DISEASE STATE EDUCATION *NON–SMALL CELL LUNG CANCER*

Disclaimer

This information is intended for your scientific and/or educational purpose and is not intended for promotional use.

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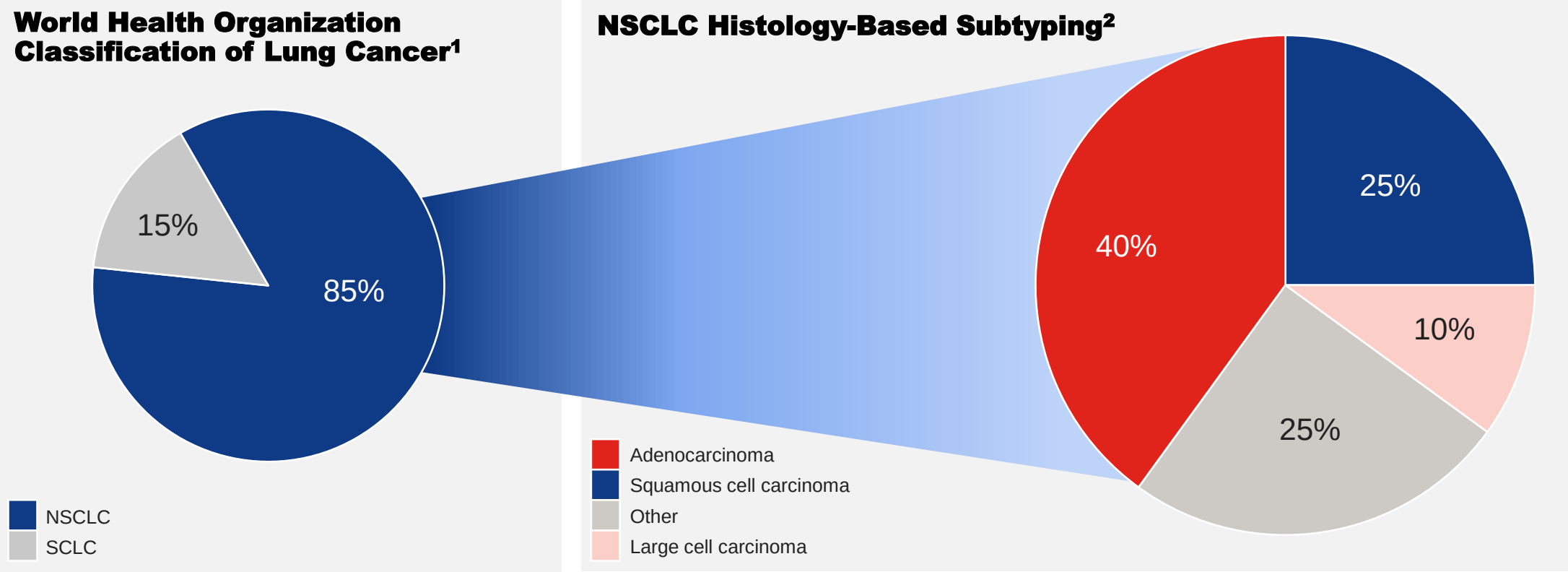
NGS = next-generation sequencing; NSCLC = non–small cell lung cancer.

Lung Cancer Overview

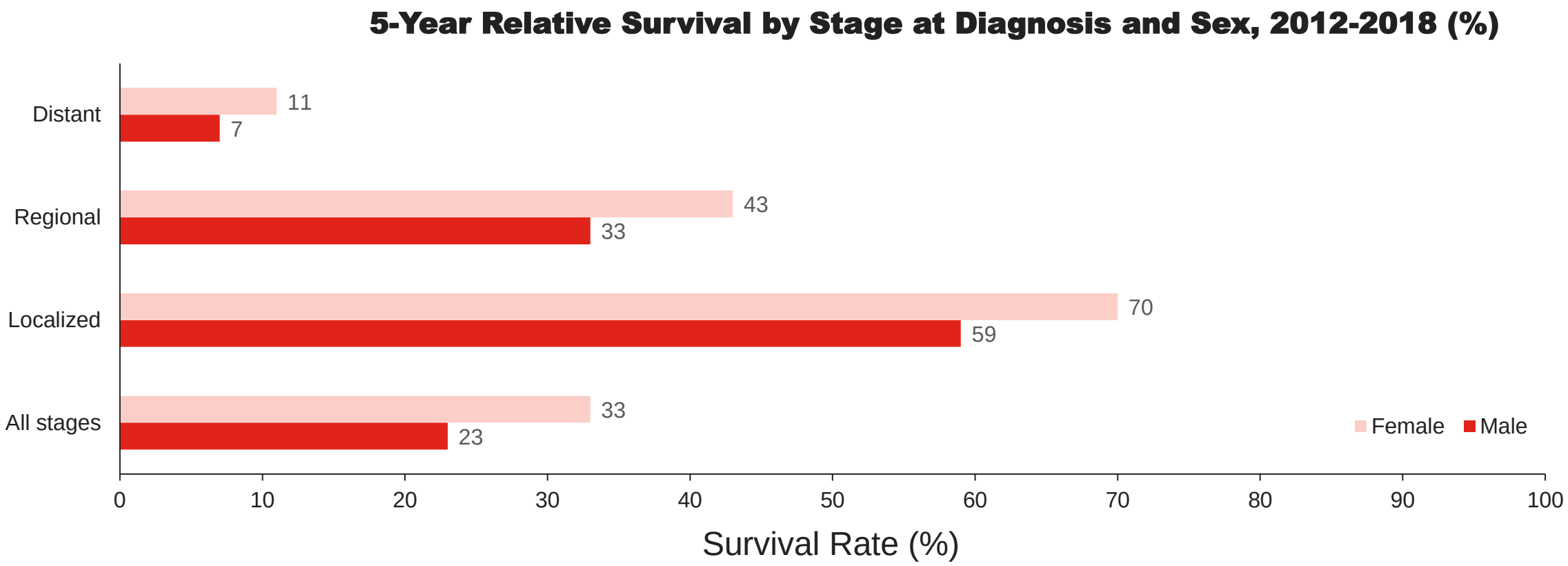
Lung Cancer Has Histologically Distinct Subtypes



SCLC = small cell lung cancer.

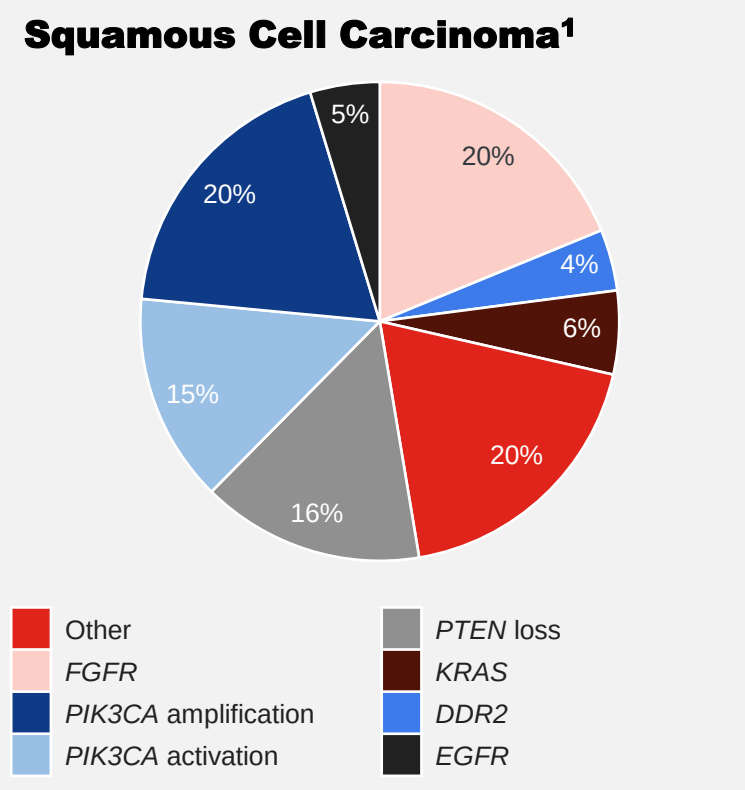
1. Dorantes-Heredia R, Ruiz-Morales JM, Cano-García F. *Transl Lung Cancer Res*. 2016;5(4):401-412. 2. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_359 (Accessed May 16, 2024).

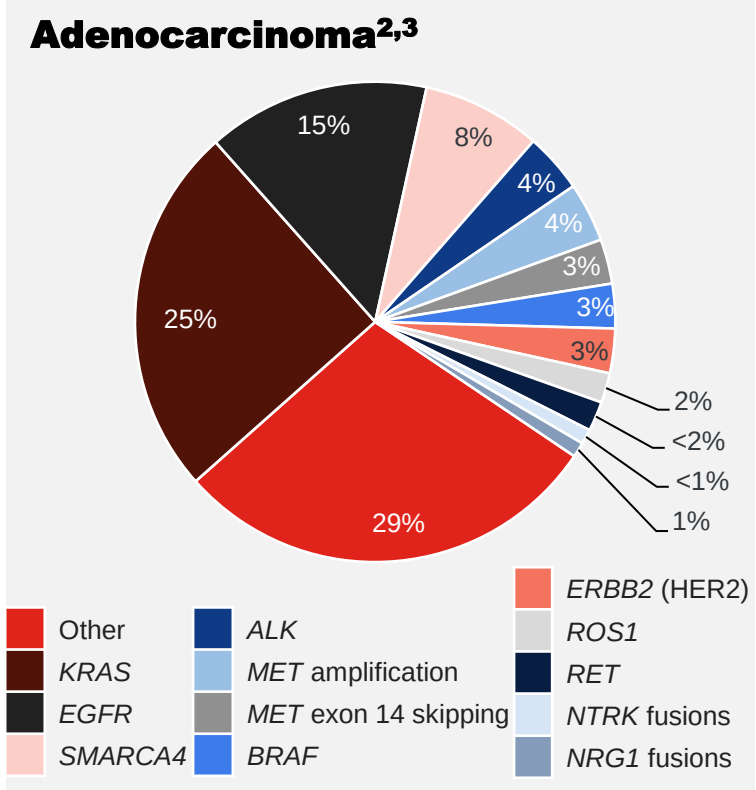
Early Detection of NSCLC Can Improve Patient Outcomes



American Cancer Society. *Cancer Facts & Figures 2023.* Atlanta: American Cancer Society; 2023.

NSCLC Is Frequently Oncogene Driven





Genomic alterations with approved targeted therapies for NSCLC[2]:

- *EGFR* mutations
- *ALK* rearrangement
- *ROS1* rearrangement
- *BRAF* V600E mutation
- *MET* exon 14 skipping
- *ERBB2* (HER2) mutations
- *NTRK* fusions
- *KRAS* G12C mutation
- *RET* rearrangement

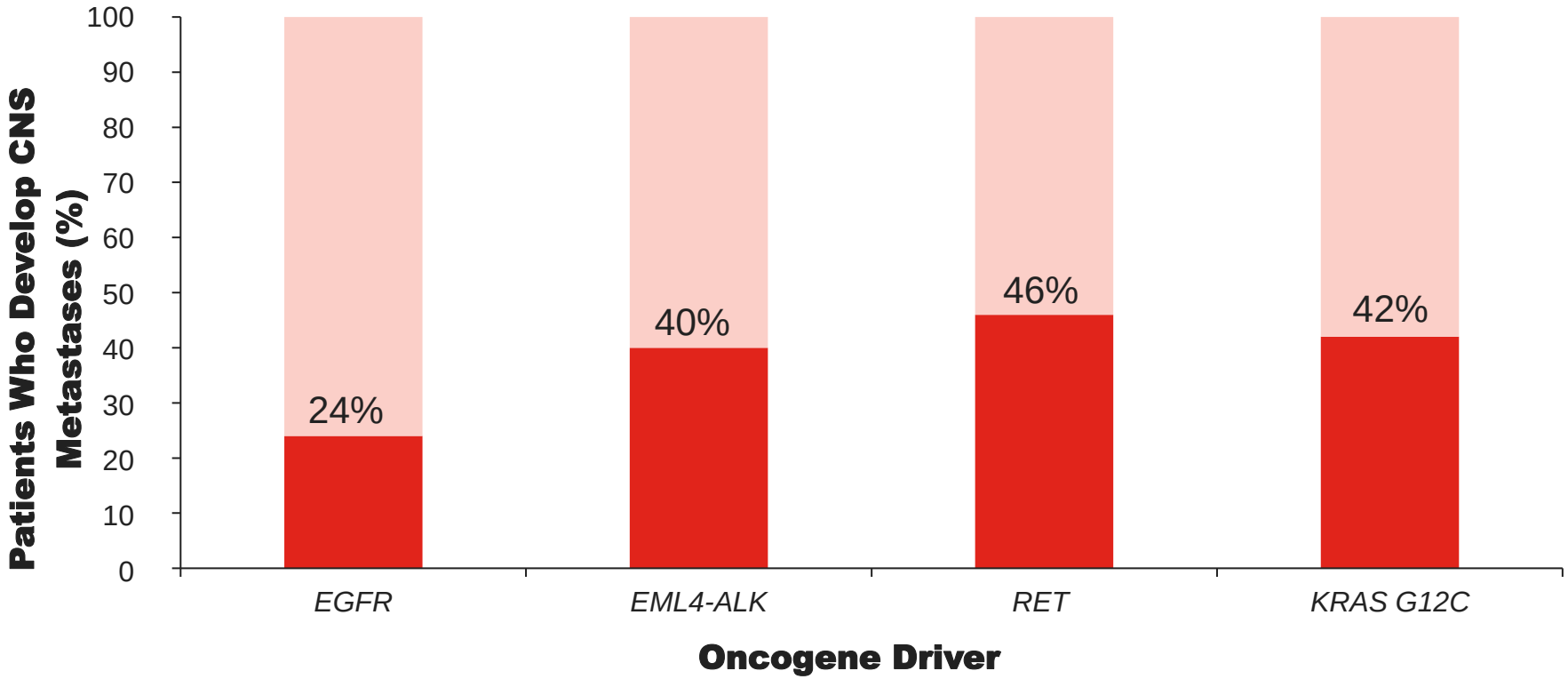
ALK = anaplastic lymphoma kinase; BRAF = v-raf murine sarcoma viral oncogene homolog B; DDR2 = discoidin domain receptor tyrosine kinase 2; EGFR = epidermal growth factor receptor; ERBB2 = avian erythroblastic leukemia viral oncogene homolog 2; FGFR = fibroblast growth factor receptor; KRAS = Kirsten rat sarcoma; MET = mesenchymal-epithelial transition factor; NRG1 = oncogenic Neuregulin 1 gene; NTRK = neurotrophic tyrosine receptor kinase; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN = phosphatase and tensin homolog; RET = rearranged during transfection; ROS1 = ROS proto-oncogene 1; SMARCA4 = SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4.

1. Lau SCM, et al. *Cancer Cell.* 2022;40:1279-1293. 2. https://www.uptodate.com/contents/personalized-genotype-directed-therapy-for-advanced-non-small-cell-lung-cancer (Accessed on December 12, 2023). 3. Deribe YL, et al. *Nat Med.* 2018;24(7):1047-1057.

Prevalence of Intracranial Metastases in Patients With NSCLC

57% of patients with NSCLC present with metastatic disease at diagnosis. Of these patients, 20% present with brain metastases, and 25-50% of patients will develop brain metastases over the course of their disease.[1]

The risk of developing CNS disease is even higher in patients with oncogene-driven NSCLC.[1-3]



CNS = central nervous system; EML4 = echinoderm microtubule–associated protein-like 4.

1. Emani V, Stinchcombe TE. *J Oncol Pract.* 2019;15(11):563-570. 2. Murciano-Goroff YR, et al. *J Thorac Oncol*. 2023;18(5):620-627. 3. Bernstein E, et al. *JCO Precis Oncol*. 2024;8:e2300447.

Diagnosing NSCLC

Diagnostic Algorithm of NSCLC[1,2]

Patient Presentation

- Medical history
- Physical examination
- Comorbidity assessment
- Performance status

Imaging and Labs

- CT of thorax and upper body
- PET-CT
- MRI of brain
- Blood cell counts
- Renal function
- Liver enzymes

Cardiopulmonary Function

- Forced expiratory vital capacity
- Forced expiratory volume in 1 second
- Diffusing capacity of the lungs for CO
- Electrocardiogram

Biopsy and Genomic Profiling

- Tissue specimen acquisition (eg, FFPE tissue, cell blocks)
- Plasma specimen acquisition
- Molecular testing (eg, NGS, PCR, FISH, IHC)

CO = carbon monoxide; CT = computed tomography; FFPE = formalin-fixed paraffin-embedded; FISH = fluorescence *in situ* hybridization; IHC = immunohistochemistry; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PET = positron emission tomography.

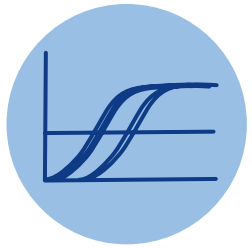
1. Remon J, Soria JC, Peters S. *Annals Oncol*. 2021;32(12):1637-1642. 2. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed December 19, 2023).

Single Analyte Diagnostic Methods Used in Precision Oncology

Protein or **Nucleic Acid** Detection Techniques

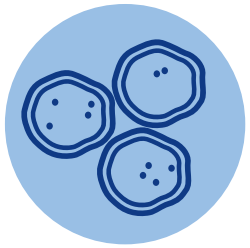
Immunohistochemistry[1-4]

- Detects protein expression
- Microscopy-based technique
- Unable to determine gene sequence or identify specific fusion partners



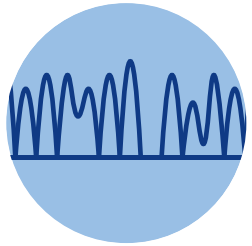
Polymerase chain reaction[3-6]

- Detects regions of interest within DNA or RNA
- Only detects known alterations



Fluorescence *in situ* hybridization[2,7]

- Visualizes specific genes/regions within a tissue sample
- Fluorescent microscopy-based technique
- Unable to determine gene sequence and limited to detection of known variations



Sanger sequencing[2,8-10]

- Detects SNVs, indels (insertions and deletions), and some fusion events in DNA
- Low-plex and low sensitivity traditional molecular method

SELECTED ASSAYS

- Variety of protein-specific antibodies available for use[4]

- ARMS-PCR[11]
- ddPCR[11]
- RT-PCR[4]
- qPCR[11]

- Variety of gene and region-specific probes available for use[4]

- PCR enrichment may be used to amplify specific DNA regions of interest for sequencing[4]

For source information, please see speaker notes.
ARMS = amplification refractory mutation system; ddPCR = droplet digital polymerase chain reaction; qPCR = quantitative polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction; SNV = single-nucleotide variant.

Comprehensive Diagnostic Methods Used in Precision Oncology

Nucleic Acid Detection Techniques

Next-generation sequencing[1-6]

- High-throughput testing of all actionable lung cancer biomarkers
- Detects all classes of genomic alterations
- Can test multiple genes of interests on limited material from biopsies or cytological samples
- Commonly used panels in NSCLC[a] include Tempus xT Gene Panel, MI® Tumor Seek™, and FoundationOne® CDx

NGS DNA tumor sequencing[7]	NGS RNA tumor sequencing[7]	NGS plasma sequencing[8]
• Allows for whole-genome or whole-exome sequencing	• Can analyze at the transcriptome level, including all types of RNA transcripts (mRNA, rRNA, tRNA, micro-RNA, and non-coding RNA) • mRNA sequencing can detect gene fusions	• Enrichment is performed on ctDNA collected by liquid biopsy • TAT is typically much shorter than that needed for tissue NGS

For source information, please see speaker notes.
[a]**This is not all-inclusive and does not represent all laboratories and tests. This list is intended for informational purposes and your considerations only, and it is based on publicly available information for these organizations.**
ctDNA = circulating tumor DNA; MI = Molecular Intelligence; mRNA = messenger RNA, rRNA = ribosomal RNA; TAT = turnaround time; tRNA = transfer RNA.

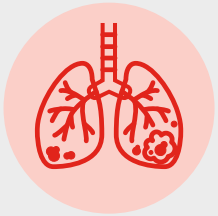
Molecular Testing Options to Identify Targetable Alterations in NSCLC

Target	Single Analyte Testing[1,2]			Comprehensive Testing[2,3]		
	PCR-based methods	FISH testing	IHC staining	NGS DNA tumor sequencing	NGS plasma sequencing	NGS RNA tumor sequencing
ALK rearrangements[1-3]	✓	✓	✓*	✓	✓	✓
BRAF mutations (including V600E)[2-4]	✓		✓*	✓	✓	✓
EGFR mutations, indels[2,3]	✓		✓	✓	✓	✓
EGFR amplification[2,3]	✓		✓	✓	✓	✓
ERBB2 (HER2) mutations[3]				✓	✓	✓
ERBB2 (HER2) amplification[3,5]	✓	✓		✓	✓	✓
HER2 protein expression[5]			✓			
KRAS mutations[3]	✓			✓	✓	✓
MET exon 14 mutation[3,6]	✓			✓	✓	✓
MET amplification[2,3]	✓	✓	✓*	✓	✓	✓
NTRK rearrangements[2,7]	✓	✓	✓	✓	✓	✓
RET rearrangements[2,3,8]	✓	✓	✓	✓	✓	✓
ROS1 rearrangements[1-3]	✓	✓	✓*	✓	✓	✓
PD-L1 protein expression[9,10]			✓			

NGS testing allows comprehensive, high-throughput testing of all recommended actionable biomarkers in lung cancer.[10]

For source information, please see speaker notes.
*Positive IHC results should be confirmed by a molecular or cytogenic method prior to initiating targeted therapy.

Post-Diagnostic Use of Biopsies

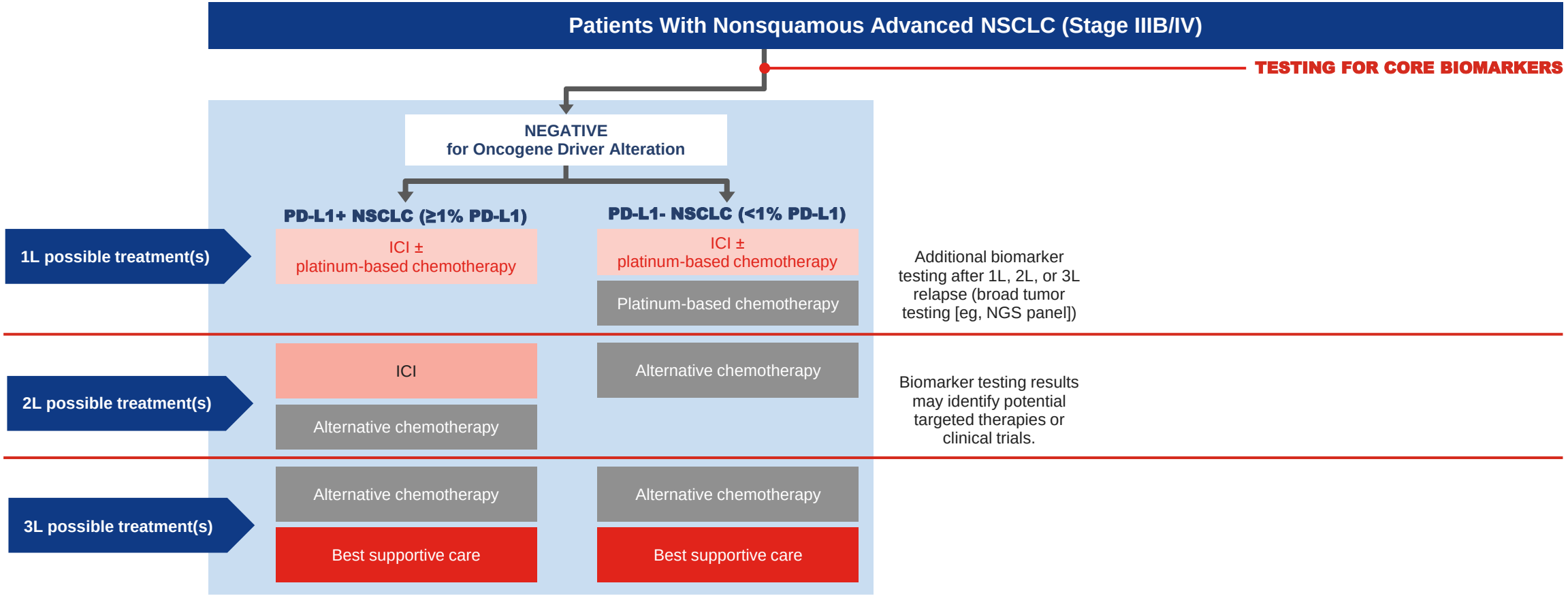
	Prognosis	Response	Resistance
Tissue 	• Repeat biopsies are often necessary to complete the range of molecular testing needed to make treatment decisions	• Not routinely used to assess treatment effect • Standard for confirming recurrence in NSCLC	• Standard of care for detection of resistance mediated by genetic mutations
Liquid 	• cfDNA can be used for early genotyping and assessment of ongoing prognosis • Can be a noninvasive approach for patients who are too sick to undergo tissue biopsy	• cfDNA may detect residual active cancer following treatment initiation • Detection of tumor mutations in cfDNA may be used to predict risk of recurrence	• Ideal for testing for resistance mechanisms due to their convenience and noninvasiveness

cfDNA = cell-free DNA.

Brown NA, Aisner DL, Oxnard GR. *Am Soc Clin Oncol Educ Book*. 2018;38:708-715.

Treatment of NSCLC

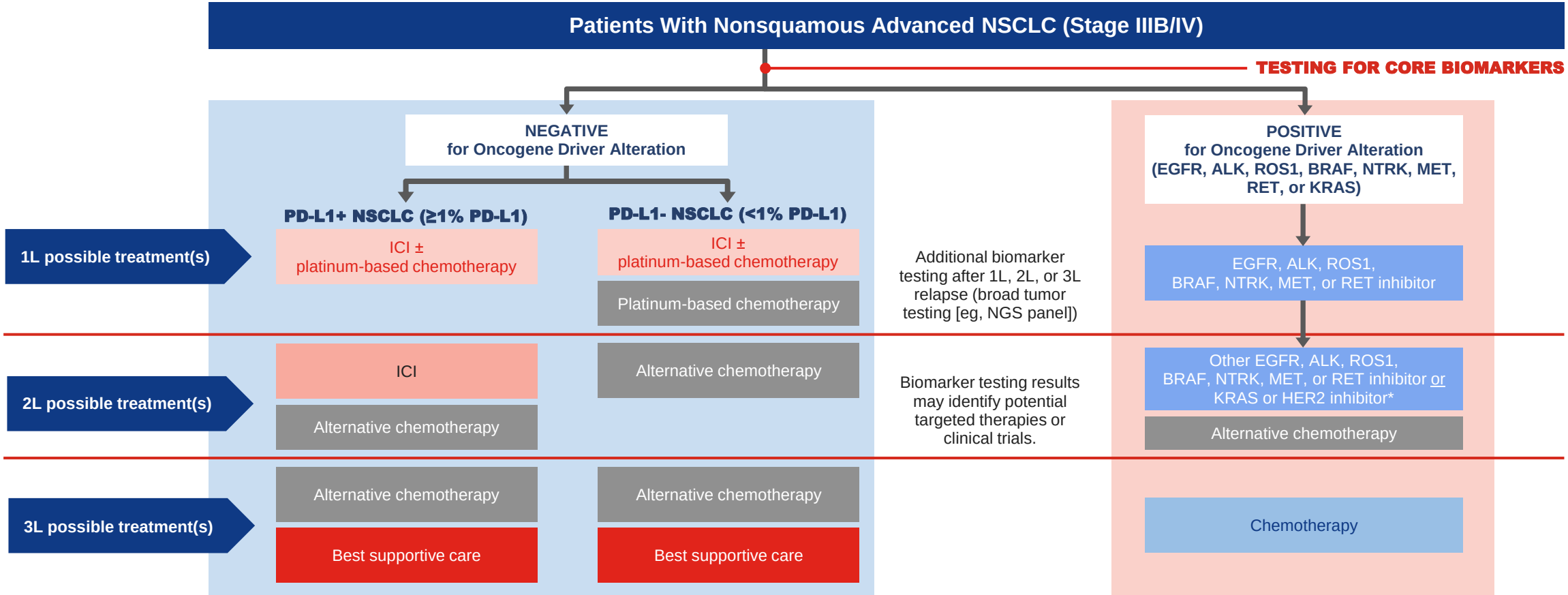
Advanced NSCLC (Nonsquamous) Treatment Journey: Biomarker Testing Is Essential to Patient Care[1-6]



*KRAS and HER2 inhibitors are approved for 2L+ therapy.
ICI = immune checkpoint inhibitor; 1L = first line; 2L = second line; 3L = third line.

1. Singh N, et al. *J Clin Oncol.* 2022;40(28):3310-3322. 2. Singh N, et al. *J Clin Oncol.* 2023;41(15):e51-e62. 3. Fam-Trastuzumab Deruxtecan-nxki [US PI]. Basking Ridge, NJ, USA: Daiichi Sankyo, Inc., 2019. 4. Adagrasib [US PI]. San Diego, CA, USA: Mirati Therapeutics, Inc., 2024. 5. Sotorasib [US PI]. Thousand Oaks, CA, USA: Amgen Inc., 2021. 6. Pembrolizumab [US PI]. Rahway, NJ, USA: Merck & Co., Inc., 2024.

Advanced NSCLC (Nonsquamous) Treatment Journey: Biomarker Testing Is Essential to Patient Care[1-6]



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FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]

EGFR alterations

ALK rearrangement

ROS1 rearrangement

BRAF V600E mutation

MET exon 14 skipping mutations

RET alterations

NTRK rearrangement

HER2 alterations

KRAS G12C mutations

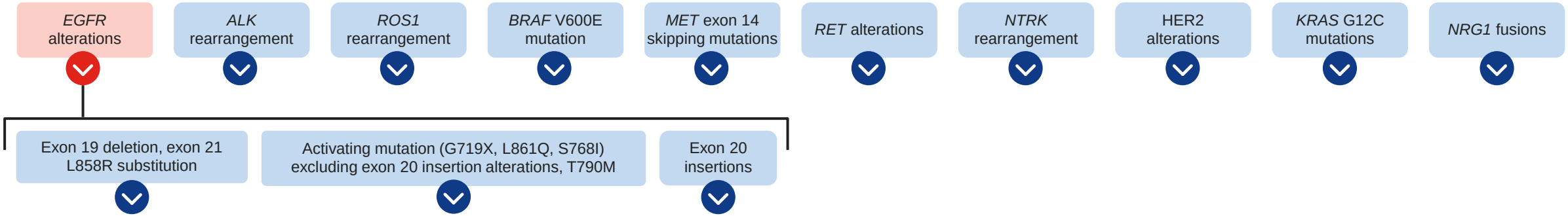
NRG1 fusions

Strength of Recommendation (ASCO) S Strong W Weak

To reveal treatment options, click on the blue arrow buttons.

For source information, please see speaker notes.
ASCO = American Society of Clinical Oncology.

FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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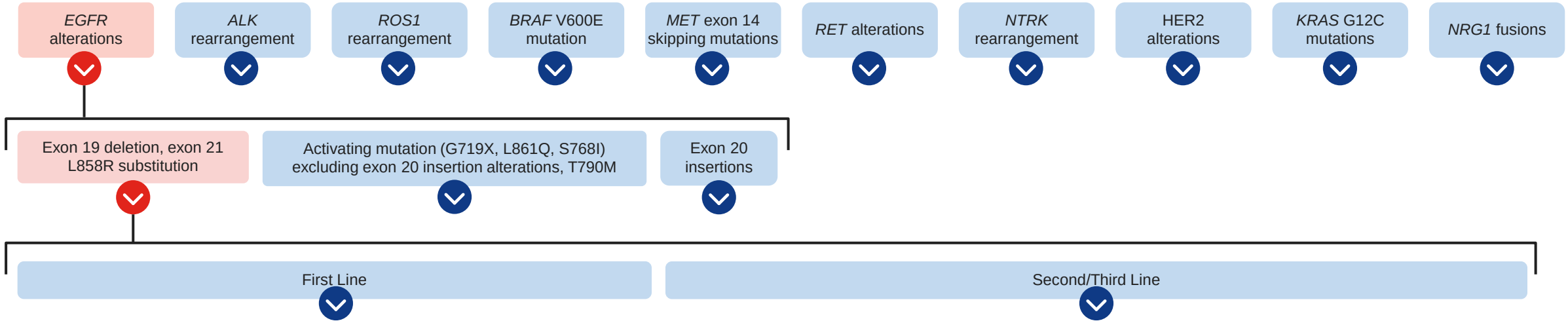
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) **S** Strong **W** Weak

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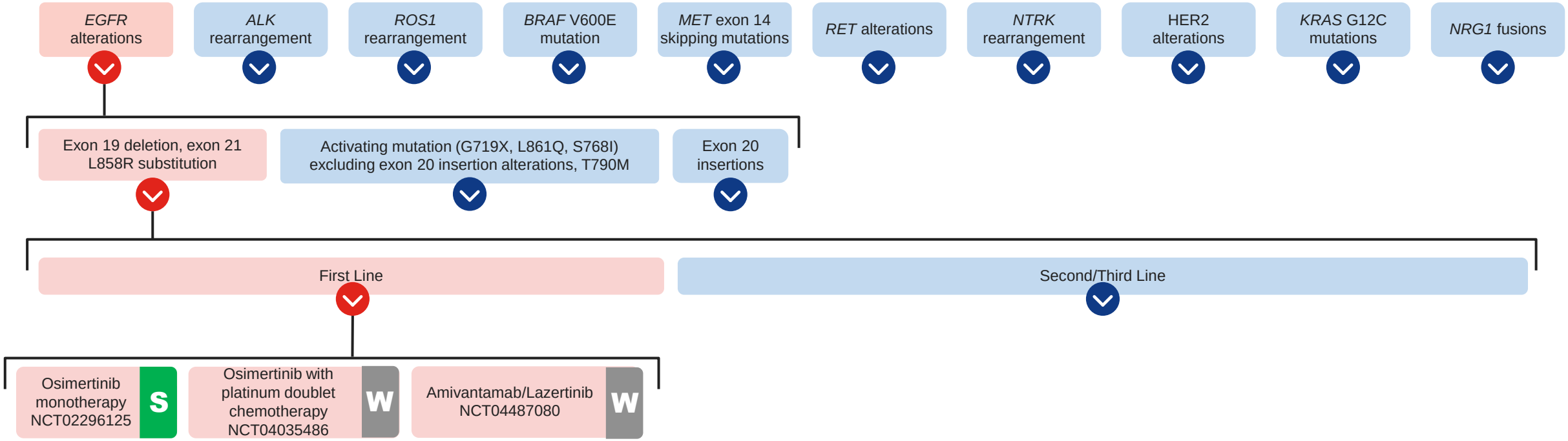
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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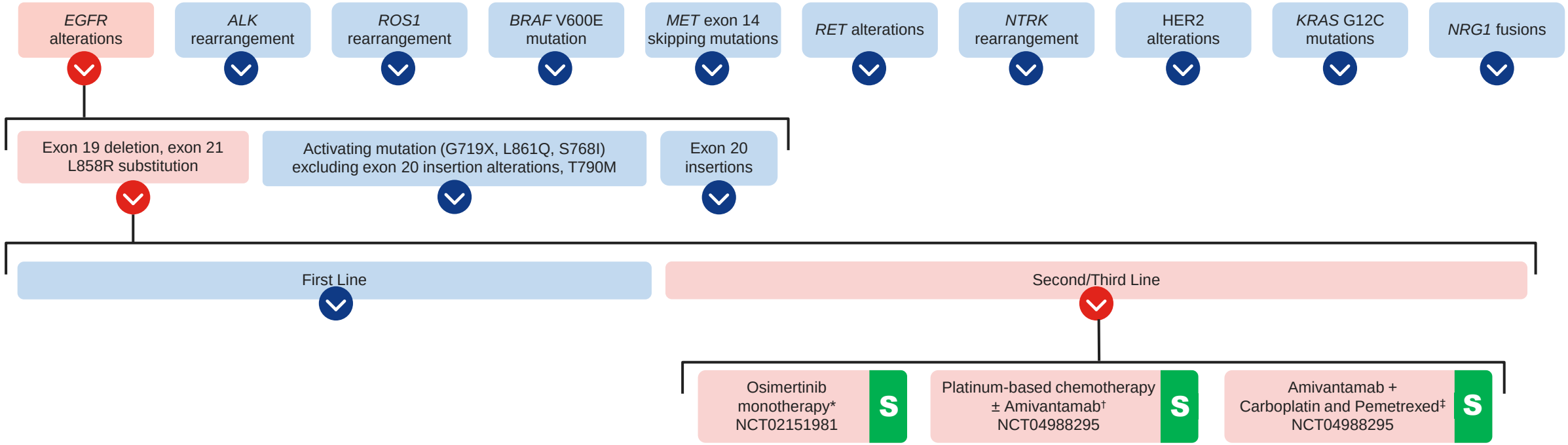
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

For source information, please see speaker notes.
*For patients that develop *EGFR* T790M resistance alterations in tumor after first- or second-generation EGFR TKIs. †For patients who have progressive disease on Osimertinib or other *EGFR* TKIs without emergent T790M or other targetable alterations. ‡For patients who have progressive disease on Osimertinib or other third-generation TKIs.
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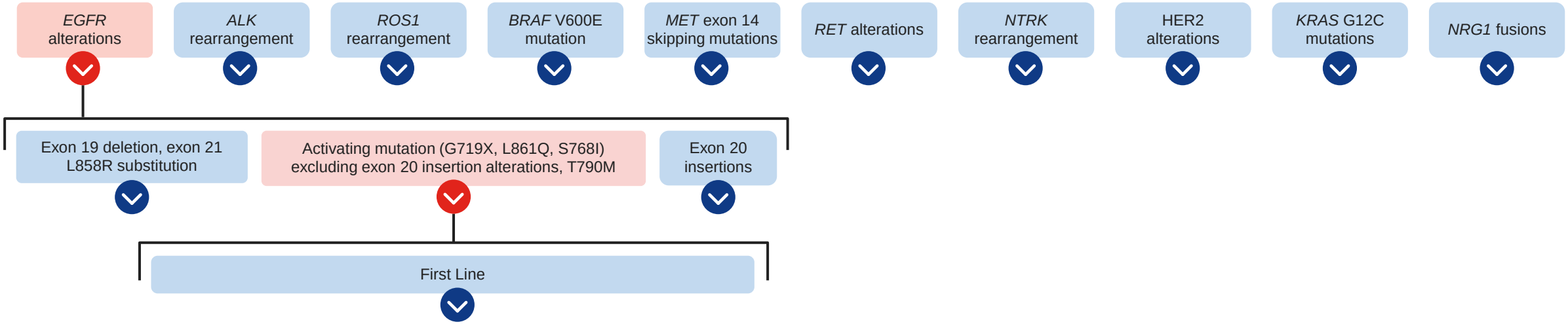
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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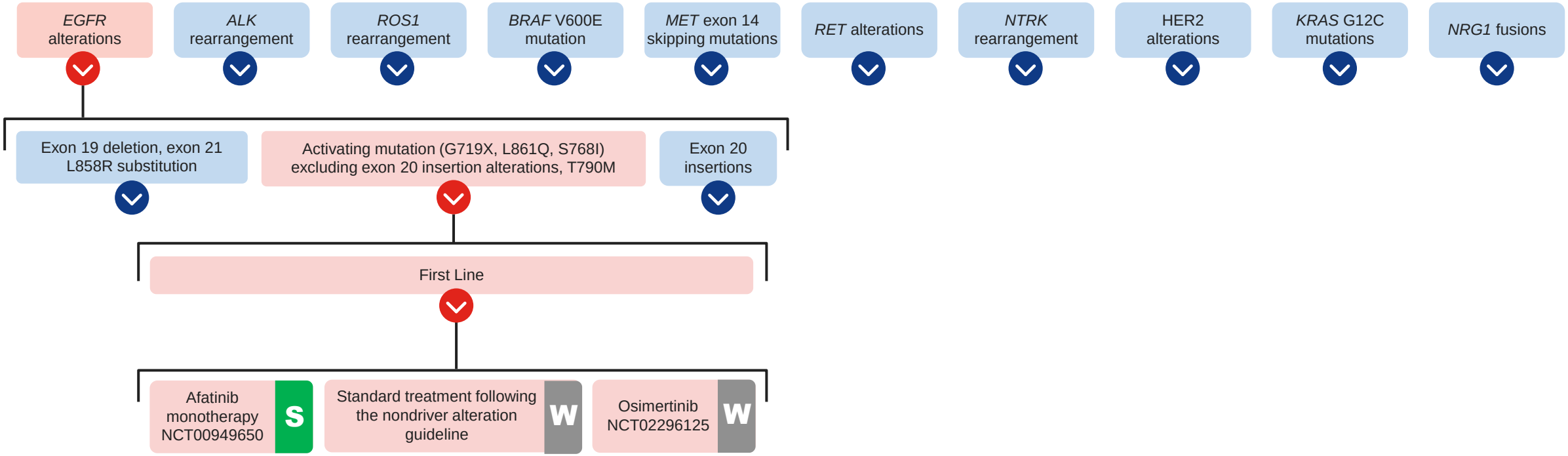

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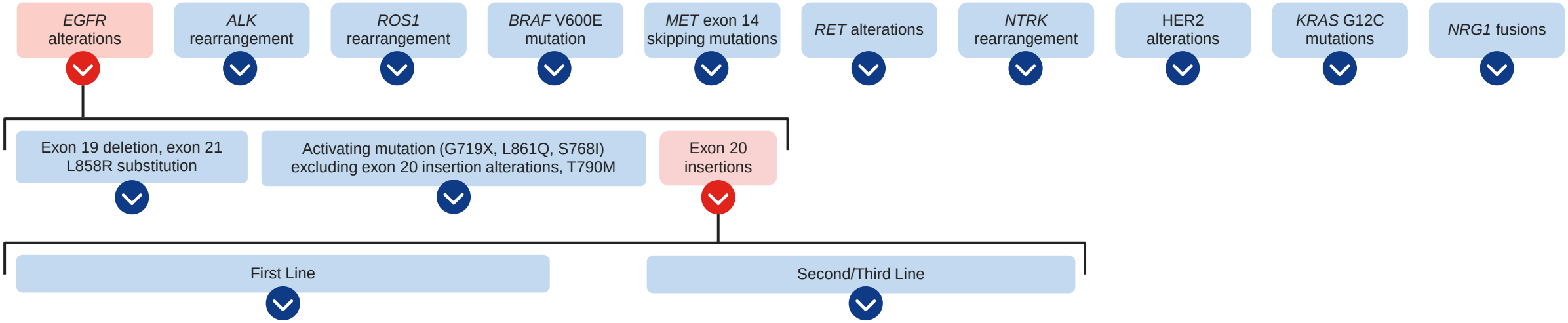

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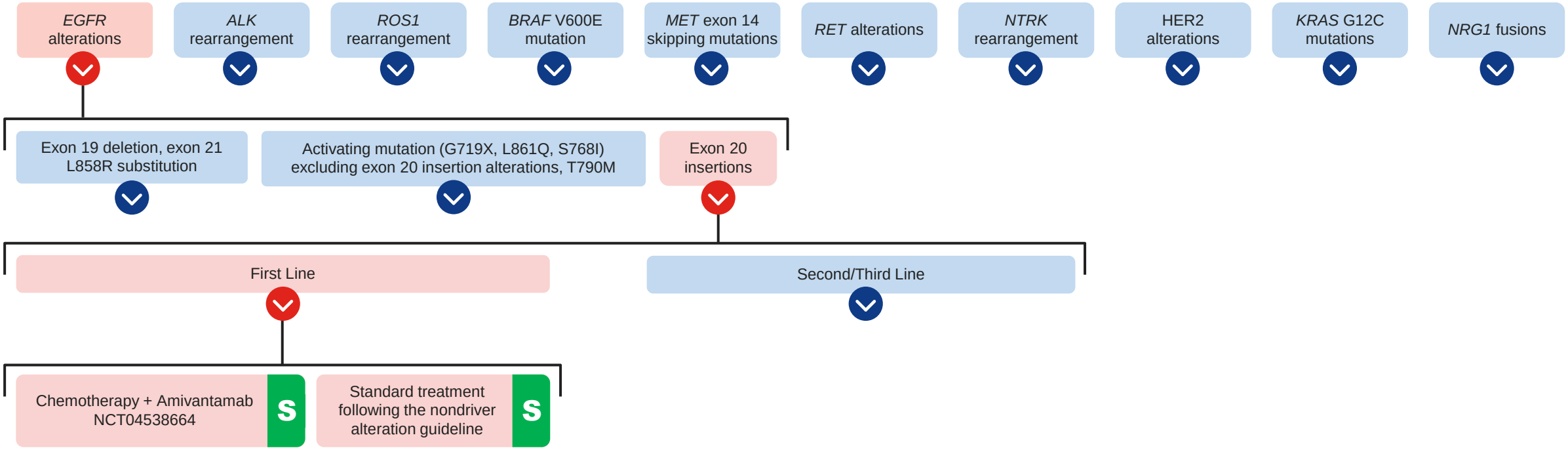

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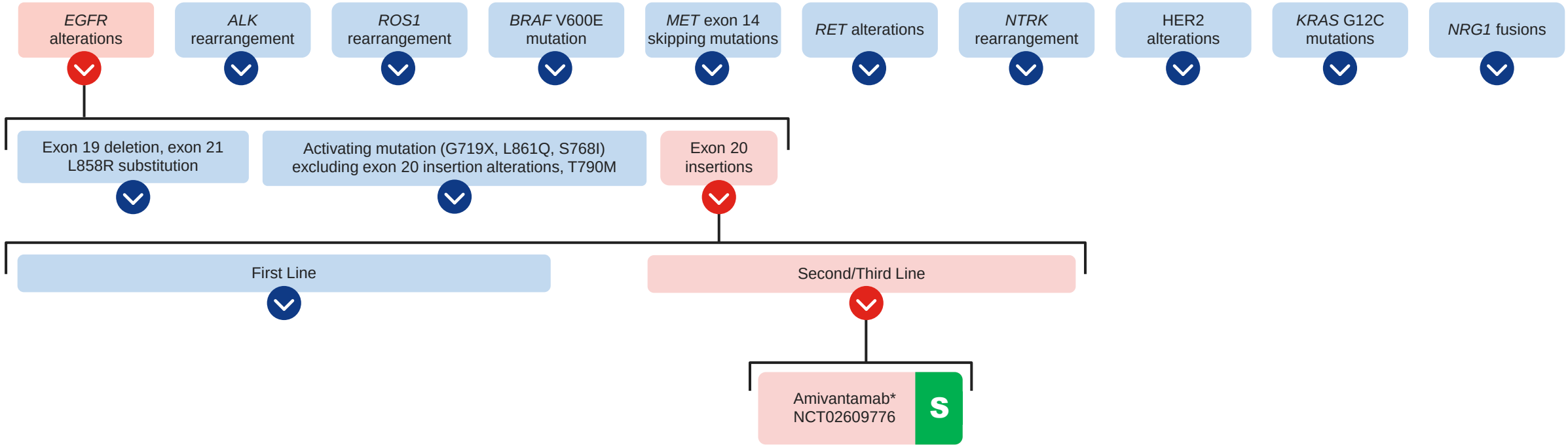

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Strength of Recommendation (ASCO) S Strong W Weak

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*For patients who received prior treatment with platinum chemotherapy.
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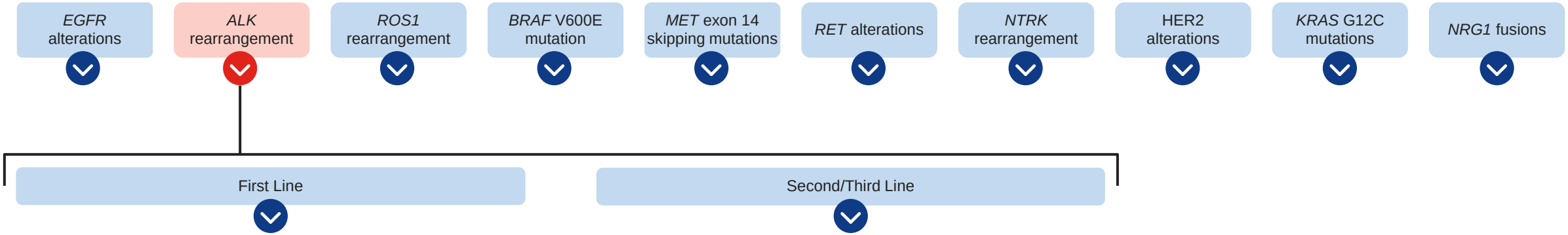
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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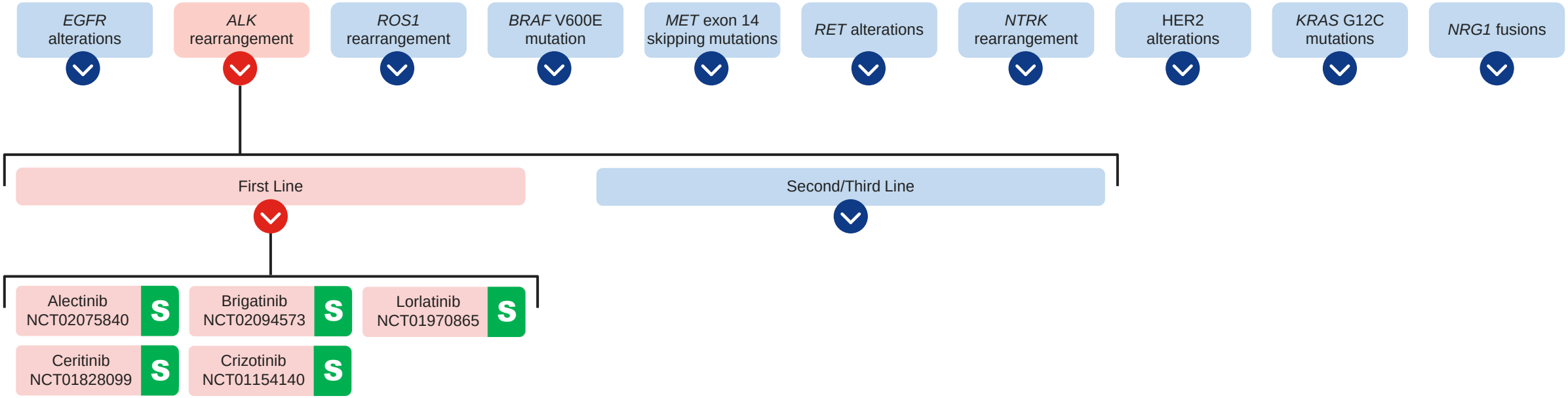

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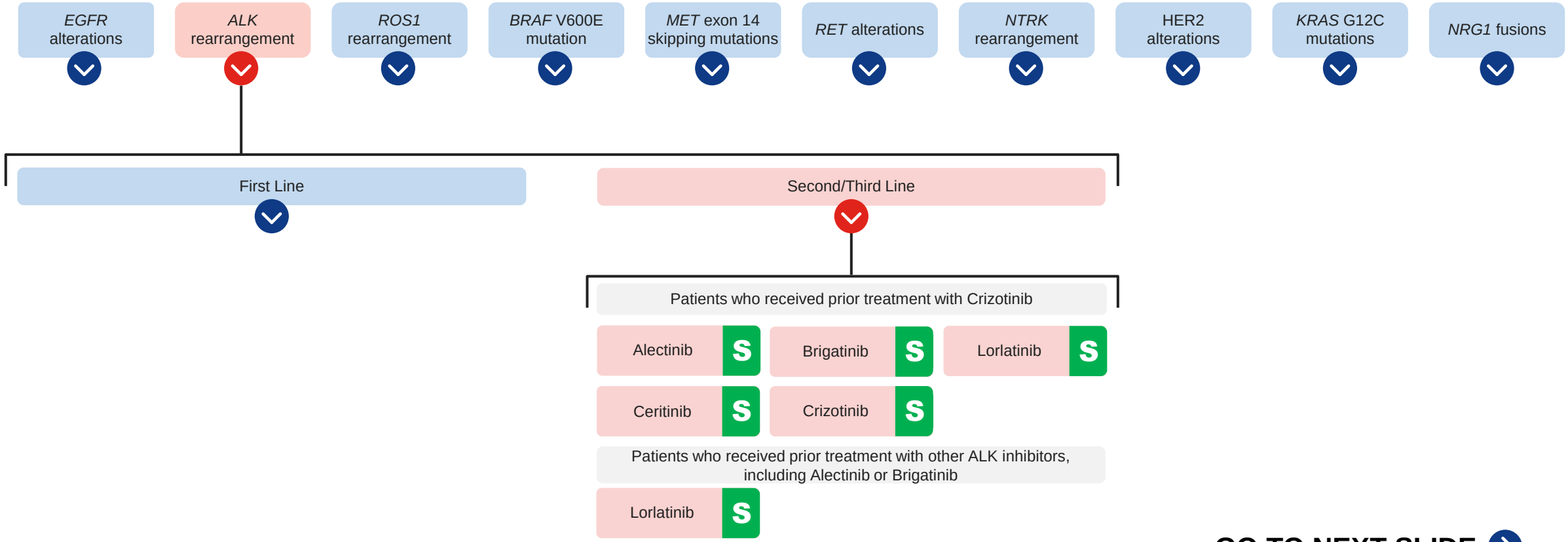

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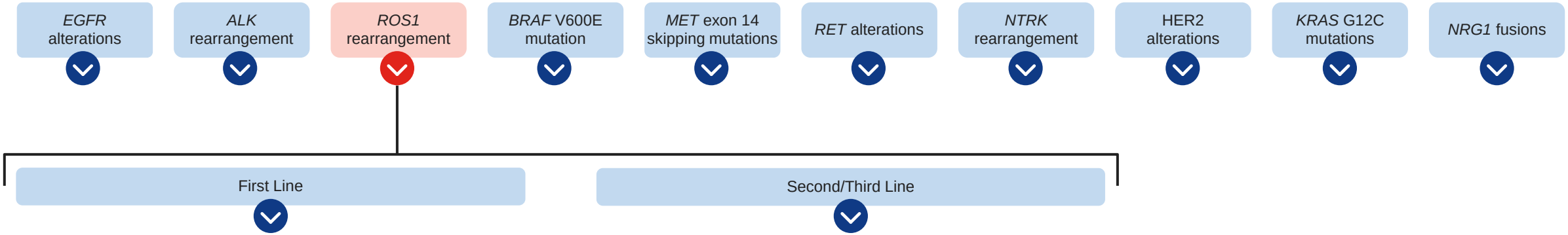

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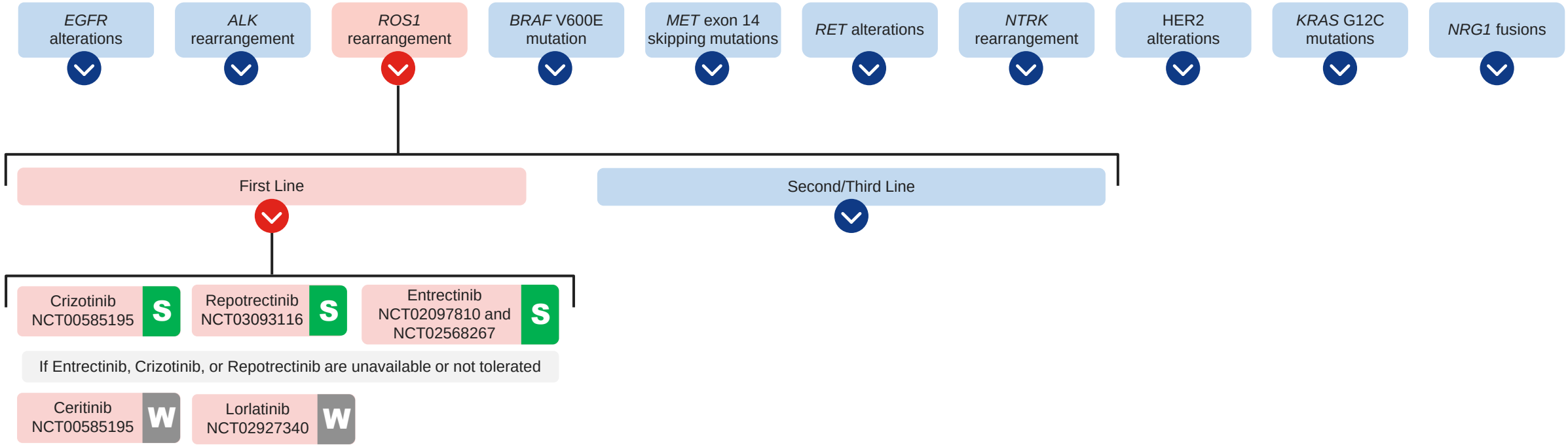

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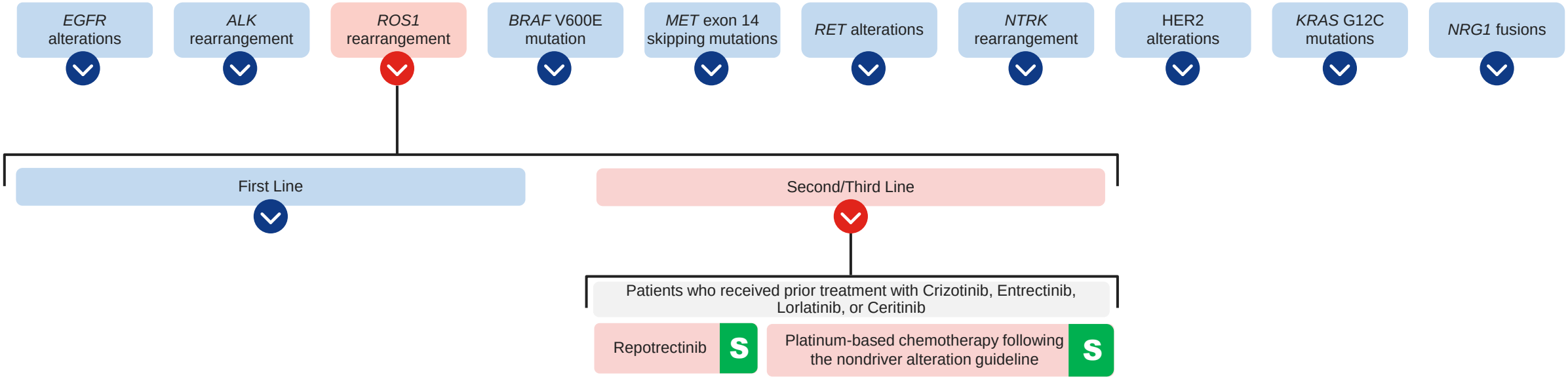

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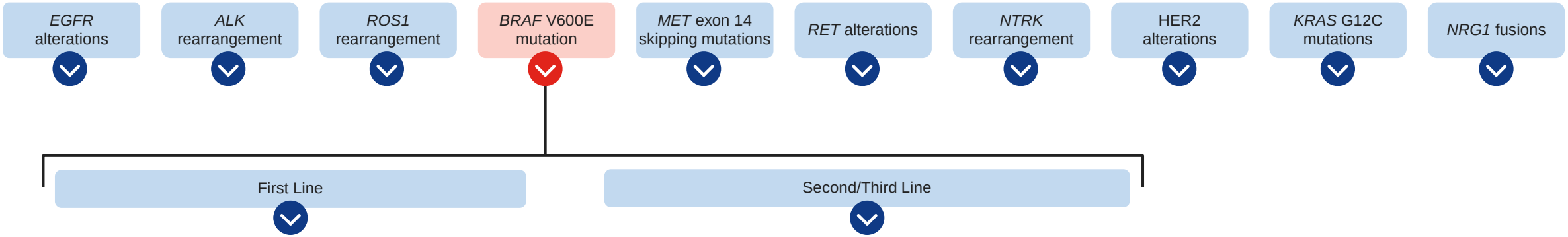

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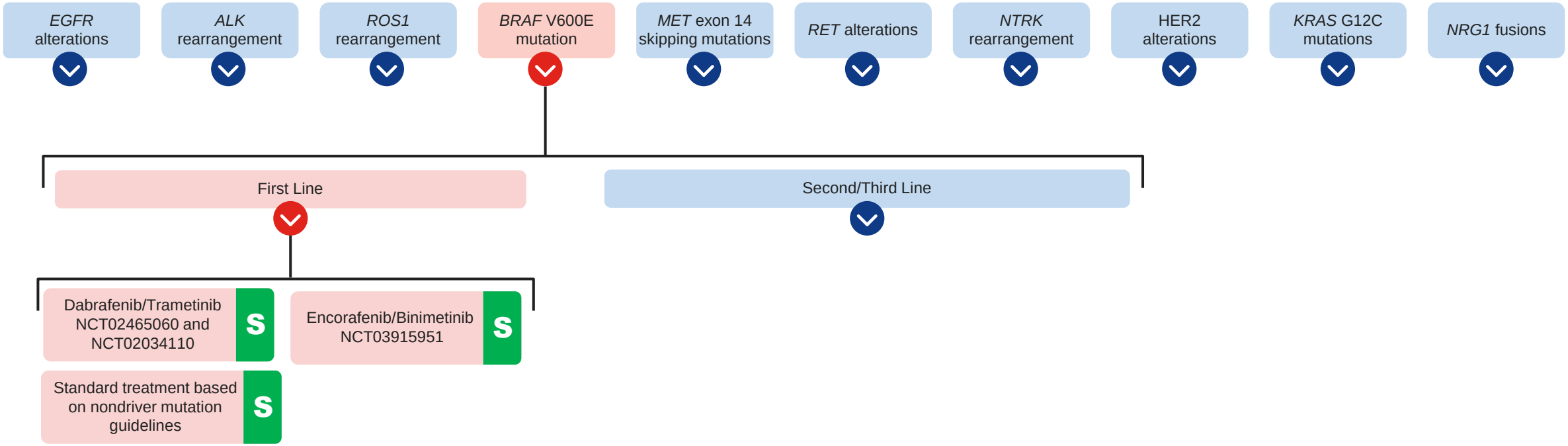
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



GO TO NEXT SLIDE

Strength of Recommendation (ASCO) S Strong W Weak

To reveal treatment options, click on the blue arrow buttons.

For source information, please see speaker notes.
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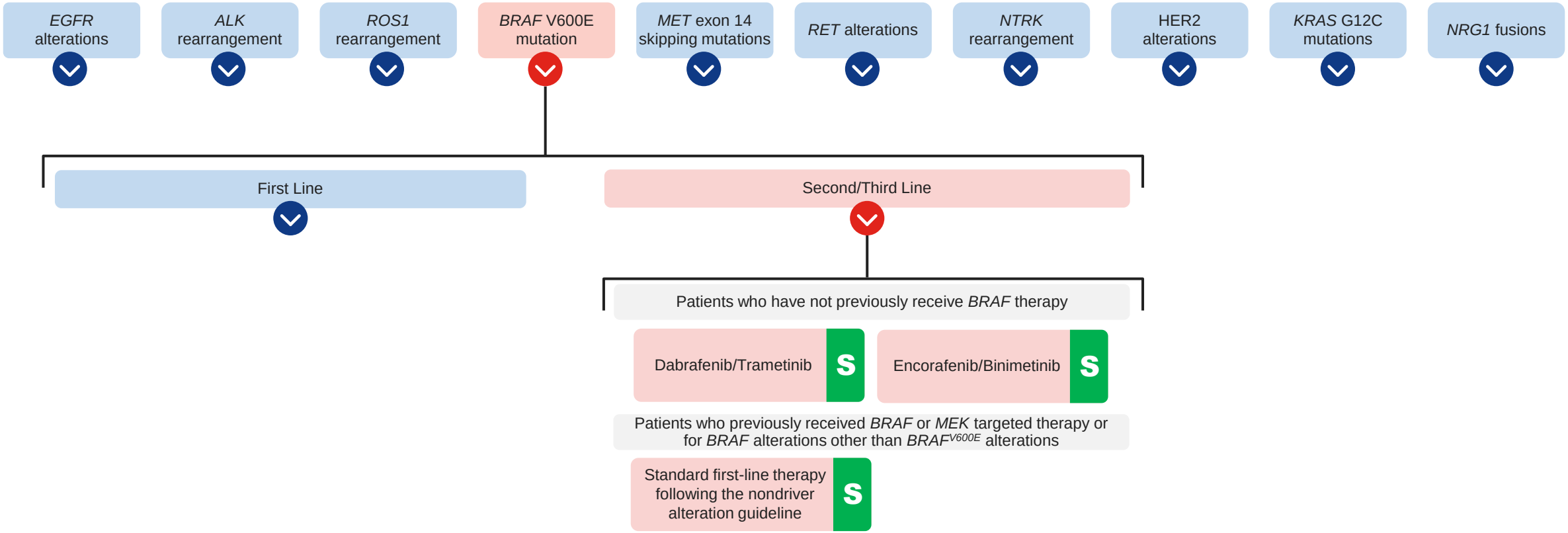
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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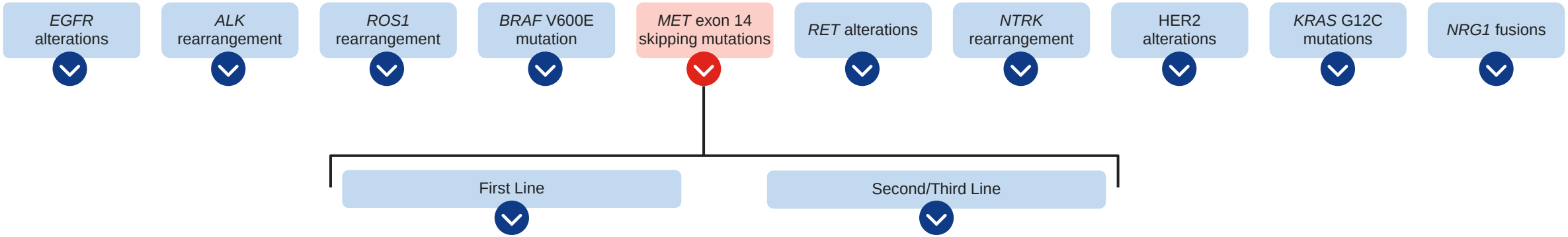
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) **S** Strong **W** Weak

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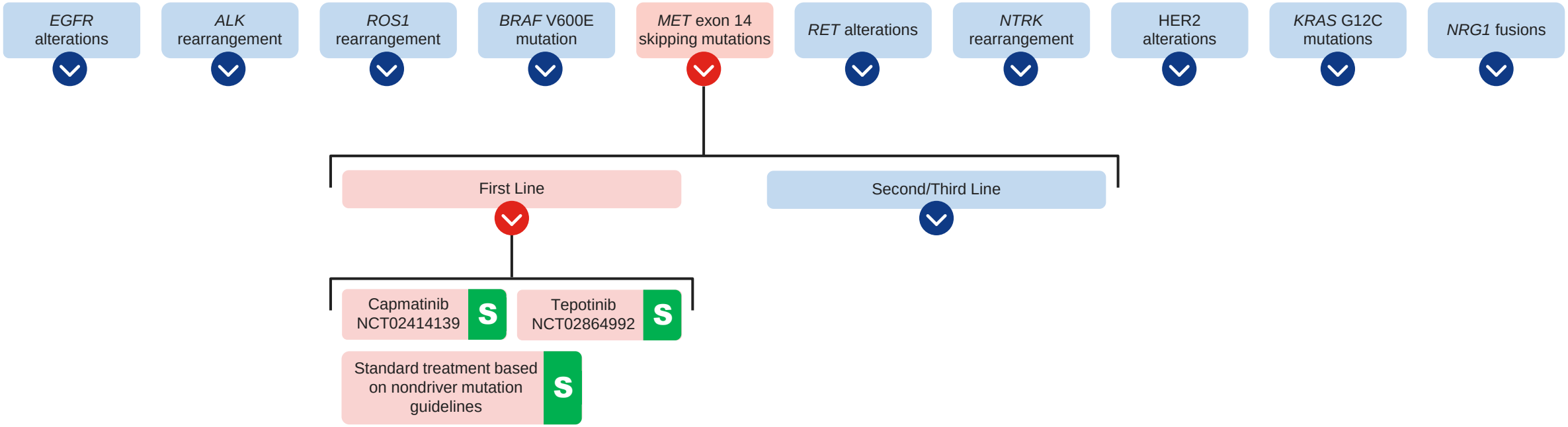
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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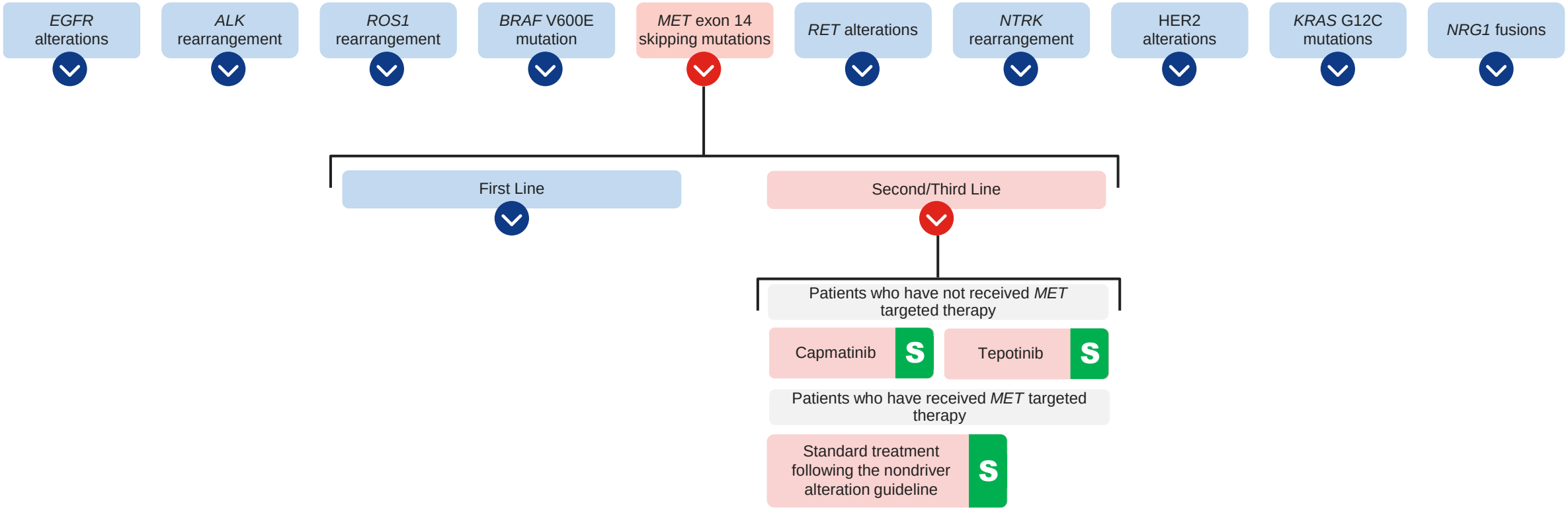
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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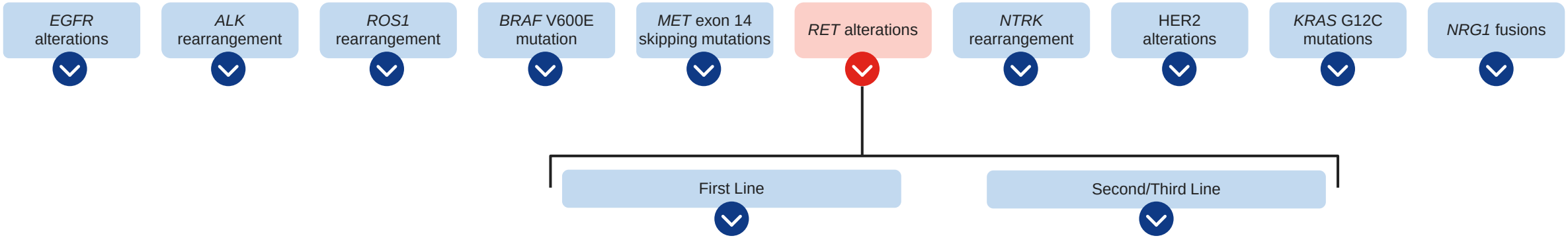
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) **S** Strong **W** Weak

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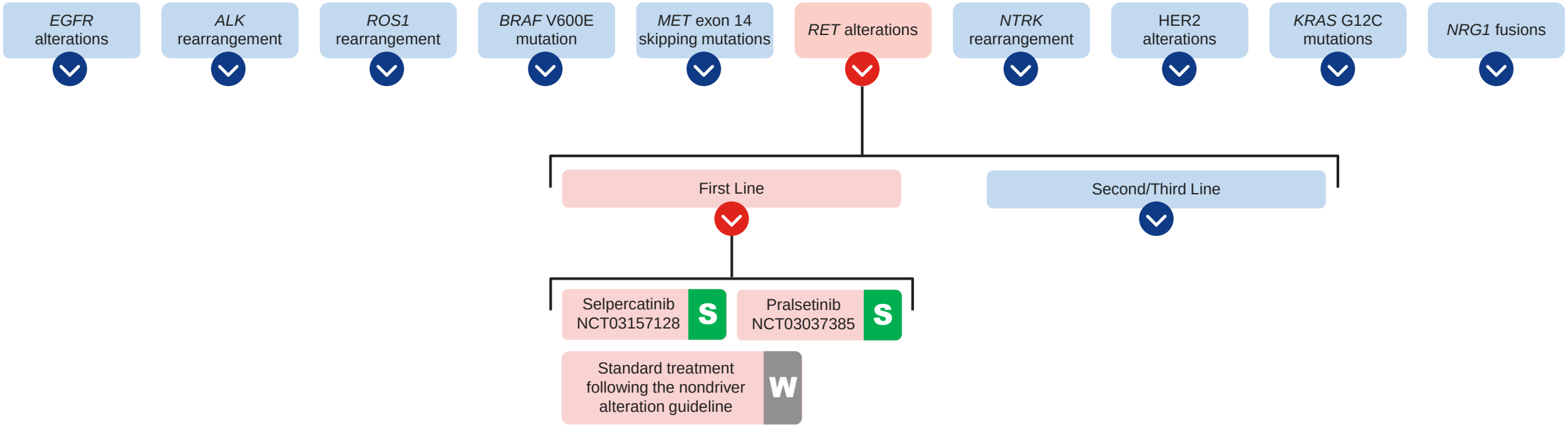
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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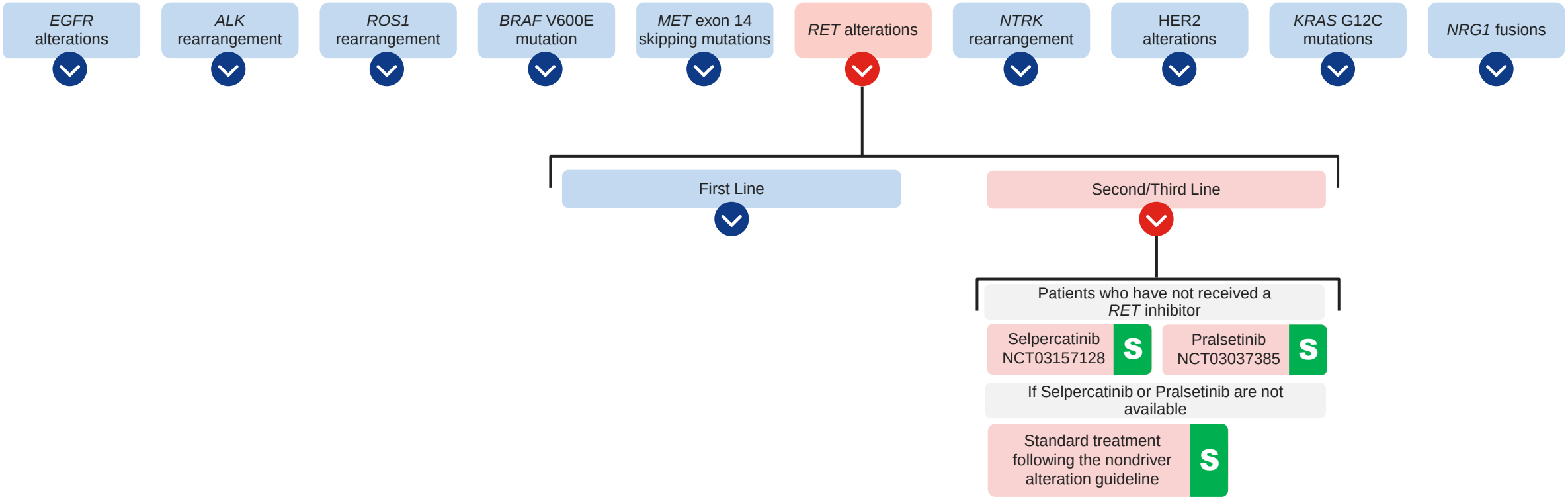
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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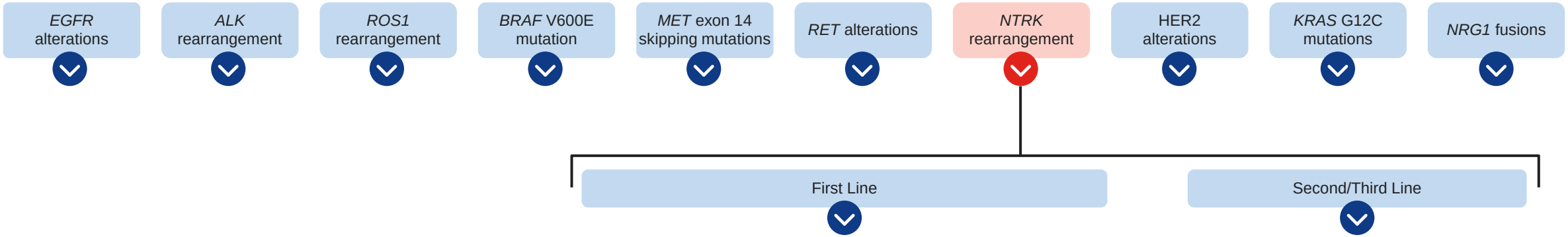
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) **S** Strong **W** Weak

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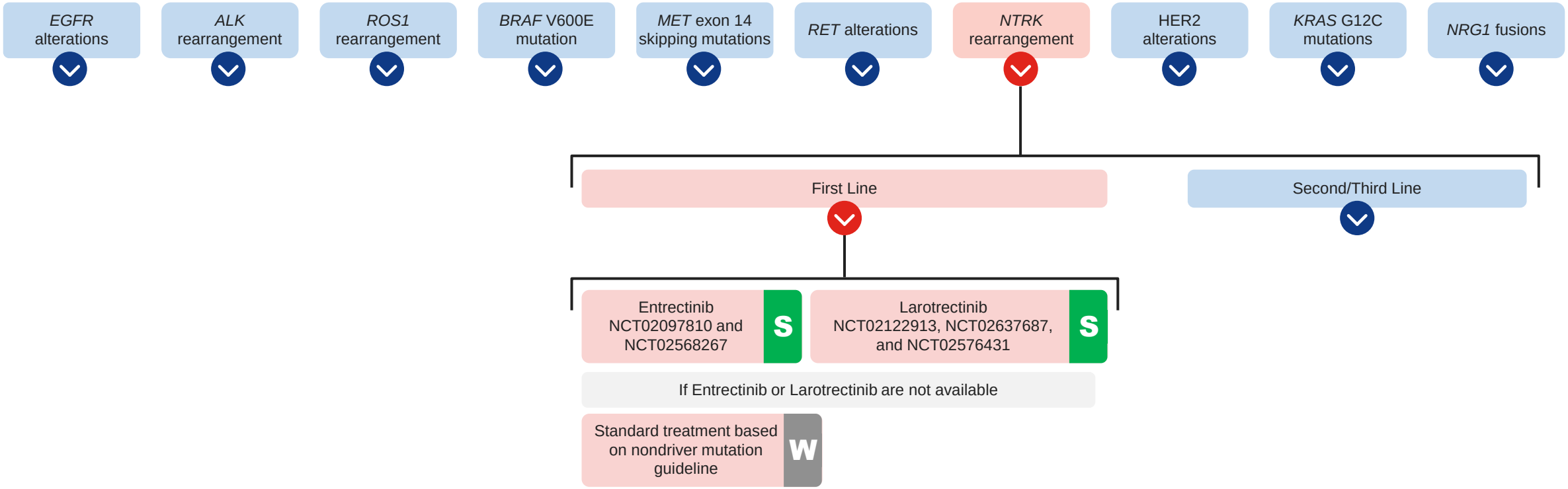
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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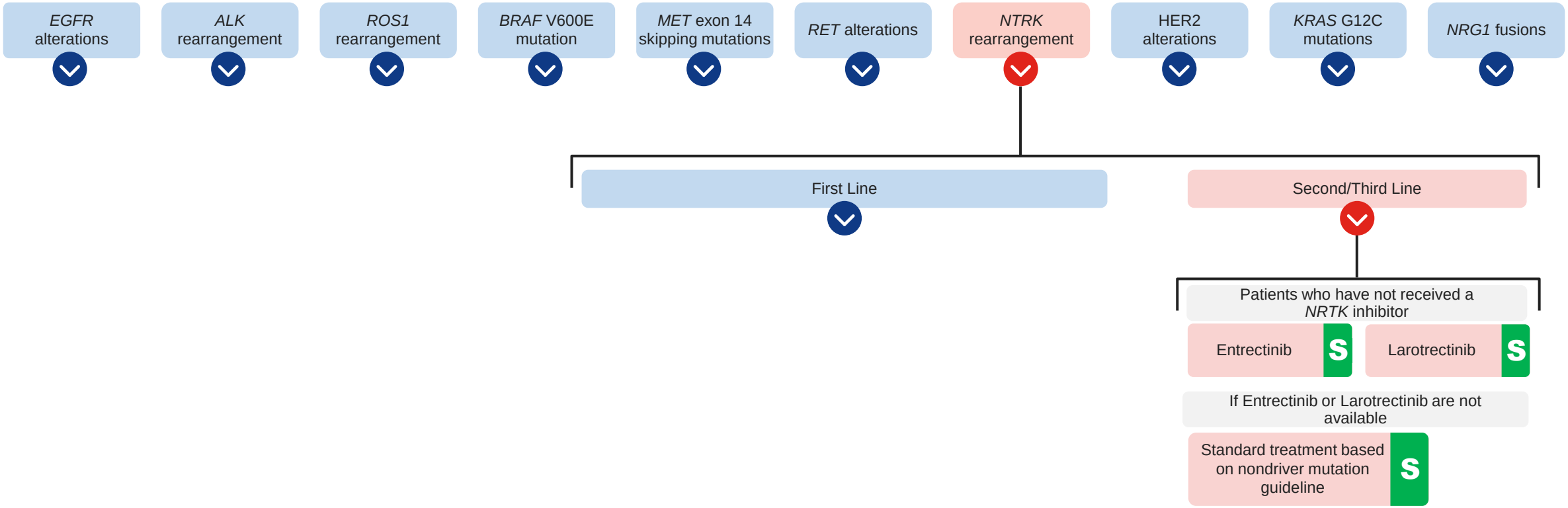
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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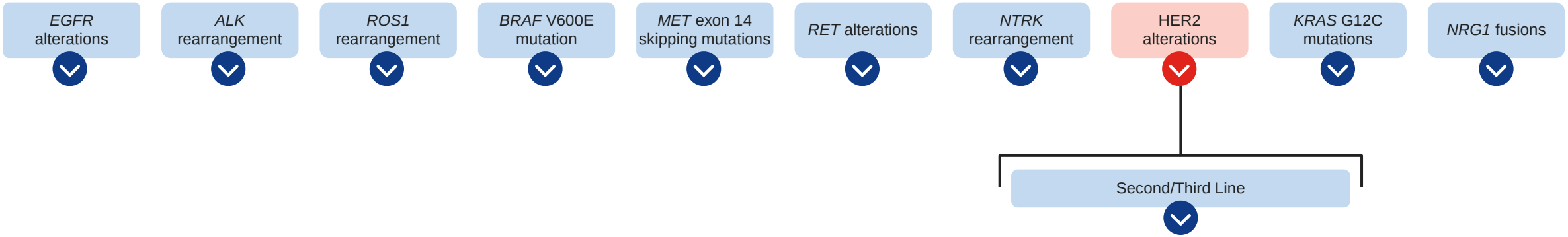
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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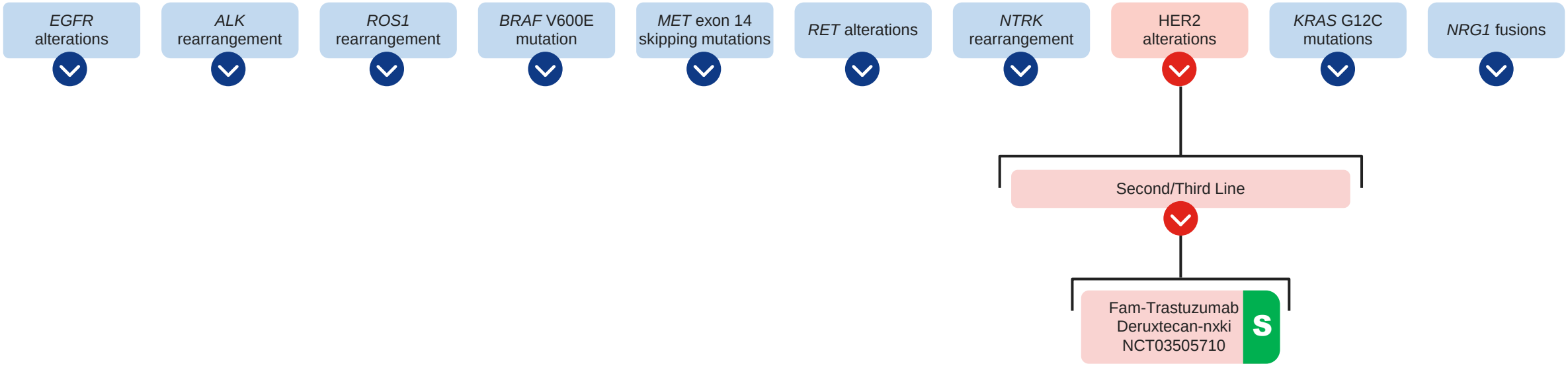
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong W Weak

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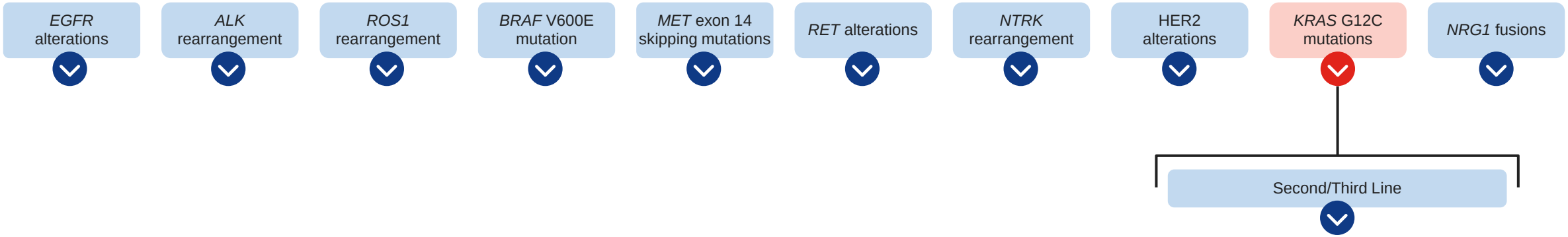
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) **S** Strong **W** Weak

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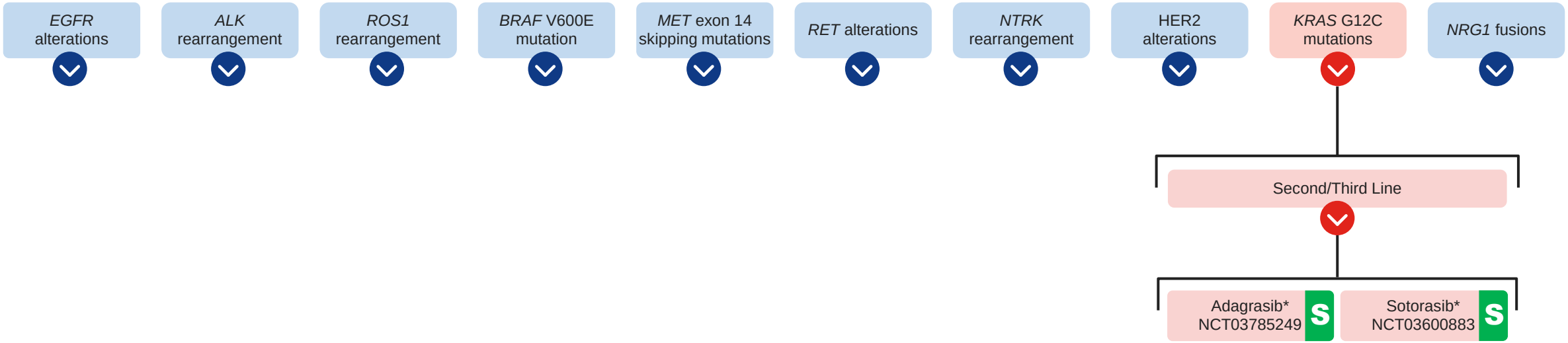
FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



To reveal treatment options, click on the blue arrow buttons.

For source information, please see speaker notes.

*Note that Adagrasib and Sotorasib are approved for patients who have received prior chemotherapy and/or anti–PD-(L)1 for patients with advanced *KRAS* G12C-mutant NSCLC. In the first-line setting, these patients should be offered standard first-line treatment with immune checkpoint inhibitor therapy and/or chemotherapy following the nondriver alteration guideline.

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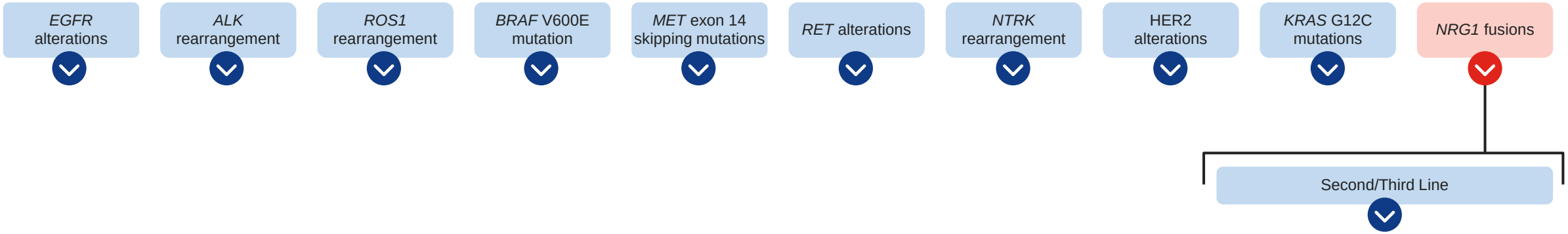
Strength of Recommendation (ASCO) S Strong W Weak

FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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For source information, please see speaker notes.

*Note that zenocutuzumab-zbco is not included in the ASCO living guideline as of June 2025. It received accelerated approval for use in advanced, unresectable, or metastatic NRG1 fusion-positive NSCLC by the US FDA in December 2024 based on ORR and DOR results from the eNRGy trial (NCT02912949).[5]

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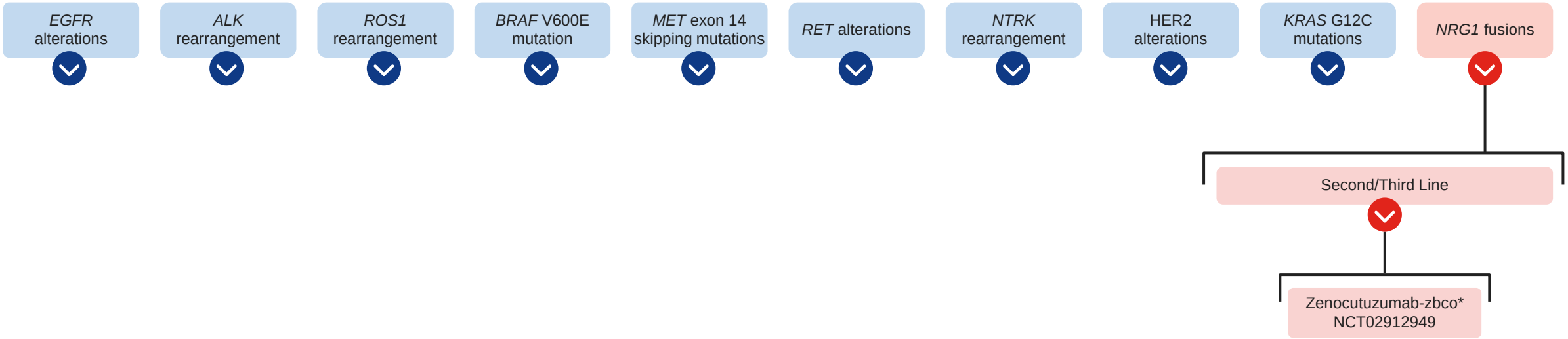
Strength of Recommendation (ASCO) S Strong W Weak

FDA-Approved Targeted Therapies for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) **S** Strong **W** Weak

FDA-Approved Drugs for Advanced NSCLC Without Driver Alteration[1,2]

Nongenomic Biomarker	FDA-Approved Drug(s) ± Chemotherapy	Studies That Led to Approval
PD-1/PD-L1 <1%	Pembrolizumab+platinum-based chemotherapy+Pemetrexed Atezolizumab+Carboplatin+Paclitaxel+Bevacizumab Atezolizumab+Carboplatin+Nab-Paclitaxel Nivolumab+Ipilimumab+chemotherapy Cemiplimab+chemotherapy Durvalumab+Tremelimumab+chemotherapy	KEYNOTE-189 (NCT02578680)[3] IMpower150 (NCT02366143)[4] IMpower130 (NCT02367781)[5] CheckMate 9LA (NCT03215706)[6] EMPOWER-Lung 3 (NCT03409614)[7] POSEIDON (NCT03164616)[8]
PD-1/PD-L1 ≥1-49%	Pembrolizumab+platinum-based chemotherapy+Pemetrexed Pembrolizumab monotherapy Atezolizumab+Carboplatin+Paclitaxel+Bevacizumab Atezolizumab+Carboplatin+Nab-Paclitaxel Nivolumab+Ipilimumab±chemotherapy Cemiplimab+chemotherapy Durvalumab+Tremelimumab+chemotherapy	KEYNOTE-189 (NCT02578680)[3] KEYNOTE-042 (NCT02220894)[9] IMpower150 (NCT02366143)[4] IMpower130 (NCT02367781)[5] CheckMate 9LA (NCT03215706)[6]; CheckMate 227 (NCT02477826)[10] EMPOWER-Lung 3 (NCT03409614)[7] POSEIDON (NCT03164616)[8]
PD-1/PD-L1 ≥50%	Pembrolizumab monotherapy Pembrolizumab+platinum-based chemotherapy+Pemetrexed Atezolizumab+Carboplatin+Paclitaxel+Bevacizumab Atezolizumab+Carboplatin+Nab-Paclitaxel Carboplatin-Paclitaxel or Nab-Paclitaxel±Pembrolizumab Cemiplimab-rwlc monotherapy Atezolizumab monotherapy Nivolumab+Ipilimumab±chemotherapy Cemiplimab+chemotherapy Durvalumab+Tremelimumab+chemotherapy	KEYNOTE-042 (NCT02220894)[9]; KEYNOTE-024 (NCT02142738)[11] KEYNOTE-189 (NCT02578680)[2] IMpower150 (NCT02366143)[4] IMpower130 (NCT02367781)[5] KEYNOTE-407 (NCT02775435)[12] EMPOWER-Lung1 (NCT03088540)[13] IMpower110 (NCT02409342)[14] CheckMate 9LA (NCT03215706)[6]; CheckMate 227 (NCT02477826)[9] EMPOWER-Lung 3 (NCT03409614)[7] POSEIDON (NCT03164616)[8]

For source information, please see speaker notes.
FDA = US Food and Drug Administration.