Introducción

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Con la colaboración de:

Bristol Myers Squibb™

Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Organizado por:

GECP
lung cancer research

Conflict of Interest Disclosure

- ✓ Honoraria
  - ✓ MSD Oncology, Pfizer, Astellas Pharma, Roche, Novartis, Janssen-Cilag, Bristol-Myers Squibb, Astra Zeneca
- ✓ Consulting of Advisory Role
  - ✓ Janssen-Cilag, MSD Oncology, Bristol-Myers Squibb, Boehringer Ingelheim
- ✓ Speaker´s Bureau
  - ✓ MSD Oncology
- ✓ Research Funding
  - ✓ Miratti Therapeutics, Astra Zeneca, Bayer, OncoMed, Astellas Pharma, Janssen-Cilag, Roche, Abbvie, Boehringer-Ingelheim, Pfizer, PharmaMar, Bristol-Myers Squibb, Novartis, Celgene, Ignyta
- ✓ Travel, Accomodations, Expenses
  - ✓ Bristol-Myers Squibb, Janssen-Cilag, Takeda, Pfizer, MSD Oncology, Roche

Incidence and Relevance of Lung Cancer

- ✓ Lung Cancer is the most important cause of cancer death in the world (21%)
- ✓ 85% are NSCLC
- ✓ Spain:
  - ✓ Incidence: 31,000 cases/year
  - ✓ Deaths: 20,000/year

Most relevant advances in recent years

- ✓ Confirmation of the effectiveness of PC screening with low-dose CT in a population at risk, currently non-smokers
- ✓ Relevance of molecular diagnosis
- ✓ Therapeutic advances
- ✓ New, more limited surgical techniques
- ✓ Role of radiotherapy in oligometastatic disease
- ✓ Consolidation of Immunotherapy
- ✓ Further development of targeted treatments

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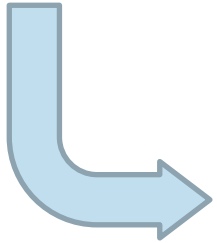
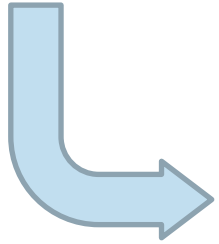
Metastatic Lung Cancer

Advances in Immunotherapy and Targeted Therapies



↓ Mortality in countries with access to new medicines



↑ Long Survivors: 20 – 25% of pat. alive to 5 years

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IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

AACR ANNUAL MEETING 2022

April 8 - 13, 2022
Ernest N. Morial Convention Center
New Orleans, Louisiana

PARIS 2022 ESMO congress

elcc European Lung Cancer Congress

ONLINE
30 MARCH - 2 APRIL 2022

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY

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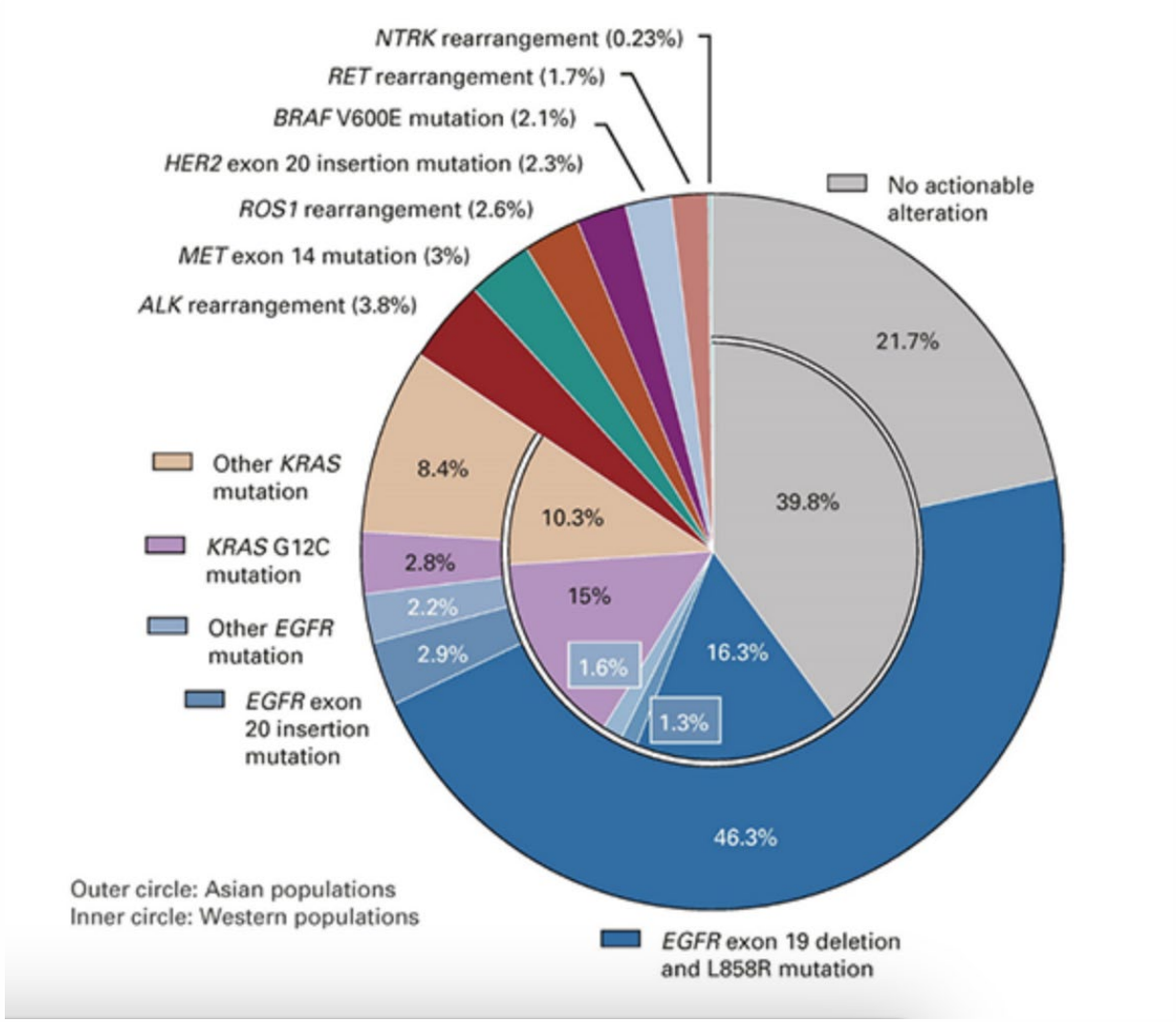
MOLECULAR TESTING FOR PATIENTS WITH ADVANCED OR METASTATIC NSCLC



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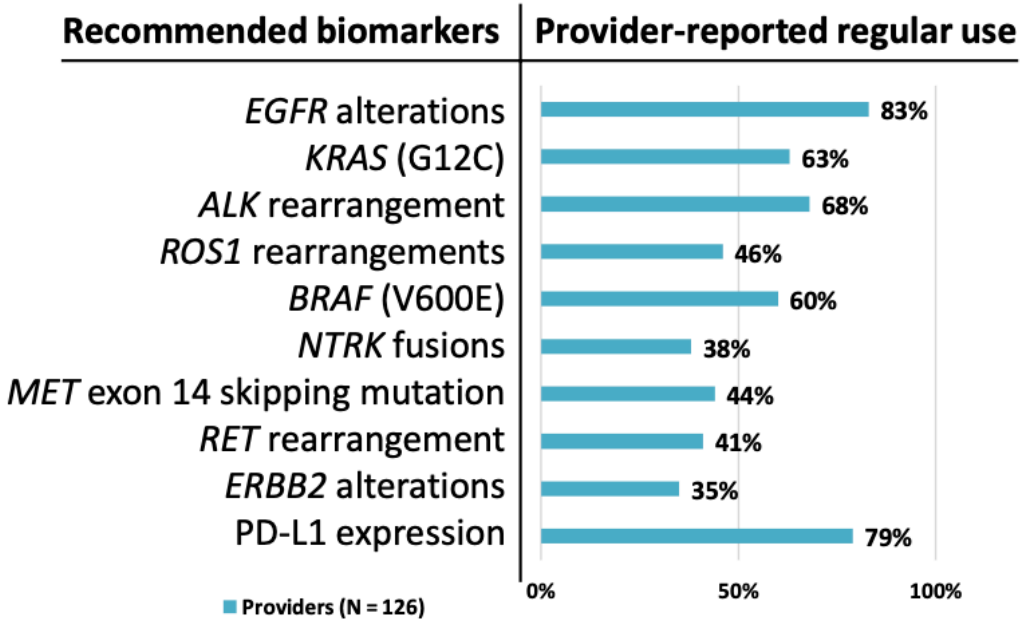
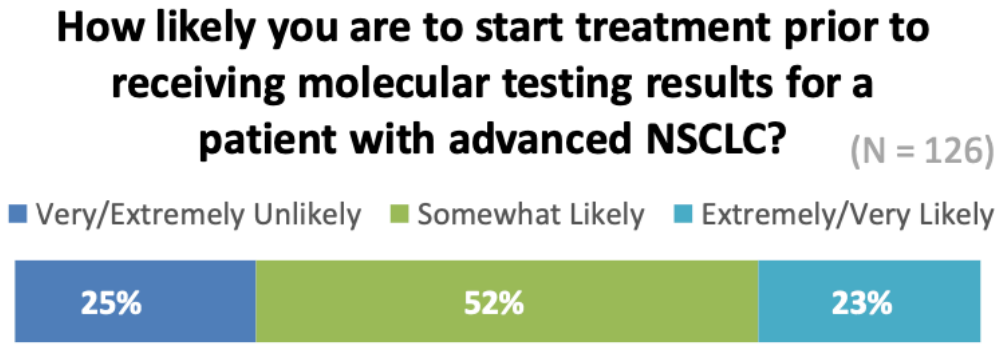
CHOOSING BIOMARKERS

- NCCN Guidelines recommend testing for the full panel of ***all 10 markers*** in NSCLC with an adenocarcinoma component. Testing should be considered for squamous cell carcinomas.
- ***Broad panel testing*** is recommended where possible (typically performed by NGS)





Top Reported Barriers to Molecular Testing

- Testing is limited by tissue specimen quantity/quality
- Long turnaround times for tests

NGS = next-generation sequencing

NCCN. Clinical Practice Guidelines: Non-Small Cell Lung Cancer. Version 4.2022. www.nccn.org. Accessed 09/15/2022; Lindeman NI, et al. *Arch Pathol Lab Med.* 2018; 142(3):321–346; Lindeman NI, et al. *J Thorac Oncol.* 2013; 8(7): 823–859; Kalemkerian GP, et al. *J Clin Oncol.* 2018; 36(9): 911-919; PRIME data on file, 2022.

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RECOMMENDED METHODS FOR MOLECULAR TESTING

		NGS*	PCR**	IHC	FISH
EGFR	Exon 19 del or L858R, S768I, L861Q, G719X, Exon 20 insertion	✓	✓		
KRAS	G12C	✓	✓		
ERBB2	Mutagenic/likely mutagenic mutations	✓	✓		
BRAF	V600E	✓	✓	✓ Some data supports utility	
ALK	Rearrangement	✓	✓	✓	✓
ROS1	Rearrangement	✓	✓	✓ With confirmatory testing	✓
RET	Rearrangement	✓	✓		✓ May under-detect
MET	Exon 14 skipping	✓	✓		
NTRK1/2/3	Rearrangement	✓	✓	✓ Complicated by baseline expression	✓ 3 probe sets needed
PD-L1	Positive IHC			✓	

***CONSIDER INCLUDING RNA-BASED TESTING TO IMPROVE DETECTION OF REARRANGEMENTS AND EXON SKIPPING**

****PCR MAY NOT DETECT NOVEL FUSION PARTNERS**

FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; PCR = polymerase chain reaction; NGS = next-generation sequencing

NCCN. Clinical Practice Guidelines: Non-Small Cell Lung Cancer. Version 4.2022. www.nccn.org. Accessed 09/15/2022; PRIME data on file, 2022.

PLASMA-BASED DNA TESTING

Plasma ctDNA testing
+
Tissue-based molecular testing

*Consider ctDNA sequencing **in parallel with tissue-based testing** to increase detection of genetic alterations*

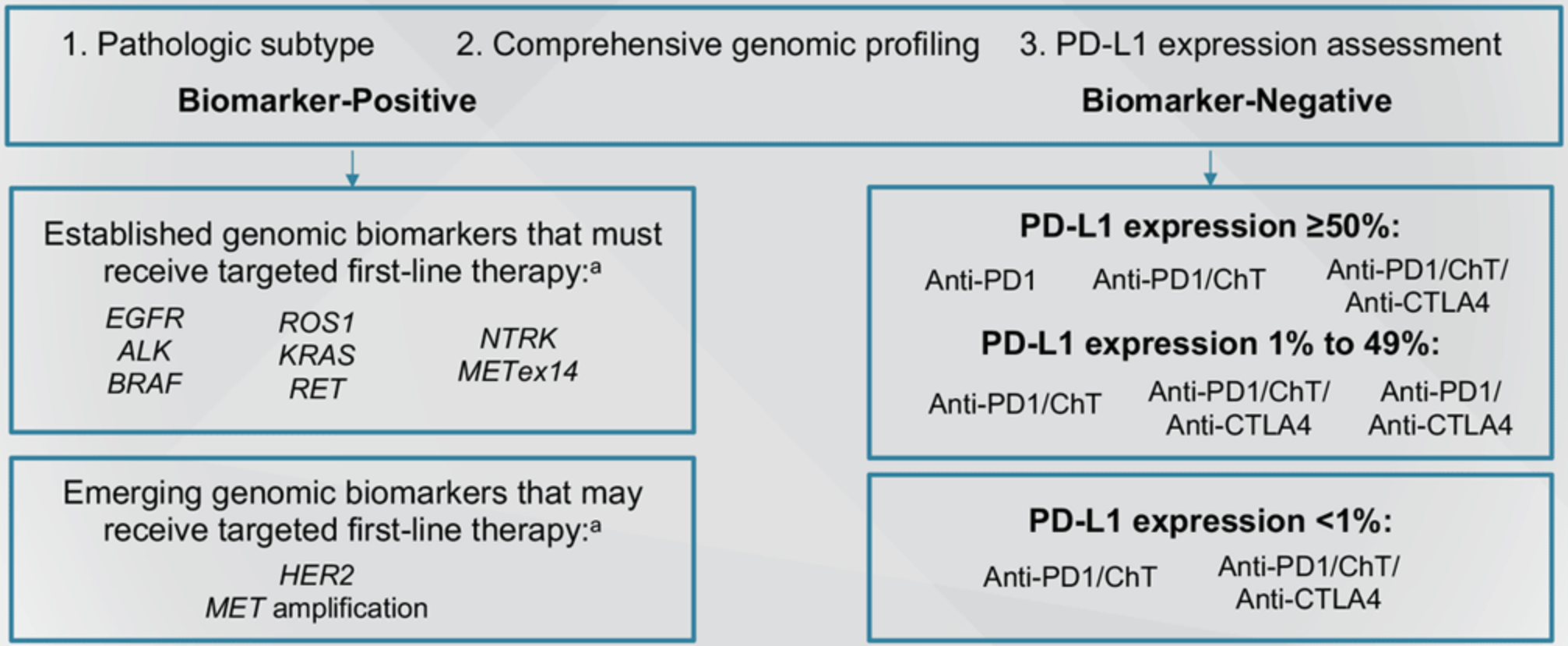
- **Plasma ctDNA testing:**
  - **May provide results faster than tissue-based testing**
  - **Can be useful when there is limited tissue sample for testing**
  - **Has been shown to identify oncogenic biomarkers that would otherwise not be detected in patients with metastatic NSCLC**

NCCN guidelines recommend plasma-based circulating tumor (ctDNA) testing:

1. If patient is medically unfit for invasive tissue sampling
2. If there is insufficient material for tissue-based molecular analysis
3. If tissue-based testing does not assess all recommended biomarkers

ctDNA = circulating tumor DNA

Overall Treatment Paradigm for Advanced NSCLC Based on Molecular Biomarker Status



[a] Where available.

Recommendations for Molecular Testing in NSCLC

- NCCN and ESMO testing recommendations are similar for metastatic NSCLC (NCCN Category 1 or 2A; ESCAT Level I or II)
- Multigene panel NGS testing can simultaneously screen for multiple actionable oncogenic drivers to identify the most appropriate course of therapy

Molecular biomarkers tested for:[a,b,1-3]

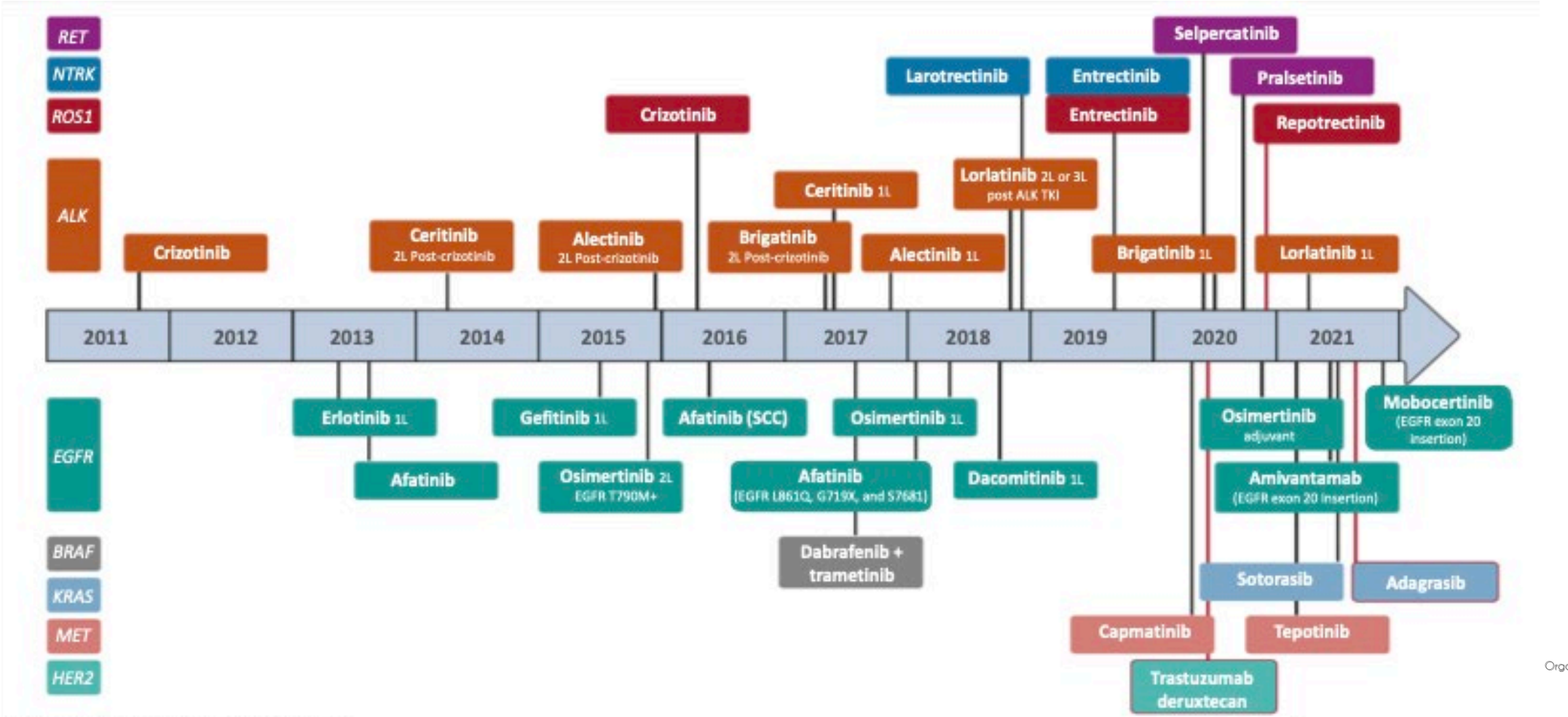
EGFR	*ROS1*	*NTRK*	
ALK	*KRAS*^{G12C}	*METex14*	*HER2*[c]
BRAF^{V600E}	*RET*	*MET* amp[c]	

Immune biomarker tested for:[b,1]

PD-L1

[a] Molecular testing is recommended for patients with metastatic adenocarcinoma, large cell, and NSCLC not otherwise specified; testing can be considered for patients with metastatic squamous cell carcinoma.
[b] Recommendations for certain individual biomarkers that should be tested but no endorsement of any specific commercially available biomarker assays or commercial laboratories.
[c] Emerging biomarker.

TARGETED THERAPY LANDSCAPE



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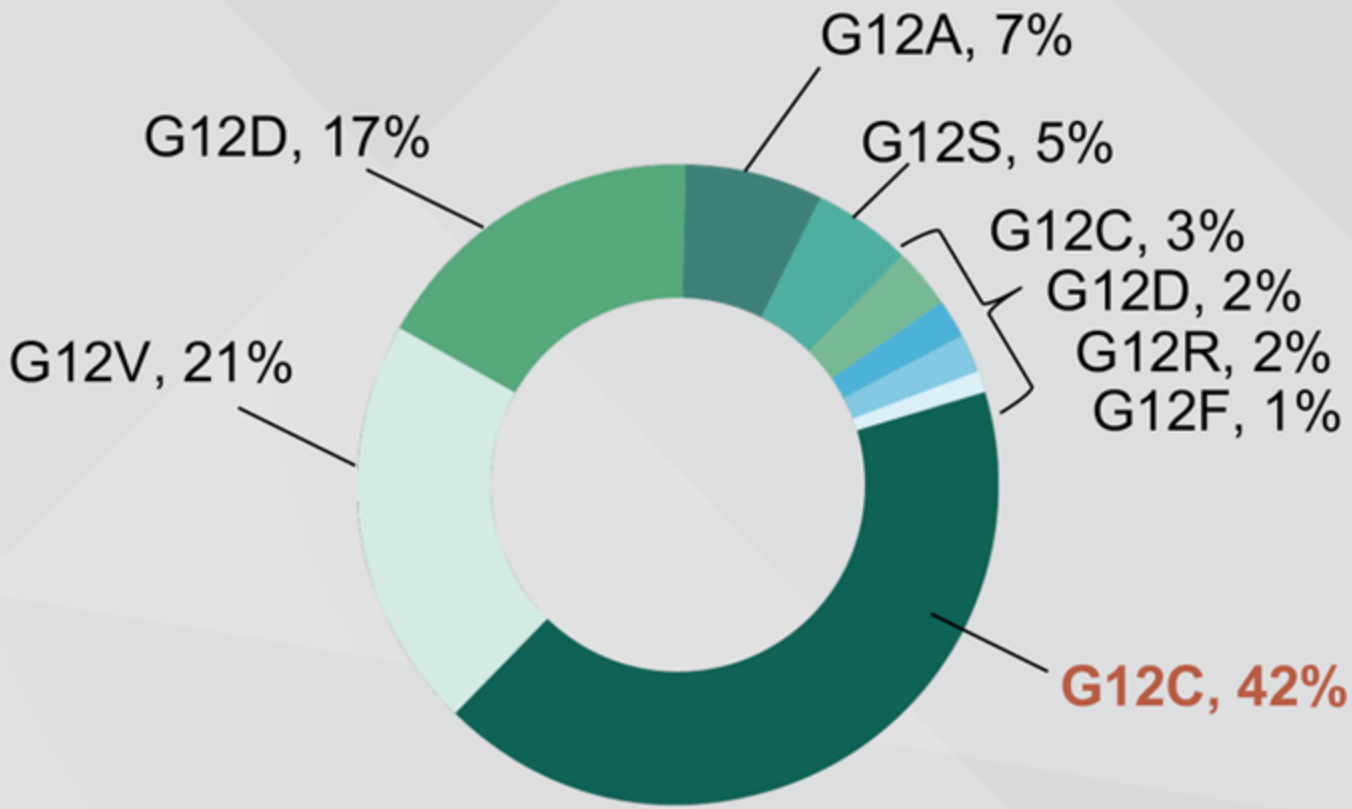
Prevalence of *KRAS* Mutations

Cancer Type[1]	*KRAS* Frequency, %
Pancreatic ductal adenocarcinoma	86
Colorectal adenocarcinoma	41
Lung adenocarcinoma	32

Population[2]	*KRAS* Frequency, %
Overall	31
Never smokers	8
Former smokers	39
Smokers	35

KRAS Alterations



Approved and Emerging Targeted Therapy for *KRAS*^{G12C}–Mutant NSCLC

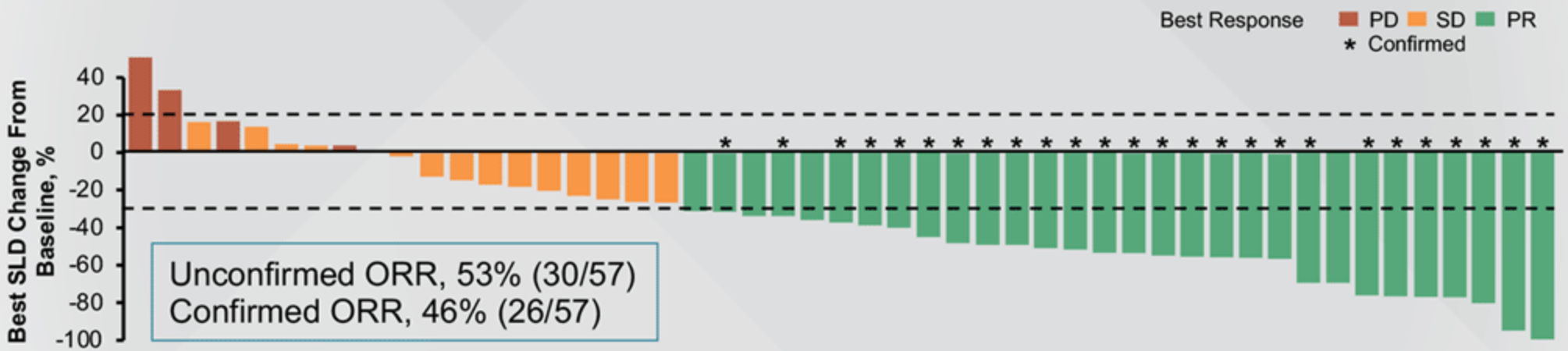
Sotorasib (Phase 1/2 CodeBreaK100)[1]	Previously Treated Patients With Mets (N = 124)
ORR	37.1%
Median DOR	11.1 mo
Median PFS	6.8 mo
Median OS	12.5
Occurrence of TRAE	69.8

Adagrasib (Phase 1/2 KRYSTAL-1)[2]	Previously Treated Patients With Mets (N = 112)
ORR	42.9%
Median DOR	8.5 mo
Median PFS	6.5 mo
Median OS	12.6 mo
Occurrence of TRAE	97.4

Investigational agents are included; refer to local regulatory bodies for status. Note that these data are from multiple trials and cannot be directly compared. See publications/references for trial information.

Emerging Monotherapy for *KRAS*^{G12C}–Mutant NSCLC

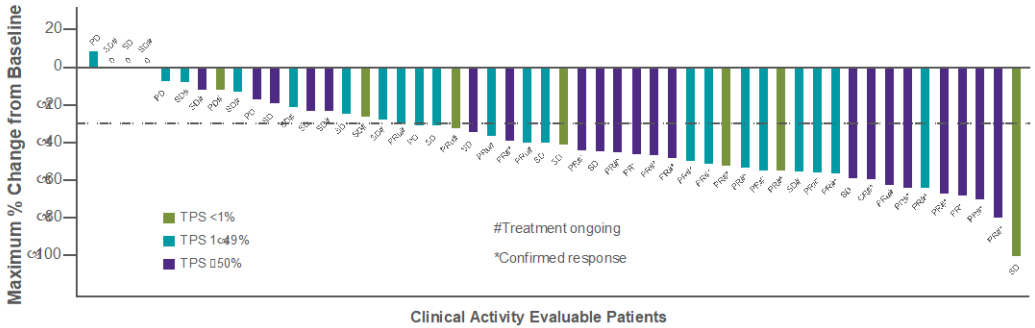
Phase 1a Trial of GDC-6036 Monotherapy in Previously Treated Patients: Antitumour Activity



TRAE resulting in modification (interruption/reduction/discontinuation; N = 59 NSCLC), 36%

Investigational agent is included; refer to local regulatory bodies for status. Note that 8 of 57 patients not included in waterfall plot. Doses ranged from 50 to 400 mg; see publication/reference for trial information.

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Best Tumor Change from Baseline



- Objective responses were observed in 49% (26/53)[a] of patients across all PD-L1 levels, with a disease control rate of 89% (47/53)
- Responses were observed in 59% (13/22)[a] of patients with PD-[illegible] with PD-L1 TPS 1–49%, and 30% (3/10)[a] with PD-L1 TPS <1%

Clinical activity evaluable population (n=53). One patient had only one post-baseline tumor assessment of PD due to new lesion; target lesions were not measured, therefore not included in the plot. Responses include target lesion tumor regression, as well as non-target lesion assessment
[a]Includes confirmed and unconfirmed CR/PR
Data as of 30 August, 2022. Median follow-up 3.5 months

NEW TRIALS WITH KRAS INHIBITORS

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Tumor Response

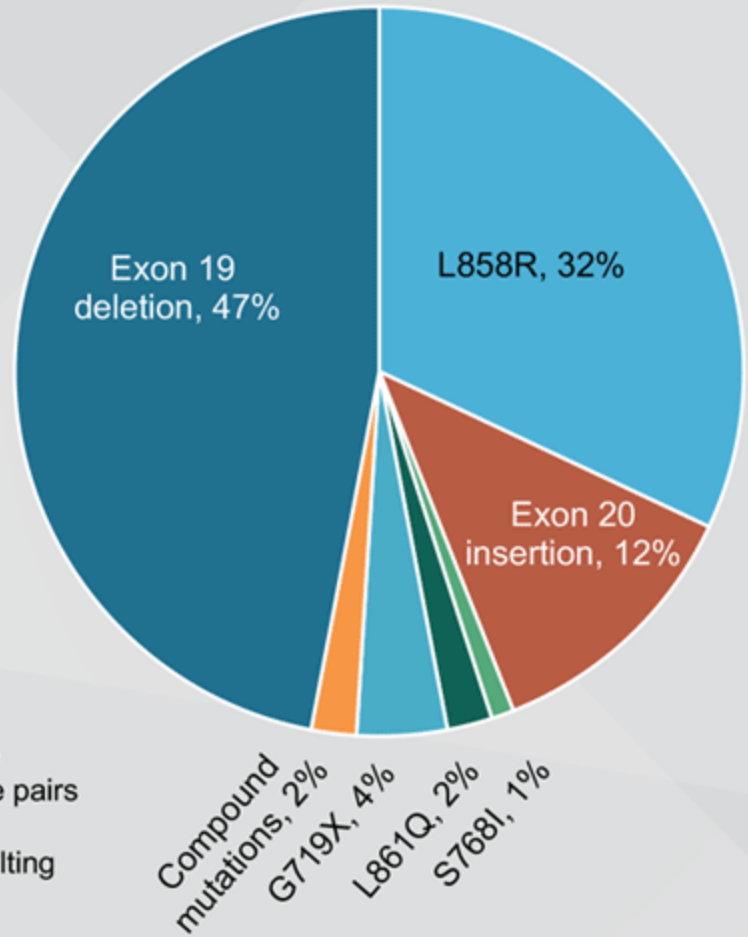
	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=53)[a,b]
Objective response rate, n (%)	26 (49)
95% CI	35–63
Best overall response, n (%)	
Complete response	1 (2)
Partial response	25 (47)
Stable disease	21 (40)
Progressive disease	6 (11)
Disease control rate, n (%)	47 (89)
95% CI	77–96

- ORR includes confirmed and unconfirmed CR/PR; 2 PRs were confirmed after data cut-off, and 3 responses remain unconfirmed, but patients remain on treatment

[a]Clinical activity evaluable population includes patients who received at least one dose of adagrasib (400 mg BID) + pembrolizumab and had measurable disease at baseline and at least one post-baseline tumor assessment. [b]In the clinical evaluable population including patients who discontinued prior to first scan for reasons not related to treatment (n=61), ORR was 43% (26/61)
Data as of 30 August, 2022. Median follow-up 3.5 months. Median duration of treatment 2.0 months

Prevalence of *EGFR* Exon 20 Insertions

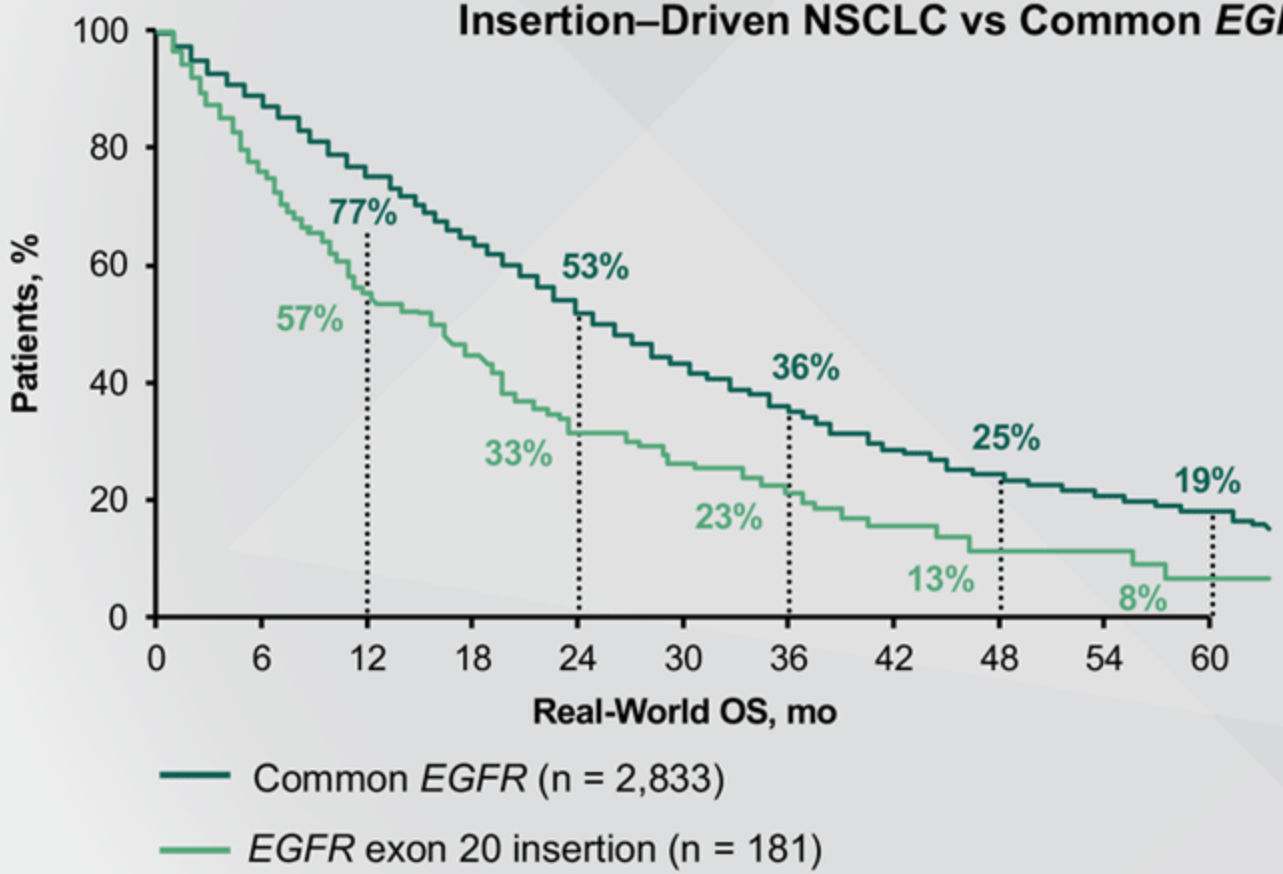
Frequency and Distribution of *EGFR* Mutations in NSCLC (N = 2,251)



EGFR exon 20 insertions include in-frame insertions and/or duplications of 3-21 base pairs between AA761-775.
S768I: missense mutation in exon 20 resulting in substitution of serine for isoleucine.

Prognosis of *EGFR* Exon 20 Insertions

Flatiron Database: Real-World Survival Outcomes in *EGFR* Exon 20 Insertion–Driven NSCLC vs Common *EGFR*



	Median Real-World OS, mo	Adjusted HR (95% CI)
Common *EGFR*	25.5	1.75 (1.5-2.1) *P* < .0001
EGFR exon 20 insertion	16.2	

Approved and Emerging Targeted Therapy for NSCLC With *EGFR* Exon 20 Insertions

Amivantamab (Phase 1 CHRYSALIS)[1]	Previously Treated Patients (N = 81)
ORR	40%
Median DOR	11.1 mo
Median PFS	8.3 mo
Median OS	22.8 mo

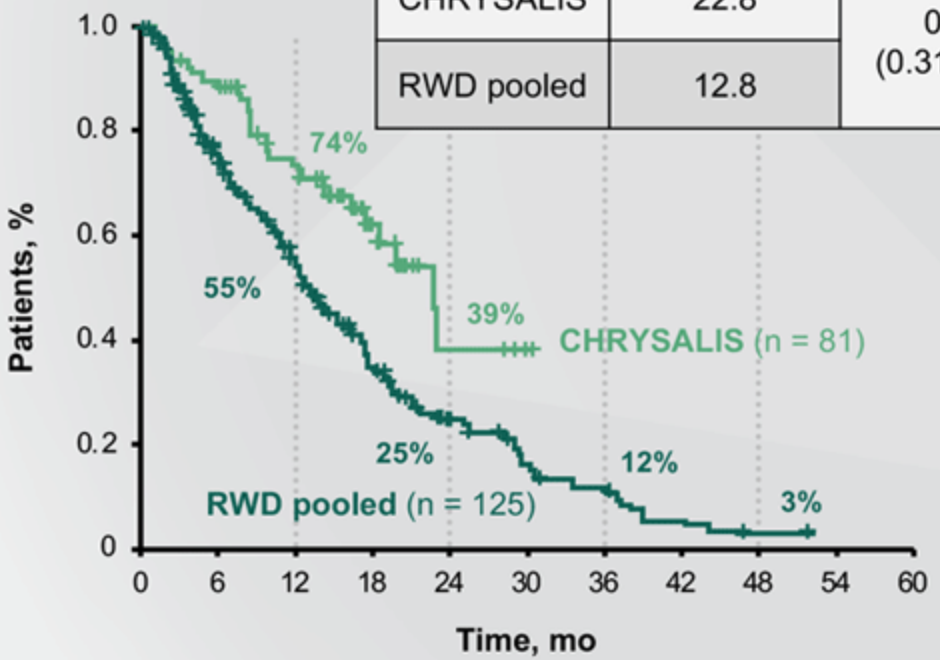
Mobocertinib (Phase 1/2 Nonrandomised)[2]	Previously Treated Patients (N = 114)
ORR	28%
Median DOR	17.5 mo
Median PFS	7.3 mo
Median OS	24.0 mo

Investigational agents are included; refer to local regulatory bodies for status. Note that these data are from multiple trials and cannot be directly compared. See publications/references for trial information.

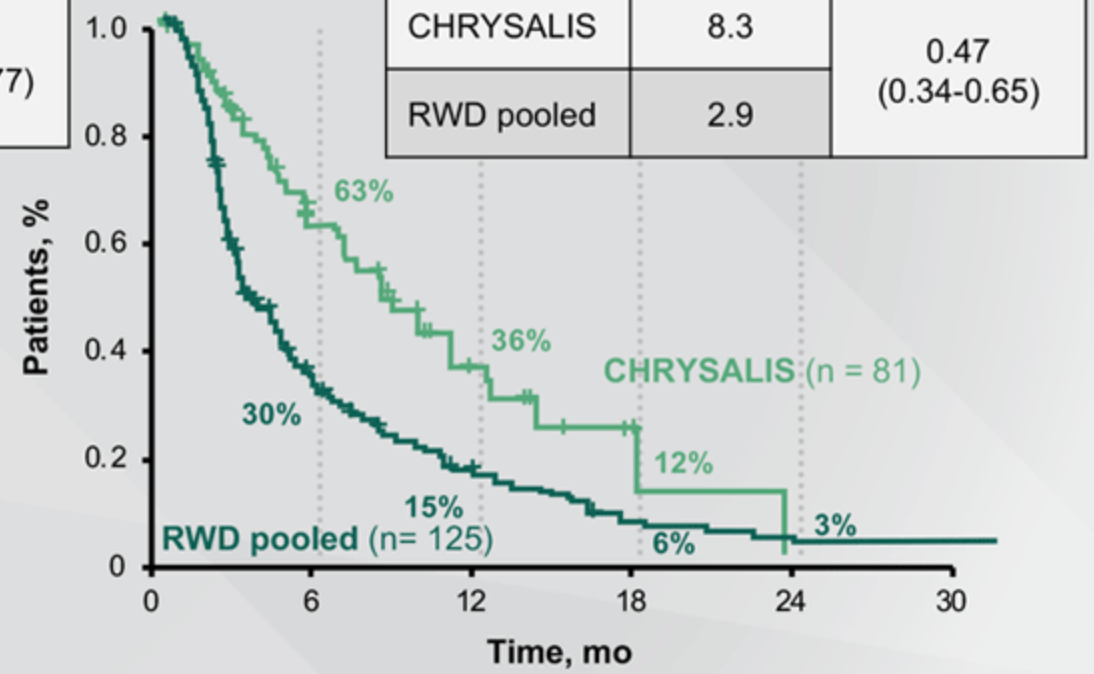
Approved Targeted Therapy for NSCLC With *EGFR* Exon 20 Insertions

Comparison of Amivantamab vs Real-World Therapy for Patient With *EGFR* Exon 20 Insertion Who Progressed After Platinum Doublet Chemotherapy

OS	Median, mo	HR vs RWE (95% CI)
CHRYSALIS	22.8	0.49 (0.31-0.77)
RWD pooled	12.8	



PFS	Median, mo	HR vs RWE (95% CI)
CHRYSALIS	8.3	0.47 (0.34-0.65)
RWD pooled	2.9	



Patient Case Scenario: Targeting *EGFR* Exon 20 Post Platinum-Based Chemotherapy

	Amivantamab (N = 81)[1]	Mobocertinib (N = 114)[2]	Poziotinib (N = 115)[3]	CLN-081 (N = 70)[4]	Sunvozertinib (N = 119)[5]	Necitumumab/ Osimertinib (N = 18)[6]
Class	EGFR MET Bispecific Ab	EGFR TKI	Pan-HER TKI	EGFR TKI	EGFR TKI	EGFR TKIs
ORR, %	40	28	14.8	36.0[a]	47.9	19.0[c]
Median DOR, mo	11.1	17.5	7.4	>15.0[b]		-
Median PFS, mo	8.3	7.3	4.2	12.0[b]	-	6.9
Median OS, mo	22.8	24.0	-	-	-	-

Investigational agents are included; refer to local regulatory bodies for status. Note that these data are from multiple trials and cannot be directly compared. See publications/references for trial information.

[a] Partial response was the best response observed. [b] Among 13 patients receiving 100 mg BID with longer-term follow-up available. [c] ORR among all patients, not just those with *EGFR* exon 20 insertion.

Approved Targeted Therapy for NSCLC With *MET* Exon 14 Skipping Mutations

Tepotinib
Phase 2 VISION[1]

	Previously Treated (n = 56)	Treatment-Naïve (n = 43)
Median PFS, mo	10.9	8.5
DOR, mo	11.1	11.8

Combined ORR, 46%

Capmatinib
Phase 2 GEOMETRY mono-1[2]

	Previously Treated (n = 69)	Treatment-Naïve (n = 28)
Median PFS, mo	5.4	12.4
DOR, mo	9.7	12.6

ORR for pretreated patients, 41%
ORR for treatment-naïve patients, 68%

Note that these data are from multiple trials and cannot be directly compared. See publications/references for trial information.

DESTINY-Lung02 for *HER2*-Mutated NSCLC: Interim Response Outcomes Associated With T-DXd

	T-DXd 5.4 mg/kg (n = 52)	T-DXd 6.4 mg/kg (n = 28)
ORR, n (%)	28 (53.8)	12 (42.9)
CR, n (%)	1 (1.9)	1 (3.6)
PR, n (%)	27 (51.9)	11 (39.3)
SD, n (%)	19 (36.5)	14 (50.0)
DCR, n (%)	47 (90.4)	26 (92.9)

Investigational regimens are included; refer to local regulatory bodies for status. See publication/reference for study information. Study is phase 2.

Introductión

Early signals of activity of PD-1/PDI1 inhibitors in NSCLC

Oct 2016 FDA expands **Pembrolizumab** indication for 1st line NSCLC with TPS >50% and approves in pretreated NSCLC

Aug 2018 FDA extends **Pembrolizumab plus Platinum Pemetrexed** in 1st line NSCLC
Aug 2018 FDA approves **Nivolumab** in 3thrd line SCLC

Feb 2018 FDA approves **Durvalumab** in stage III

Oct 2018 Pembrolizumab in combination with chemotherapy FDA approves in 1st SqCC NSCLC

Ipilimumab plus Nivolumab in NSCLC and Mesothelioma

Cemiplimab for PD-L1 >50%

Ipilimumab plus Nivolumab plus CT in NSCLC

Nivolumab plus CT Neoadj stage II-IIIA NSCLC

Mar 2015: FDA approved **Nivolumab** for pretreated SqCC NSCLC

Mar 2017 FDA grants **Pembrolizumab** for MSI High solid tumors

Dec 2018 FDA approves **Atezolizumab** plus CT plus bevacizumab in non Sq NSCLC

Jun 2019 FDA approved 3rd line SCLC

Durvalumab plus CT in advanced SCLC

Atezolizumab for adjuvant PD-L1 early stage NSCLC

Oct 2015 FDA extends **Nivolumab** for pretreated non SqCC NSCLC
Oct 2015 FDA approves **Pembrolizumab** for pretreated NSCLC with TPS >1%

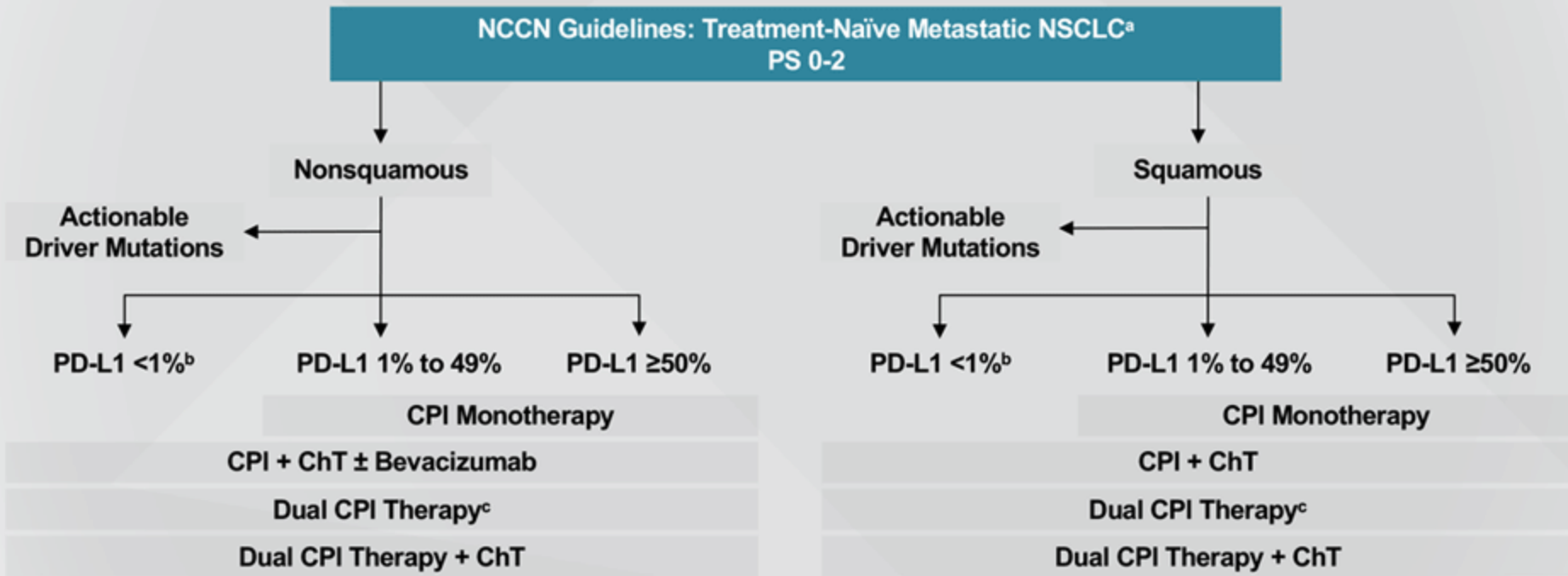
Mar 2017 FDA approves **Pembrolizumab plas CT** for 1st line nonSq NSCLC

Mar 2019 FDA approves **Atezolizumab plus CT** in advanced SCLC

Adap from Adv Exp Med Biol 2020

Fundación GECP lung cancer research

Impact of PD-L1 Expression on the Management of NSCLC Without Driver Mutations



See publications/references for further information. [a] Treatment regimens listed are not comprehensive. See the NCCN Guidelines for NSCLC for detailed recommendations, including treatment regimens. [b] CPI is recommended for eligible patients with PS 0-1. [c] Dual CPI therapy for patients with PD-L1 <1% is not FDA-approved.

Note that CPI monotherapy for PD-L1 1–49% and dual CPI therapy (regardless of PD-L1 status) are not EMA-approved. Treatment pathways by PD-L1 status continue to be refined based on outcomes from ongoing clinical trials.

What Challenges has ITP in advanced NSCLC

- ✓ ITP vs Ch-ITP for PD-L1 high expresión
- ✓ Treatment Options after Progresssion on First-Line ITP
- ✓ Role of ITP in advanced with driver-positive NSCLC
- ✓ How overcome the resistance to ITP
- ✓ Rechallenge
- ✓ Special Populations (elderly, poor ECOG, PS 2)
- ✓ Predicitive biomarkers, role of ctDNA
- ✓ Treatment duration
- ✓ Optimal approach to PD-L1 negative NSCLC

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New therapeutic evidence on NSCLC

- ✓ Benefit of Osimertinib on early EGFR+, resectable NSCLC and the reduction in risk of CNS recurrence or death (ADAURA trial)
- ✓ The Issue of Adjuvant ITP on driver negative NSCLC resectable (IMPower 010 and Keanote-091/Pearls), and the relationship between ctDNA-defined subgroups and DFS
- ✓ New evidence of the role of neoadjuvant chemotherapy and immunotherapy in resectable NSCLC (NADIM and NADIM 2 trials)
- ✓ Consolidation of the results with CT+ RT → Durvalumab on unresectable stages IIIA, IIIB NSCLC (PACIFIC trial)
- ✓ Expectations and Realities of Conjugated Antibodies and Bispecific Antibodies

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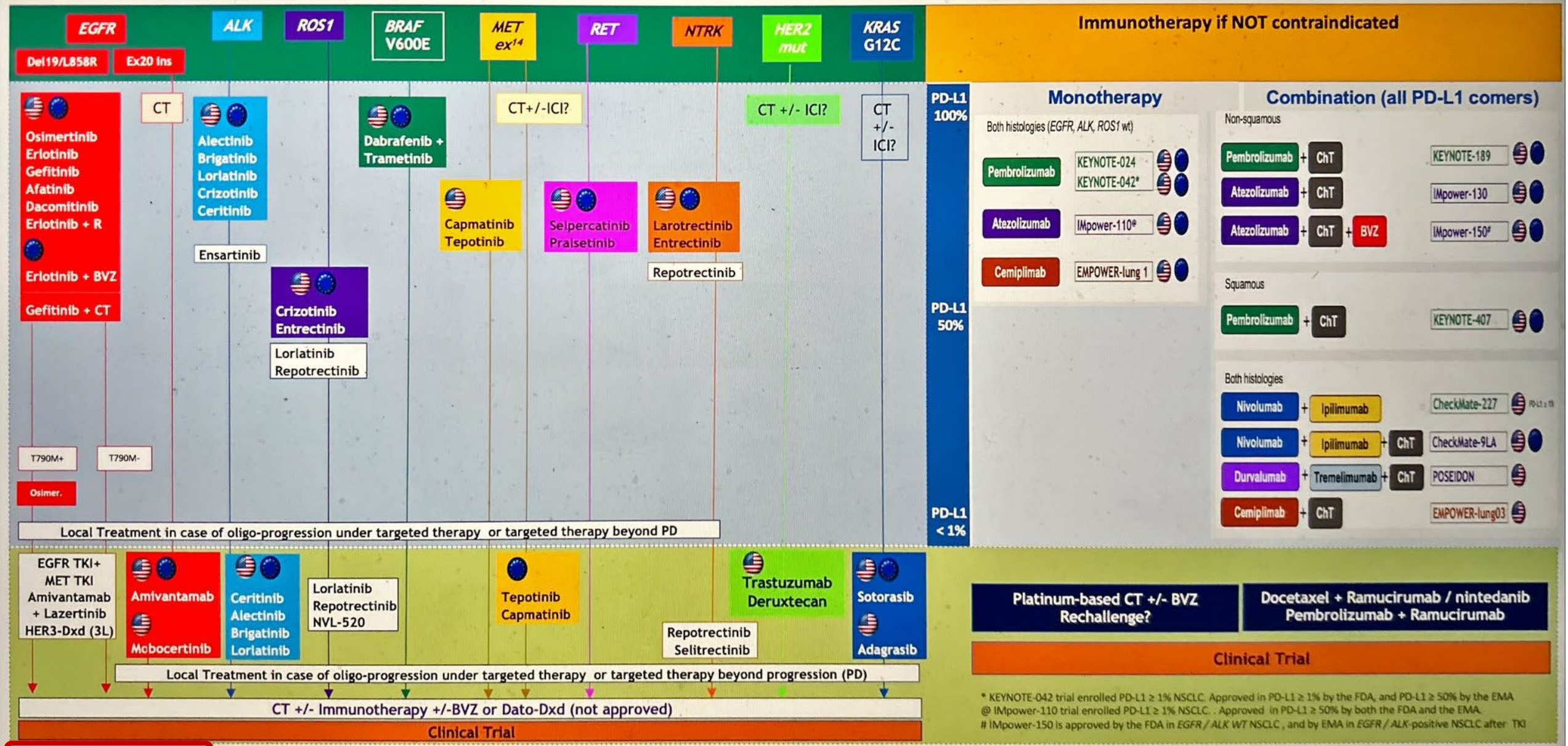
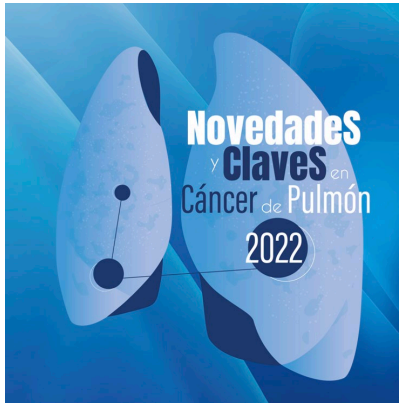
We start 2023 with this new treatment paradigm in aNSCLC



Novedades y Claves en Cáncer de Pulmón
Programa Científico



- ✓ **Introducción**
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  - ✓ A. Cantero. H. Regional Universitario de Málaga
- ✓ **Estadios Iniciales y enfermedad localmente avanzada**
  - ✓ M. Saigi. H. Germans Trias i Pujol. Badalona
- ✓ **Enfermedad Metastásica**
  - ✓ F.J. García Navalón. H. Son Llatzer. Palma de Mallorca
- ✓ **Cáncer de Pulmón Microcítico y otros tumores**
  - ✓ A. López. H. Univesitario Severo Ochoa. Madrid
- ✓ **Conclusiones**
  - ✓ R. Palmero. H. Duran i Reynals. Hospitalet de Llobregat

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