DISEASE STATE EDUCATION *NON–SMALL CELL LUNG CANCER*

Disclaimer

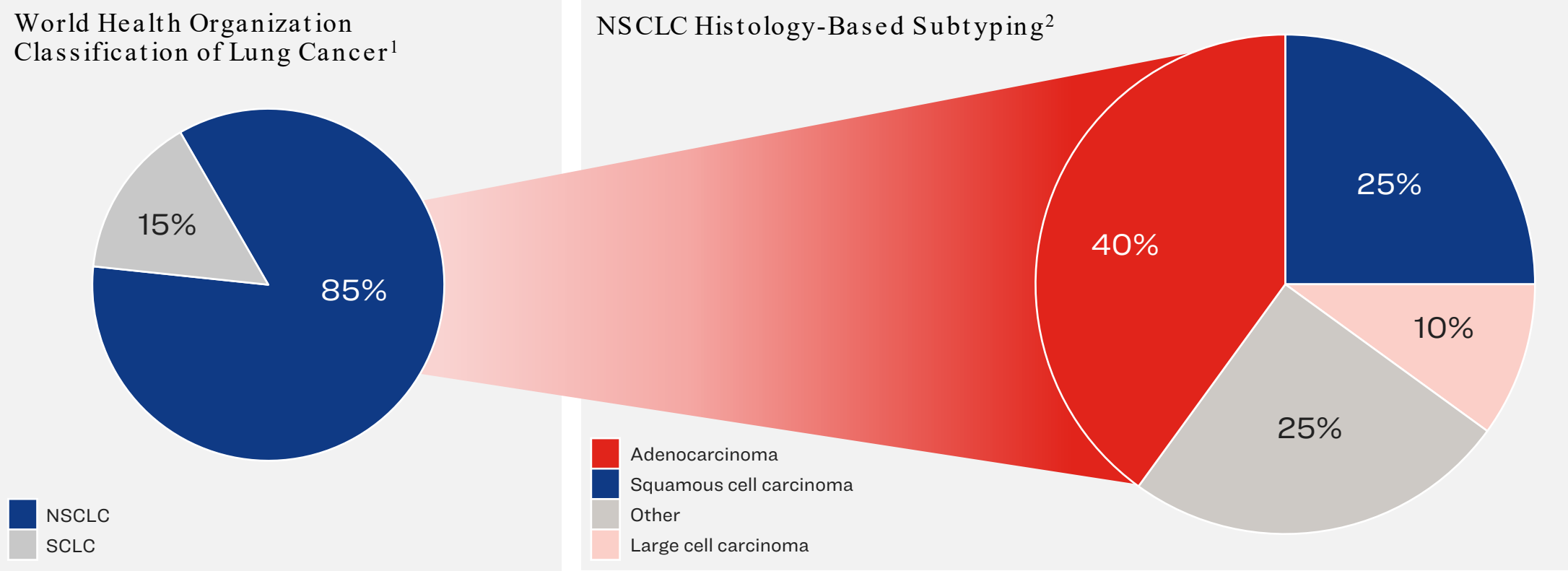
This information is intended for your scientific and/or educational purpose and is not intended for promotional use.

Table of Contents

Click on the specific tab to navigate to the corresponding section.
NGS = next-generation sequencing; NSCLC = non–small cell lung cancer.

Lung Cancer Overview

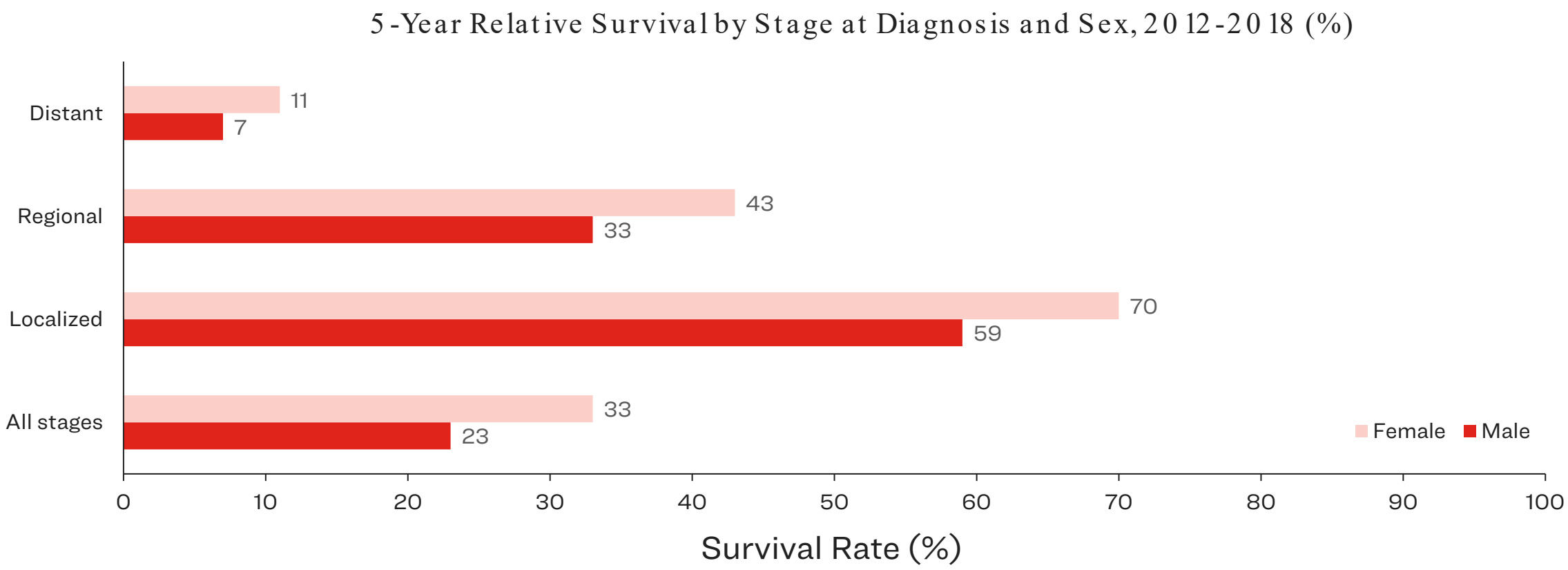
Lung Cancer Has Histologically Distinct Subtypes



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).

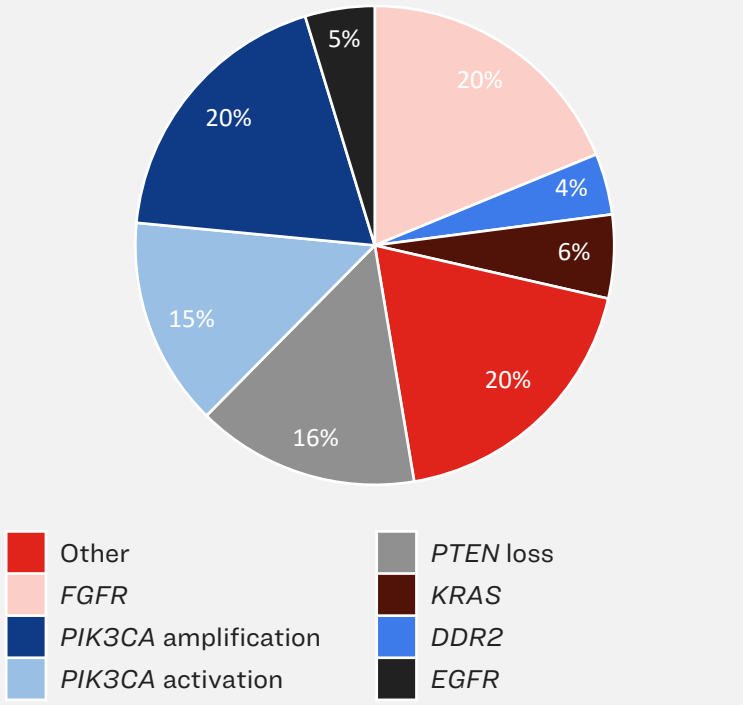
Early Detection of NSCLC Can Improve Patient Outcomes



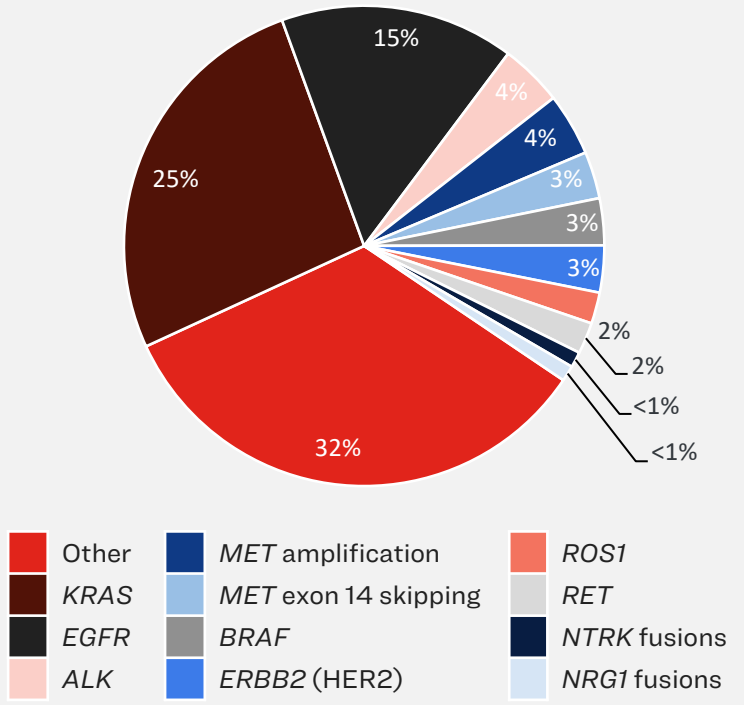
American Cancer Society. *Cancer Facts & Figures 2023.* Atlanta: American Cancer Society; 2023.

NSCLC Is Frequently Oncogene Driven

Squamous Cell Carcinoma[1]



Adenocarcinoma[2]



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

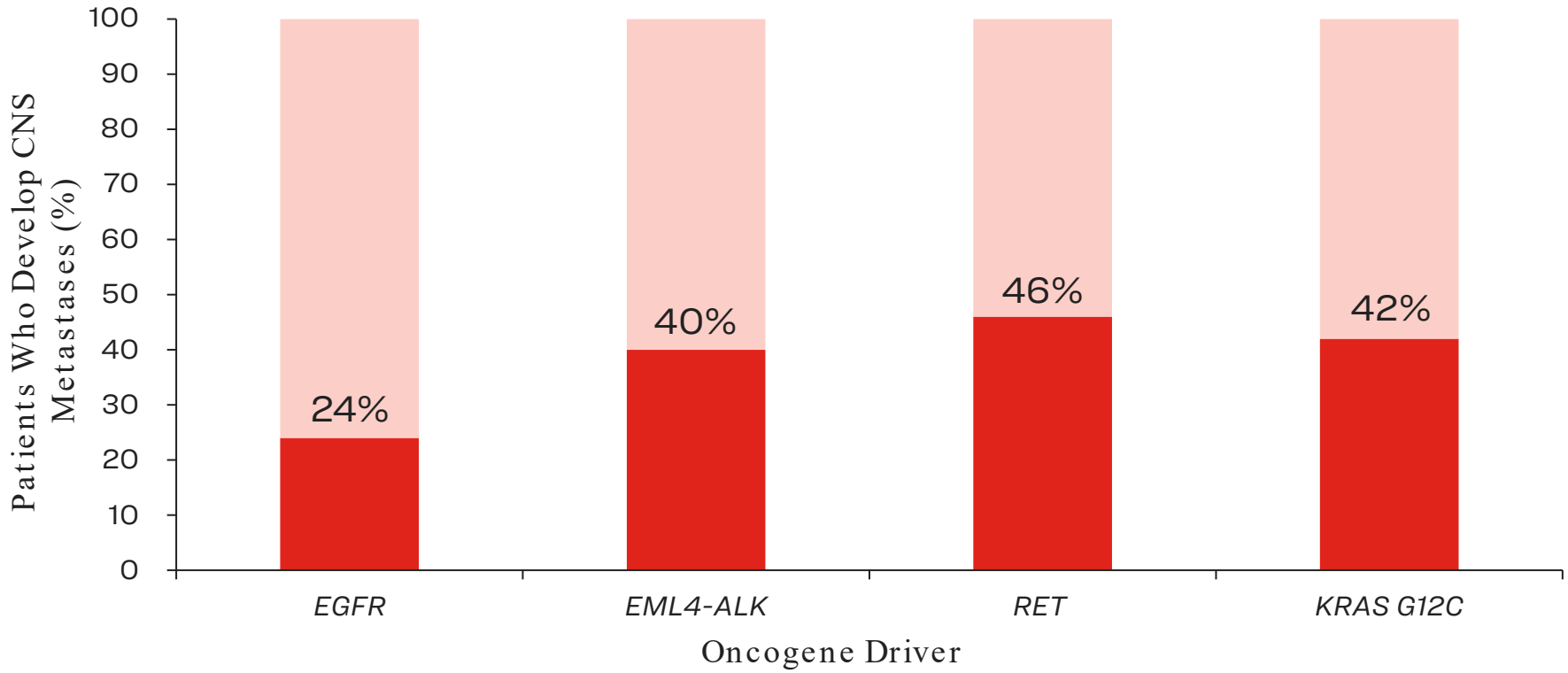
- *EGFR* mutations
- *ALK* rearrangement
- *ROS1* rearrangement
- *BRAF* V600E mutation
- *MET* exon 14 skipping
- *ERBB2* (HER2) mutations
- *NTRK* fusions
- *KRAS* point mutations
- *RET* rearrangement

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.

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).

Prevalence of CNS 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.

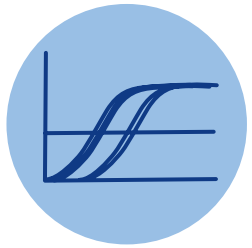
1. Remon J, Soria JC, Peters S. *Annals Oncol*. 2021;32(12):1637-1642. 2. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed December 19, 2023).

Single Analyte Diagnostic Methods Used in Precision Oncology

Protein or **Nucleic Acid** Detection Techniques

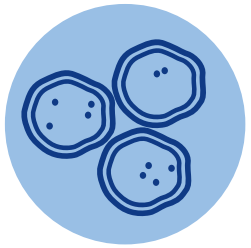
Immunohistochemistry[1-4]

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



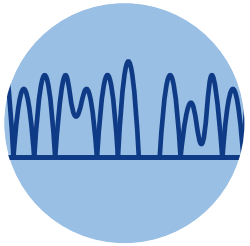
Polymerase chain reaction[3-6]

- 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.

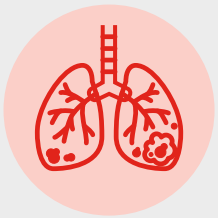
Molecular Testing Options to Identify Targetable Alterations in NSCLC

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

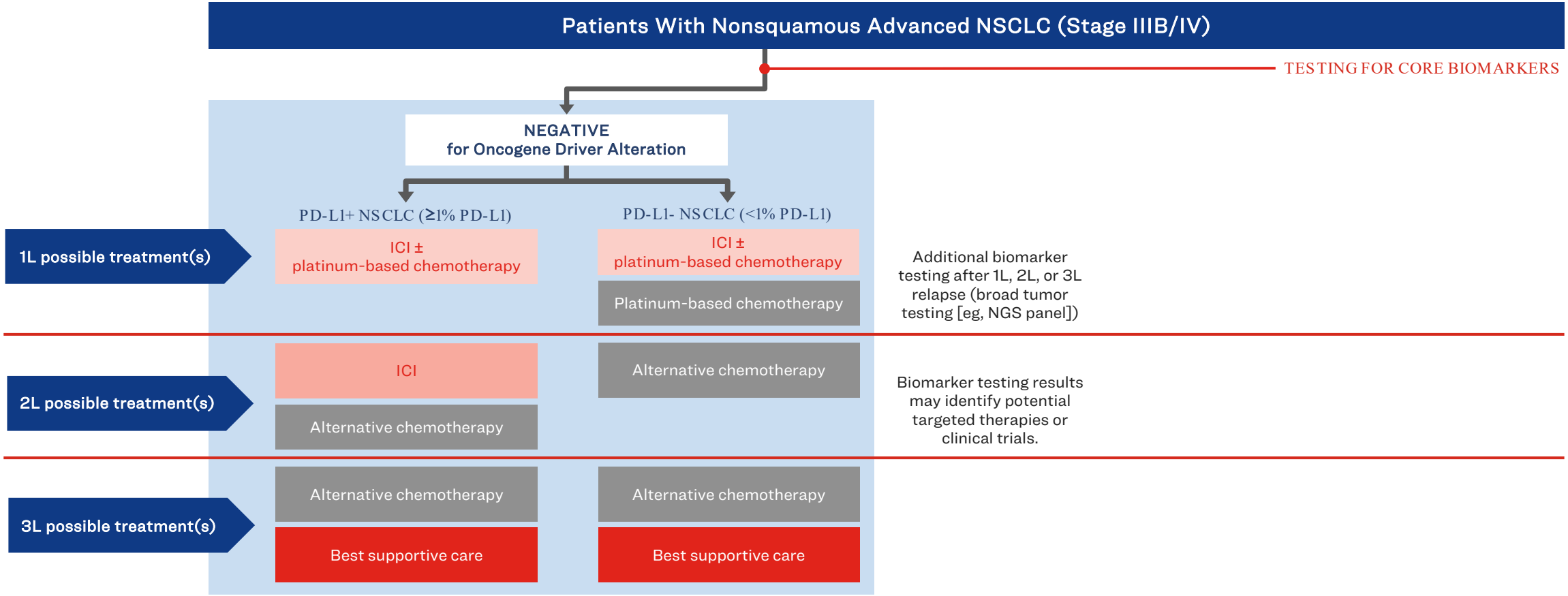
	Prognosis	Response	Resistance
Tissue 	• Repeat biopsies are often necessary to complete the range of molecular testing needed to make treatment decisions	• Not routinely used to assess treatment effect • Standard for confirming recurrence in NSCLC	• Standard of care for detection of resistance mediated 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.

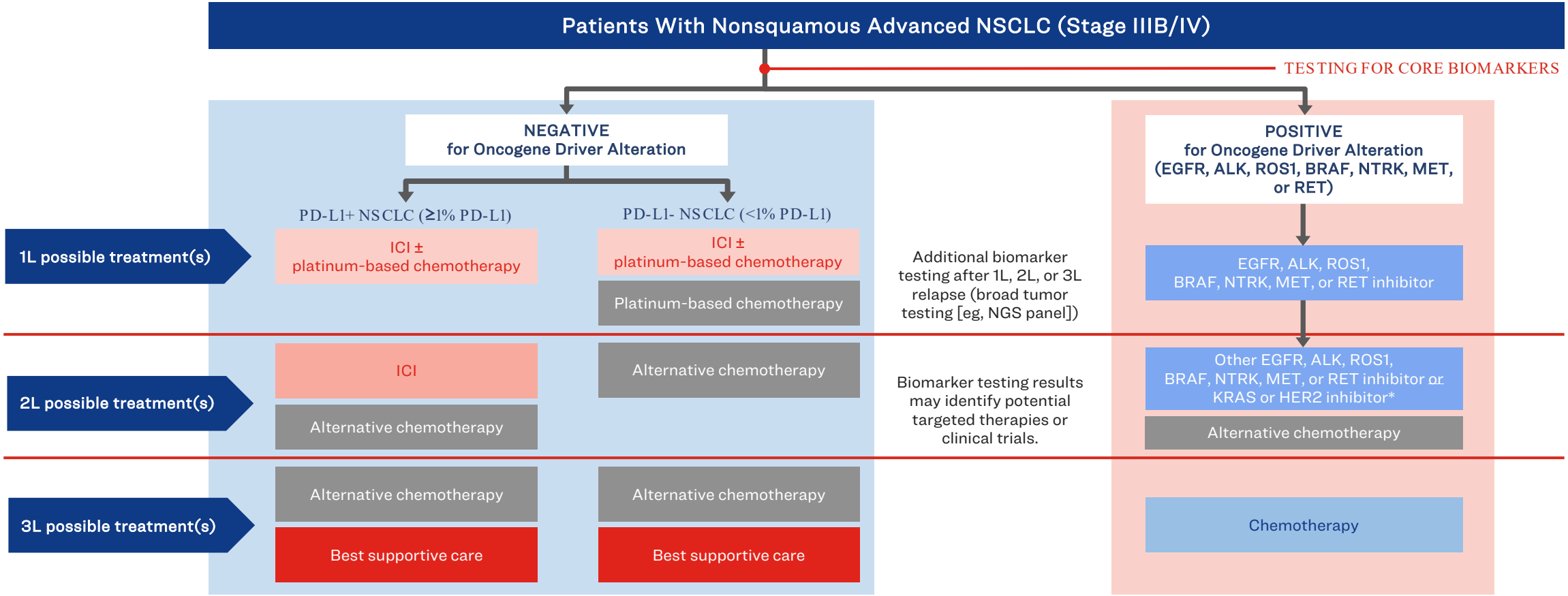
Treatment of NSCLC

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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NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]

- *EGFR* alterations
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- *ROS1* rearrangement
- *BRAF* V600E mutation
- *MET* exon 14 skipping mutations
- *RET* alterations
- *NTRK* rearrangement
- HER2 alterations
- *KRAS* mutations

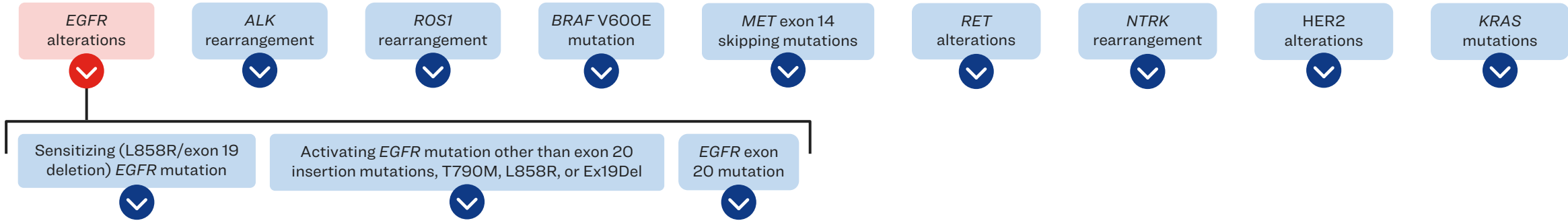
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

ASCO = American Society of Clinical Oncology.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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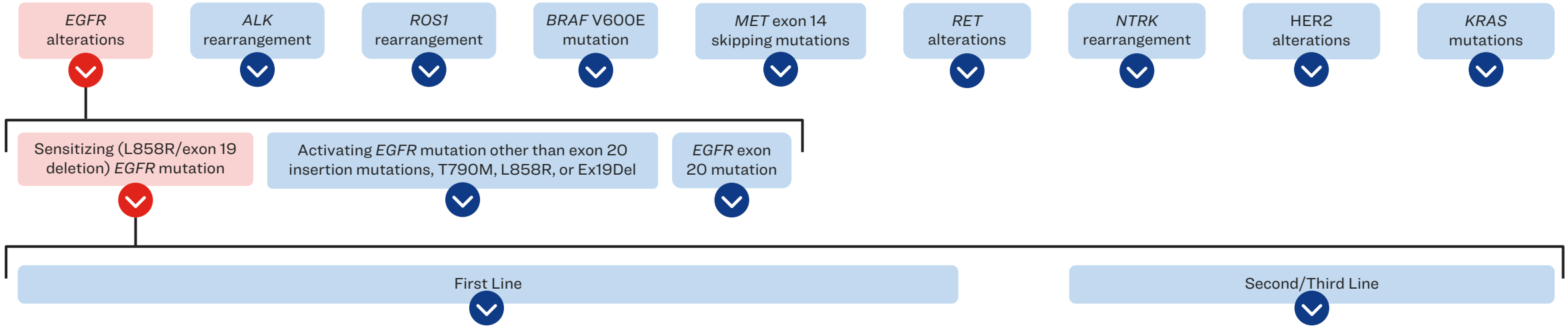

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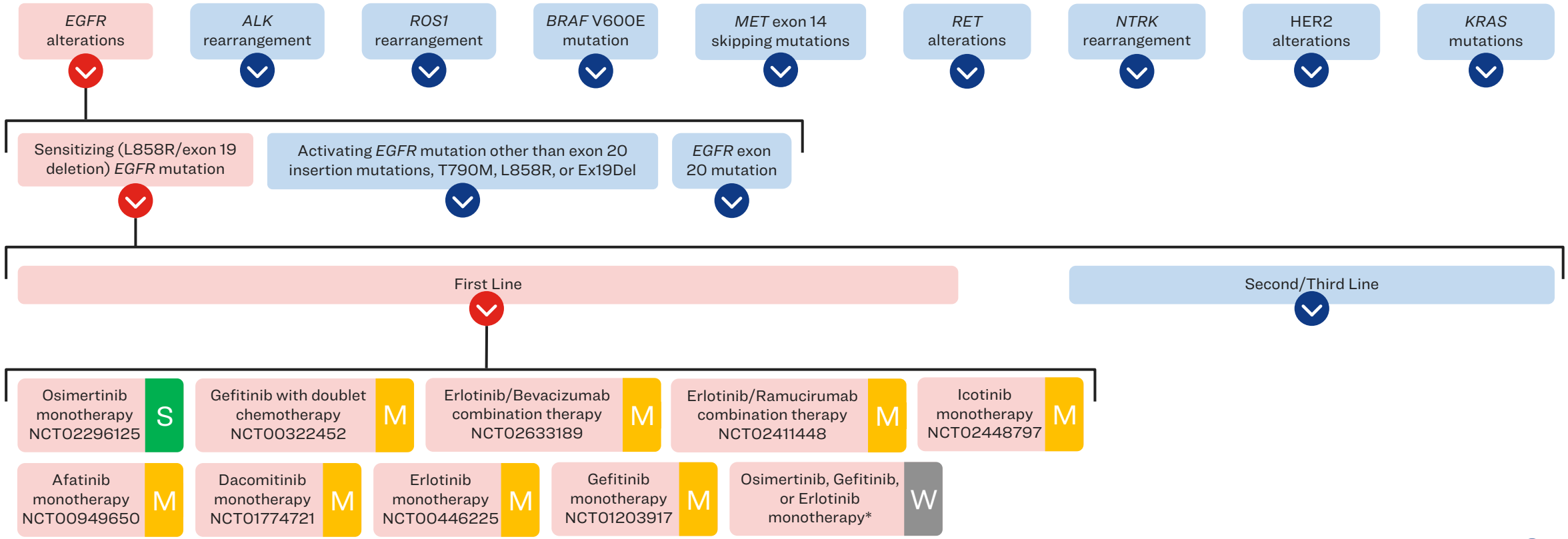

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*For PS 3.
Ex19Del = exon 19 deletion; PS = performance status.

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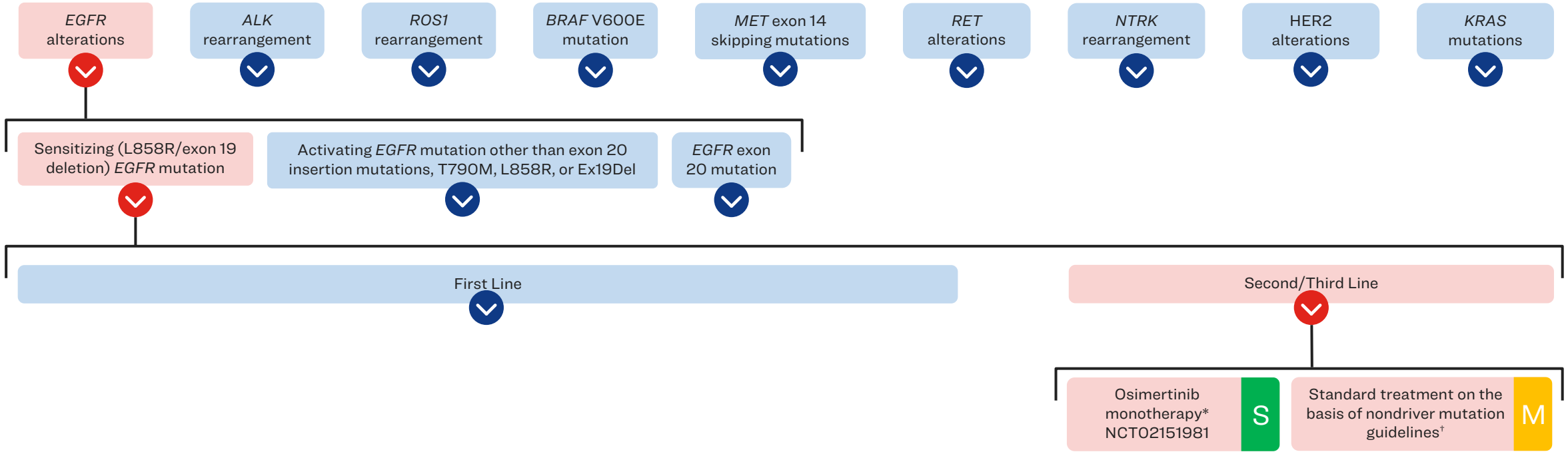
NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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*For PS 0-2 who have had previous EGFR-targeted therapy (who did not receive Osimertinib) and subsequently have an *EGFR* T790M resistance mutation. †For patients with any *EGFR* mutation who have progressed on EGFR TKIs with no T790M mutation or whose disease has progressed on Osimertinib.

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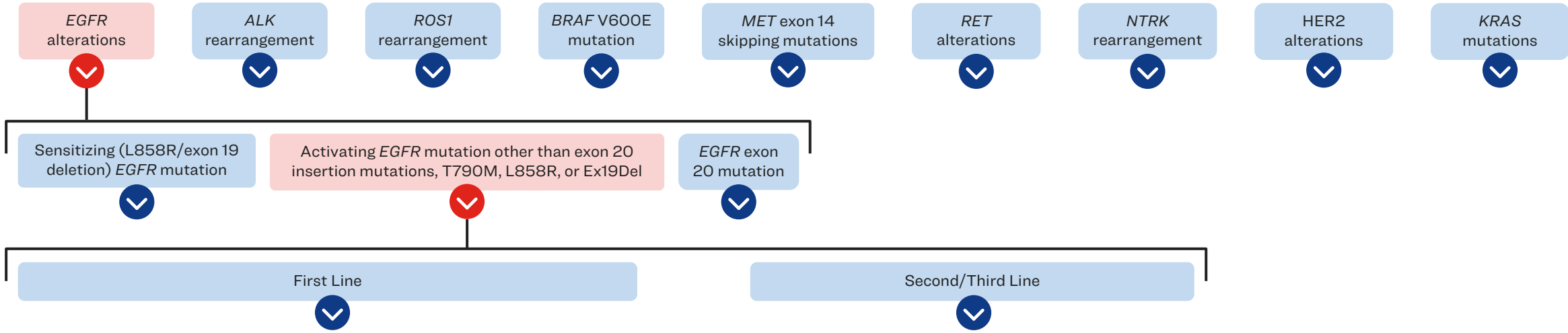
NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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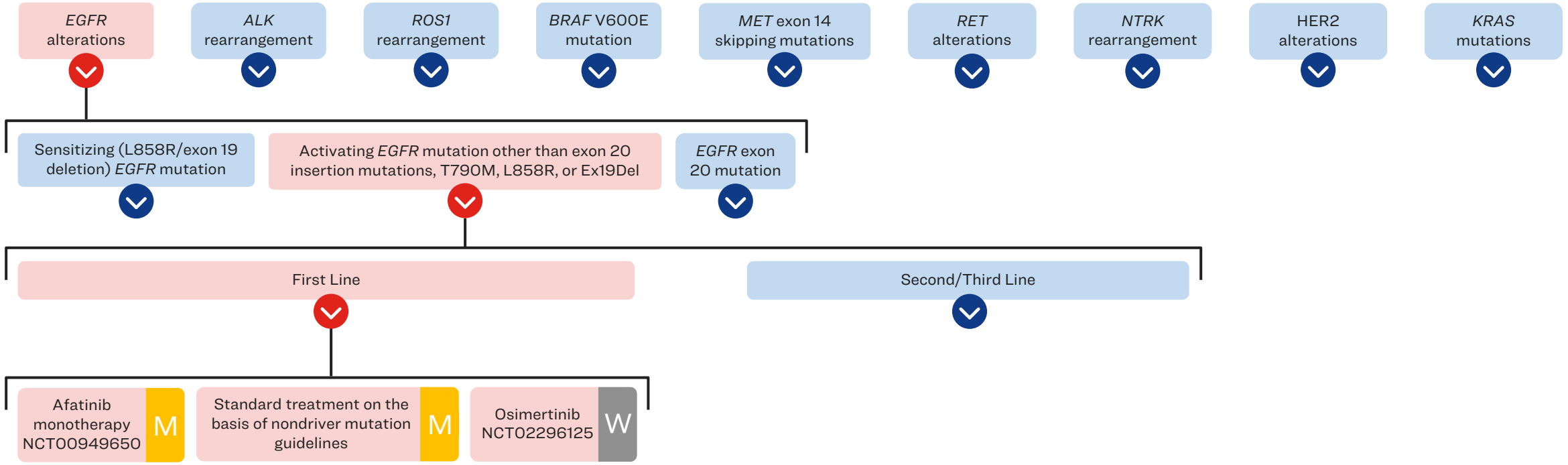

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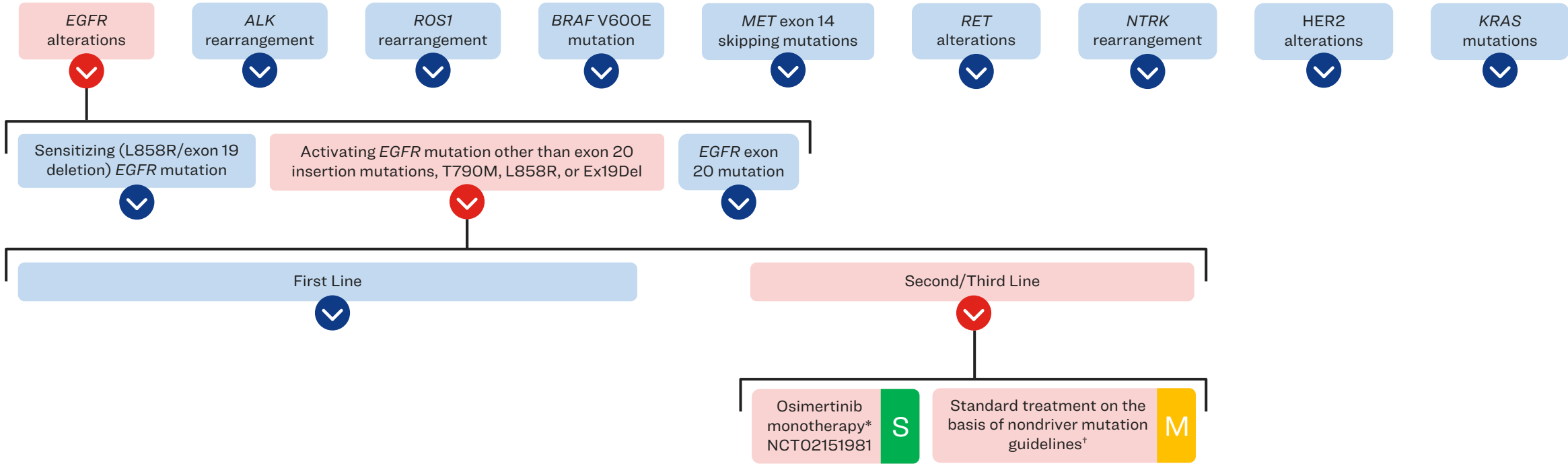

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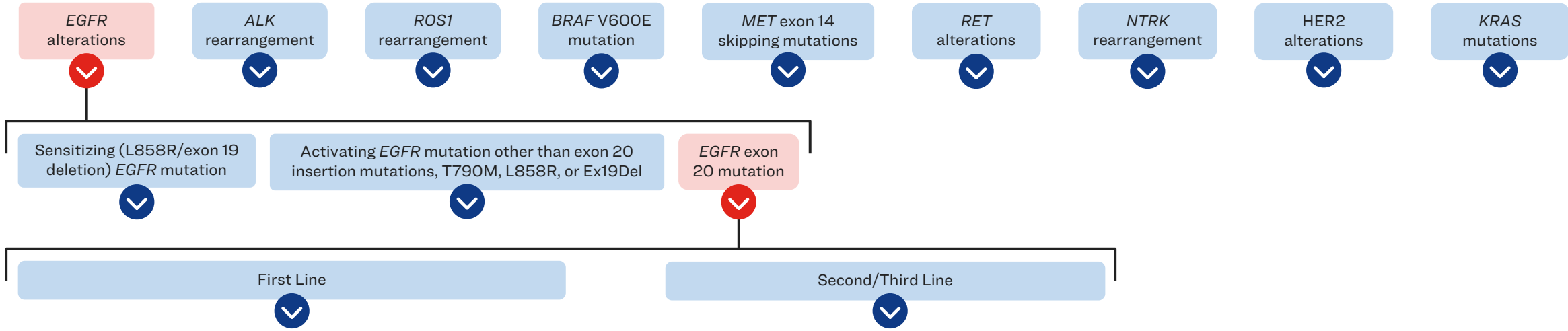

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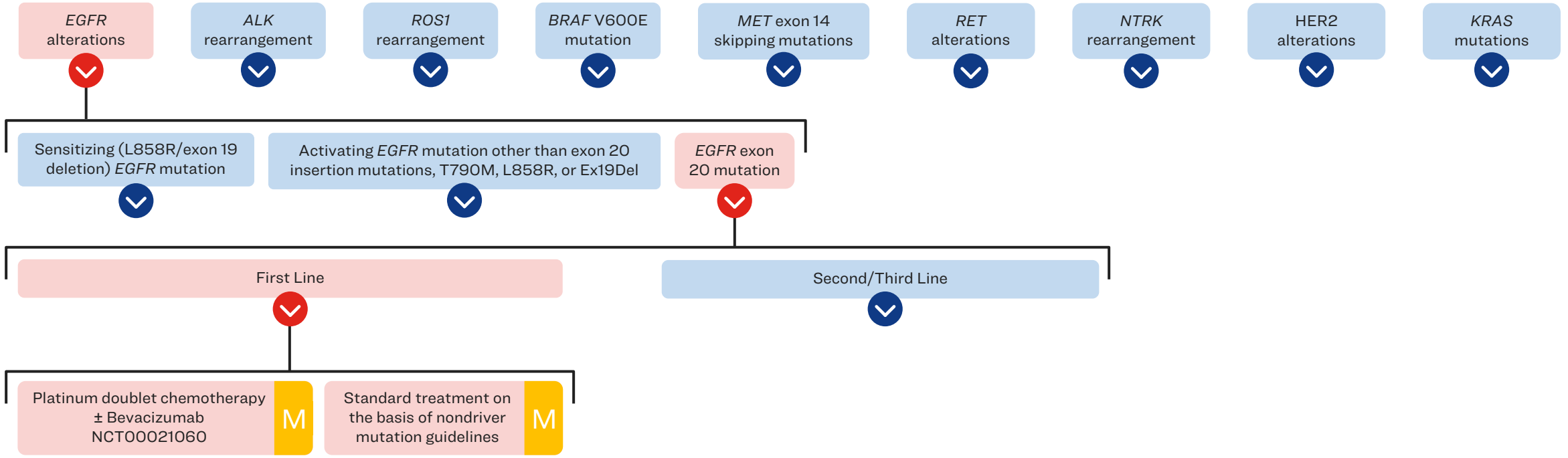

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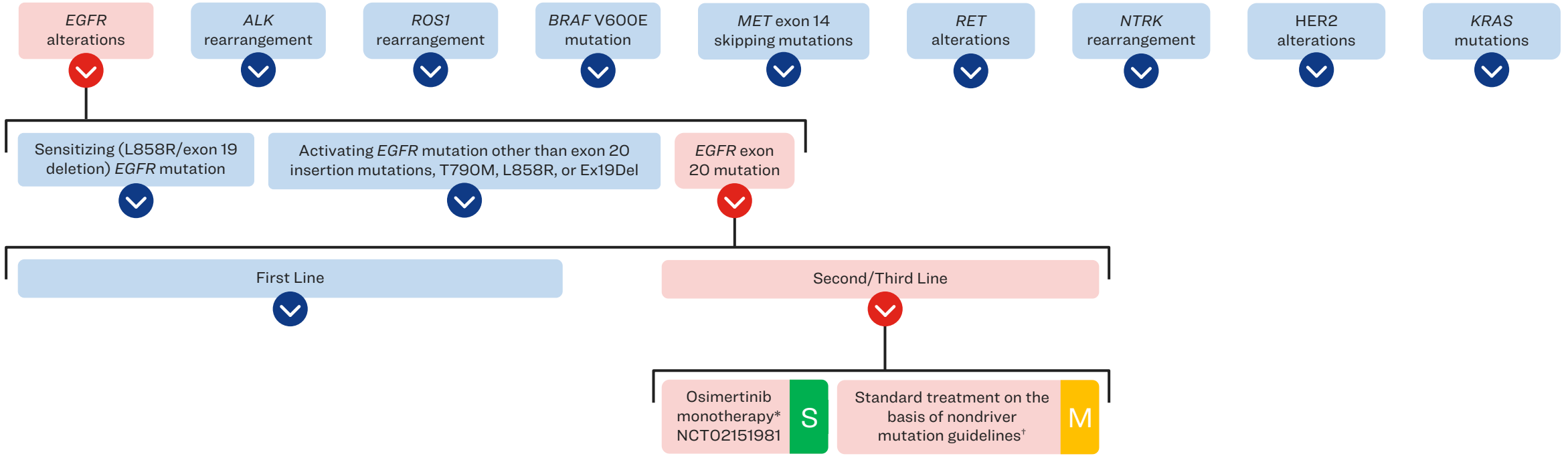

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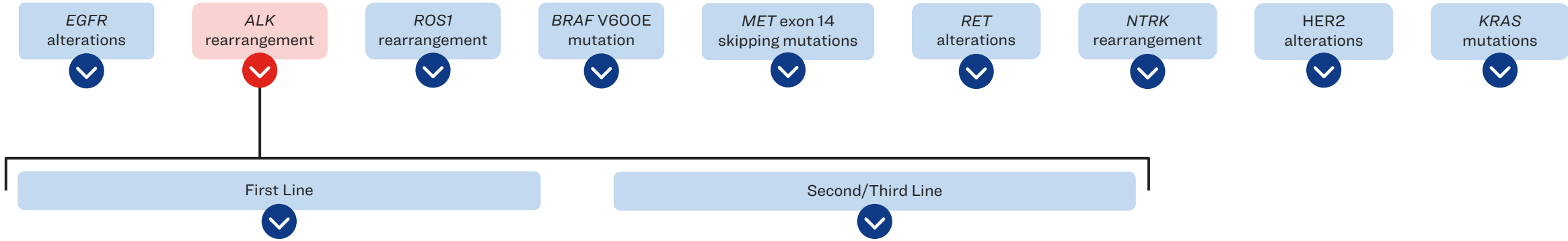

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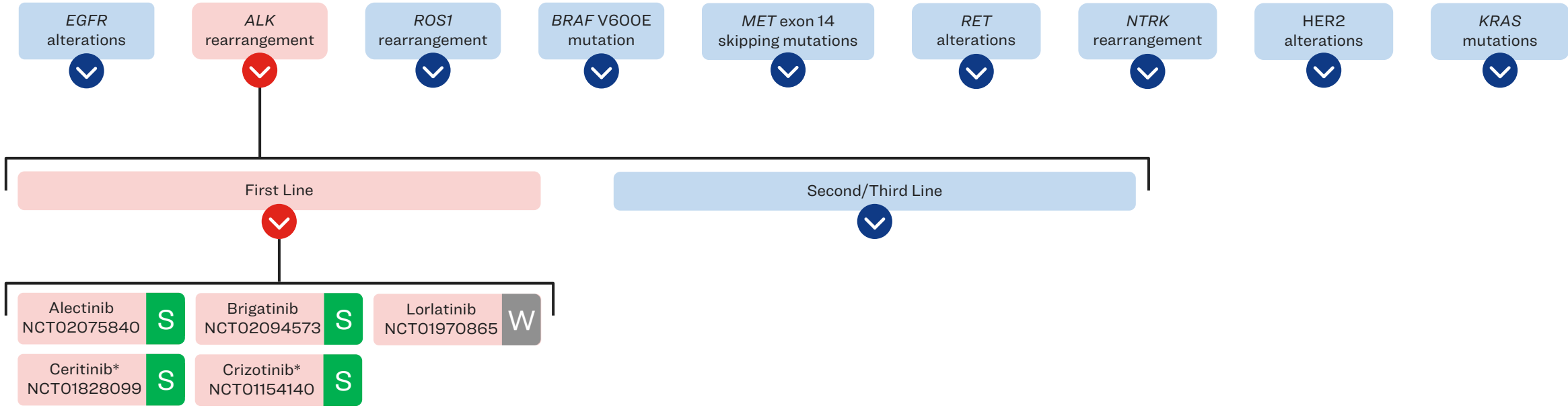

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To reveal treatment options, click on the blue arrow buttons.

For source information, please see speaker notes.
*PS 0-2 treatment options if Alectinib, Brigatinib, or Lorlatinib unavailable.
PS = performance status.

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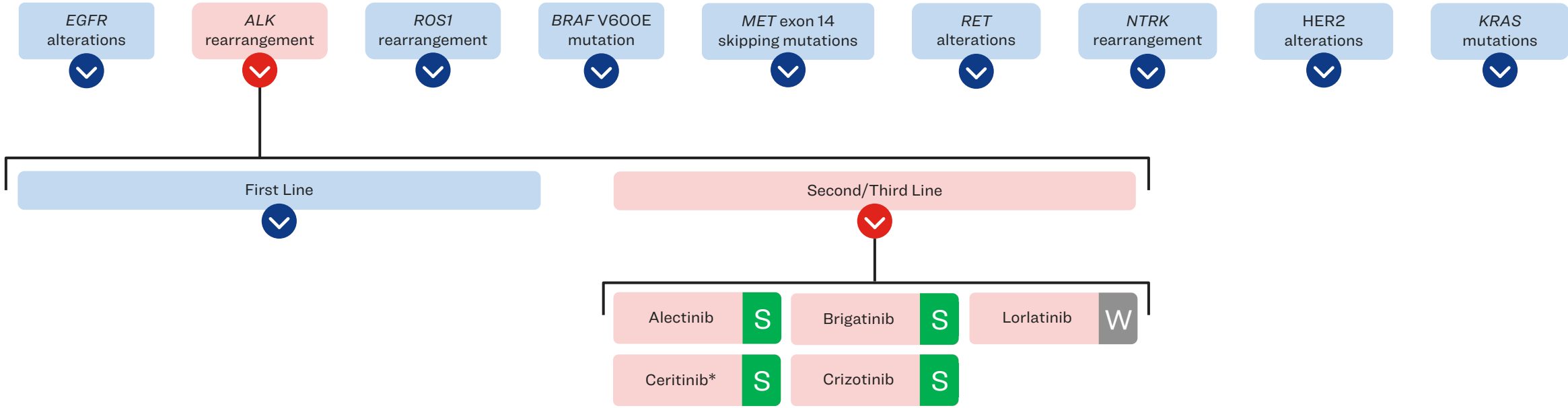

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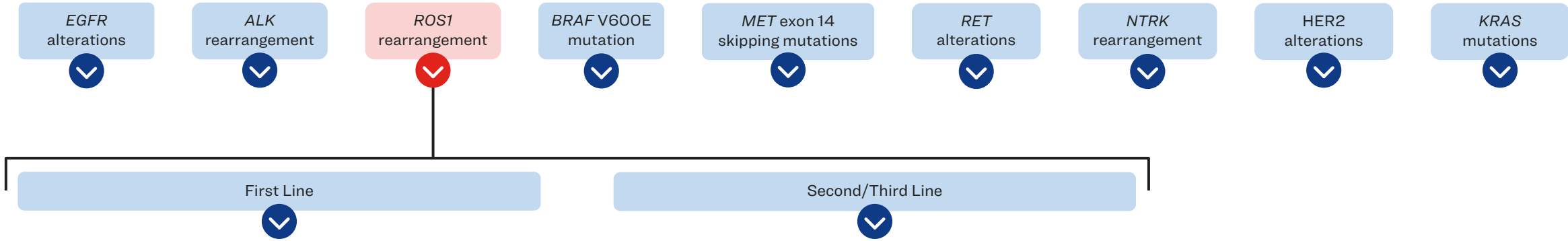

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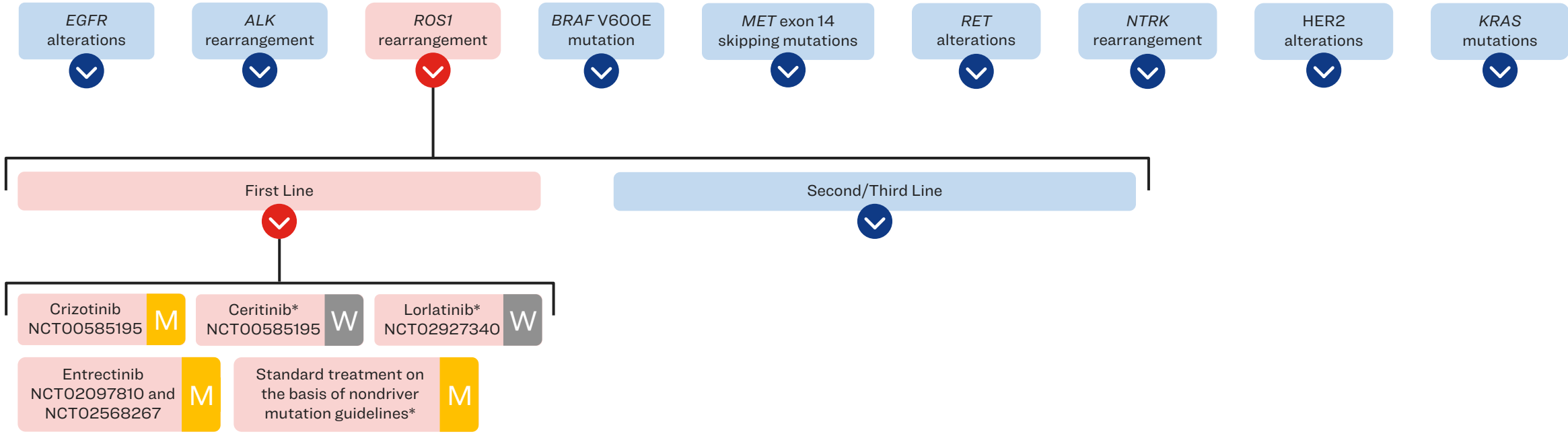

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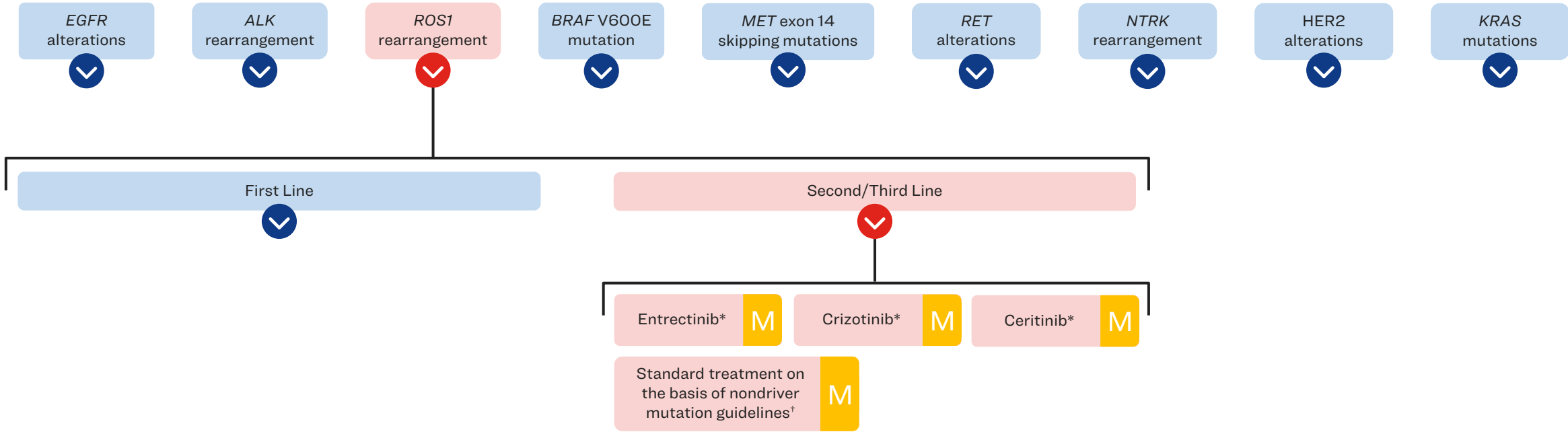
NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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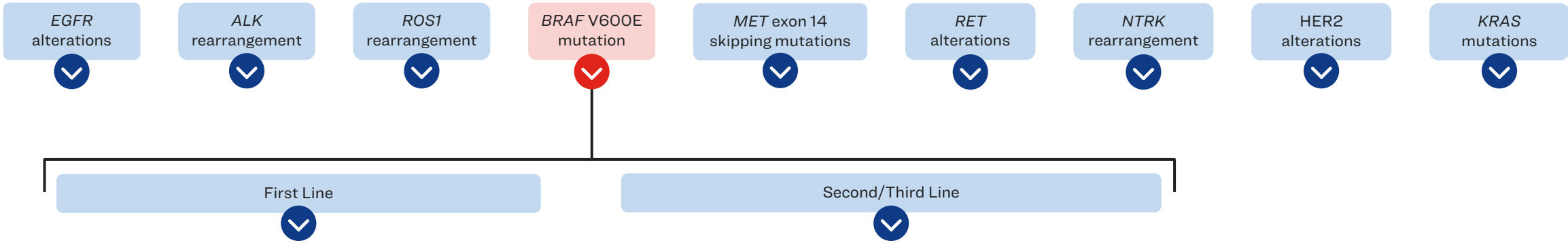
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

*Previously received nontargeted therapy. †Previously received ROS1-targeted therapy.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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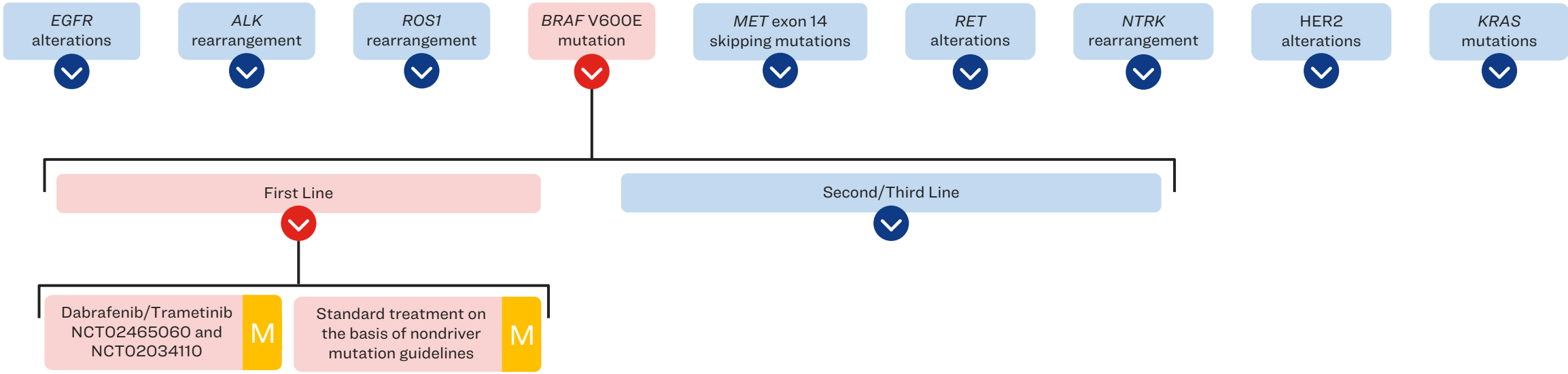
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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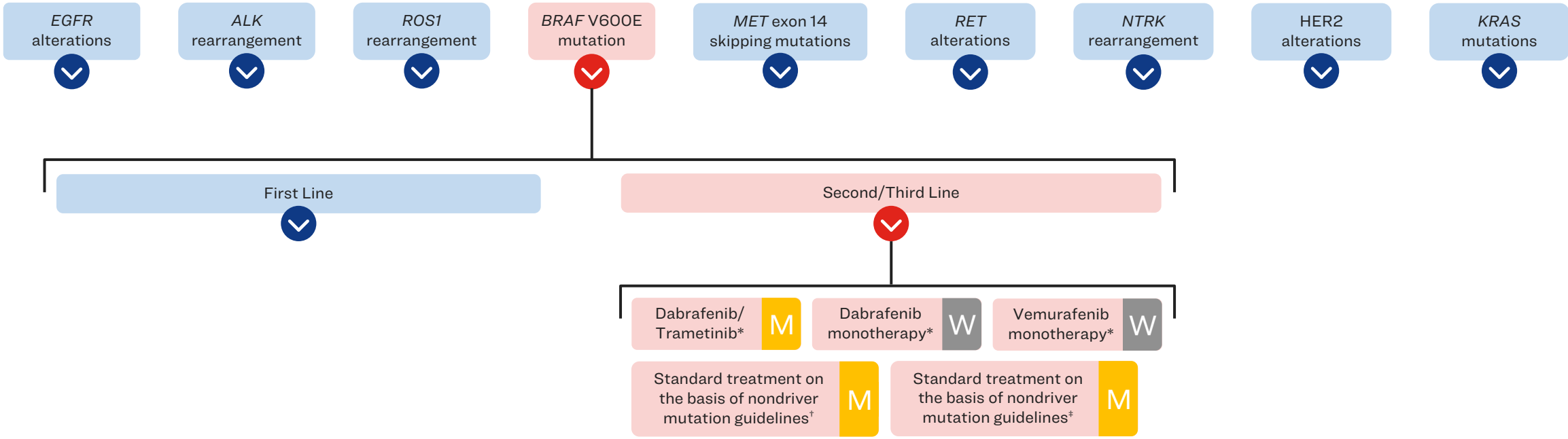
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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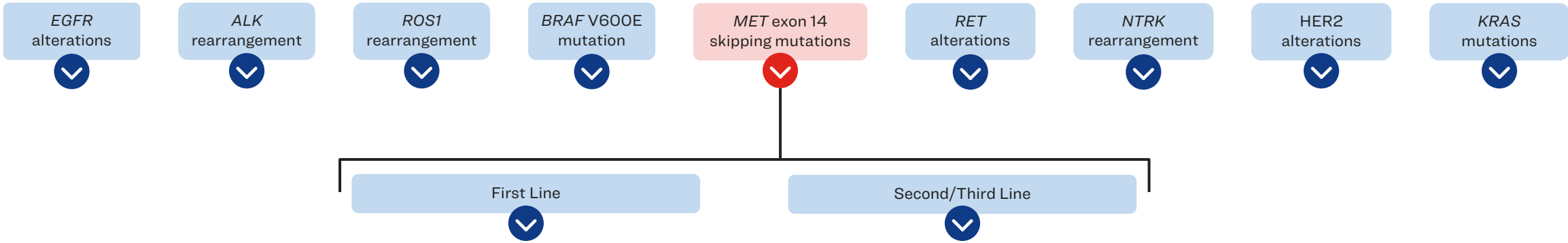
To reveal treatment options, click on the blue arrow buttons.

For source information, please see speaker notes.

*Patients who did not previously receive BRAF-targeted therapy. †Patients who previously received BRAF/MEK-targeted therapy. ‡Patients who previously received chemotherapy, immunotherapy, and BRAF-targeted therapy or *BRAF* mutation outside of V600E.

Strength of Recommendation (ASCO) S Strong M Moderate W Weak

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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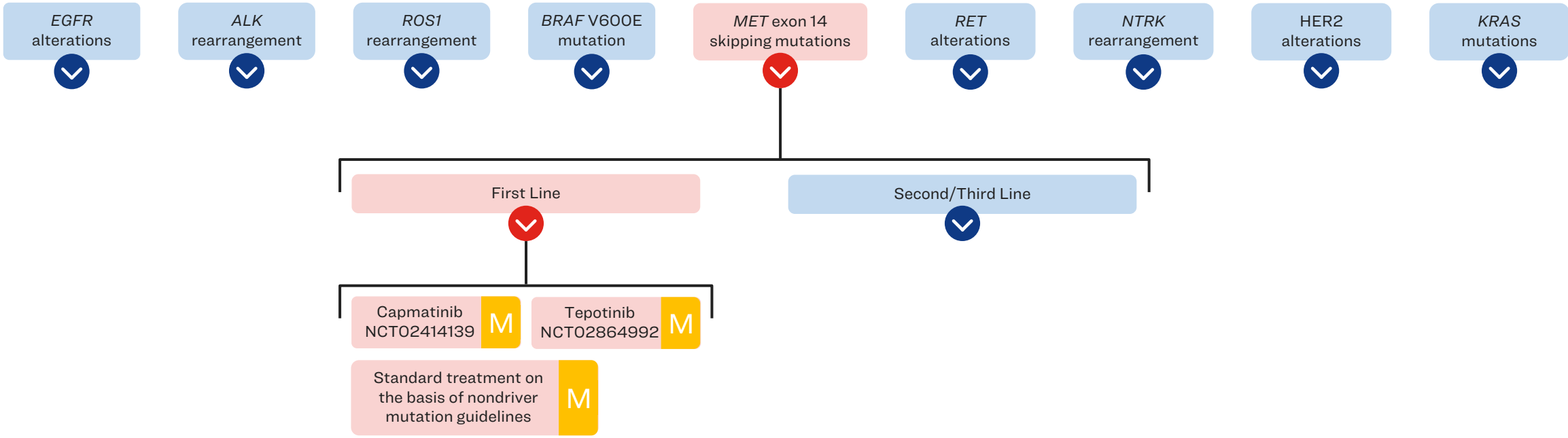
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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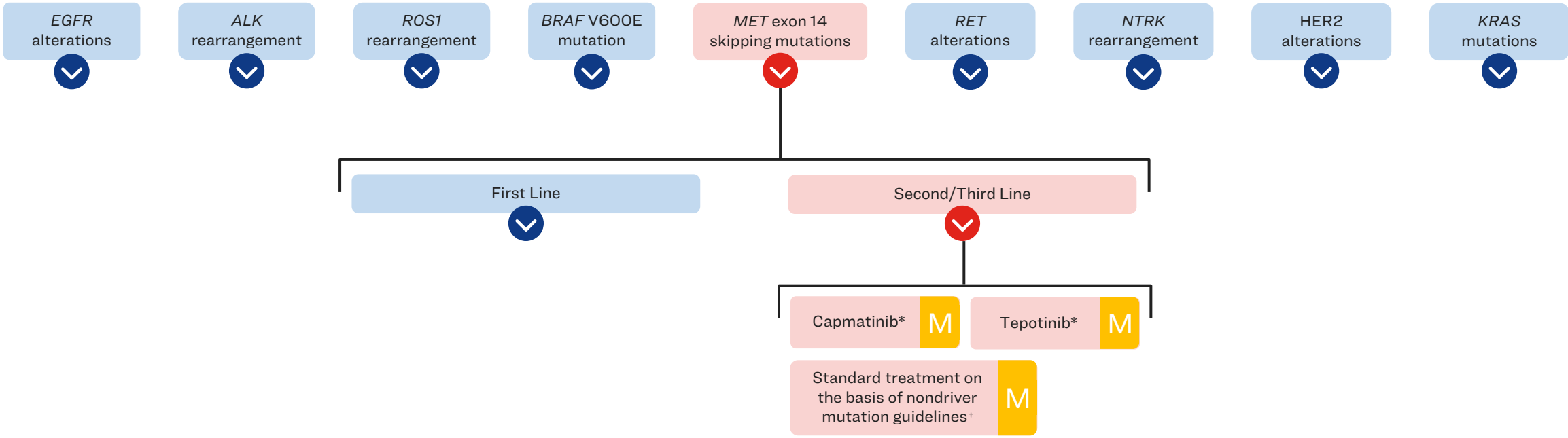
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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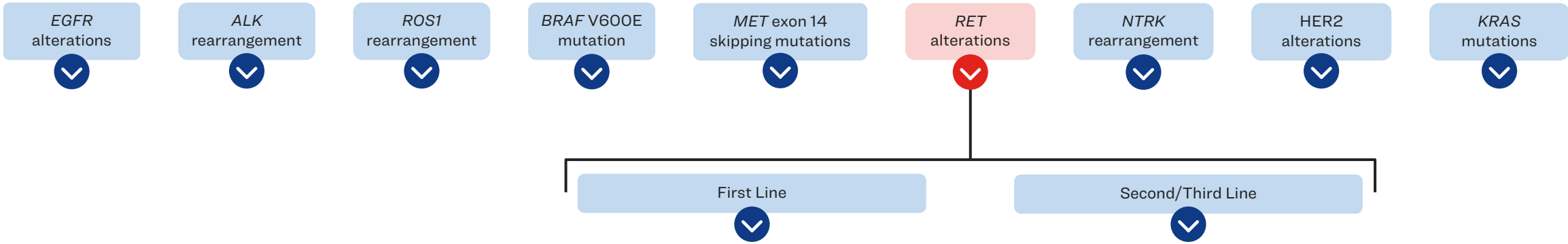
To reveal treatment options, click on the blue arrow buttons.

For source information, please see speaker notes.

*Previously received or been ineligible for 1L chemotherapy with or without immunotherapy. †Previously received MET-targeted therapy or *MET* abnormalities other than exon 14 skipping mutations.

Strength of Recommendation (ASCO) S Strong M Moderate W Weak

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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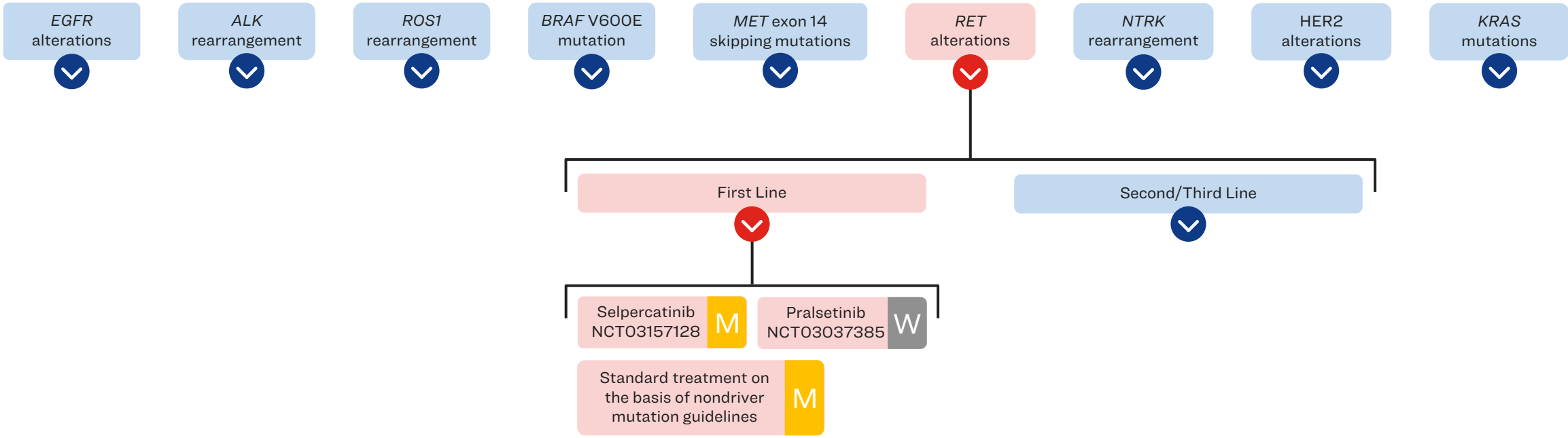
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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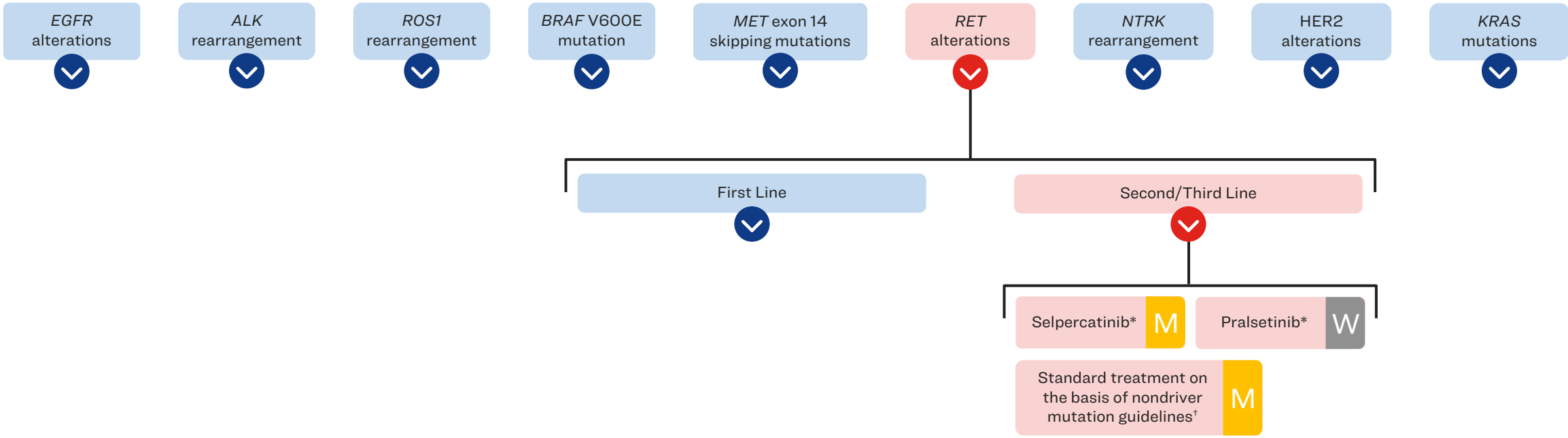
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for **Advanced** Biomarker-Driven NSCLC[1-4]



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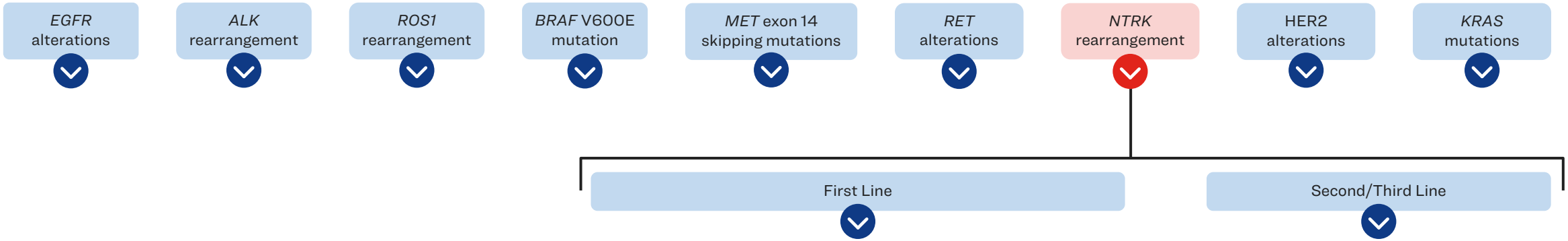
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

*Did not receive RET-targeted therapy. †Previously received RET-targeted therapy.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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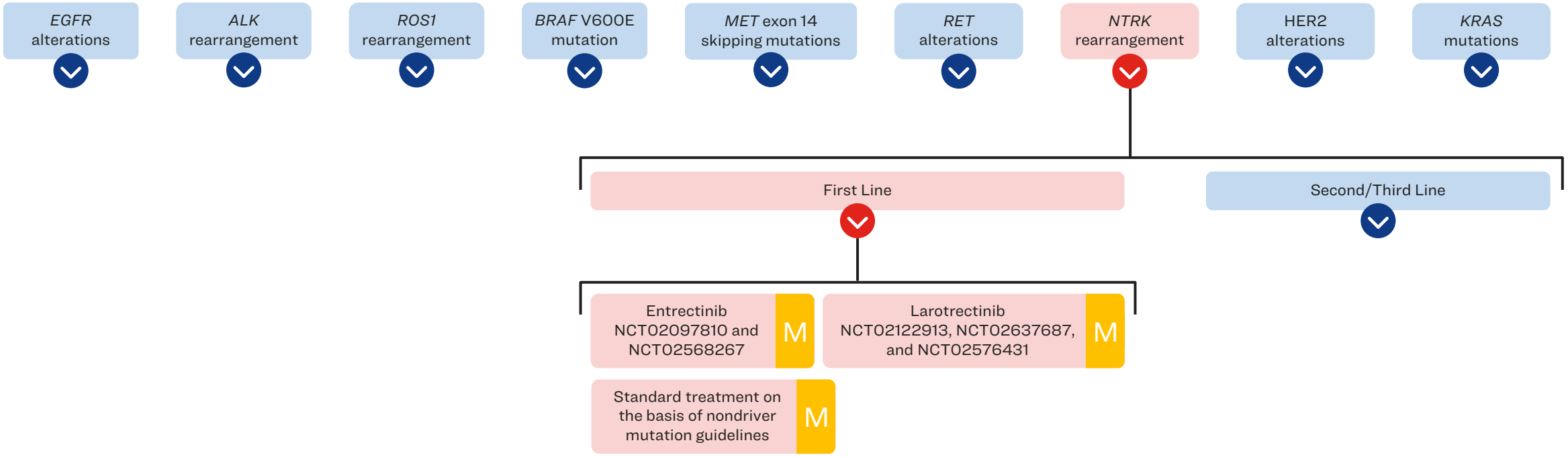
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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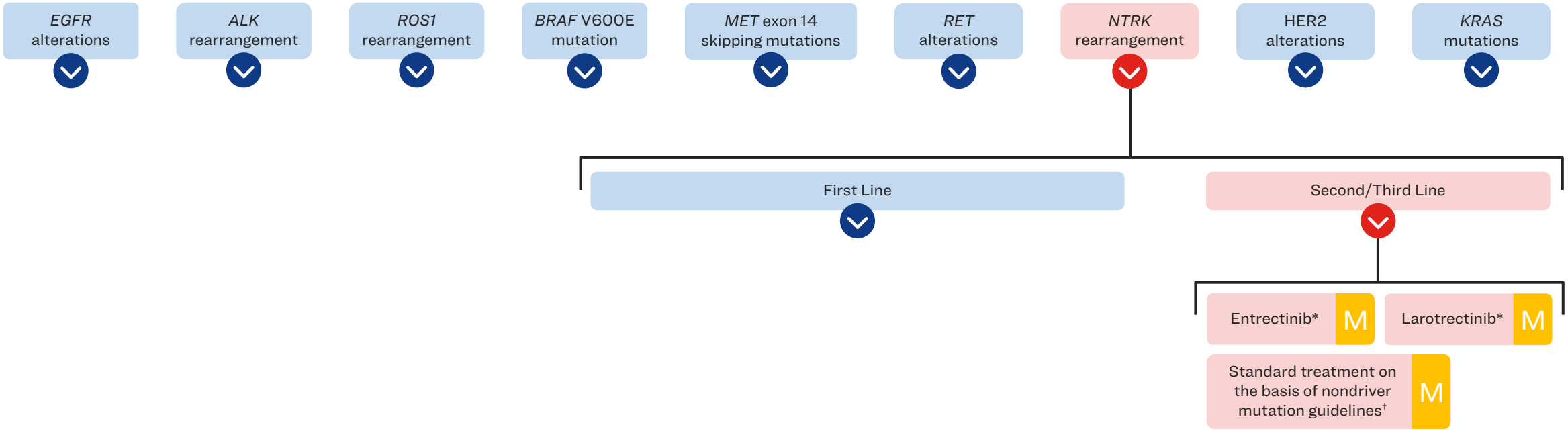
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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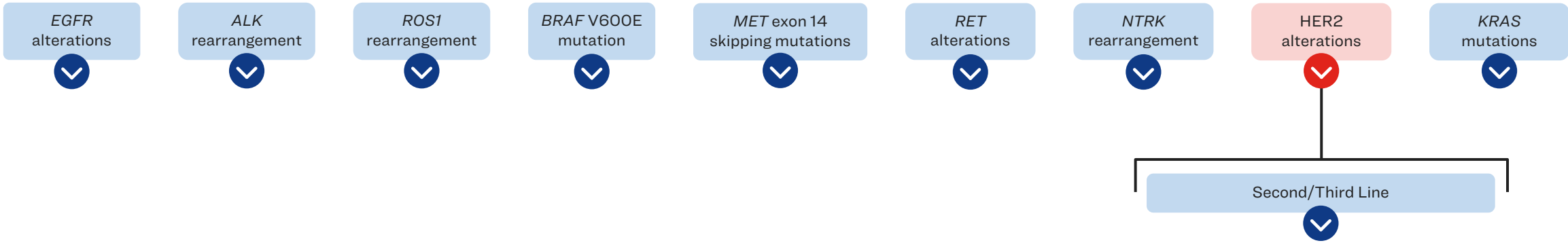
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

*Did not receive an *NTRK* inhibitor. †Previously received an *NTRK* inhibitor.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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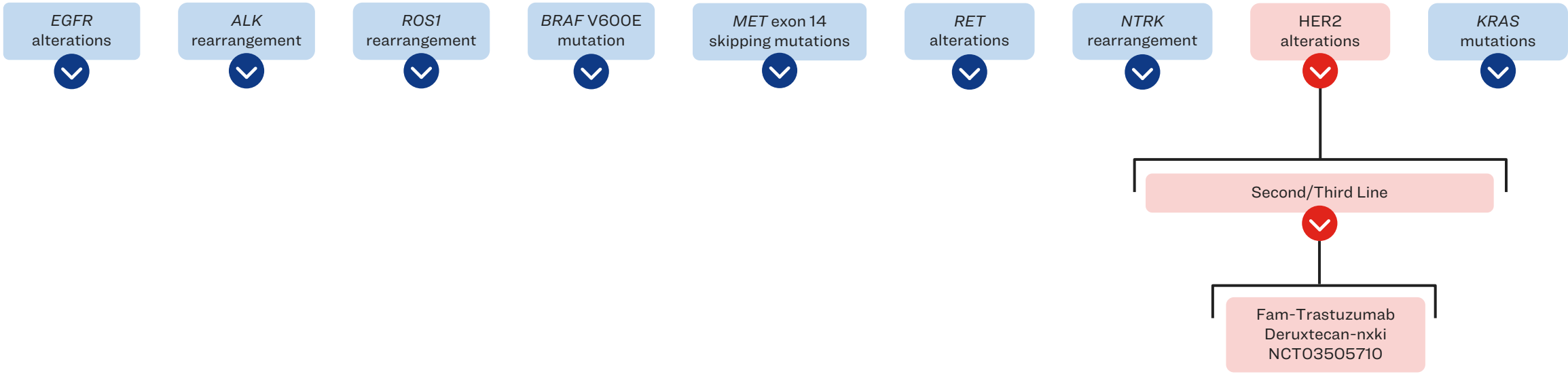
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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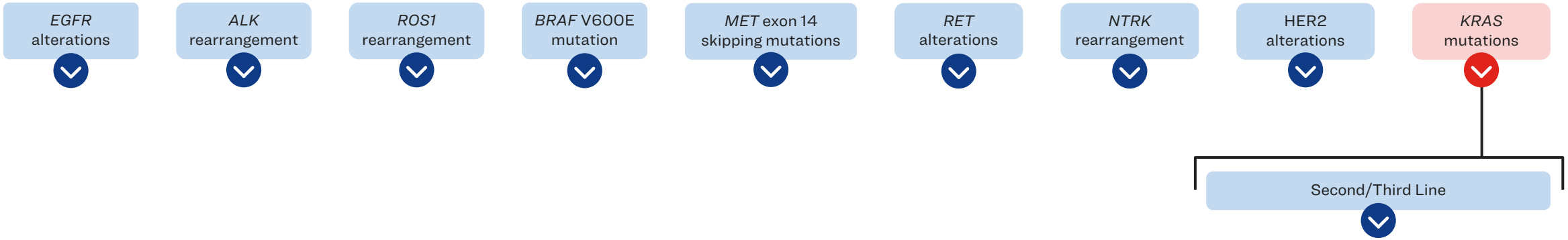
Strength of Recommendation (ASCO) **S** Strong **M** Moderate **W** Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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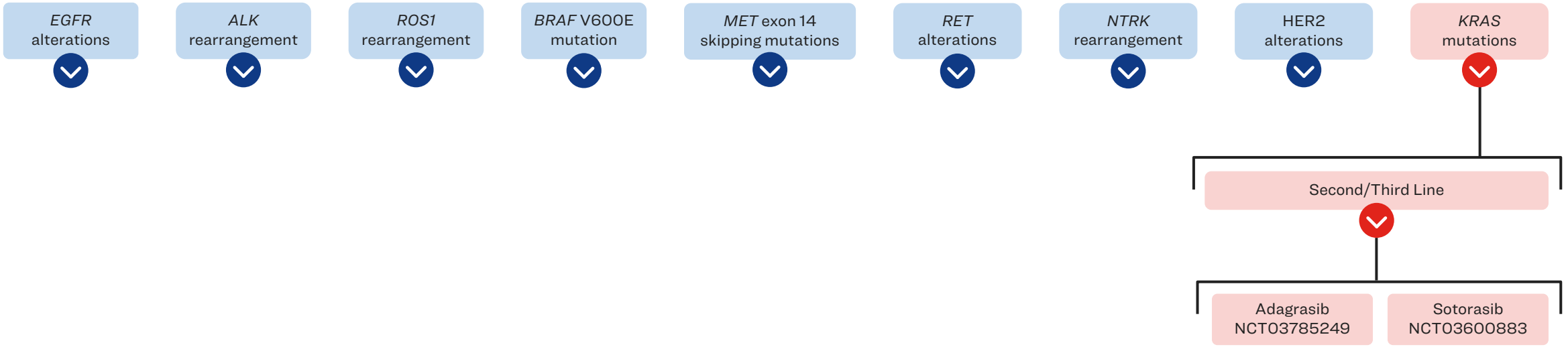
Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

NSCLC (Nonsquamous) Treatment Journey: Targeted Therapy for Advanced Biomarker-Driven NSCLC[1-4]



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Strength of Recommendation (ASCO) S Strong M Moderate W Weak

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

For source information, please see speaker notes.

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 ACPB Atezolizumab+Carboplatin+Nab-Paclitaxel Nivolumab+Ipilimumab+chemotherapy	KEYNOTE-189 (NCT02578680)[3] IMpower150 (NCT02366143)[4] IMpower130 (NCT02367781)[5] CheckMate 9LA (NCT03215706)[6]
PD-1/PD-L1 ≥1-49%	Pembrolizumab+platinum-based chemotherapy+Pemetrexed Pembrolizumab monotherapy ACPB Atezolizumab+Carboplatin+Nab-Paclitaxel Nivolumab+Ipilimumab±chemotherapy	KEYNOTE-189 (NCT02578680)[3] KEYNOTE-042 (NCT02220894)[7] IMpower150 (NCT02366143)[4] IMpower130 (NCT02367781)[5] CheckMate 9LA (NCT03215706)[6]; CheckMate 227 (NCT02477826)[8]
PD-1/PD-L1 ≥50%	Pembrolizumab monotherapy Pembrolizumab+platinum-based chemotherapy+Pemetrexed ACPB Atezolizumab+Carboplatin+Nab-Paclitaxel Carboplatin-Paclitaxel or Nab-Paclitaxel±Pembrolizumab Cemiplimab-rwlc monotherapy Atezolizumab monotherapy Nivolumab+Ipilimumab+chemotherapy	KEYNOTE-042 (NCT02220894)[7]; KEYNOTE-024 (NCT02142738)[9] KEYNOTE-189 (NCT02578680)[2] IMpower150 (NCT02366143)[4] IMpower130 (NCT02367781)[5] KEYNOTE-407 (NCT02775435)[10] EMPOWER-Lung1 (NCT03088540)[11] IMpower110 (NCT02409342)[12] CheckMate 9LA (NCT03215706)[6]; CheckMate 227 (NCT02477826)[8]

For source information, please see speaker notes.
ACPB = Atezolizumab+Carboplatin+Paclitaxel+Bevacizumab; FDA = US Food and Drug Administration.

NSCLC (Nonsquamous) Treatment Journey: Treatment Options in Early-Stage NSCLC

Treatment Options for Stage IA-IIIA NSCLC	
AJCC Stage	Treatment
IA	Surgery or definitive radiation (for medically inoperable patients)
IB	Surgery followed by adjuvant systemic therapy or neoadjuvant ICI-chemotherapy followed by surgery For unresected Stage III: definitive concurrent chemoradiation followed by consolidation PD-L1 inhibitor
IIA	
IIB	
IIIA	

*For patients with sensitizing *EGFR* mutations. †For patients with ≥1% PD-L1.
AJCC = American Joint Committee on Cancer.
Godoy LA, et al. *Biomarker Research.* 2023;11:7.

Adjuvant Therapy for Early-Stage NSCLC Without a Known Driver Alteration

Drug	Clinical Trial	Trial Title	Trial Status	Key Findings
Atezolizumab[1,2]	IMpower010 (NCT02486718)	Study to Assess Safety and Efficacy of Atezolizumab (MPDL3280A) Compared to Best Supportive Care Following Chemotherapy in Patients With Lung Cancer [IMpower010]	Ongoing	• Improved DFS vs. best supportive care in Stage II-IIIA NSCLC
Durvalumab[3,4]	AEGEAN (NCT03800134)	A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer (AEGEAN)	Ongoing	• Improved event-free survival vs. placebo • Higher incidence of pathological complete response vs. placebo
Nivolumab[5,6]	CheckMate-816 (NCT02998528)	A Neoadjuvant Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Versus Chemotherapy Alone in Early Stage Non-Small Cell Lung Cancer (NSCLC) (CheckMate 816)	Ongoing	• Improved event-free survival and number of pathological complete responses in patients receiving Nivolumab+chemotherapy vs. chemotherapy alone
Pembrolizumab[7-10]	KEYNOTE-671 (NCT03425643)[7,8]	Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (MK-3475-671/ KEYNOTE-671)	Ongoing	• Improved event-free survival vs. placebo • Improved major pathological response vs. placebo
	KEYNOTE 091 (NCT02504372)[9,10]	Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS)	Ongoing	• Improved DFS vs placebo
Toripalimab[11,12]	Neotorch (NCT04158440)	Phase III Study of Toripalimab Versus Placebo Plus Chemotherapy in Resectable NSCLC	Ongoing	• Improved event-free survival vs. chemotherapy at interim analysis

Note: Cross-trial comparisons are for illustrative purposes only and should be interpreted with caution.
For source information, please see speaker notes.
DFS = disease-free survival.

Adjuvant Therapy for *EGFR*-Mutant Early-Stage NSCLC

Drug	Clinical Trial	Trial Title	Trial Status	Key Findings
Osimertinib[1,2]	ADAURA (NCT02511106)	AZD9291 Versus Placebo in Patients With Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy	Ongoing	• Sustained, clinically meaningful improvement in DFS • Lower overall recurrences • Demonstrated CNS efficacy
Icotinib[3,4]	CORIN (NCT02264210)	Icotinib for Completed Resected IB NSCLC With EGFR Mutation	Ongoing	• Improvement in DFS at 3-year follow-up (mDFS not reached) • 77% reduction in risk of disease recurrence or death • Demonstrated CNS efficacy
Gefitinib[5,6]	ADJUVANT (NCT01405079)	Gefitinib Versus Vinorelbine/Platinum as Adjuvant Treatment in Stage II-IIIA (N1-N2) NSCLC With EGFR Mutation	Completed	• mOS of 75.5 months (not significantly different from standard chemotherapy) • Statistically significant improvement in mDFS compared to standard chemotherapy
Afatinib[7,8]	NCT01746251	Adjuvant Afatinib in Stage I-III NSCLC With EGFR Mutation	Completed	• RFS was improved in patients treated with adjuvant Afatinib for 2 years compared to adjuvant Afatinib for 3 months • mOS not reached
Erlotinib[9,10]	SELECT (NCT00567359)	Erlotinib in Patients With Resected, Early Stage NSCLC With Confirmed Mutations in the EGFR	Completed	• The 2-year DFS of 88% was significantly higher than the historical control of 76% • 5-year DFS of 56% • 5-year OS of 86%

Note: Cross-trial comparisons are for illustrative purposes only and should be interpreted with caution.
For source information, please see speaker notes.
mDFS = median disease-free survival; mOS = median overall survival; OS = overall survival; RFS = recurrence-free survival.

Adjuvant Therapy for Other Biomarker-Driven Early-Stage NSCLC

Drug	Gene Target	Clinical Trial	Trial Title	Trial Status	Key Findings
Alectinib[1,2]	*ALK*	ALINA (NCT03456076)	A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With ALK Positive Non-Small Cell Lung Cancer	Ongoing	• DFS benefit of Alectinib vs. chemotherapy in both study populations (Stage II-IIIA and Stage IB-IIIA) • Clinically meaningful CNS-DFS benefit observed in the Stage IB-IIIA population
Alectinib[3,4]	*ALK*	ALNEO (NCT05015010)	Alectinib in Neo-adjuvant Treatment of Stage III NSCLC	Ongoing	Awaiting data disclosure
Crizotinib[5]	*ALK*	ALCHEMIST (NCT02201992)	Crizotinib in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer That Has Been Removed by Surgery and ALK Fusion Mutations	Ongoing	Awaiting data disclosure
Capmatinib[6,7]	*MET* exon 14 skipping	GEOMETRY-N (NCT014926831)	Phase II of Neoadjuvant and Adjuvant Capmatinib in NSCLC	Ongoing	Awaiting data disclosure
Selpercatinib[8,9]	*RET*	LIBRETTO-432 (NCT04819100)	A Study of Selpercatinib After Surgery or Radiation in Participants With Non-Small Cell Lung Cancer	Ongoing	Awaiting data disclosure

Note: Cross-trial comparisons are for illustrative purposes only and should be interpreted with caution.
For source information, please see speaker notes.

A Study of Multiple Therapies in Biomarker-Selected Patients With Resectable Stages IB-III NSCLC

NAUTIKA1 (NCT04302025) Trial Design

Phase 2, nonrandomized, open-label trial

Key enrollment criteria:

- Resectable, untreated Stage IB-IIIB NSCLC
- Molecular testing results confirming at least 1 of the following abnormalities:
  - *ALK* fusion
  - *ROS1* fusion
  - *NTRK1/2/3* fusion
  - *BRAF* V600E mutation
  - *RET* fusion
  - PD-L1 expression
  - *KRAS* G12C mutation
- ECOG PS 0 or 1

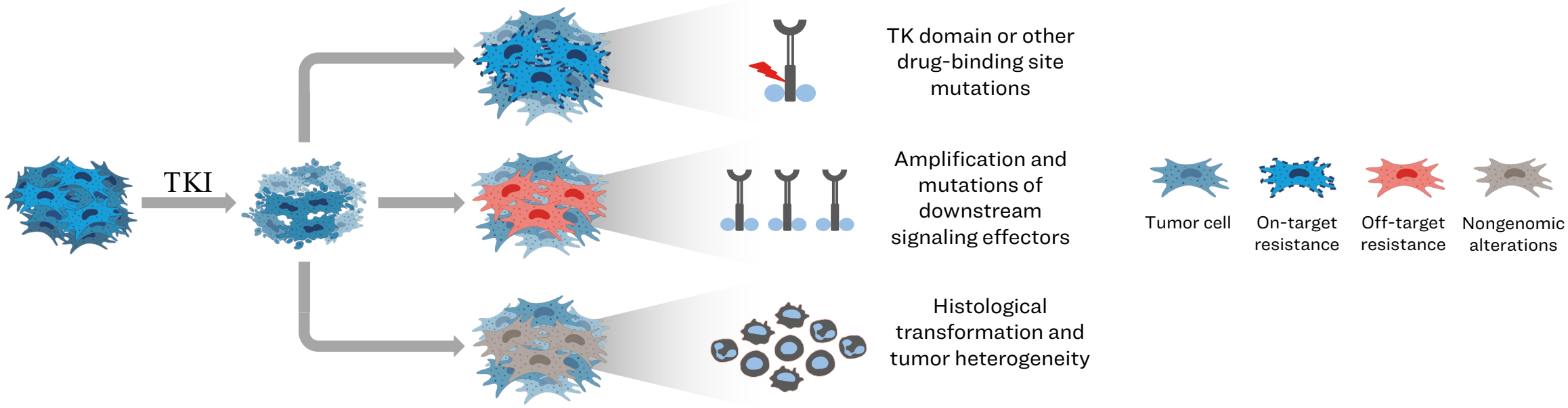
Therapies being investigated include:

- Alectinib (*ALK*)
- Entrectinib (*ROS1*/*NTRK*)
- Vemurafenib (*BRAF*)
- Cobimetinib (*BRAF*)
- Pralsetinib (*RET*)
- Atezolizumab (*PD-L1*)
- Divarasib (*KRAS* G12C)

ECOG = Eastern Cooperative Oncology Group; PS = performance status.
https://clinicaltrials.gov/study/NCT04302025?term=NCT04302025&rank=1 (Accessed January 30, 2024).

Considerations for Targeted Therapies: Acquired Resistance to TKIs[1-4]

Acquired resistance: emerge after therapy initiation and contribute to progression despite TKI therapy



TK = tyrosine kinase; TKI = tyrosine kinase inhibitor.

1. Waarts MR, et al. *J Clin Invest.* 2022;132(8):e154943. 2. Boumahdi S, de Sauvage FJ. *Nat Rev Drug Discov.* 2020;19:39-56. 3. Shen Z, et al. *Front Oncol.* 2022;12:1033484. 4. Wang X, Zhang H, Chen X. *Cancer Drug Resist.* 2019;2:141-160.