Unmet Needs in Lung Cancer

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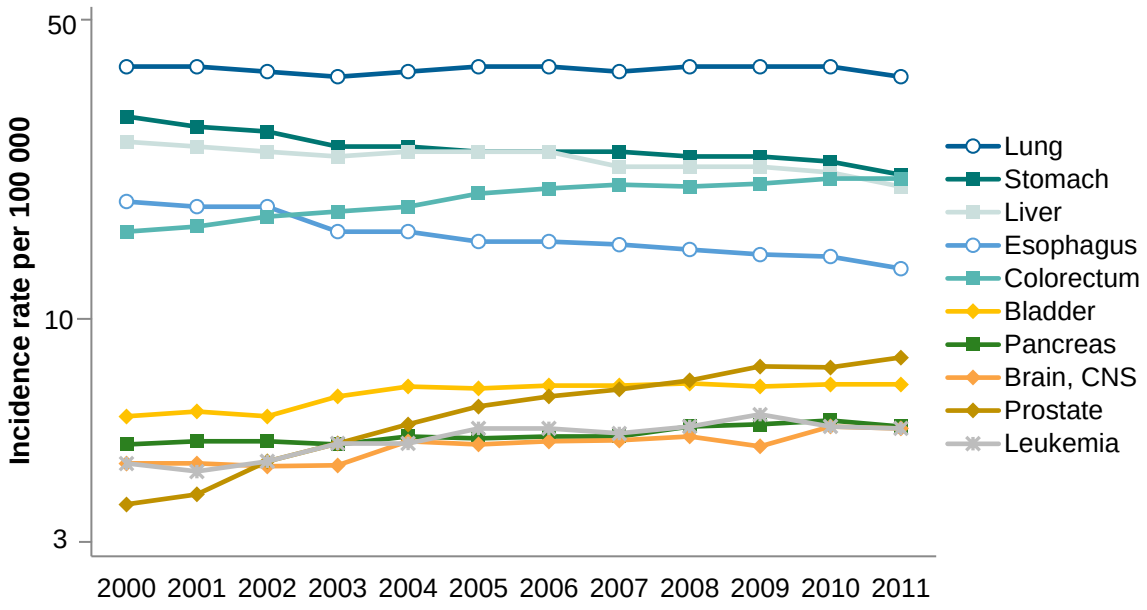
Lung Cancer Is the Most Common Cancer Type in China

Cancer Statistics in China, 2015

Wanqing Chen, PhD, MD; Rongshou Zheng, MPH; Peter D. Baade, PhD; Siwei Zhang, BMedSc; Hongmei Zeng, PhD, MD; Freddie Bray, PhD; Ahmedin Jemal, DVM, PhD; Xue Qin Yu, PhD, MPH; Jie He, MD

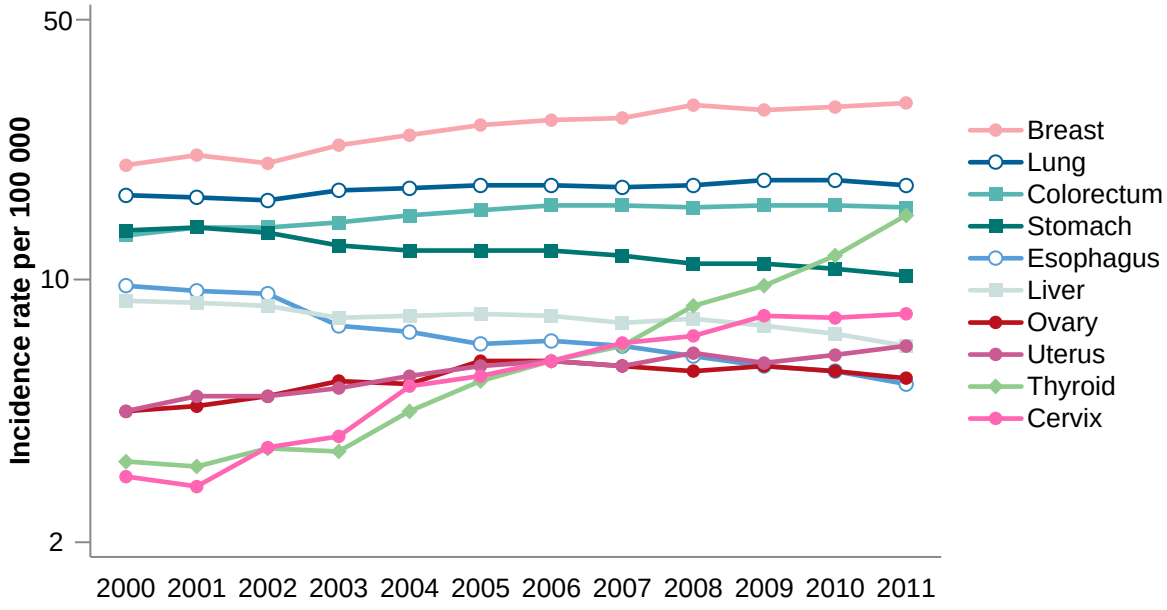
Incidence Rates for Males in China (2000–2011)

Trends in Incidence Rates (Age-Standardized to the Segi Standard Population) for Selected Cancers for Males: China, 2000 to 2011



Incidence Rates for Females in China (2000–2011)

Trends in Incidence Rates (Age-Standardized to the Segi Standard Population) for Selected Cancers for Females: China, 2000 to 2011



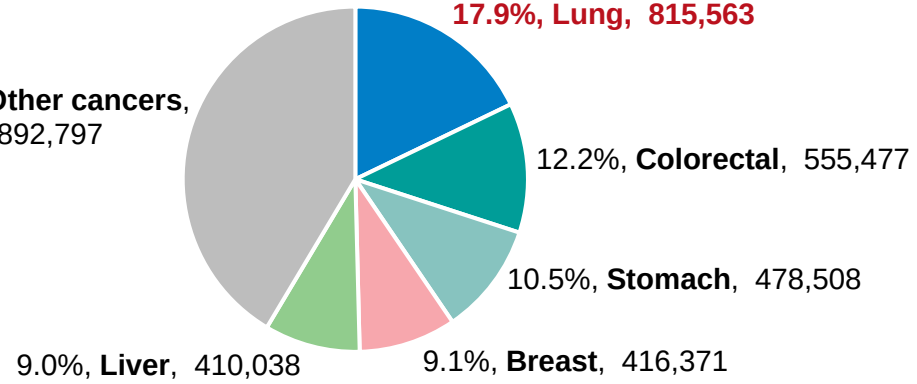
Abbreviation: CNS (central nervous system).

Source: Wanqing Chen, et al. CA Cancer J Clin 2016 Mar-Apr;66(2):115-32.

Lung Cancer Incidence and Mortality in China Are Higher Than in US

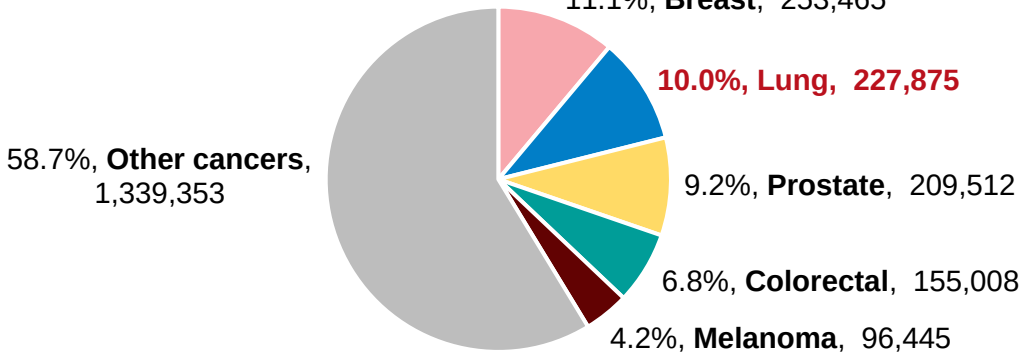
China Has ~4x New Cases vs. US

China



Total: 4,568,754

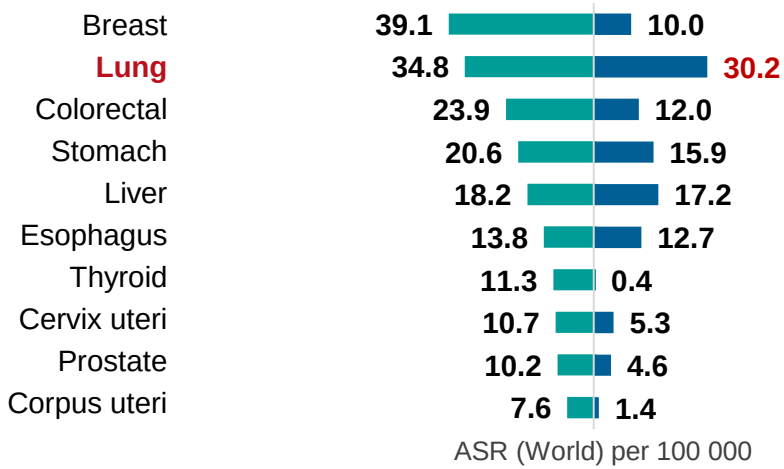
United States



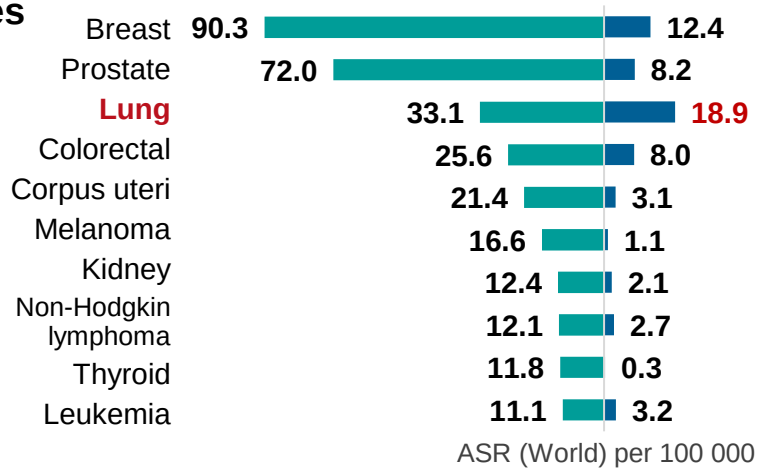
Total: 2,281,658

Mortality in China is 60% Higher than US

China



United States



Source: GLOBOCAN 2020.

Most Patients Are Diagnosed at Advanced Stage with Poor Prognosis
Overall Survival Rate Has Not Significantly Improved Over Time

Low Survival Rate in Advanced-Stage Patients[1]

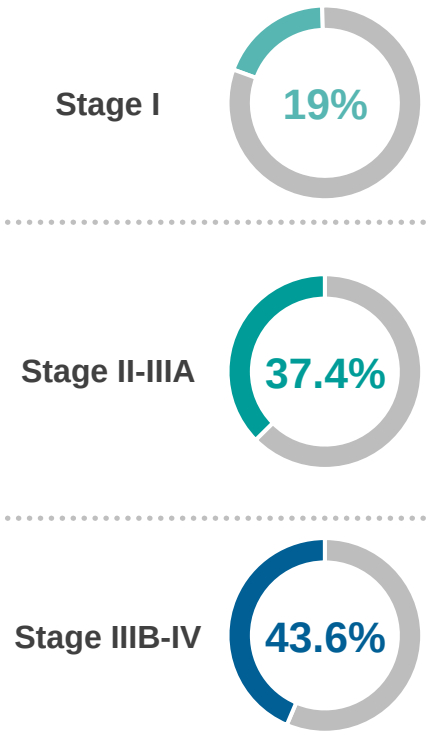
Overall survival by clinical stage

7th Edition	Events/N	MST	24 Months	60 Months
IA	1119/6303	NR	93%	82%
IB	768/2492	NR	85%	66%
IIA	424/1008	66.0	74%	52%
IIB	382/824	49.0	64%	47%
IIIA	2139/3344	29.0	55%	36%
IIIB	2101/2624	14.1	34%	19%
IV	664/882	8.8	17%	6%

Most Patients Are Diagnosed at Advanced Stage[2]

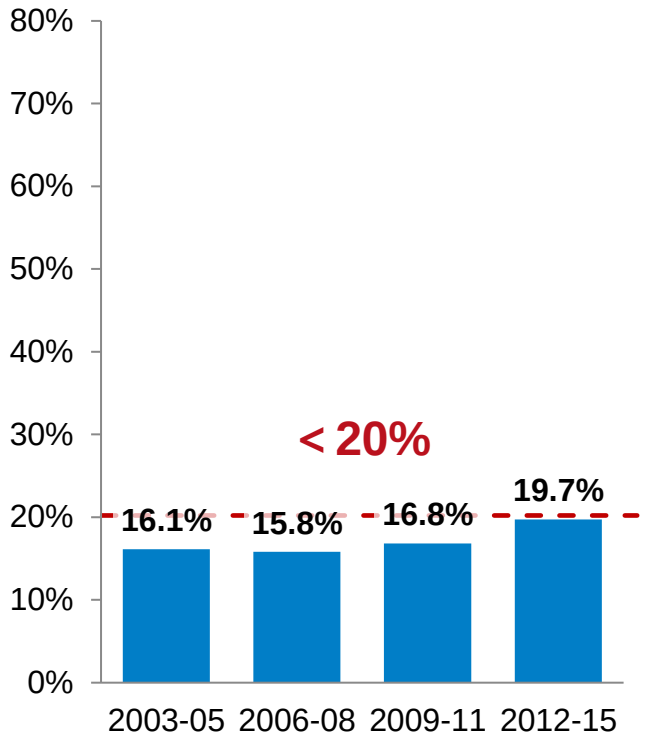
Lung cancer patients selected in seven regions in China

(N=7184, 2005.1-2014.12, TNM 7th)



Five-Year Survival Rate in China Still < 20%[3]

Five-year relative survival rates of lung cancer in China (2003–2015)

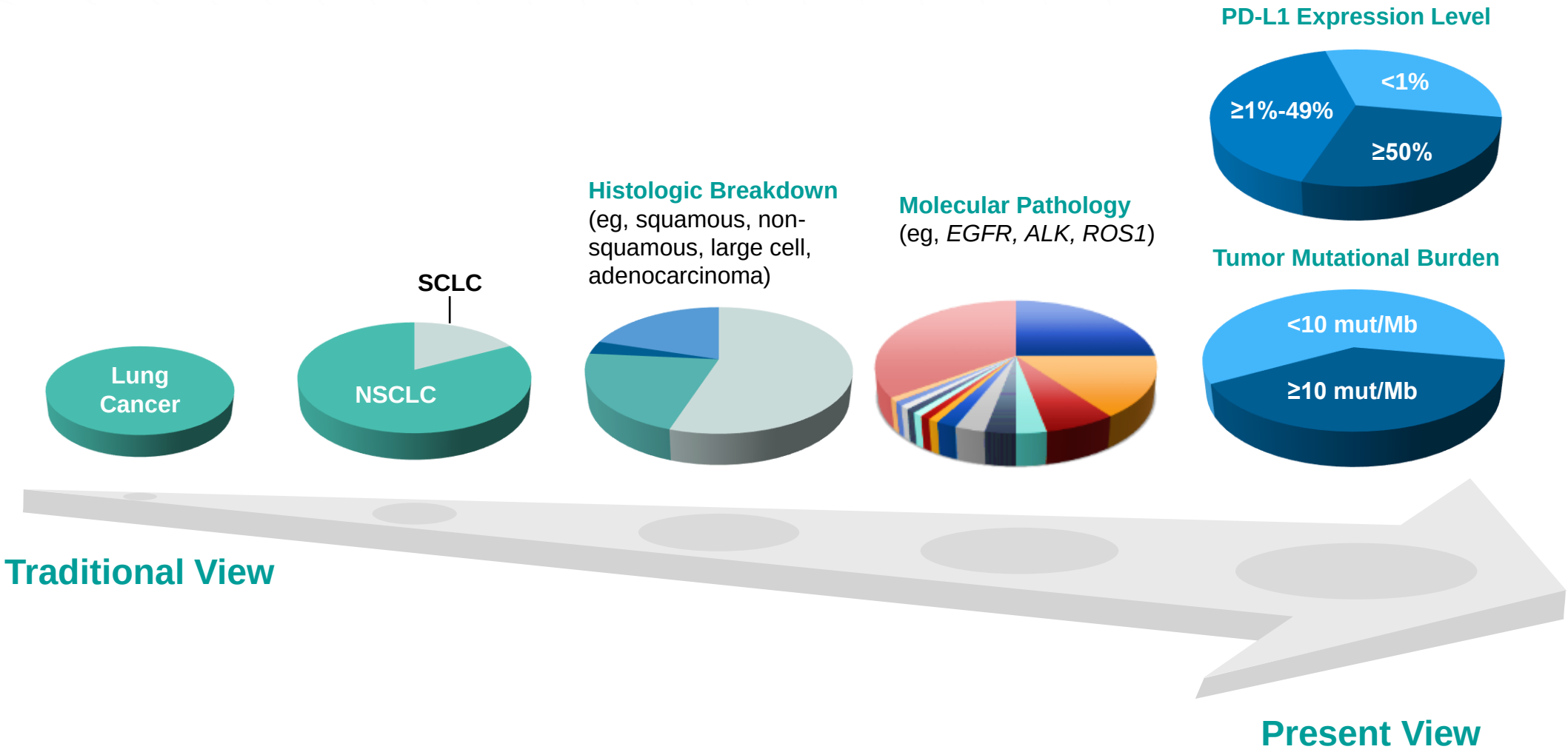


Source: (1) Goldstraw P, et al. Thorac Oncol. 2016 Jan;11(1):39-51; (2) Ju-Fang Shi, et al. Lung Cancer Journal, Volume 128, P91-100, 2019 Feb; (3) Hongmei Zeng, et al. The Lancet Volume 6, 2018.

What Have We Achieved in the Past Several Years?

NSCLC is leading the search for precision medicines

Evolution of Therapy in Lung Cancer Under Precision Medicine



Source: WA Cooper, et al. Pathology. 2011;43:103; CJ Langer, et al. JCO. 2010;28:5311; J Galon, et al. Immunity. 2013;39:11; W Pao, et al. Lancet Oncol. 2011;12:175; G Krigsfeld, et al. AACR 2017. Abstr CT143. MD Hellmann, et al. NEJM. 2018;378:2093.

Targeted Therapy Has Become Standard of Care for *EGFR*-Mutated NSCLC

EGFR Mutated Advanced NSCLC[1,2]

Osimertinib, erlotinib, afatinib, gefitinib, dacomitinib

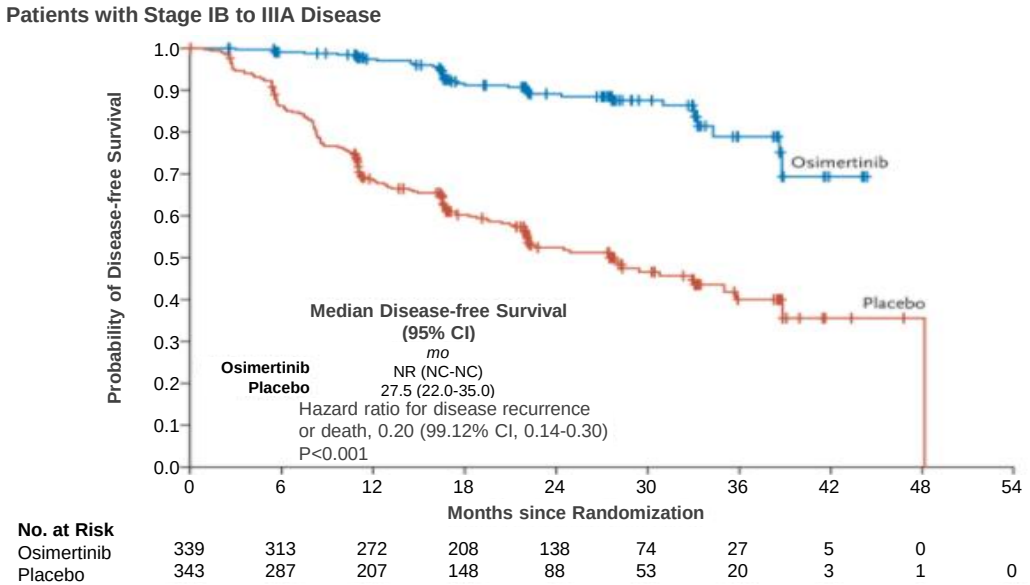
Progression

EGFR T790M mutation positive	EGFR T790M mutation negative or previous osimertinib
Osimertinib	**CT±Bev**

Selected EGFR TKI Trials[3]

Year	Generation	Study	Treatment
2009	1st generation	IPASS	Gefitinib vs Chemo
2011	1st generation	OPTIMAL	Erlotinib vs chemo
2013	2nd generation	LUX-Lung3	Afatinib vs Chemo
2017	2nd generation	ARCHER 1050	Dacomitinib vs gefitinib
2017	3rd generation	AURA3	Osimertinib vs Chemo/T790M+
2018	3rd generation	FLAURA	Osimertinib vs 1st generation TKI

Adjuvant Therapy (IB-IIIA) – ADAURA[4]



Clinical Trials Ongoing with Potential to Include (Neo)Adjuvant and Maintenance Treatment After Chemo/radiation in Stage III

NeoADAURA *(NCT04351555)*	LAURA *(NCT03521154)*

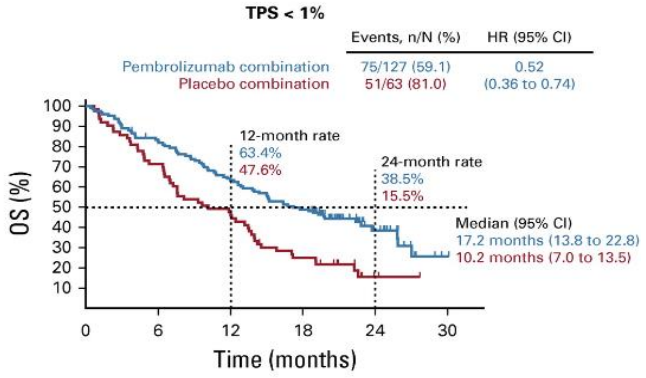
Source: (1) NCCN guideline v5.0 2021; (2) CSCO NSCLC guideline; (3) Lung Cancer (Auckl). 2020 Oct 7;11:73-103; (4) N Engl J Med. 2020 Oct 29;383(18):1711-1723.

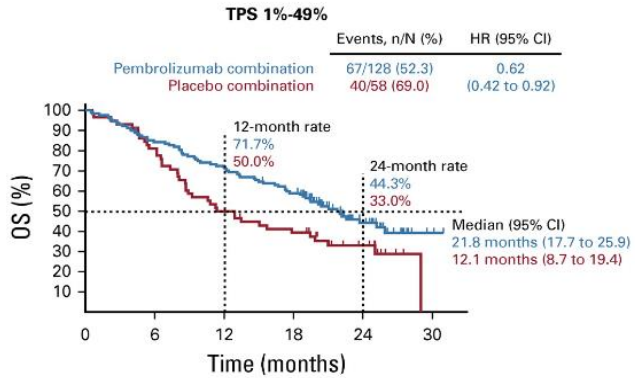
Immune Checkpoint Inhibitors
Another Breakthrough for NSCLC Without Driver Mutations

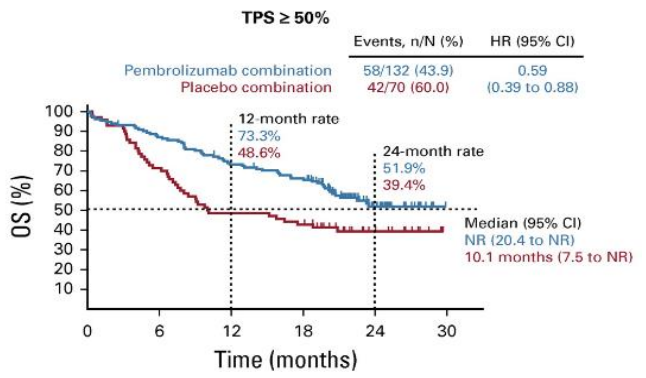
Selected Immune Checkpoint Inhibitor Clinical Studies

KEYNOTE-189[1]

Pembrolizumab + CT for Adv NSCLC

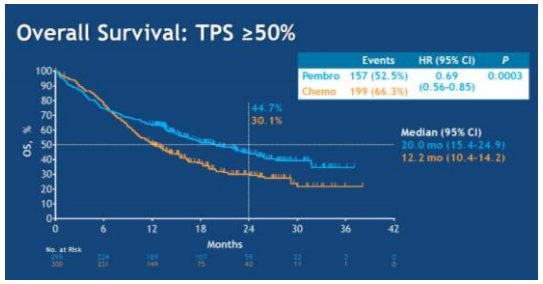


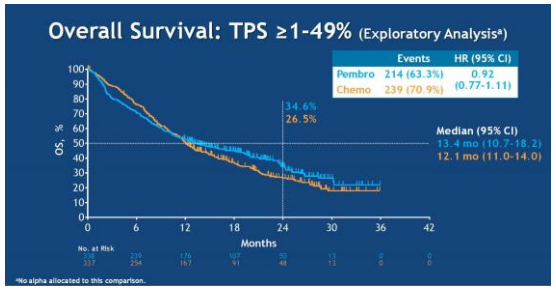




KEYNOTE-042[2]

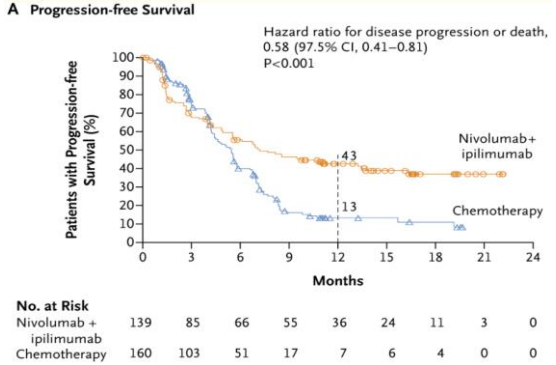
Pembrolizumab for Adv NSCLC (PD-L1 TPS≥ 1%)





Checkmate 227[3]

Nivolumab + Ipilimumab for Adv NSCLC TMB high



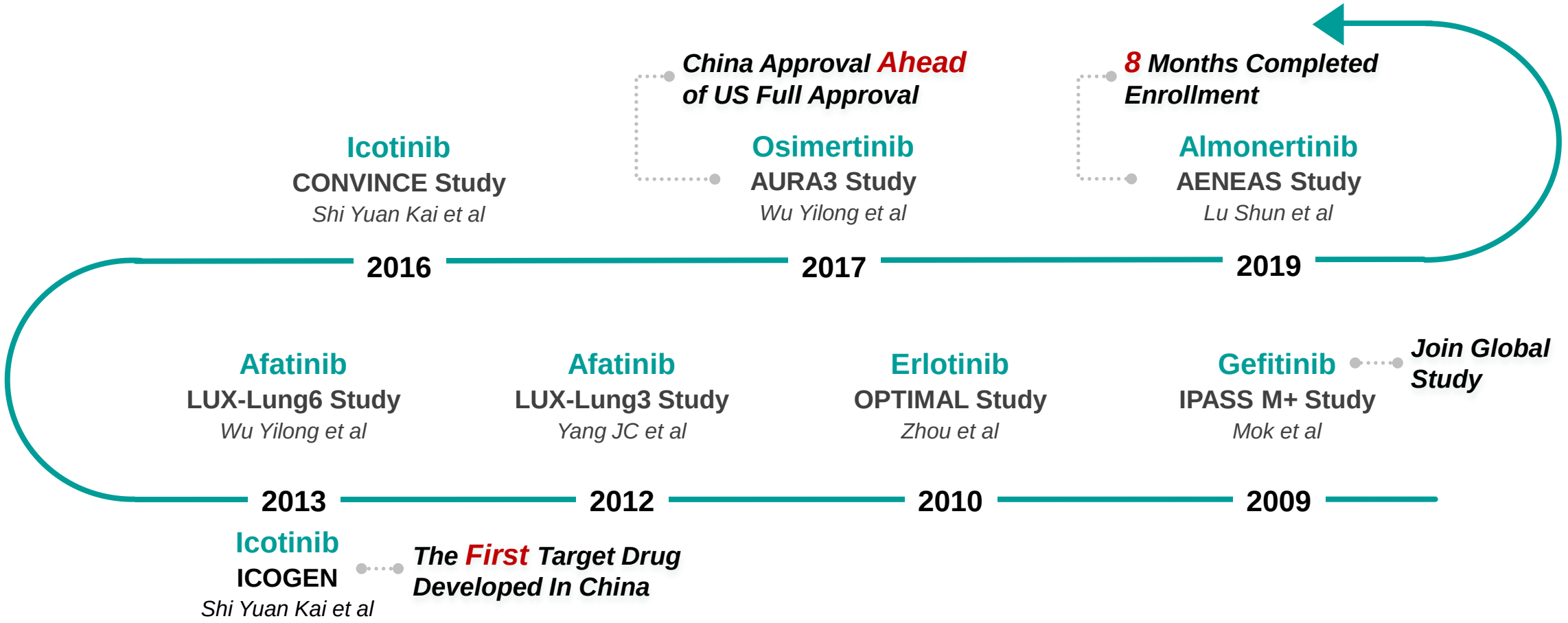
**Tumor Mutational Burden, TMB; Advanced, Adv; Chemotherapy, CT*

- **ICI has become SoC for NSCLC without driver mutation**
- **More biomarkers are being explored to identify appropriate patients**

Source: (1) S Gadgeel, et al. J Clin Oncol. 2020 May 10;38(14):1505-1517; (2) Gilberto Lopes. ASCO 2018; (3) MD Hellmann, et al. N Engl J Med 2018; 378:2093-2104.

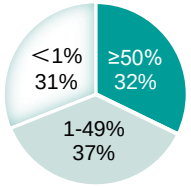
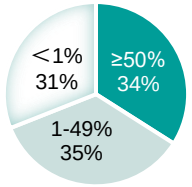
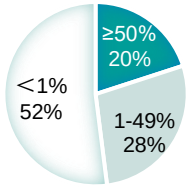
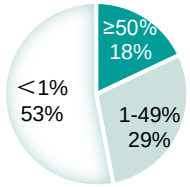
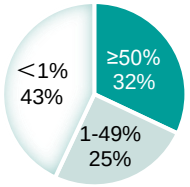
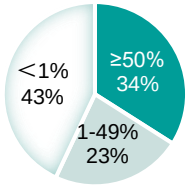
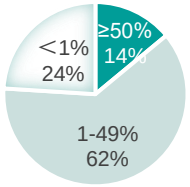
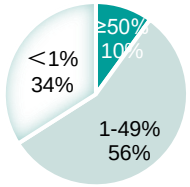
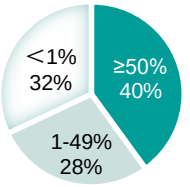
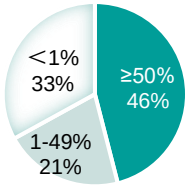
China Participated in Historic Transformation

Chinese Investigators Are More Experienced and Leading More Clinical Trials



Source: (1) Mok, et al. NEJM 2009; (2) Zhou, et al. ESMO 2010; (3) Yang JC, et al. ASCO 2012; (4) Wu Yilong, et al. 2013 ASCO; (5) Shi Yuankai, et al. 2013 Lancet Oncology; (6) Shi Yuankai, et al. 2016 ASCO.

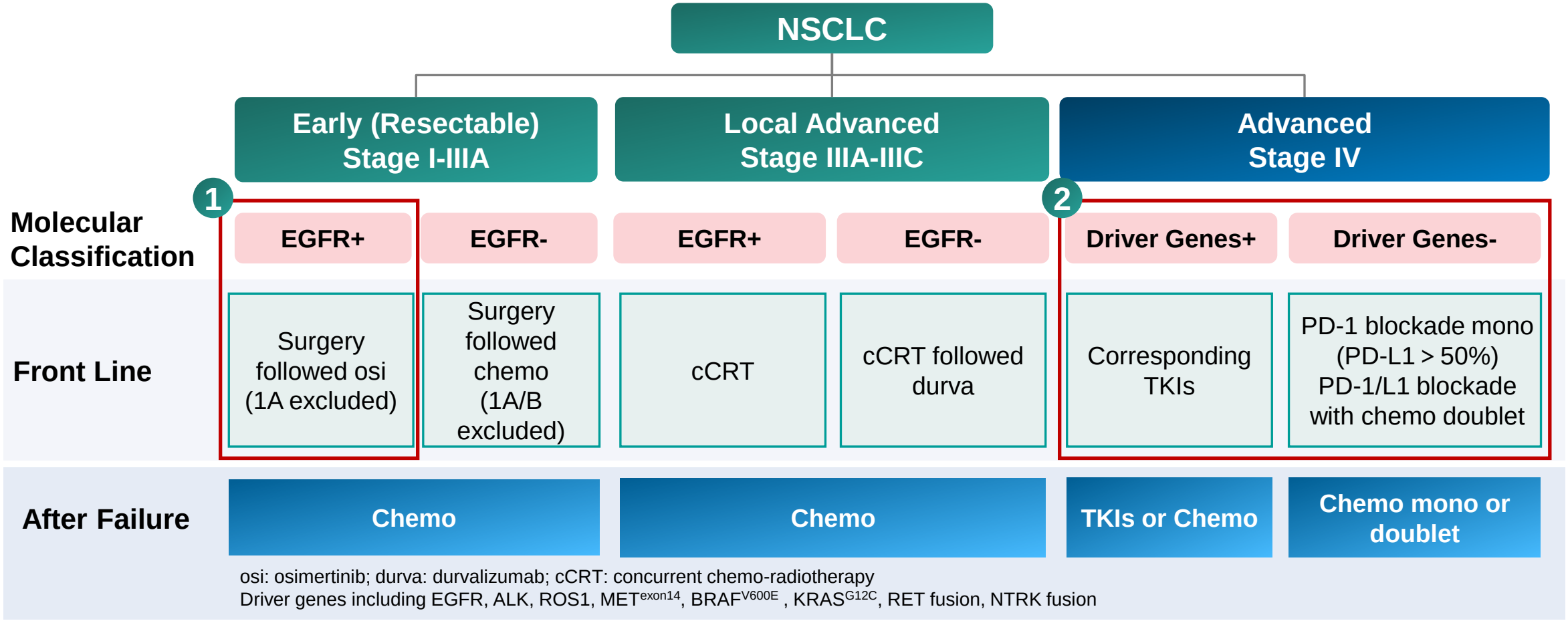
Continued Innovation in Drug Development Is Needed

	Immune Checkpoint Inhibitors Combined with Chemotherapy[1-5]									
Study	**KEYNOTE-189**		**IMpower 130**		**RATIONALE 304**		**CameL**		**ORIENT 11**	
Patient	N=616		N=679		N=334		N=419		N=397	
Treatment	Pembrolizumab+ CT	CT	Atezolizumab+ CT	CT	Tislelizumab+ CT	CT	Camrelizumab+ CT	CT	Sintilimab+ CT	CT
PD-L1 Expression*										
mPFS (Month)	**8.8**	**4.9**	**7.2 (7[#])**	**6.4 (5.5[#])**	**9.7 (8.5[#])**	**7.6 (5.6[#])**	**11.3**	**8.3**	**8.9**	**5.0**
PFS HR (95% CI)	**0.52** (0.43–0.64, p <0.001) **0.53** ([#] by Investigator) (0.43-0.63, p < 0.00001)		**0.75** (0.63-0.91) **0.64** ([#] by Investigator) (0·54–0·77, p <0.0001)		**0.645** (0.462, 0.902, p=0.0044) **0.561** ([#] by Investigator) (0.411-0.767, p=0.0001)		**0.61** (0.46-0.80, p=0.0002)		**0.482** (0.362-0.643, p < 0.0001)	
OS HR (95% CI)	**0.49** (0.38–0.64, p <0.001)		**0.79** (0·64–0·98, p=0.033)		**0.685** (Not mature) (0.422-1.110, p=0.0612)		**0.72** (Not mature) (0.52-1.01, p=0.027)		**0.609** (Not mature) (0.400,0.926, p= 0.019)	
ORR (%)	47.6	18.9	49.2	31.9	57.4	36.9	60	39.1	51.9	29.8
irAE (%)	22.7	11.9	-	-	25.7	NA	77.6 (RCEP)	-	43.2	36.6

* IMpower130: PD-L1 high (TC3 or IC3) correspond to PD-L1≥50% group; PD-L1-low (TC1/2 or IC1/2) correspond to PD-L1 1-49% group; PD-L1 negative correspond to PD-L1＜1% group.
# assessment by investigator.
Abbreviations: CT (chemotherapy), irAE (immune-related adverse events), RCEP (reactive capillary endothelial proliferation).
Source: (1) L Gandhi, et al. N Engl J Med, 2018. 378(22): 2078-2092 (KEYNOTE189); (2) H West, et al. Lancet Oncol, 2019. 20(7): 924-937 (IMpower130); (3) Shun Lu, et al. ESMO 2020(RATIONALE304); (4) Caicun Zhou, et al. 2019 WCLC (Camel). (5) Li Zhang, et al. 2020 WCLC Presidential Symposium (ORIENT11).

EGFR TKIs and ICIs
Firmly Established as Standard of Care in Treating NSCLC in China

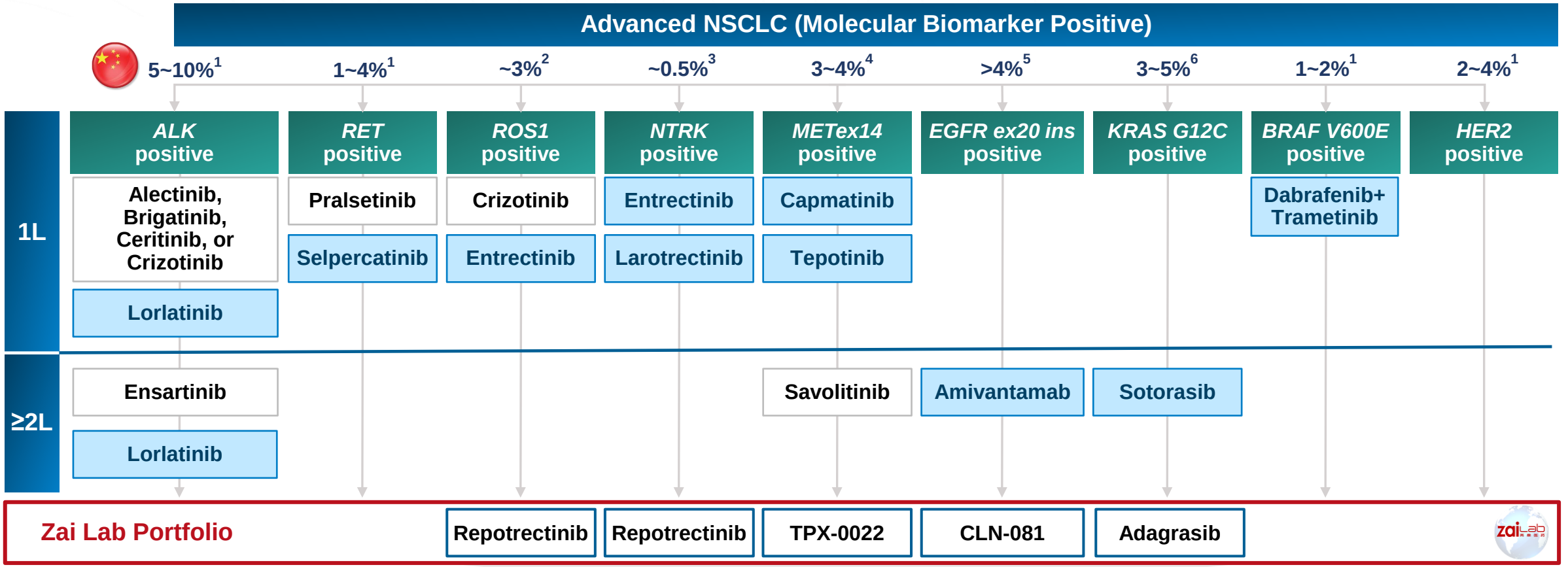
1. Third-generation EGFR TKIs have moved forward to early stage
2. Molecular pathology decides treatment regimen in advanced stage



osi: osimertinib; durva: durvalizumab; cCRT: concurrent chemo-radiotherapy
Driver genes including EGFR, ALK, ROS1, MET^{exon14}, $BRAF^{V600E}$, $KRAS^{G12C}$, RET fusion, NTRK fusion

Source: CSCO NSCLC guideline 2020.

Chinese Patients Need More Choices for Driver Mutations Beyond EGFR



FDA approved, NMPA not approved

More Clinical Trials Needed to Establish Better Treatment Paradigms in Each of These Populations

Source: FDA, NMPA, NCCN guideline 2021 V5.0., CSCO NSCLC guideline.
Note: (1) Chinese Journal of Pathology. 2021.50(6):583-591; (2) Clinical and the prognostic characteristics of lung adenocarcinoma patients with ROS1 fusion in comparison with other driver mutations in East Asian populations, 2014; and Frost & Sullivan; (3) NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls, 2020; (4) Turning Point Therapeutics presentation, December 2020; (5) Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology - mainland China subset analysis of the PIONEER study, 2015; (6) KRAS G12C mutations in Asia: a landscape analysis of 11,951 Chinese tumor samples, 2020; Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients, 2020; The prevalence and concurrent pathogenic mutations of KRASG12C in Northeast Chinese non-small-cell lung cancer patients, 2021.

Differentiated Drugs Are Needed
ROS1 as Example

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non–Small-Cell Lung Cancer

Yi-Long Wu, James Chih-Hsin Yang, Dong-Wan Kim, Shun Lu, Jianying Zhou, Takashi Seto, Jin-Ji Yang, Noboru Yamamoto, Myung-Ju Ahn, Toshiaki Takahashi, Takeharu Yamanaka, Allison Kemner, Debasish Roychowdhury, Jolanda Paolini, Tiziana Usari, Keith D. Wilner, and Koichi Goto

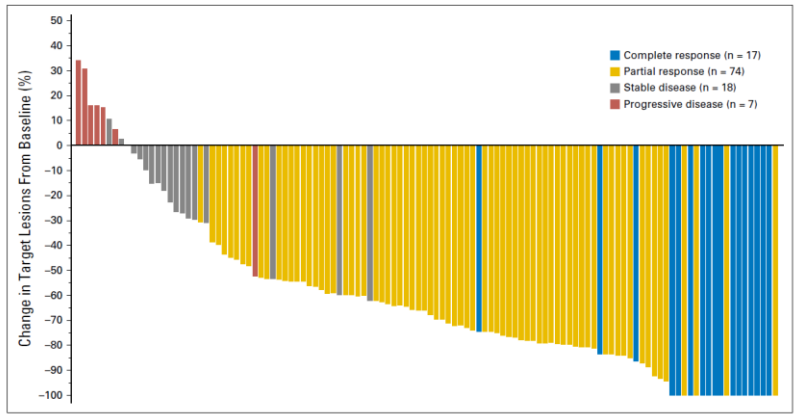
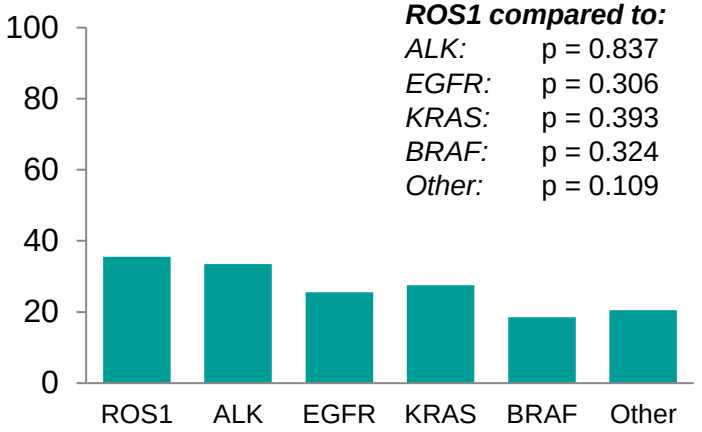


Fig 1. Best percent change in the target tumor burden from baseline as assessed by independent radiology review. Number of patients is based on the response-evaluable population that excludes early death, indeterminate, and patients with nontarget lesions only.

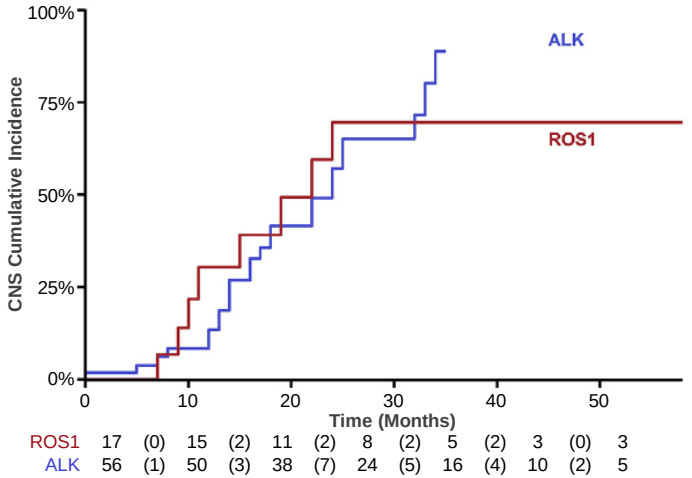
- ORR by IRR : 71.7% (95% CI, 63.0% to 79.3%)[1]
- Lack of intracranial efficacy
- Crizotinib approved in China

CNS-Penetrating TKI Needed

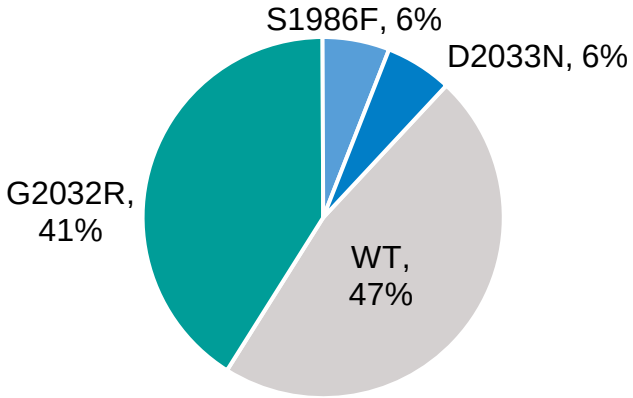
Incidence of brain metastases across oncogene groups[2]



CNS progression in patients with ROS1+ and ALK+ NSCLC on Crizotinib[2]



Resistant to Crizotinib[3]



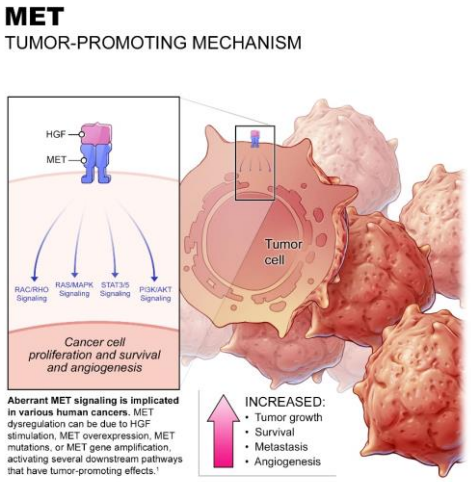
Treatment is urgently needed after crizotinib resistance

Source: (1) Yi-Long Wu et al. J Clin Oncol 36:1405-1411; (2) Patil T et al. JTO 2018; (3) Gainor JF et al. JCO Precis Oncol. 2017.

zai Lab

Trial Experience Is Increasing Beyond EGFR Mutation
MET ex14 as Example

2005



MET ex14 first reported in NSCLC[1]

2016

savolitinib

Phase II Study Initiate
(NCT02897479)

Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring *MET* exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study

Prof Shun Lu, MD • Prof Jian Fang, MD • Prof Xingya Li, MD • Prof Lejie Cao, MD • Prof Jianying Zhou, MD • Prof Qisen Guo, MD • et al. Show all authors

2020.5

capmatinib

2021

tepotinib – 2021.2

savolitinib – 2021.6

Experience Sharing

- Deeply understand disease
- Team collaboration to find positive patients
- Communication with CDE

Need more trials addressing treatment needs of mutations beyond EGFR

Source: (1) Cancer Res. 2005 Feb 15; 65(4): 1479-88.

NSCLC is Characterized by High Level of Unmet Clinical Needs
Despite Recent Progress and Encouraging Prospects

Unmet Clinical Needs in NSCLC

- Access to broad molecular testing
- Low survival rates
- Turnaround times for testing
- Tissue availability
- Diagnosis at advanced stage
- 2L options for patients resistant to immunotherapy
- Therapy sequence for patients with actionable mutations

Opportunities in NSCLC

- Generalization of broad molecular testing by NGS
- Use of liquid biopsy
- Re-biopsy In ≥ 2L
- Personalization of treatment
- Potentially curative immunotherapy and targeted therapy in 1L
- Increase in treatment options in ≥ 2L

Abbreviations: 1/2L (first/second line), NGS (next-generation sequencing).

What Will We Need in the Future?

1. **More Testing as More Targeted Therapies Are Approved**
2. **Resolving Drug Resistance**
3. **New Technologies**

Challenge: Many Driver Mutations Still Not Being Tested in China

Guidelines on Clinical Practice of Molecular Tests in Non-Small Cell Lung Cancer in China

Mandatory	Expansion
• EGFR	• MET
• ALK	• BRAF V600E
• ROS1	• HER2
	• RET
	• NTRK
	• KRAS

- Receiving PD-L1 testing if EGFR, ALK negative

NCCN Guidelines Version 5.2021 Non-Small Cell Lung Cancer

Mandatory
• EGFR (eg, exon19 deletion or L858R)
• ALK
• ROS1
• MET ex14 Skipping
• EGFR exon20 Insertion
• KRAS G12C
• BRAF V600E
• NTRK1/2/3
• RET

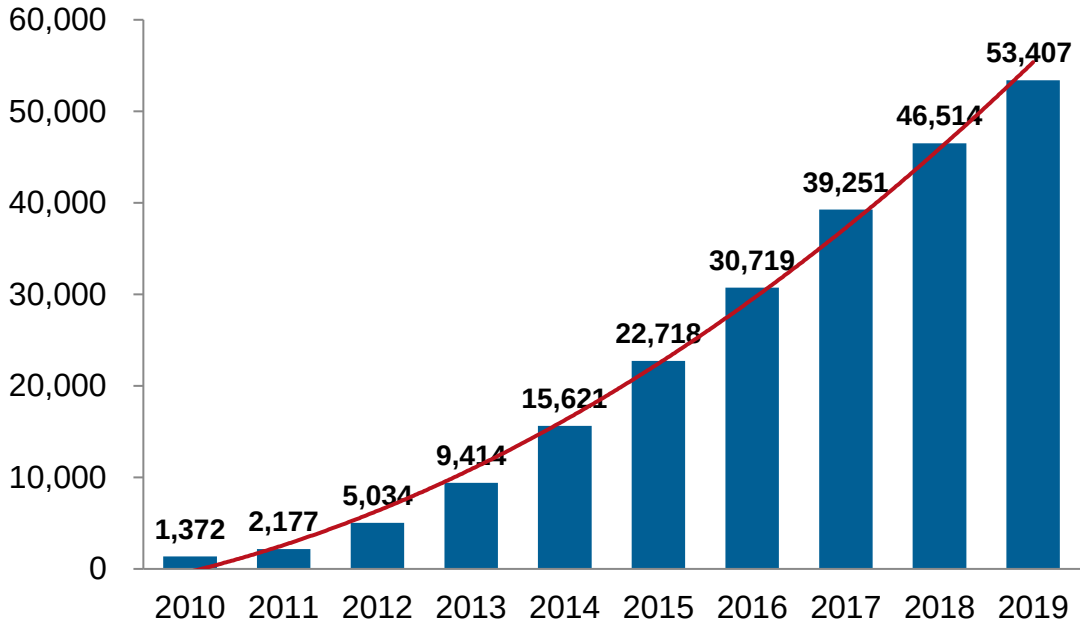
- Receiving PD-L1 testing at the same time

- Some patients may not receive recommended expansion testing
- Testing order may miss some mutations beyond EGFR and ALK

Opportunity: Continued Growth in Biomarker Testing in China

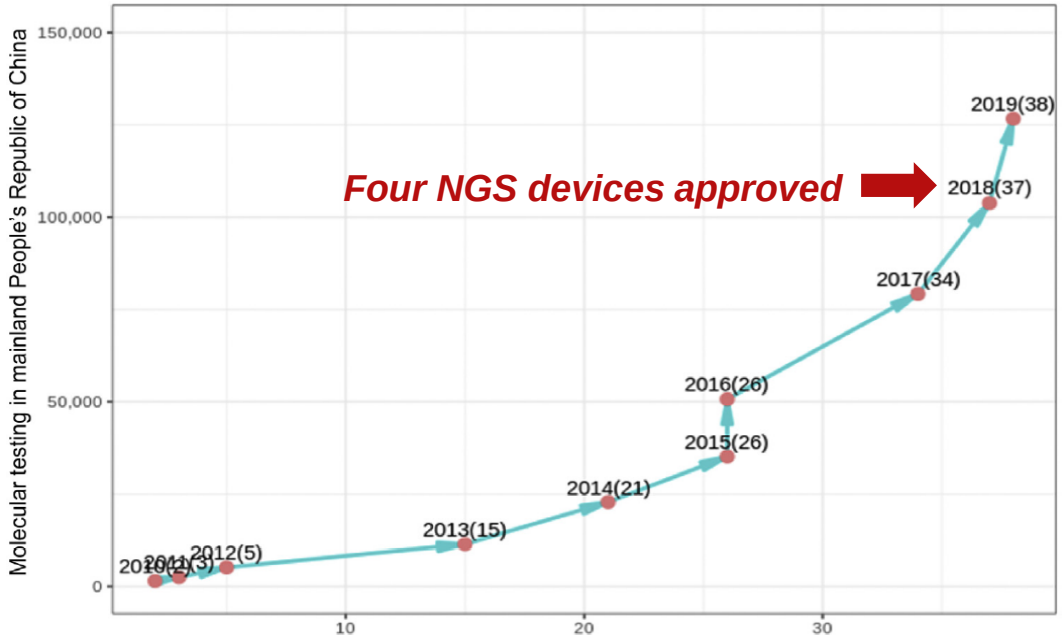
Molecular Testing Has Increased Significantly Over Past 10 Years

Number of molecular tests in NSCLC by year, based on 49 surveyed hospitals



NGS Testing Has Expanded Since 2018

Timeline of IVD devices approved by NMPA from 2010 to 2019 based on 49 surveyed hospitals

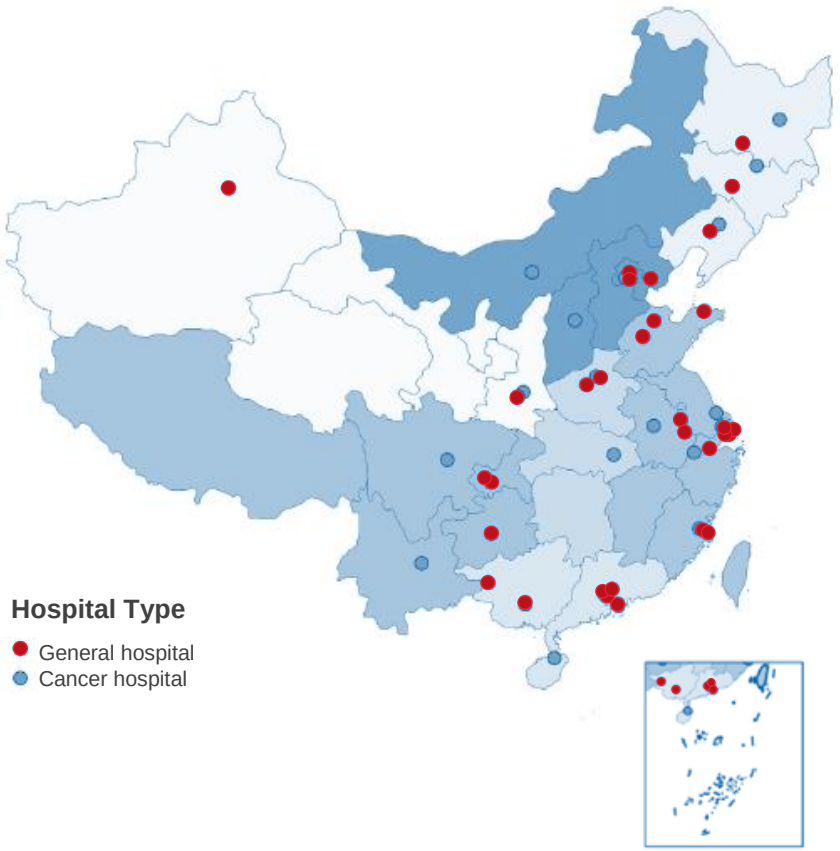


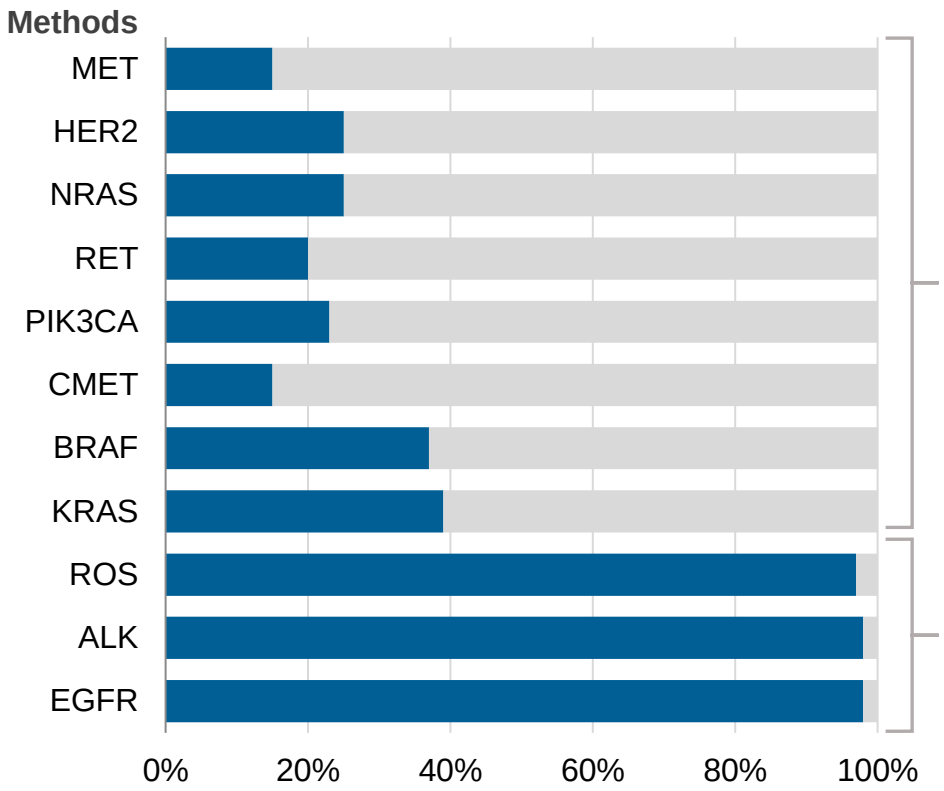
Increased use of NGS panels can aid physicians in selecting therapies, especially with rapid development of targeted agents beyond EGFR TKIs

Abbreviation: NMPA (National Medical Products Administration), IVD (In vitro diagnostic device).
Source: W Li, et al. JTO Clinical and Research Reports Vol. 2 No. 4: 100163.

Testing Is Expected to Increase in China with More Targeted Therapies Being Approved and Use of NGS

Proportion of Molecular Testing in 49 Hospitals (2017-2019)





Testing remains low without targeted drugs being approved;

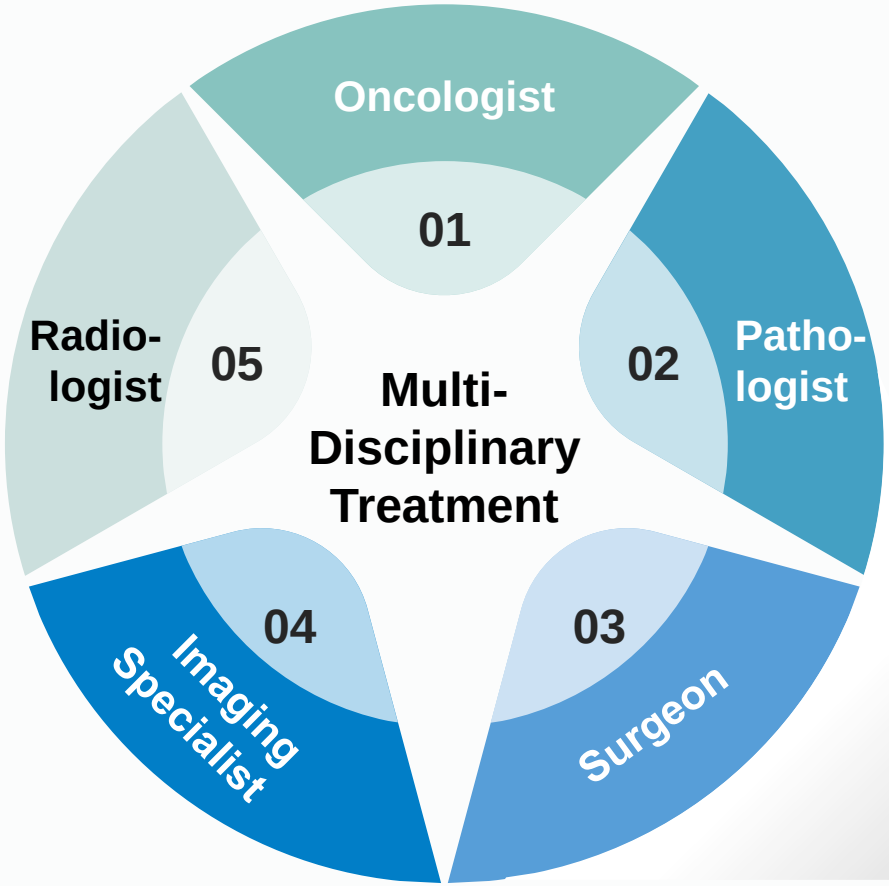
NGS testing has been a main driver

Testing rates become high as targeted drugs are marketed in China

Source: W Li, et al. JTO Clinical and Research Reports Vol. 2 No. 4: 100163.

More Attention Needed for Patients With Other Mutations

Outpatient Focus on Mutation



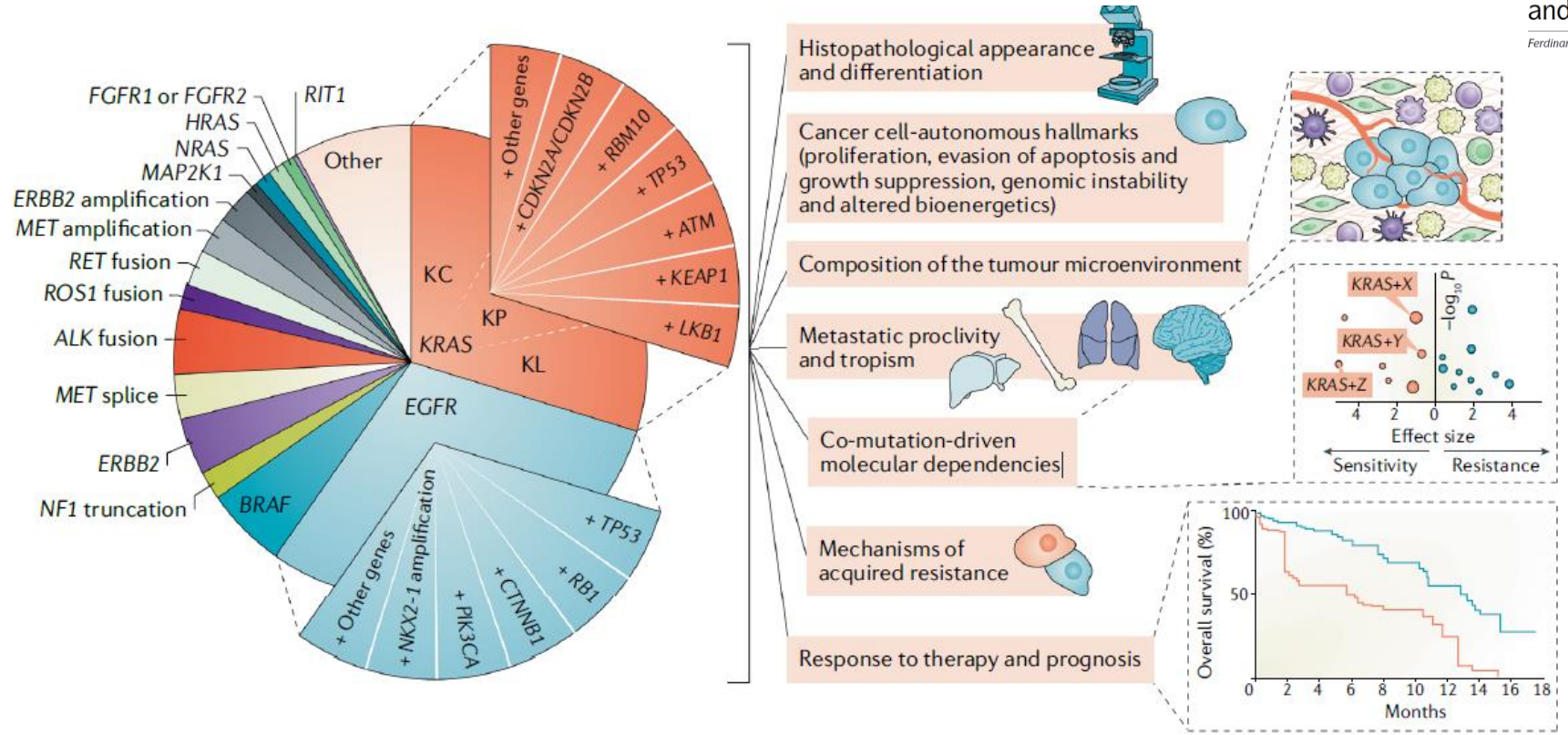
Clinical Study Group

- Increase patient testing rate
- Recommend suitable drug or trials for every patient

In the Future, We May Need Highly Personalized Therapeutic Approaches

Next-Generation Model for Molecular Stratification of LCC

(Only KRAS and EGFR Co-Occurring Genomic Alterations Are Depicted Graphically)



nature reviews cancer

Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy

Ferdinandos Skoulidis* and John V. Heymach

Moving beyond a single gene, we need more precise testing and drugs for different patient subgroups

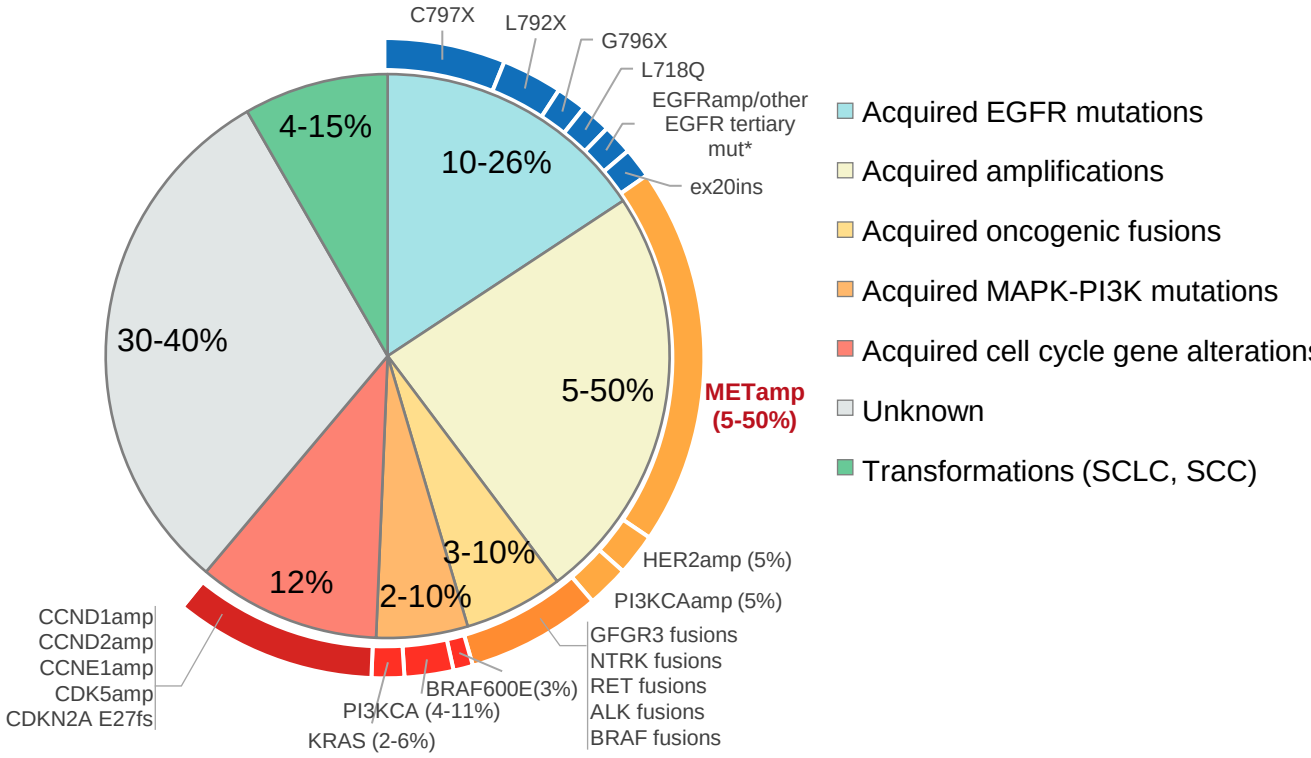
Abbreviation: LCC (lung adenocarcinoma).

Source: F Skoulidis, et al. Nature Reviews Cancer volume 19, pages495–509 (2019).

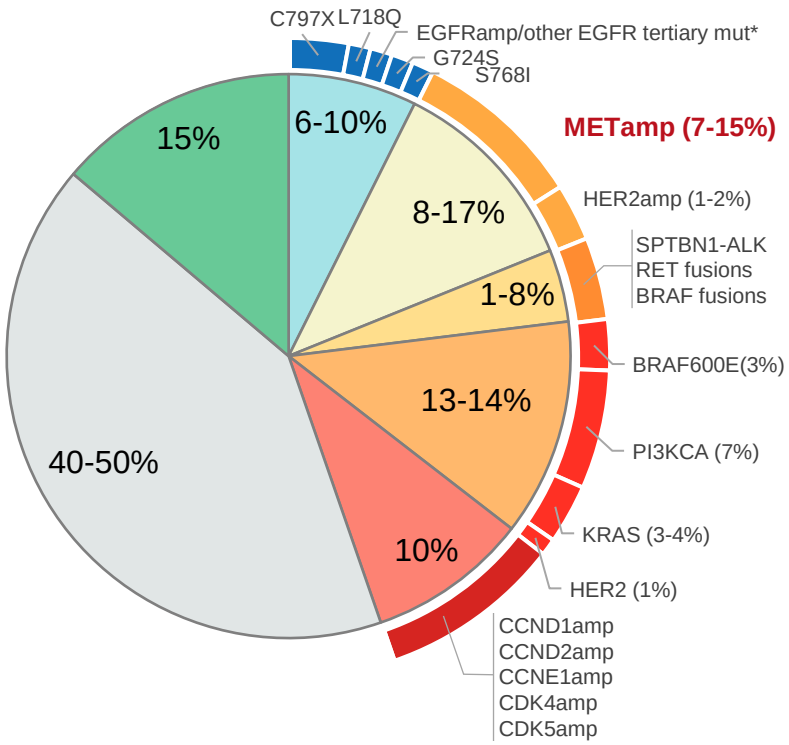
zai Lab

Drug Resistance Remains Key Issue
EGFR Resistance as Example

Resistance Mechanisms to EGFR TKI (Second-line Osimertinib)



Resistance Mechanisms to EGFR (First-line Osimertinib)



Future directions for resistant mechanism

- Retesting is important
- Different ways to resolve drug resistance, such as combination with MET inhibitor, next-generation drugs

Source: A Leonetti, et al. British Journal of Cancer (2019) 121:725–737.

Ongoing Trials Aim to Resolve MET Amplification Resistance
EGFR Resistance as Example

Study	Phase	Patients	N	Drug	ORR (%)	PFS (months)	DoR (months)
Non-selective MET inhibitor for treating MET Amp solid tumors							
NCT03993873	I	*MET* mutation including MET Amp Solid Tumor	120	**TPX-0022**	N/A	N/A	N/A
EGFR-TKI+MET-TKI							
TATTON[1]	Ib	• FISH (MET GCN≥5 or MET/CEP7≥2) • NGS (MET GCN≥5) • IHC 3+	344	Savolitinib+Osimertinib	62-67%	9.0-11.1	9.7-11.0
INSIGHT[2]	II	• MET GCN≥5 or MET/CEP7≥2 • MET IHC 3+	18 (Ib); 31 (II)	Tepotinib+Gefitinib	*MET Amp*: 67% MET IHC 3+: 68%	*MET* Amp: 16.6 MET IHC 3+: 8.3	19.8/8.7
NCT01610336[3]	II	• MET GCN≥6 • MET IHC 3+	100	Capmatinib+Gefitinib	MET GCN≥6: 47% MET IHC 3+: 32%	MET GCN≥6: 5.49 MET IHC 3+: 5.45	5.6
INSIGHT[2]	II	• MET GCN≥5 or MET/CEP7≥2 • MET IHC 3+	18 (Ib); 31 (II)	Chemotherapy	*MET Amp*: 43% MET IHC 3+: 33%	*MET* Amp: 4.2 MET IHC 3+: 4.4	2.8
AcSé[4]	II	• MET GCN≥6	25	Crizotinib	32	3.2	N/A

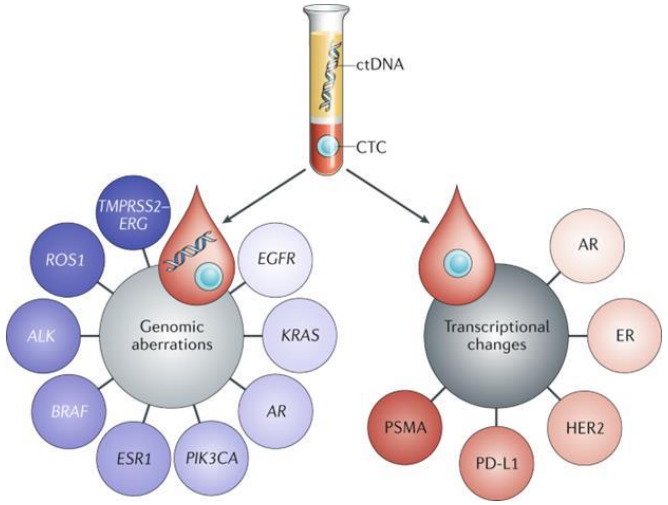
Abbreviations: FISH (Fluorescence in situ hybridization), CEP7 (Centromere 7), GCN (Gene Copy Number), IHC (Immunohistochemistry).

Source: (1) Han JY,et al. 2020WCLC.FP14.03; (2) Wu YL, et al. Lancet Respir Med.2020 Nov;8(11):1132-1143; (3) Wu YL,et al.J Clin Oncol.2018;36(31):3101-3109; (4) Moro-Sibilot D,et al. Ann Oncol. 2019 Dec 1;30(12):1985-1991.

New Advances from Diagnosis to Treatment Options

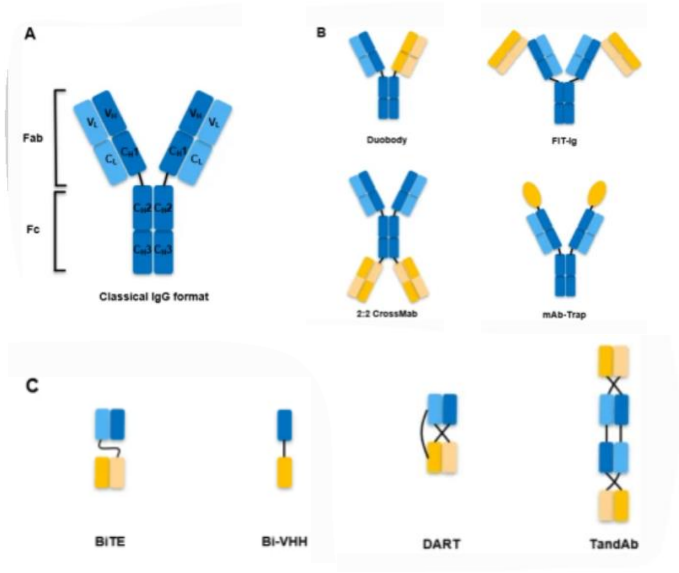
Liquid Biopsies[1]

- Cell-free DNA (cfDNA)
- Circulating tumor DNA (ctDNA)

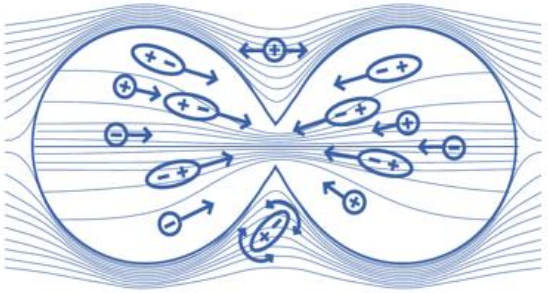


Antibodies[2]

- Bispecific antibody
- Antibody-drug conjugate (ADC)



Tumor Treating Fields[3]



Source: (1) K Pantel, et al. Nature Reviews Clinical Oncology volume 16, pages409–424 (2019); (2) Shuyu Huang, et al. Journal of Cancer Research and Clinical Oncology 2020; 146(12): 3111–3122; (3) Novocure disclosure.

Summary

- **Lung cancer is most common cancer type and leading cause of cancer death in China, with five-year survival rate less than 20%**
- **NSCLC leads precision medicine for cancer treatment**
  - ✓ **Target therapy has become SoC for EGFR-mutated NSCLC**
  - ✓ **Immune checkpoint inhibitors have become SoC for NSCLC without driver mutations, and more biomarkers are being explored for select patients**
  - ✓ **China witnessed and participated In historic transformation**
- **Significant unmet needs exist in China for NSCLC patients with driver mutations beyond EGFR**
  - ✓ **Beyond EGFR TKIs, access to other targeted drugs in China is low**
- **Molecular testing is booming, but increased testing is mainly driven by EGFR and ALK; testing is expected to increase in China as more targeted therapies are approved and with increased use of NGS**
- **Drug resistance is still a barrier in clinic; we should understand more about resistant mechanisms and explore different methods to resolve drug resistance**
- **New technologies will provide additional options and potential for improved survival**