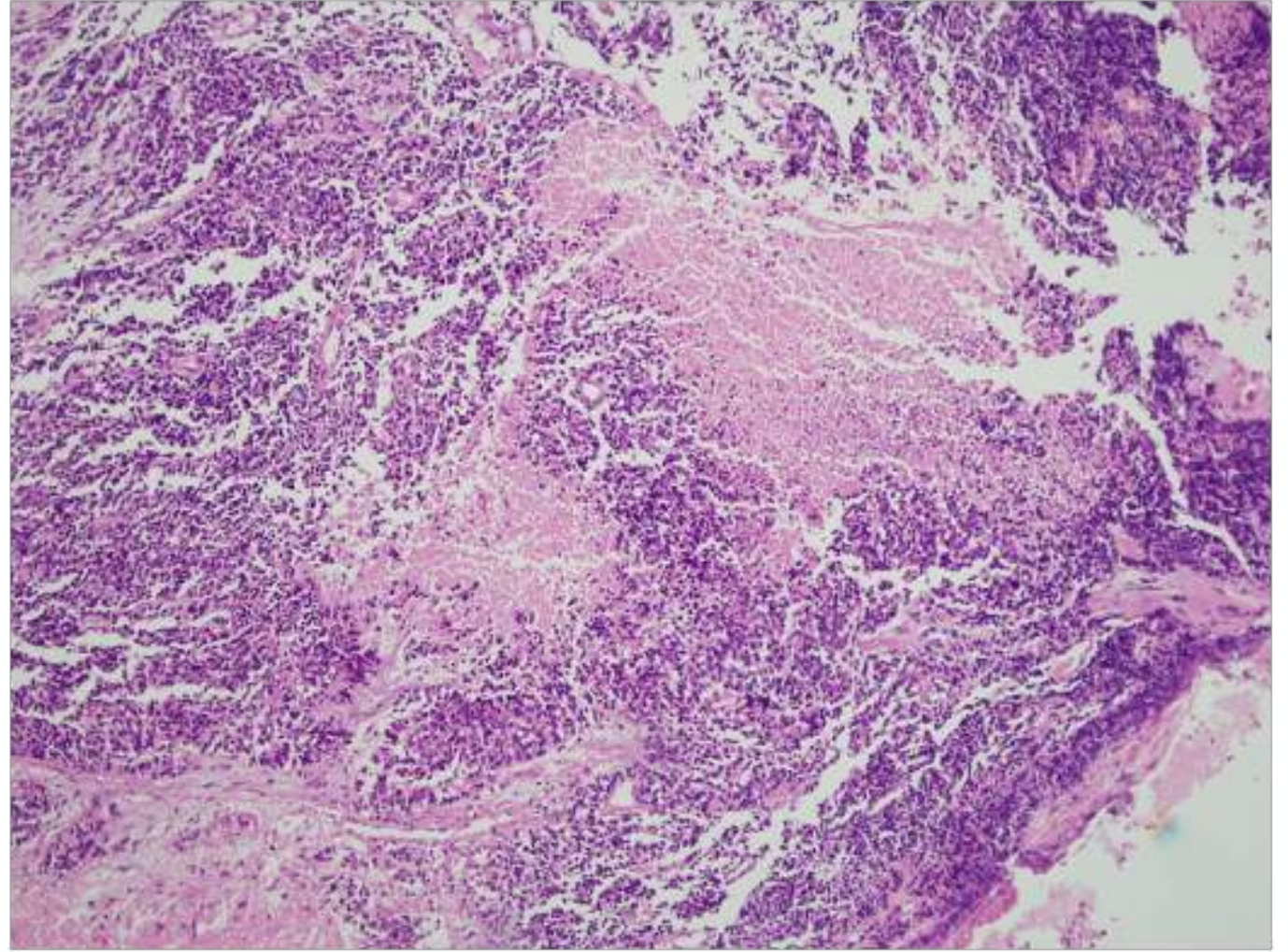
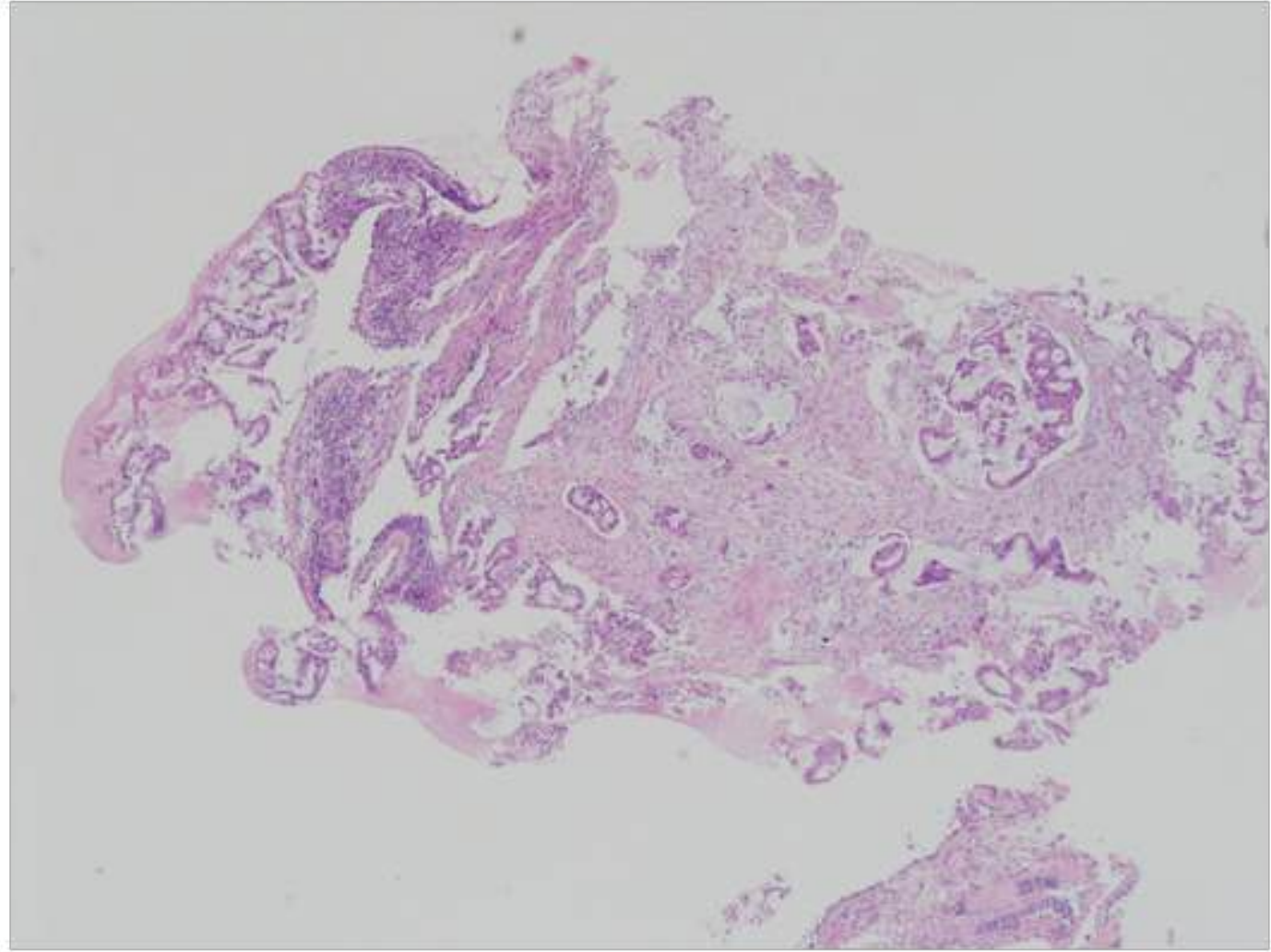
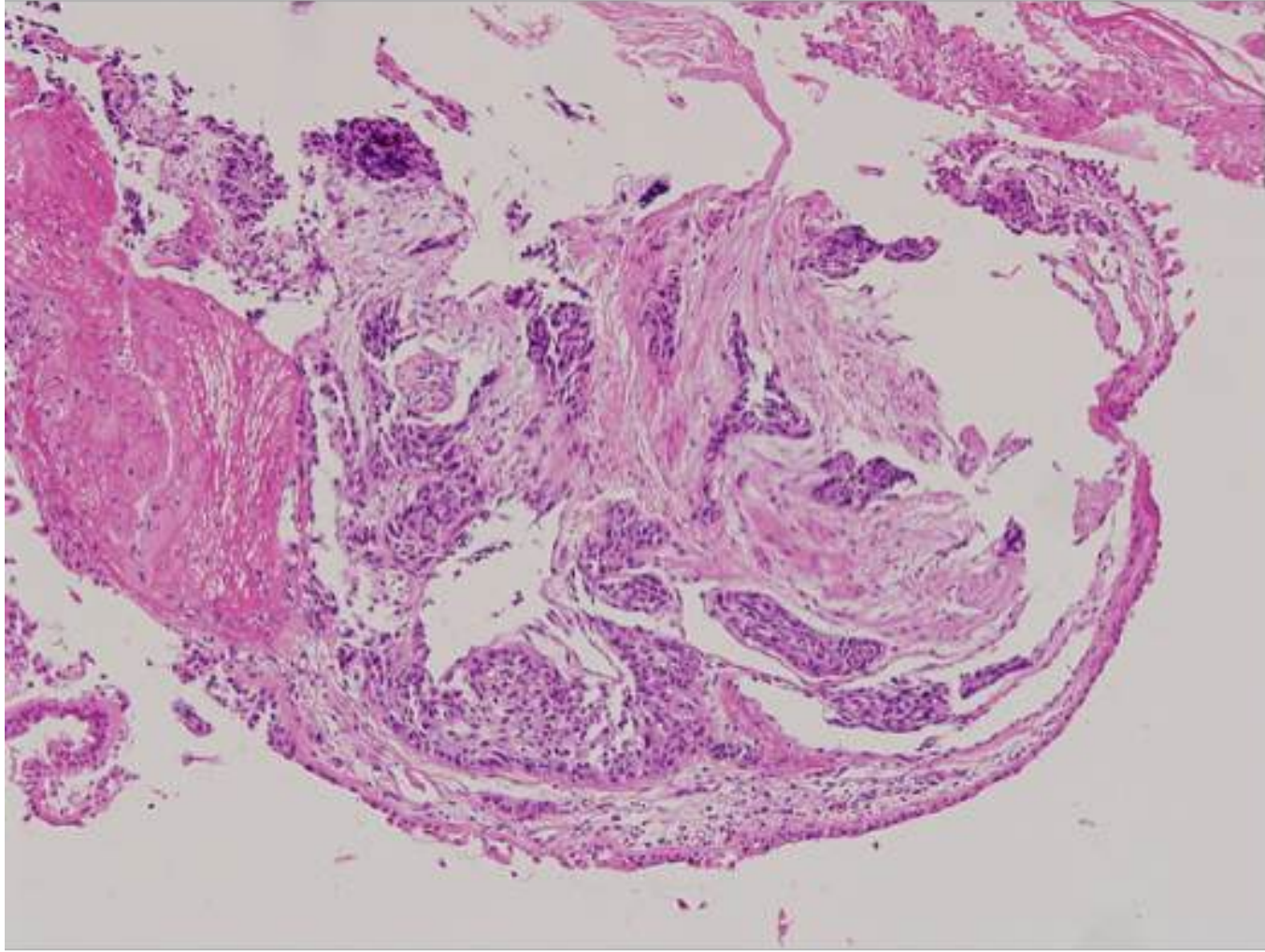


Endobronchial Ultrasound - TBNA

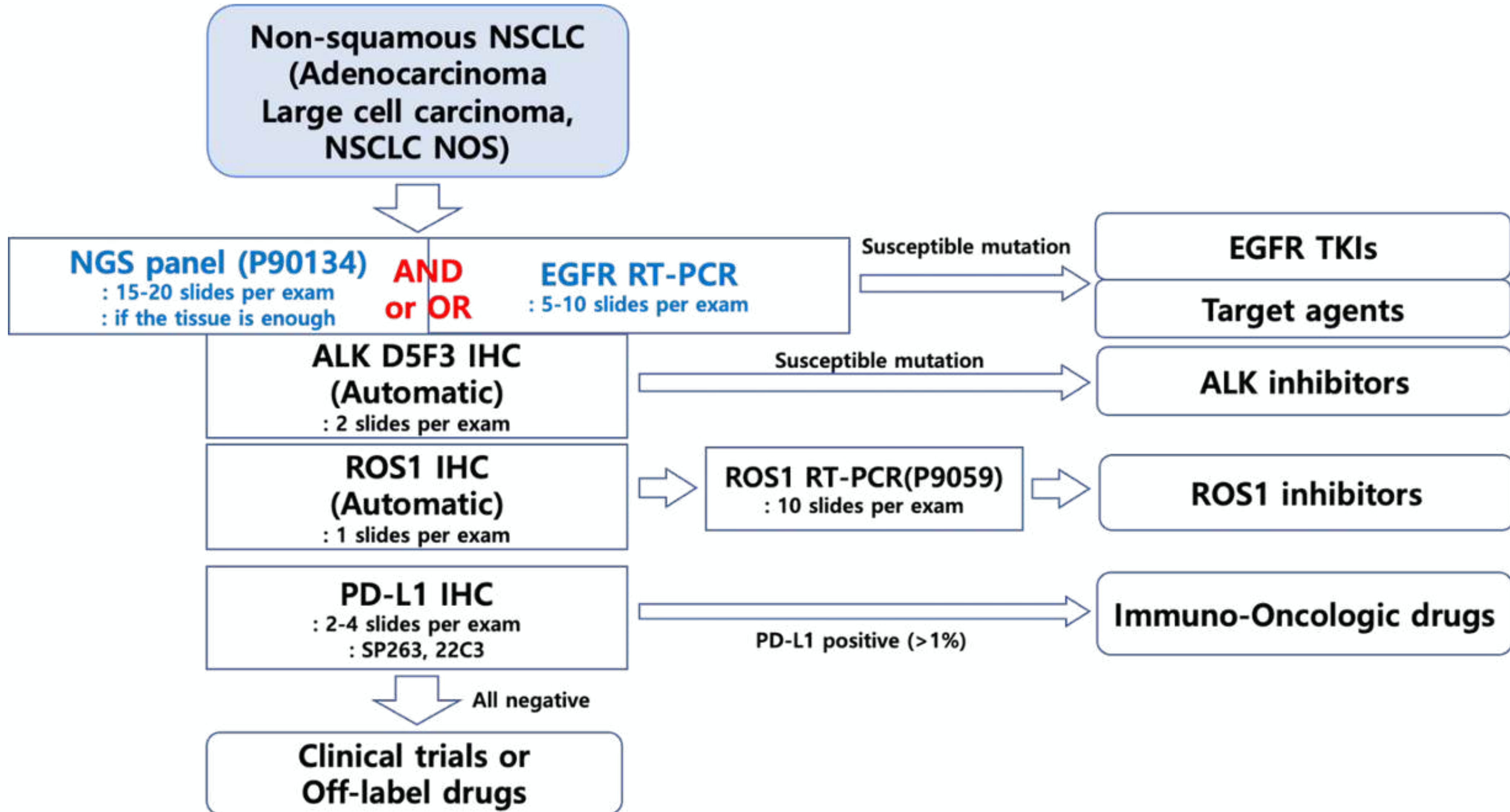


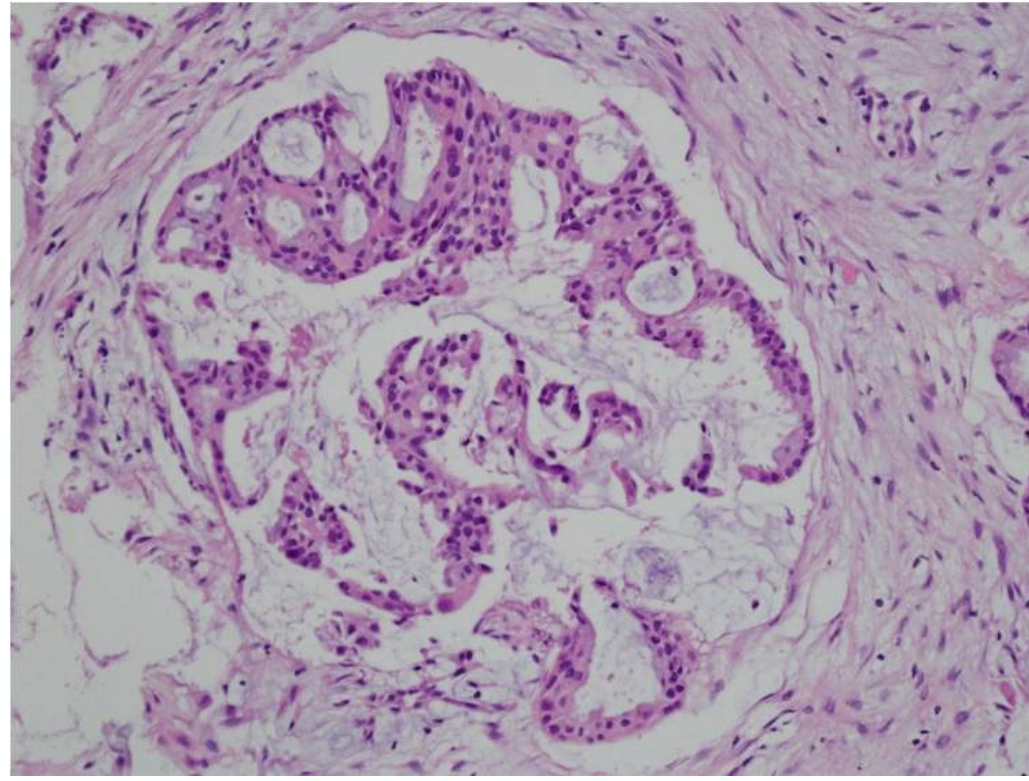
Endobronchial Ultrasound - TBNA



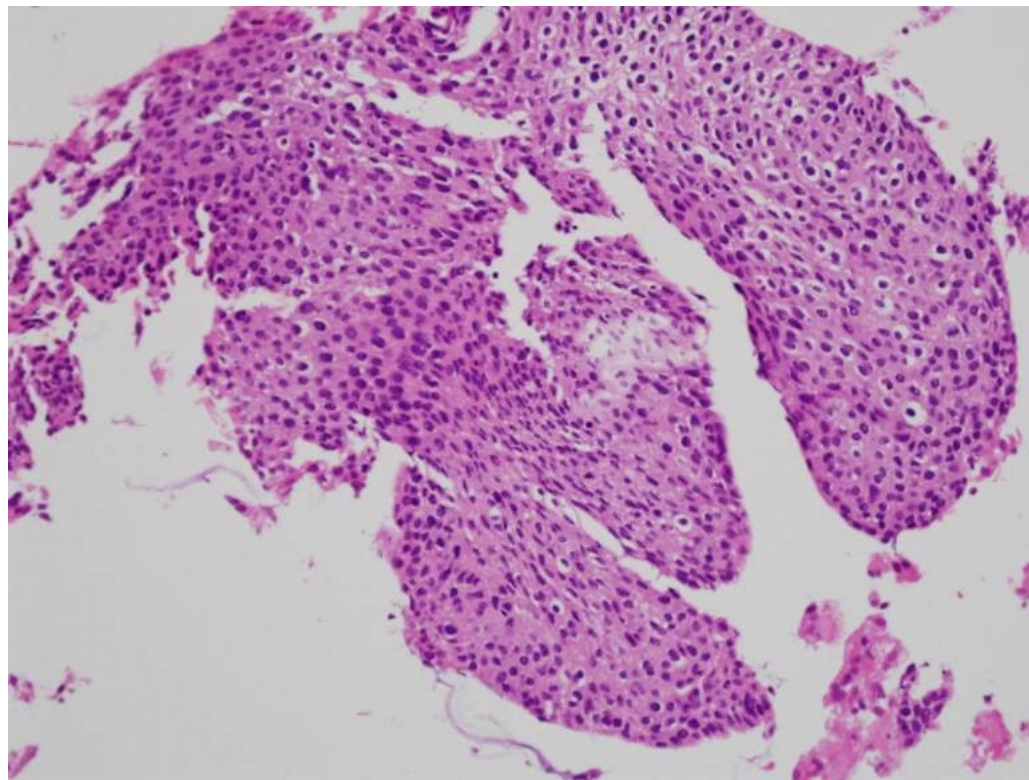


Molecular testing in AMC





Adenocarcinoma



Squamous Cell Carcinoma



EGFR mutation

NGS Panel

ALK IHC

ROS1 IHC - ROS1 RT PCR

PD-L1 IHC

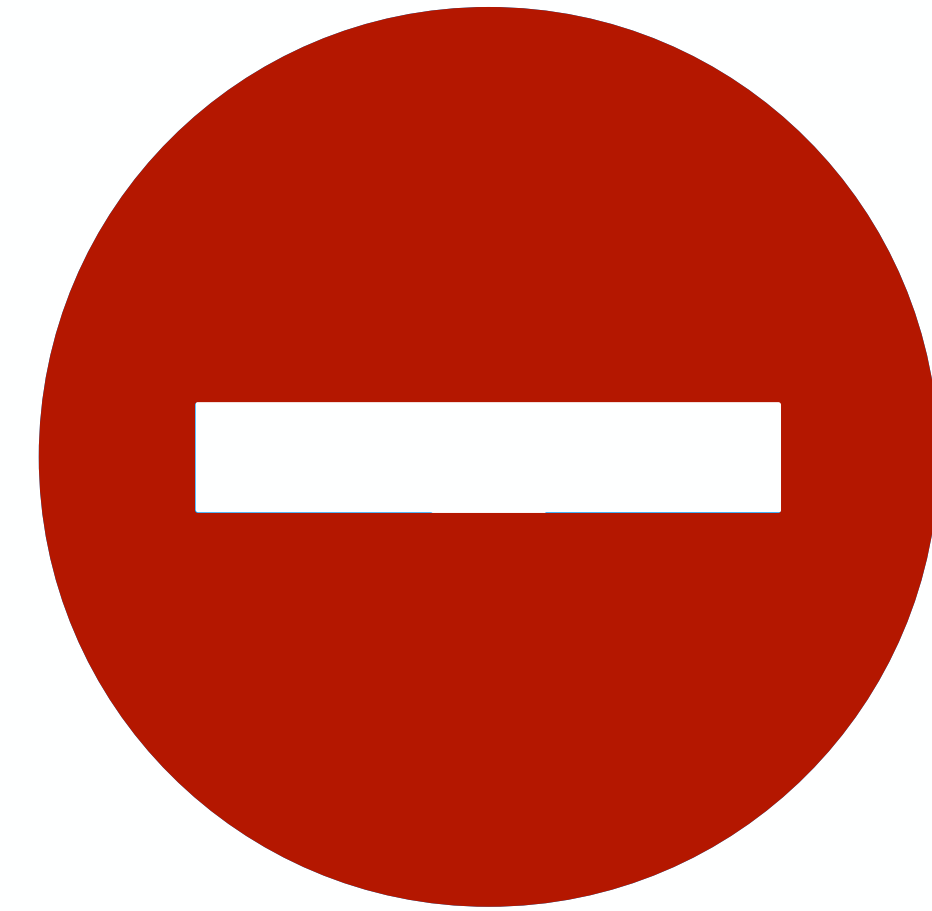
EGFR mutation

ALK IHC

ROS1 IHC - ROS1 RT PCR

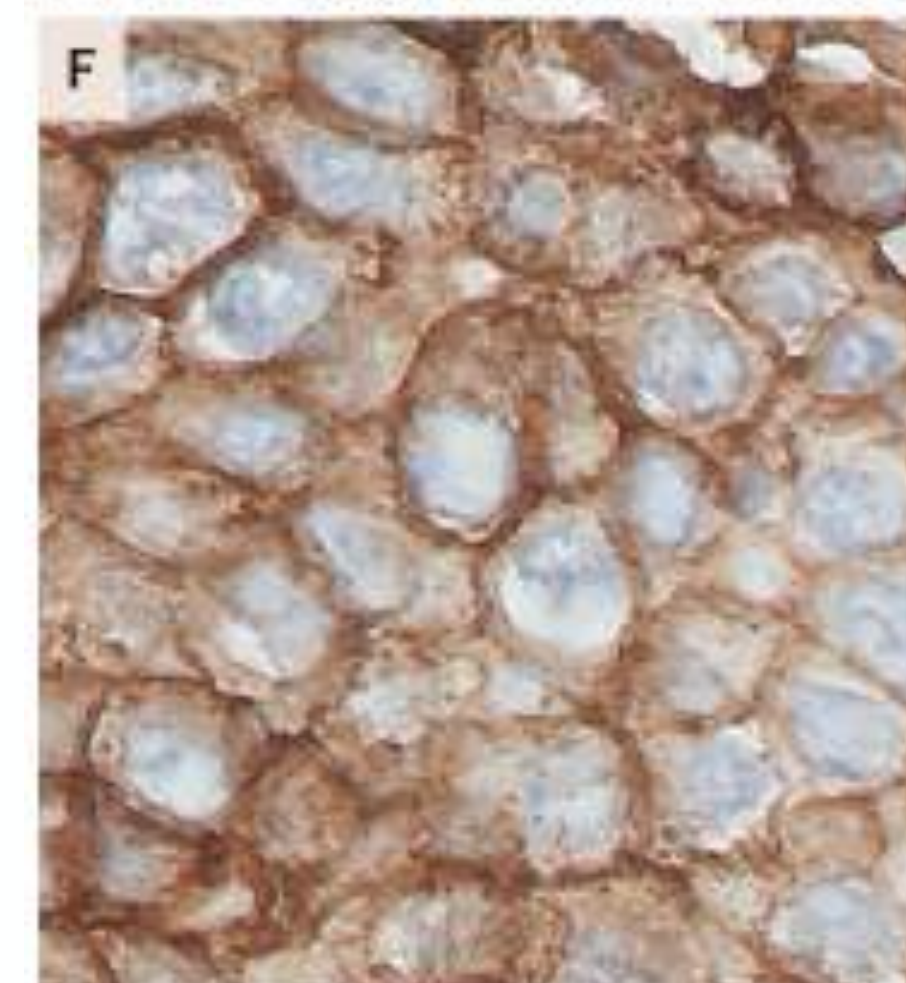
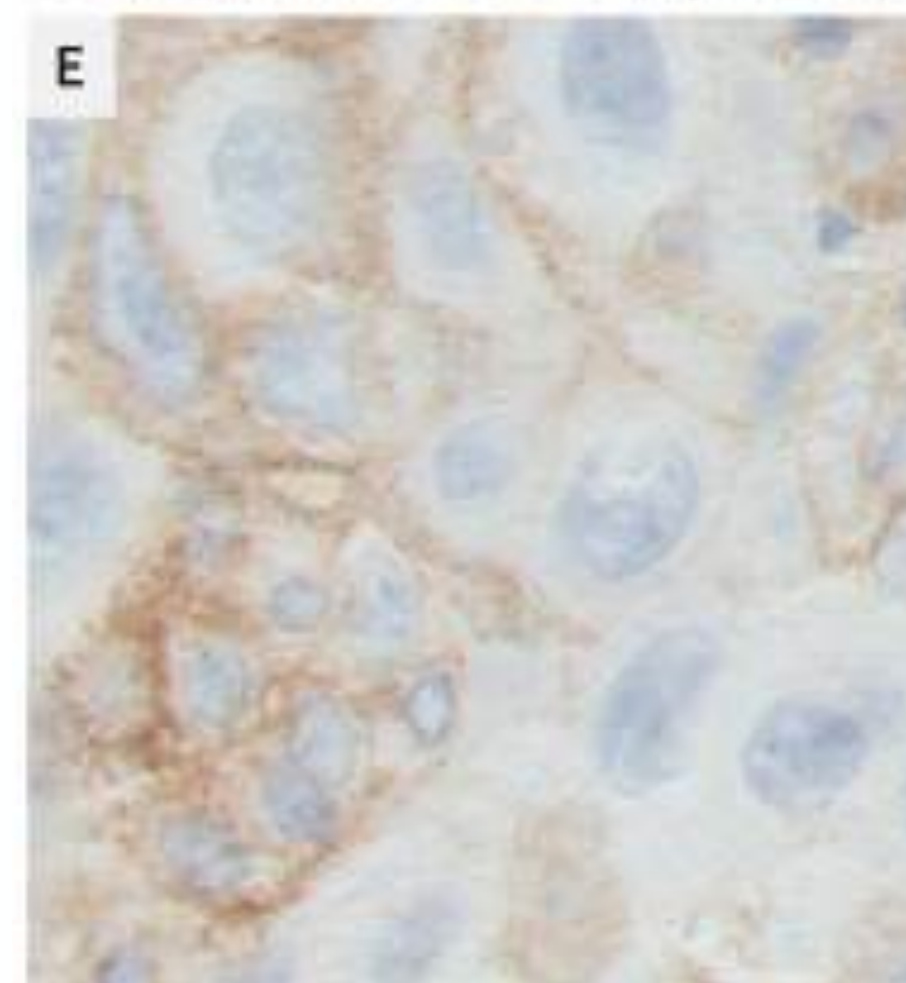
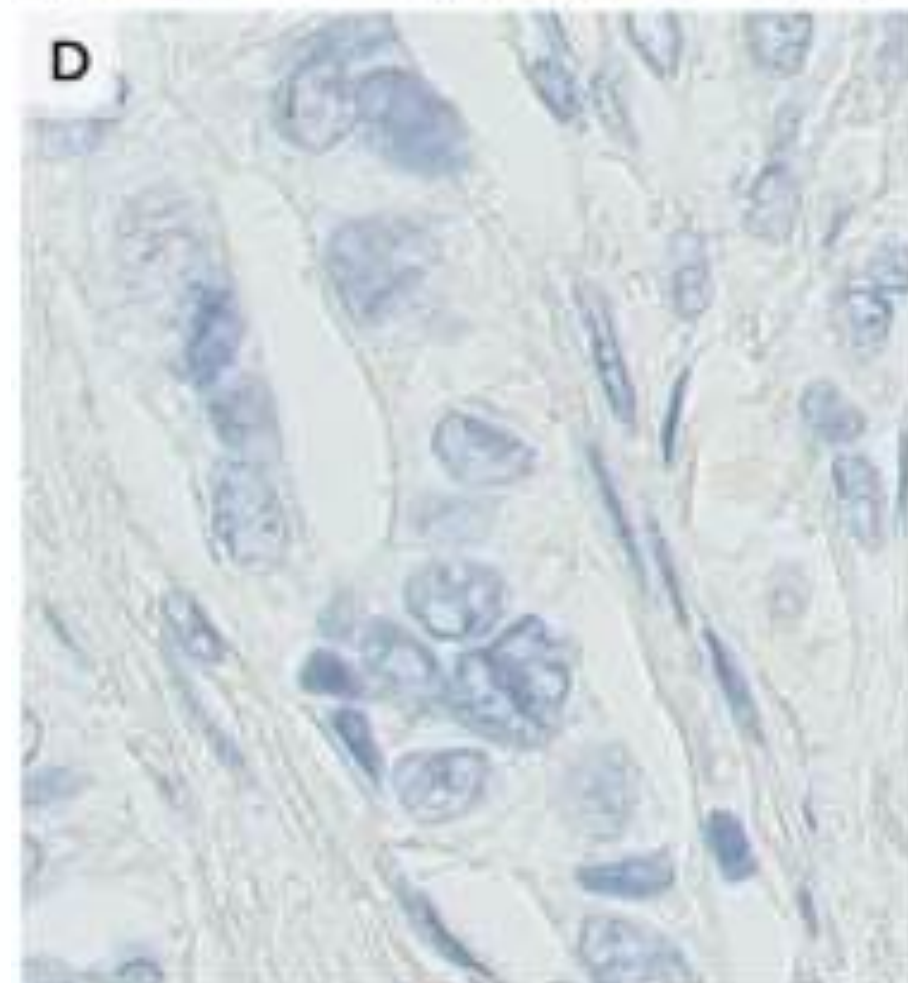
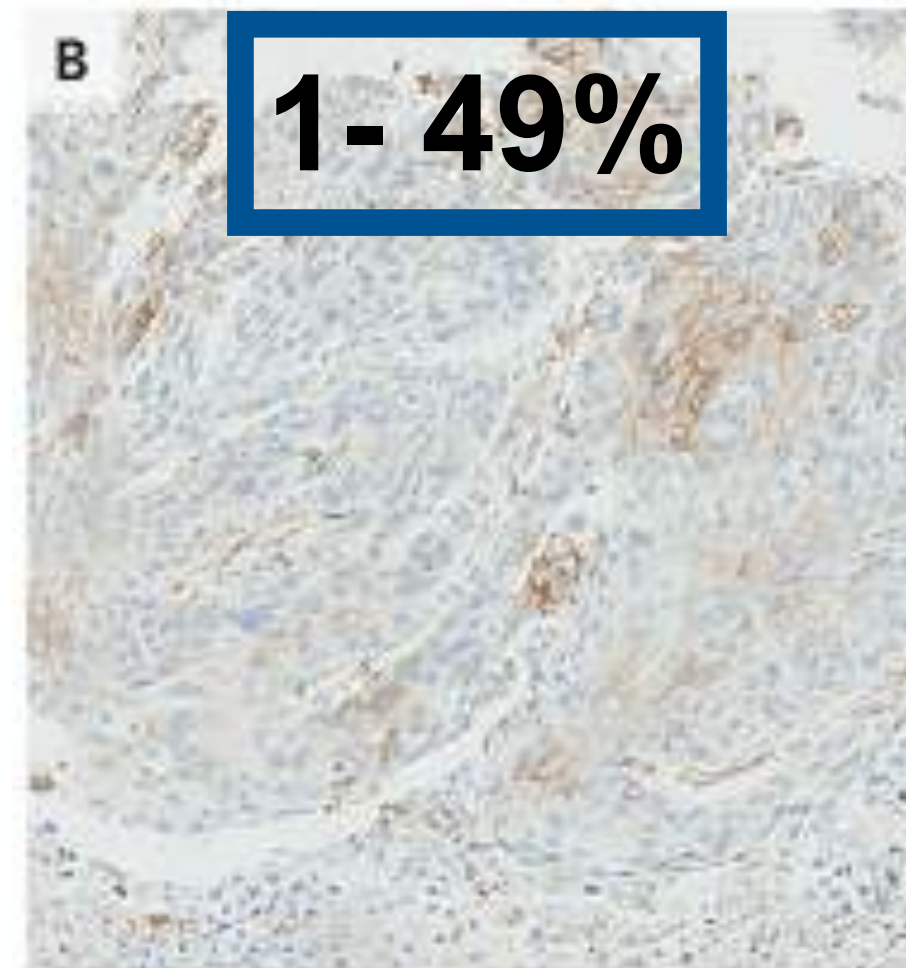
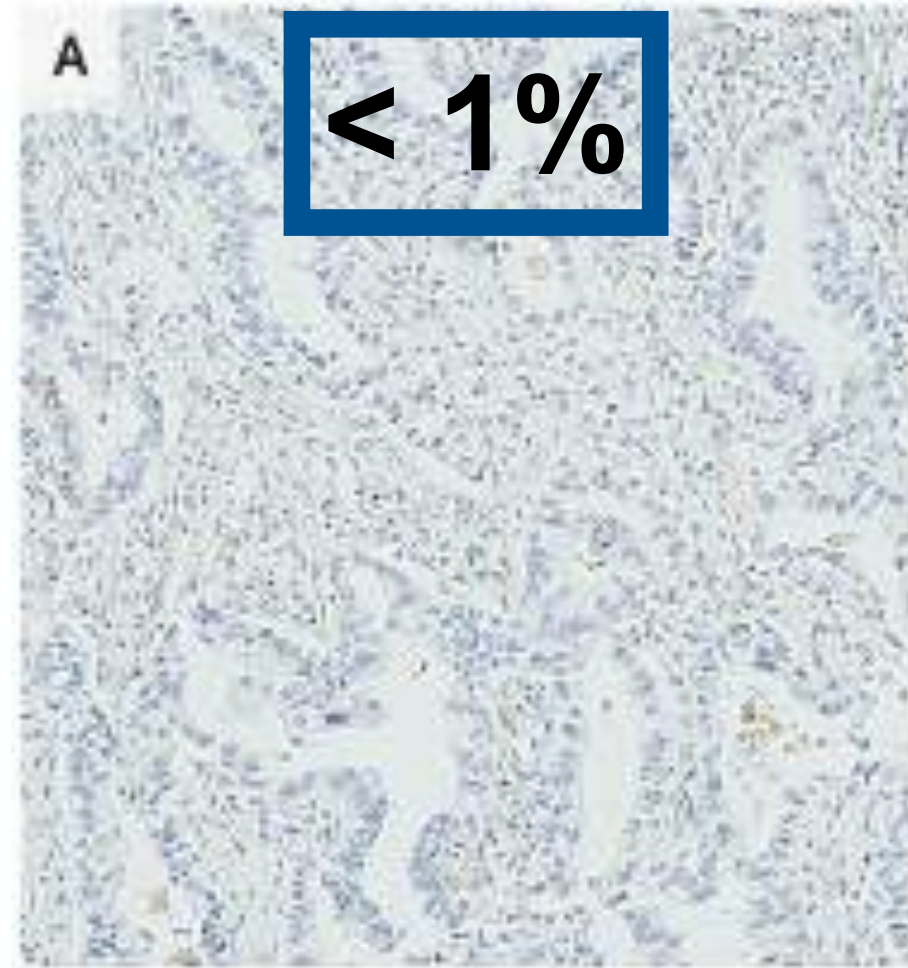
NGS Panel

RAF, RET, C-MET, KRAS, NTRK

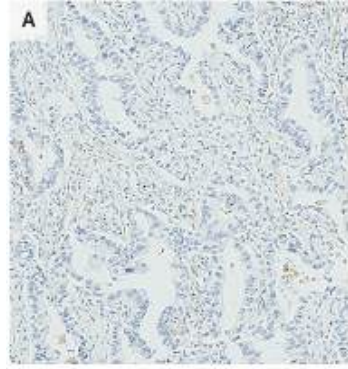


PD-L1 IHC

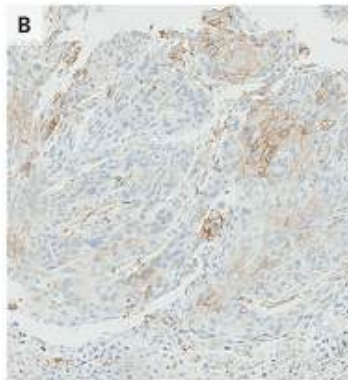
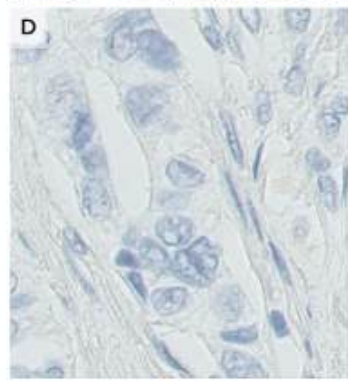
PD-L1 IHC



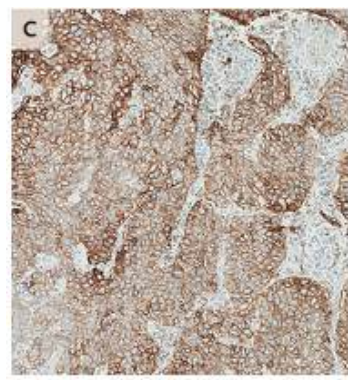
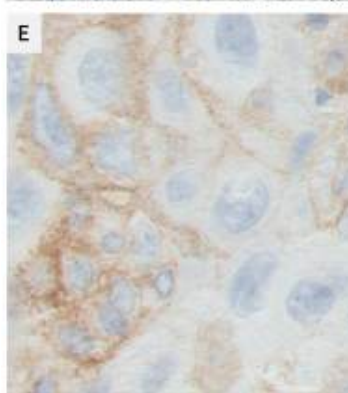
PD-L1 IHC



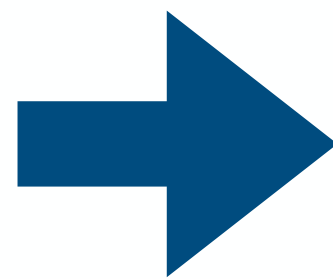
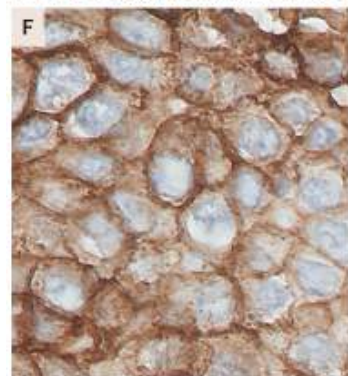
< 1%



1- 49%



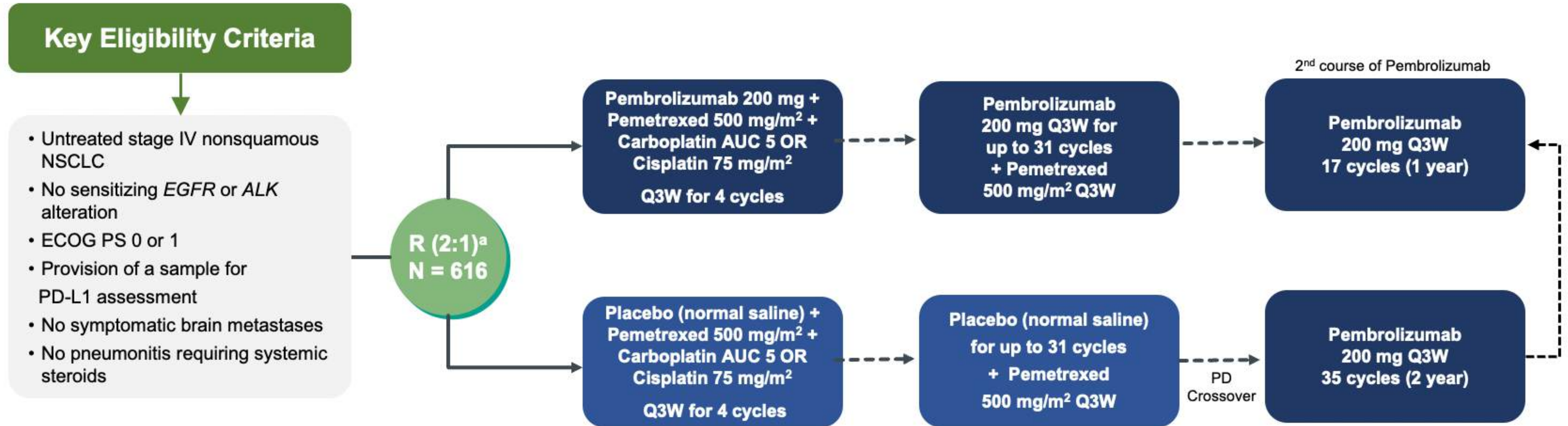
≥ 50%



**Pembrolizumab/carboplatin/pemetrexed
Pembrolizumab/cisplatin/pemetrexed**

**Pembrolizumab Alone
Tislelizumab/carboplatin/pemetrexed**

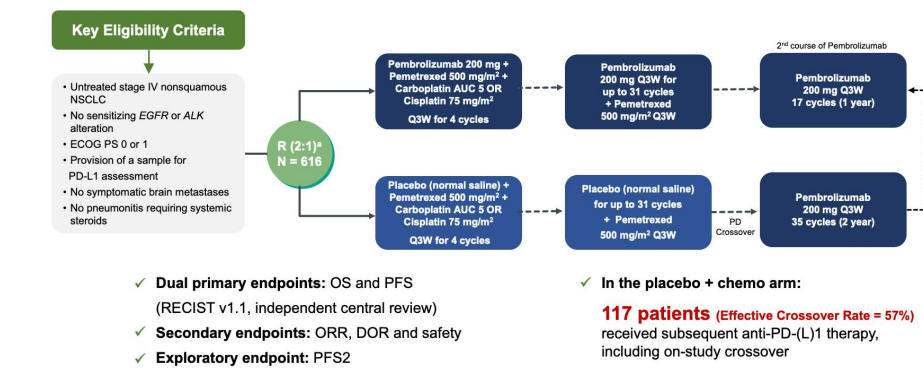
KEYNOTE-189 Study Design



- ✓ **Dual primary endpoints:** OS and PFS (RECIST v1.1, independent central review)
- ✓ **Secondary endpoints:** ORR, DOR and safety
- ✓ **Exploratory endpoint:** PFS2

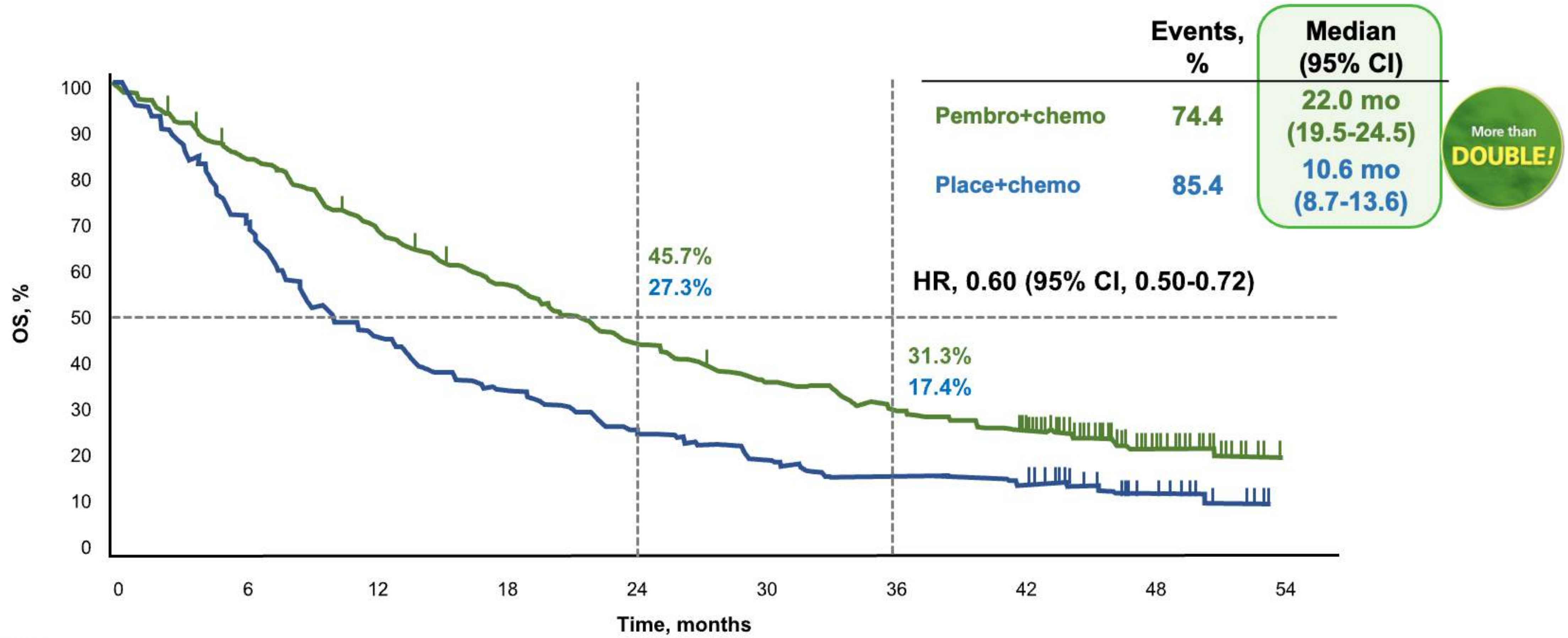
- ✓ **In the placebo + chemo arm:**
117 patients (Effective Crossover Rate = 57%) received subsequent anti-PD-(L)1 therapy, including on-study crossover

PFS2 defined as time from randomization to investigator-assessed disease progression that led to cessation of second-line therapy, start of third-line therapy, or death. a. Randomization was stratified by: PD-L1 expression (TPS ≥ 1% vs <1%), platinum chemotherapy (cisplatin vs carboplatin), and smoking status (never vs former/current). b. Patients who had SD or better after completing 35 cycles of pembrolizumab or had stopped trial treatment after achieving CR and received ≥ 8 cycles of treatment, but then experienced PD, could receive second-course pembrolizumab for 17 cycles (~1 year) if they had received no new anticancer therapy since the last dose of pembrolizumab. c. Patients could cross over to pembrolizumab monotherapy after PD per RECIST v1.1 by blinded independent central review.



Overall Survival, ITT Population

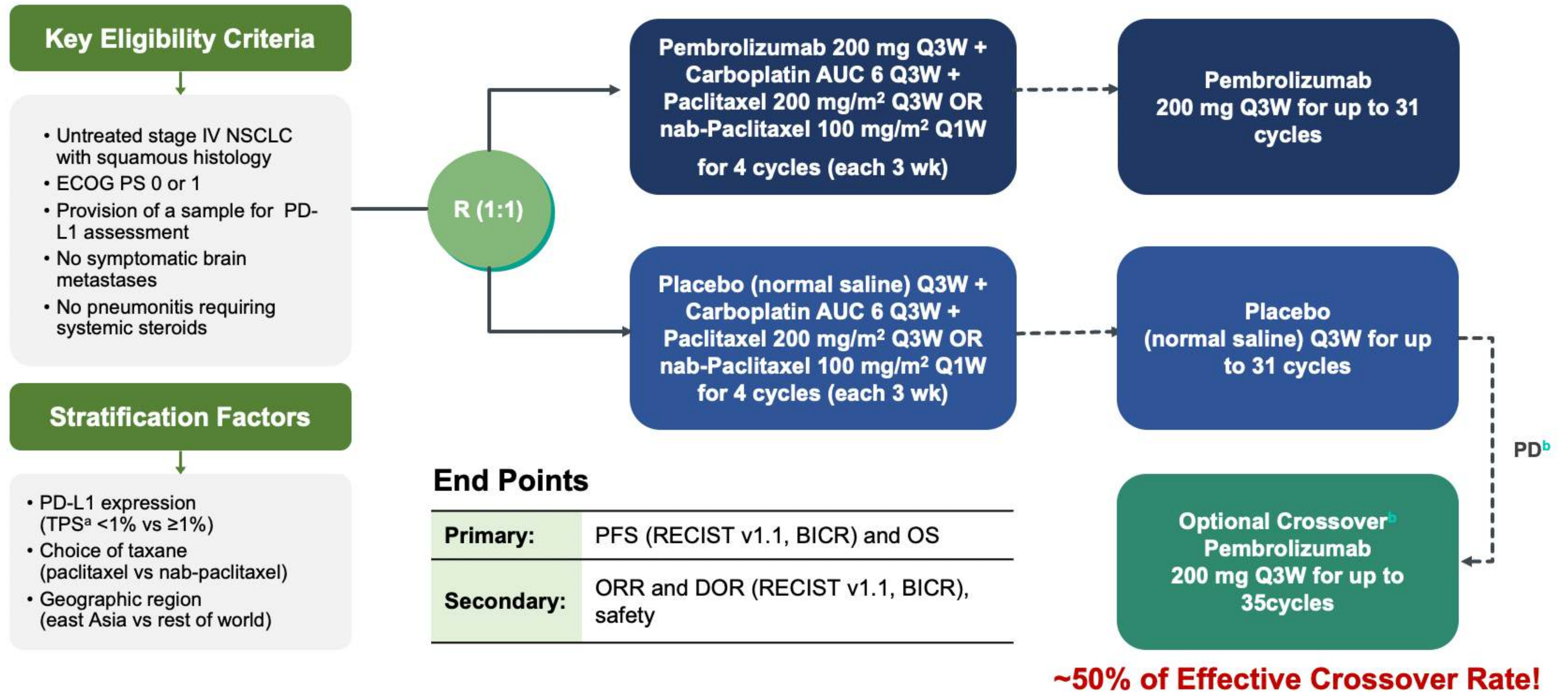
No sensitizing *EGFR* or *ALK* alteration



| No.at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|------------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| Pembro + chemo | 410 | 347 | 283 | 234 | 184 | 149 | 125 | 99 | 28 | 0 |
| Placebo + chemo | 206 | 149 | 98 | 72 | 55 | 42 | 34 | 29 | 10 | 0 |

KEYNOTE-407 Study Design (NCT02775435)

Squamous Cell Carcinoma

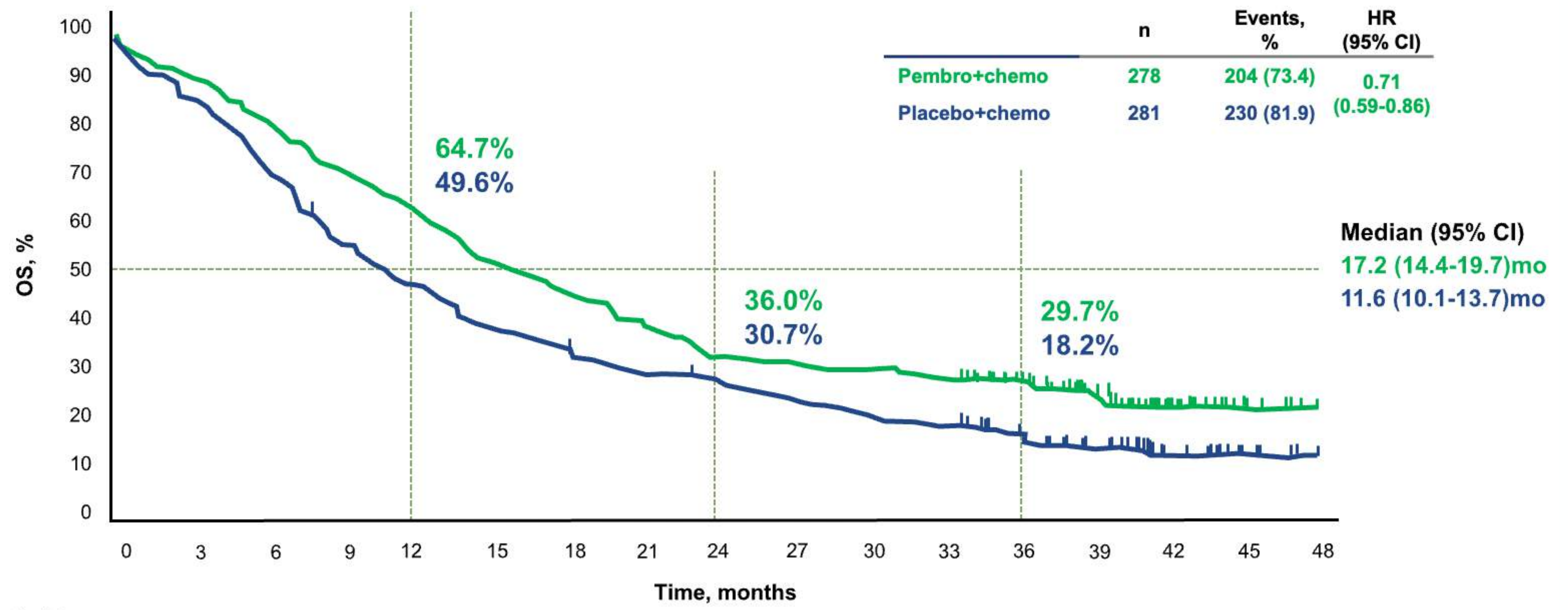
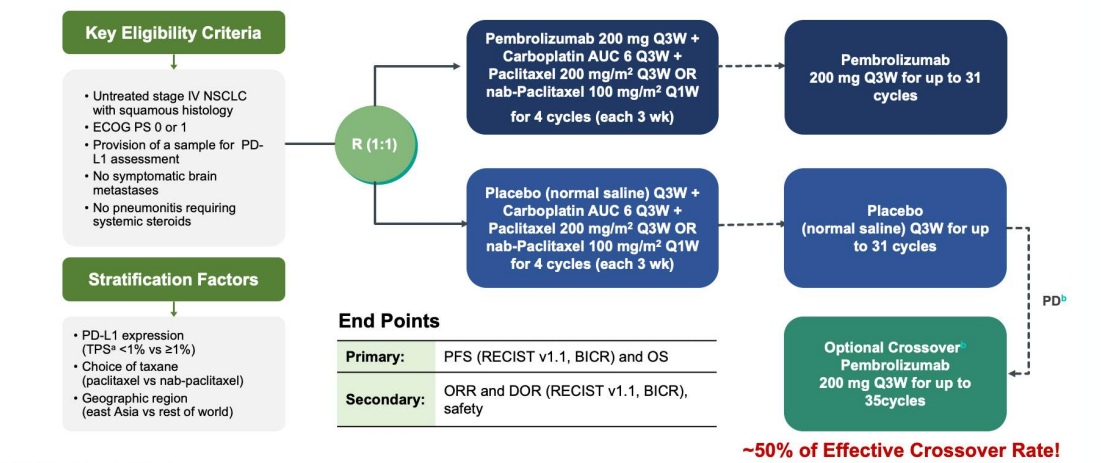


BICR=blinded independent central radiologic review

a. Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 HC 22C3 pharmDx assay. b. Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

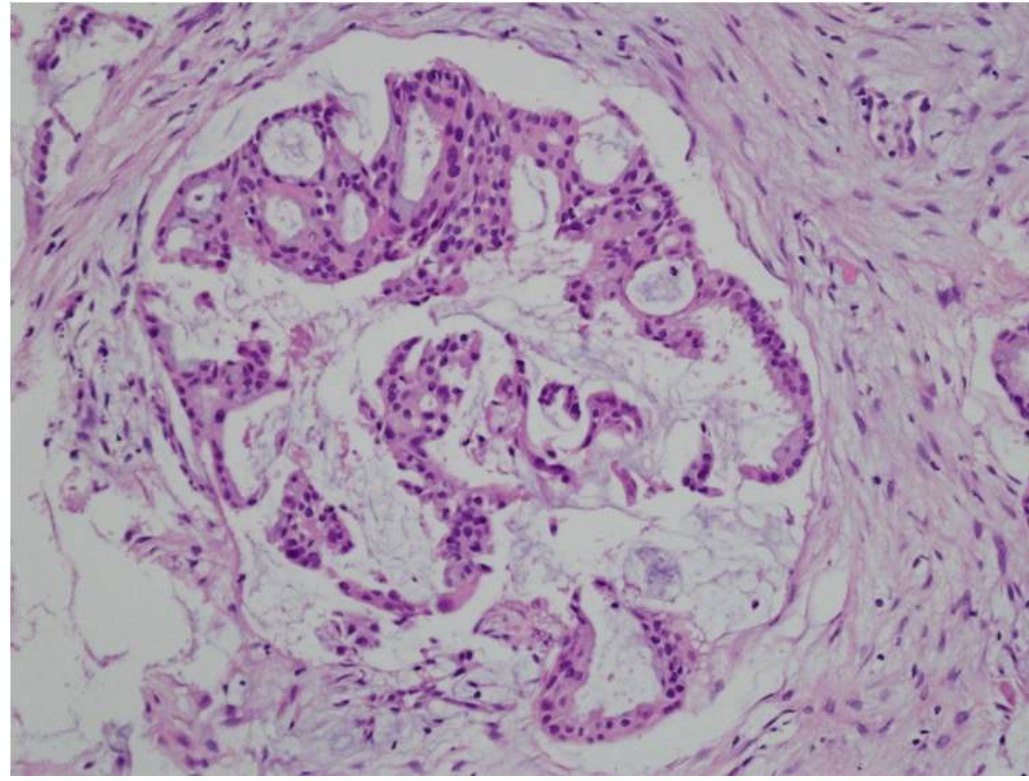
Overall Survival^a

KEYNOTE-407 Study Design (NCT02775435)

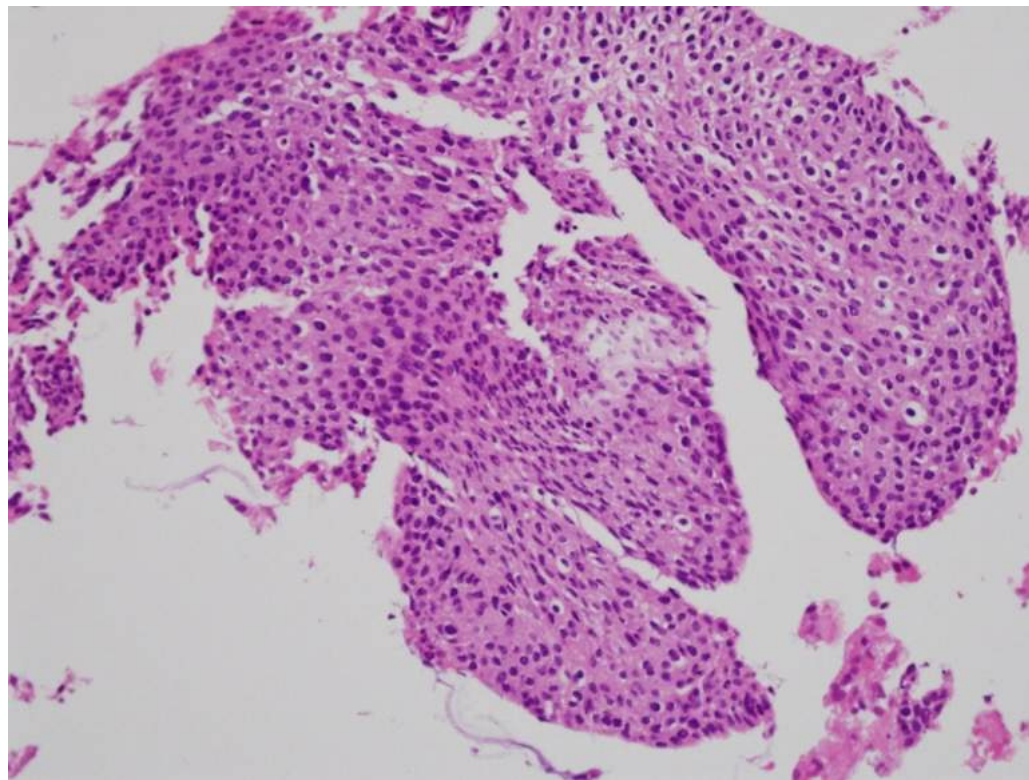


| No.at risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|
| Pembro + chemo | 278 | 256 | 232 | 203 | 180 | 150 | 134 | 117 | 100 | 93 | 91 | 84 | 65 | 44 | 18 | 5 | 0 |
| Placebo + chemo | 281 | 245 | 210 | 163 | 137 | 113 | 100 | 87 | 83 | 70 | 62 | 58 | 42 | 29 | 14 | 4 | 0 |

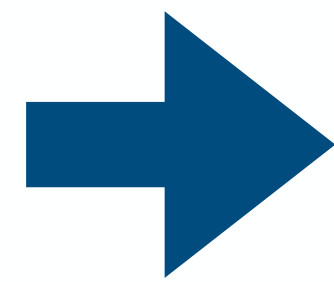
a. ITT population.
Data cutoff date: Sep 30, 2020
A Rhobinson, et al. KN407. Presented at ELCC 2020.



Adenocarcinoma



Squamous Cell Carcinoma



Pembrolizumab/carboplatin/paclitaxel
Tislelizumab/caboplatin/paclitaxel

Small Cell Lung Cancer



Limited Stage



Extensive Stage



Limited Stage

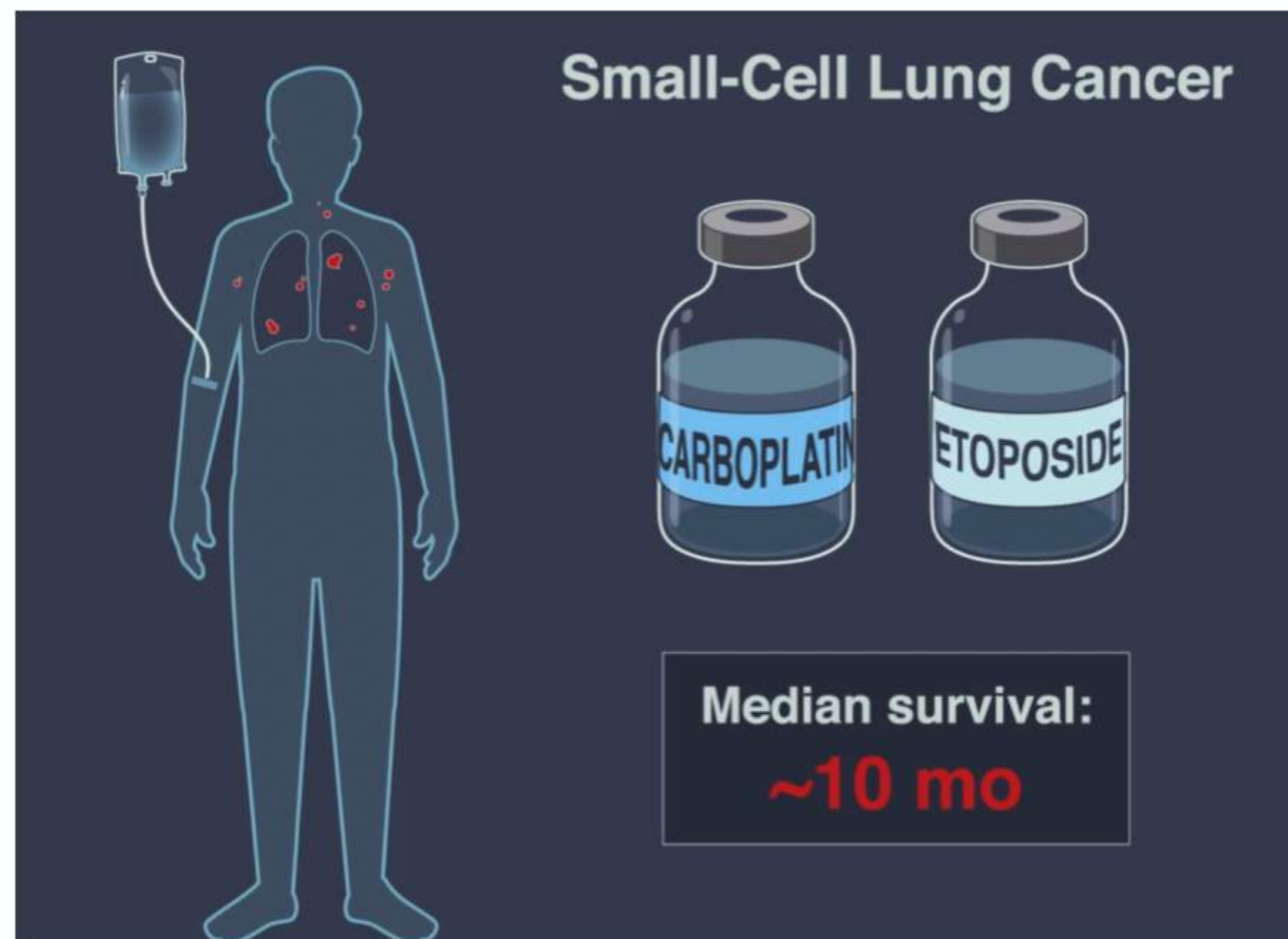
➔ **Definitive Concurrent Chemoradiation**



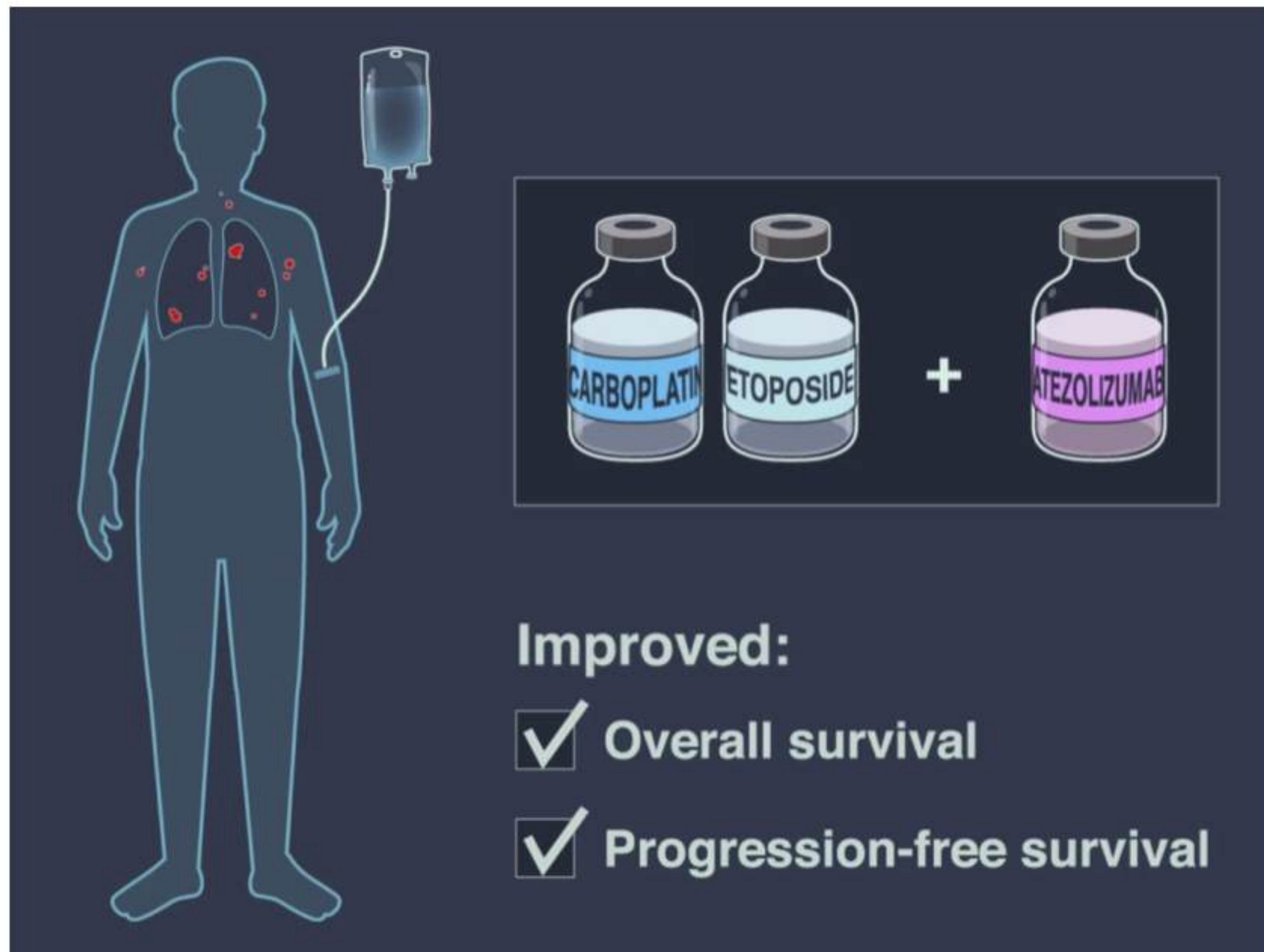
Extensive Stage

➔ **Atezolizumab/Etoposide/Carboplatin**

Small-Cell Lung Cancer



Median survival:
~10 mo



Improved:

- ✓ Overall survival
- ✓ Progression-free survival

First study in over 20 years to show a **clinically meaningful improvement in OS** over the current SoC in 1L ES-SCLC

IM power133 LUNG

403 patients with untreated ES-SCLC

Randomisation 1:1

Co-primary endpoints: **OS and PFS**

Atezolizumab + carboplatin/etoposide
Atezolizumab maintenance

4 cycles
Until PD/loss of clinical benefit

Placebo + carboplatin/etoposide
Placebo maintenance

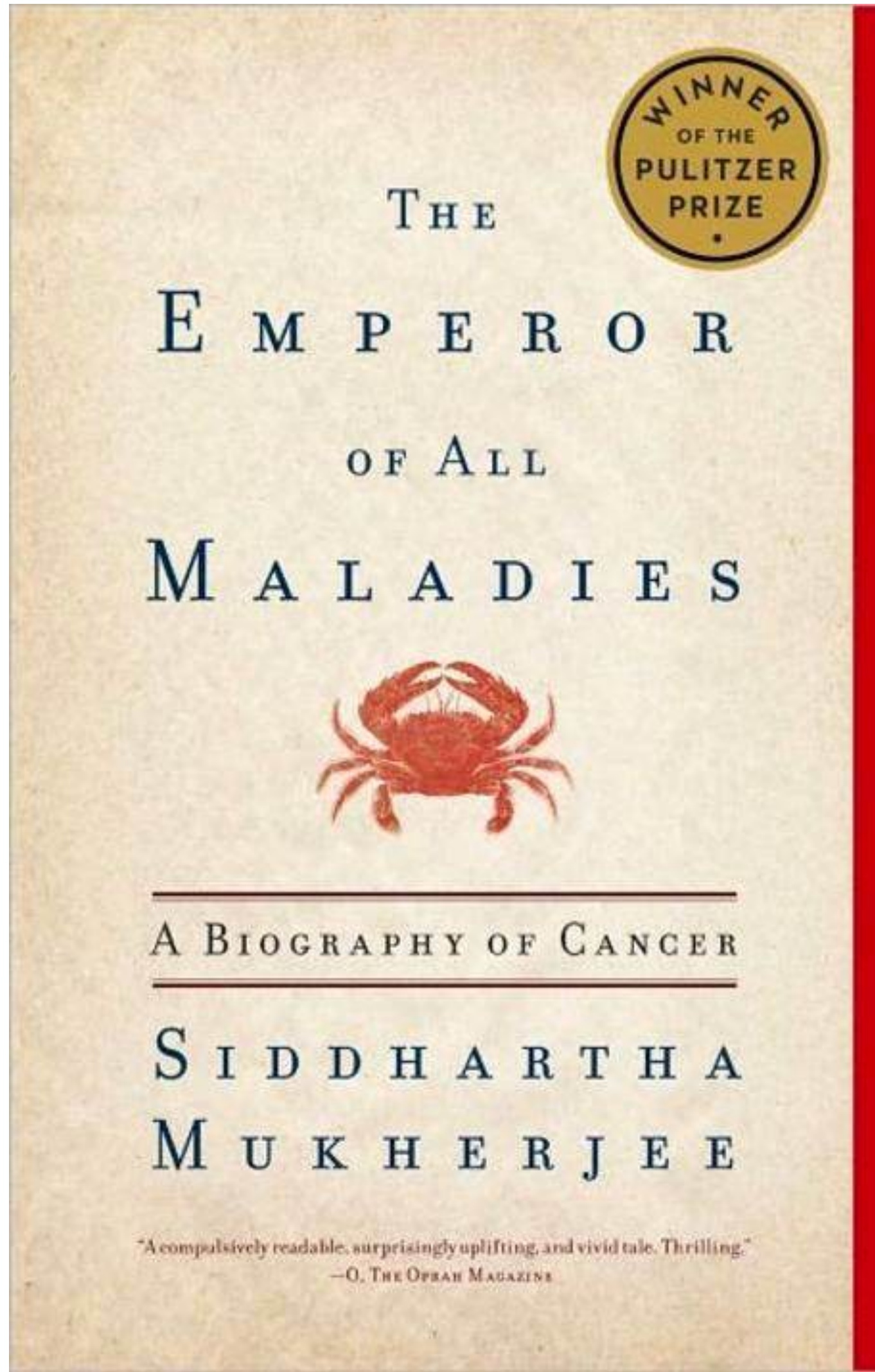
PFS: Median **5.2 mo** **HR 0.77** $p=0.017$ Median **4.3 mo**

OS: Median **12.3 mo** **HR 0.70** $p=0.0069$ Median **10.3 mo**

12-month OS: **51.7%** **Δ 13.5%** **38.2%**

Improved:

- ✓ Overall survival
- ✓ Progression-free survival



THE EMPEROR OF ALL MALADIES : A BIOGRAPHY OF CANCER

암: 만병의 황제의 역사

싯다르타 무케르지
이한음 옮김

2011년 풀리처상 일반 논픽션 부문 수상
2010년 「뉴욕 타임스 북 리뷰」 논픽션 부문 "올해의 책" 선정
「뉴욕 타임스 북 리뷰」 논픽션 부문 베스트셀러
아마존 베스트셀러

매혹적이고 긴박감이 넘치고 가슴 뭉클한 이 책은 암 치료의 미래에 대해서도 흥미로운 전망을 보여준다.
암의 탈신화화를 원하는 사람들에게 희망과 미래를 약속하는 책이다.

까지

싯다르타 무케르지, 이한음 역 - 암: 만병의 황제의 역사

이 책을 읽으면
항암제와 화학 요법의
기작을
알게 됩니다.

(바이오 전공자,
약은 항체 의약품밖에 모름)

그리고 항암제를 쓰던 의사들이
저만큼 아무것도 몰랐다는 사실도
알게 됩니다.

실험이 성공해도
결과가 왜 잘 나오는지
모르는 게 딱 나랑 똑같네.

(아닙니다)