BLA 761222 ODAC

Sintilimab BLA in non-squamous NSCLC

U.S. Food & Drug Administration

Oncologic Drugs Advisory Committee

February 10, 2022

Innovent | Lilly

Introduction

Lana Shiu, MD

Senior Vice President, Global Regulatory Affairs

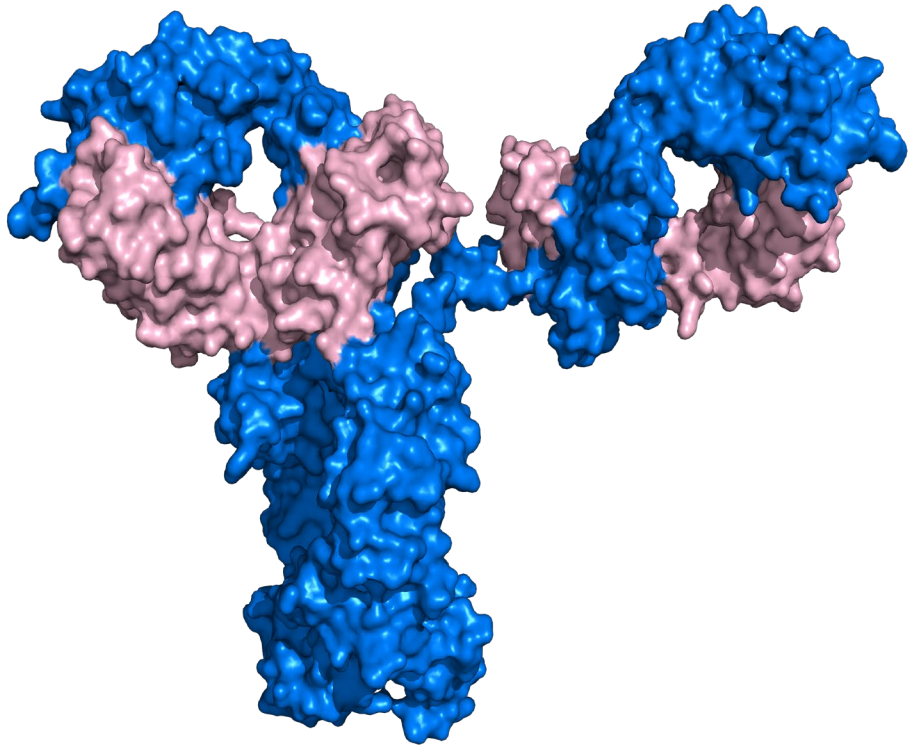
Innovent Biologics USA, Inc.

Introduction to Innovent Biologics

- Global biopharmaceutical company headquartered in Suzhou, China
- 6000+ employees on 4 continents
- 6 products commercialized in China
- >25 products in development
- Mission to develop high-quality and affordable medicines
- Collaboration with Eli Lilly since 2015

Sintilimab Is a Novel PD-1 Inhibitor

- Recombinant fully human IgG4 monoclonal antibody
- Binds PD-1 with high affinity (Kd of 0.07 nM) and exhibits potent PD-1 signaling blockade
- Well-tolerated in multiple GLP toxicity studies including repeat-dose in monkeys (200 mg/kg) up to 26 weeks



Wang J, et al. *mAbs.* 2019;11(8):1443-1451.
Zhang S, et al. *Antib Ther*. 2018;1(2):65-73.

Sintilimab Demonstrated Positive Efficacy Results in 9 Pivotal Studies

	Target Indication (Study Name)	N	Met Primary Endpoint	Regulatory Status in China (Approved)
	1L Non-squamous NSCLC (ORIENT-11)[1,2]	397	✓	✓
	1L Squamous NSCLC (ORIENT-12)[3]	357	✓	✓
	2L Squamous NSCLC (ORIENT-3)	290	✓	
	EGFR TKI failed NSCLC (ORIENT-31)	600	✓	Submitted
	r/r classic Hodgkin's Lymphoma (ORIENT-1)[4,5]	96	✓	✓
	1L Esophageal Squamous Cell Carcinoma (ORIENT-15)[6]	676	✓	Submitted
	2L Esophageal Squamous Cell Carcinoma (ORIENT-2)[7]	190	✓	
	1L Gastric Cancer (ORIENT-16)[8]	650	✓	Submitted
	1L Hepatocellular Carcinoma (ORIENT-32)[9]	595	✓	✓

- Approved for 4 indications in China
- Post-marketing safety data on more than 170,000 patients

1. Yang Y, et al. *J Thorac Oncol*. 2020;15(10):1636-1646; 2. Yang Y, et al. *J Thorac Oncol*. 2021;16(12):2109-2120; 3. Zhou C, et al. *J Thorac Oncol*. 2021;16(9):1501-1511;
4. Shi Y, et al. *Lancet Haematol*. 2019;6(1):e12-e19; 5. Shi Y, et al. *J Clin Oncol*. 2018;36(15 suppl): Abstract 7536; 6. Shen L, et al. *Ann Oncol*. 2021;32(suppl 5):S1330. Abstract LBA52;
7. Xu J, et al. *J Clin Oncol*. 2020;38(15 suppl):Abstract 4511; 8. Xu J, et al. *Ann Oncol*. 2021;32(suppl 5):S1331. Abstract LBA53; 9. Ren Z, et al. *Lancet Oncol*. 2021;22(7):977-990.

Proposed Indication and Dosing

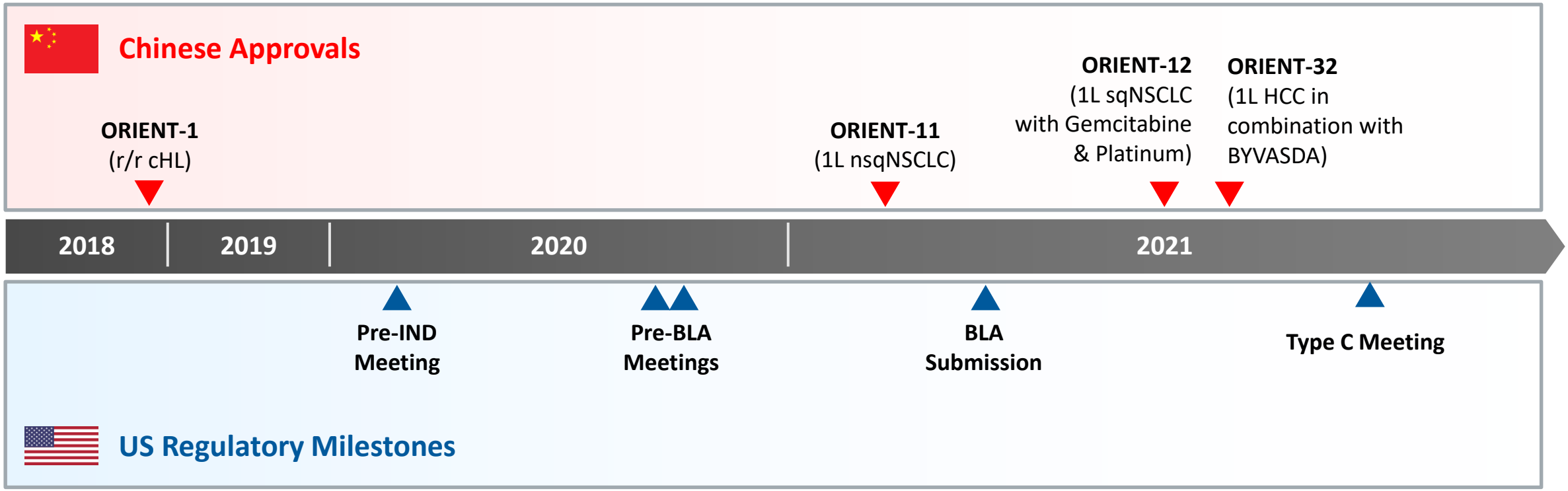
Indication

Sintilimab in combination with pemetrexed and platinum-based chemotherapy is indicated for the first-line treatment of patients with Stage IIIB, IIIC, or Stage IV non-squamous non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations

Dosing Regimen

200 mg via IV every 3 weeks

Regulatory History of Sintilimab in China and US



Why We Are Here Today

- Discuss the applicability of ORIENT-11 to support a US approval
- Address key review issues noted in the FDA Briefing Document

- US Regulations and ICH Guidelines provide the Framework for the Use of Foreign Data to support FDA Approval
  - *21CFR314.106(b)* (Foreign Data as the Sole Basis for Marketing Approval)
  - ICH E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data)

What You Will Hear Today

Treatment Landscape	• Non-squamous NSCLC diagnosis, staging, and treatment are similar in US and China • Pemetrexed + platinum chemotherapy is the most commonly used chemotherapy regimen in nsqNSCLC in US and China
Efficacy	• ORIENT-11 met the primary endpoint of PFS at interim analysis • Analysis of OS showed a robust and clinically meaningful treatment effect
Safety	• Sintilimab + chemotherapy has an acceptable safety profile consistent with that of approved PD-1/L1 inhibitors
Applicability to the US Population	• Clinical practice standards are similar in the US and China • PK/PD profile is insensitive to ethnicity, based on analysis of intrinsic factors • Efficacy and safety of sintilimab in US population will be similar to those in ORIENT-11

Agenda

Introduction	Lana Shiu, MD Sr. Vice President, Global Regulatory Affairs, Innovent Biologics USA, Inc.
Treatment Landscape in NSCLC	Mark A. Socinski, MD Advent Health Cancer Institute
ORIENT-11 Efficacy and Conduct	Eduard Gasal, MD President, Innovent Biologics USA, Inc.
Safety	Maria Fernanda Fernandes, MD Sr. Medical Advisor, Global Patient Safety Oncology, Eli Lilly
Applicability to US Population	David R. Ferry, MD, PhD Vice President, Oncology Medical Strategy, Eli Lilly

Additional Experts

Misako Nagasaka, MD, PhD

Associate Clinical Professor
University of California, Irvine

Eli Lilly

Ben Anderson, PhD (Moderator)
Global Product Leader

Eric Dozier, MBA
Vice President, Oncology

Yong Lin, PhD
Principal Research Scientist, Biostatistics

Lan Ni, PhD
Head of Global PK/PD & Pharmacometrics

Matthew Rotelli, PhD
Sr. Advisor, Bioethics

Treatment Landscape in NSCLC

Mark A. Socinski, MD
Executive Medical Director
Advent Health Cancer Institute
Member, Thoracic Oncology Program

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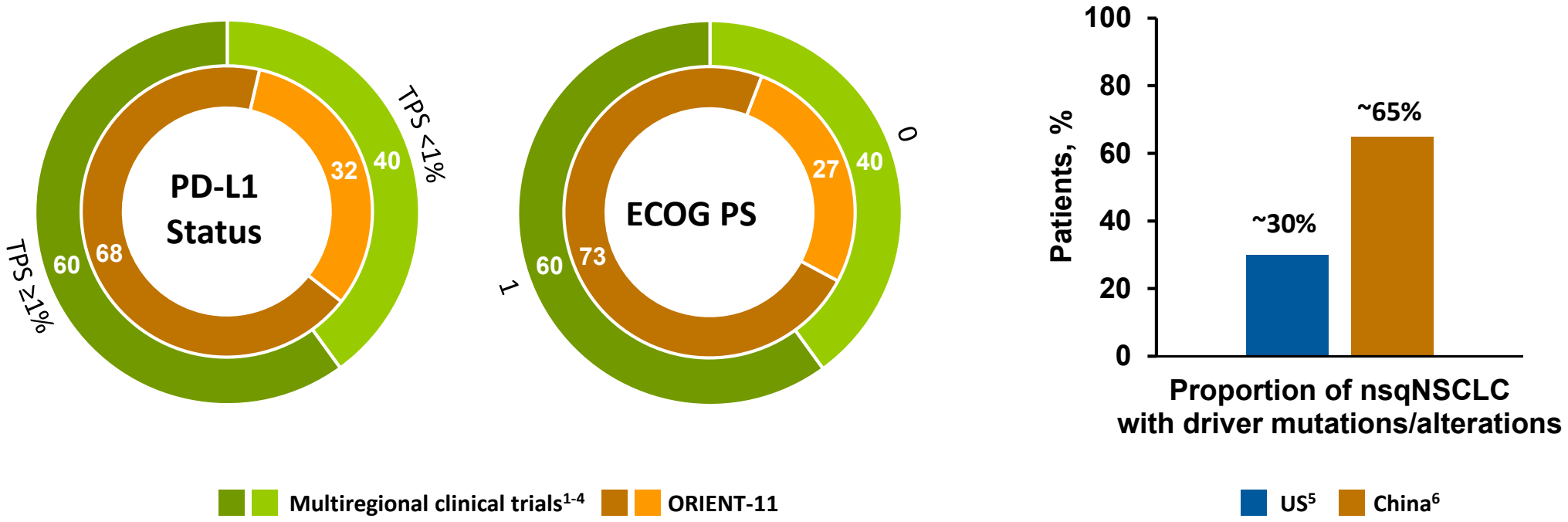
Epidemiology and Treatment Landscape of Stage IV NSCLC in the United States

- Lung cancer was the leading cause of cancer deaths in the US in 2018[1]
  - Estimated 235,000 cases in 2021
  - Estimated 132,000 deaths in 2021
- ~80% of lung cancer is NSCLC[1]
- Current clinical practice for Stage IV NSCLC
  - Comprehensive genomic testing for oncogenic driver mutations/alterations (*EGFR*, *ALK*, *ROS1*, *RET*, etc.)
  - Patients without genomic alterations are treated with chemo-immunotherapy or single-agent immunotherapy depending on PD-L1 status

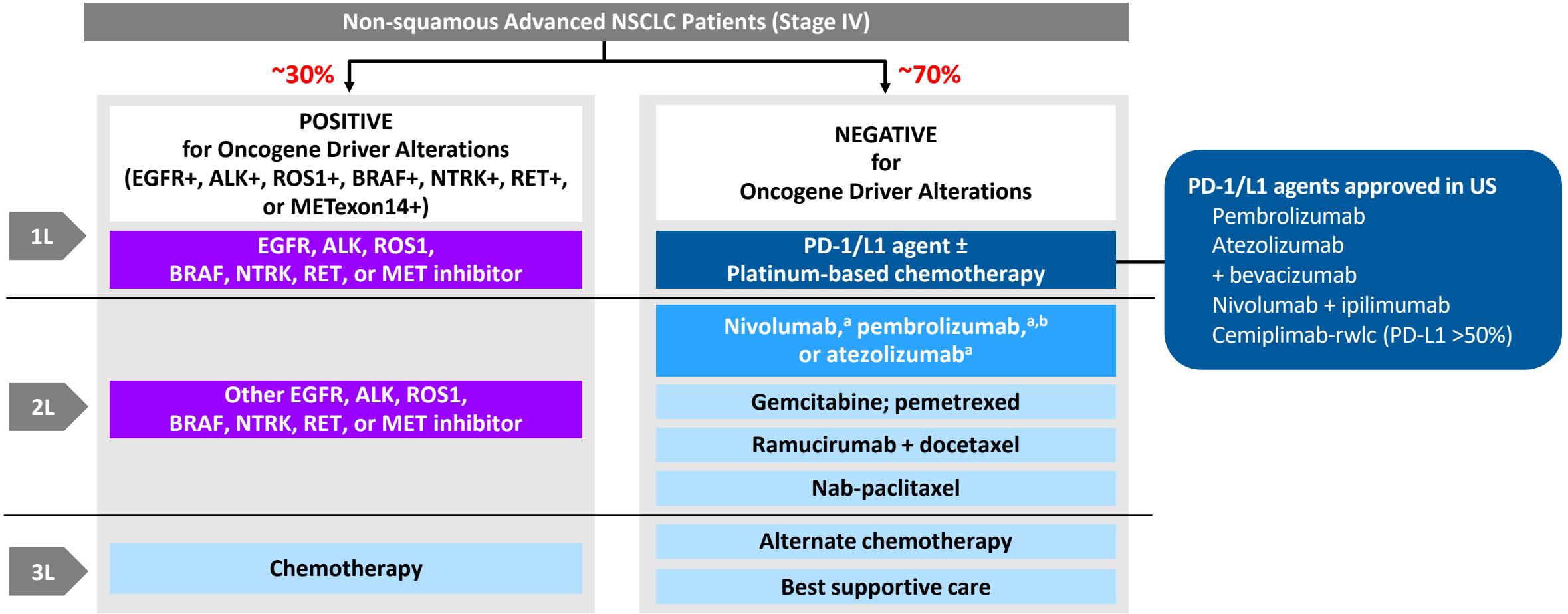
1. Siegel RL, et al. *CA Cancer J Clin*. 2021;71(1):7-33.

Key Characteristics of Stage IV Nonsquamous NSCLC



1. Gandi et al. *N Engl J Med*. 2018;378:2078-2092; 2. West H, et al. *Lancet Oncol*. 2019;20(7):924-937;
3. Socinski MA, et al. *N Engl J Med*. 2018;378(24):2288-2301; 4. Reck M, et al. *J Clin Oncol*. 2020;38(suppl 15):9501;
5. Campbell JD, et al. *JAMA Oncol*. 2017;3;801-809; 6. Meng H, et al. *Front Genet*. 2019;10:1008.

Current Treatment Algorithm for nsqNSCLC in the United States

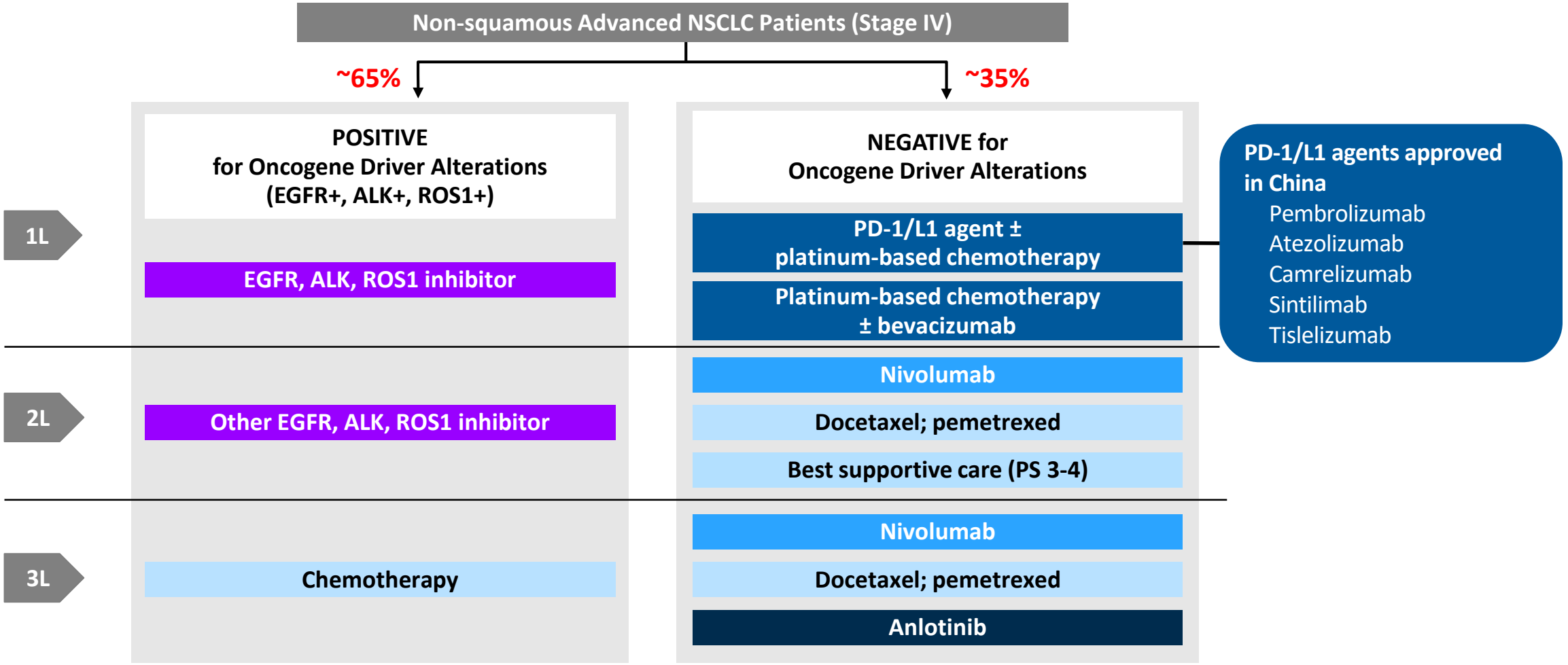


[a] For patients not previously treated with immunotherapy; [b] Pembrolizumab is approved for NSCLC patients with PD-L1≥1%.

ALK=Anaplastic Lymphoma Kinase; BRAF=v-raf Murine Sarcoma Viral Oncogene Homolog B; EGFR=Epidermal Growth Factor Receptor; KRAS=Kirsten Rat Sarcoma Viral Oncogene Homolog; MET=Circulating Hepatocyte Growth Factor; NTRK=Neurotrophic Tyrosine Receptor Kinase; RET=Ret Proto-oncogene; ROS1=ROS Proto-oncogene.

1. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed May 10, 2021). 2. Hirsch FR, et al. *Lancet*. 2017;389(10066):299-311.

Current Treatment Algorithm for NSCLC in China



NSCLC CSCO guidelines, 2021. Accessed at http://www.csco.ac.cn/

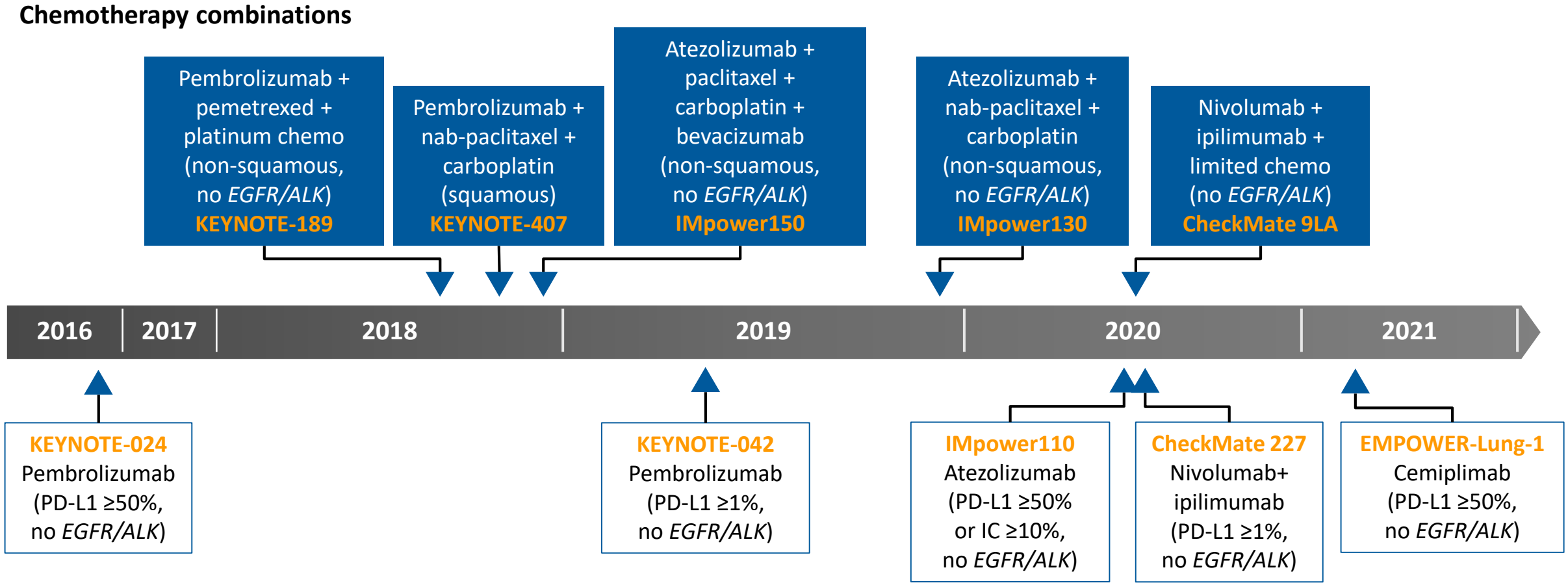
Diagnostic and Treatment Standards in US and China Are Similar

Factor	United States	China
Treatment guidelines	NCCN 2021 version 4[1]	CSCO 2021[2]
Staging system	AJCC Cancer Staging Manual, 8th edition[3]	
Pathology	2015 WHO classification	
Standard genetic testing[a]	*EGFR, ALK*	
PD-L1 biomarker testing	PD-L1 CDx per product label	
1L immunotherapy options for patients without driver alterations[b]	Pembrolizumab + chemo Pembrolizumab for PD-L1 ≥1% or atezolizumab for PD-L1 ≥50% Atezolizumab + bevacizumab + chemo Nivolumab + ipilimumab + chemo Nivolumab + ipilimumab for PD-L1 TPS ≥1% Cemiplimab for PD-L1 ≥50%	Sintilimab, atezolizumab, camrelizumab, or tislelizumab + chemo
SoC chemotherapy backbone	Platinum-based chemo: cisplatin or carboplatin with Pemetrexed/Bevacizumab/Gemcitabine/Docetaxel/Paclitaxel/Vinorelbine	

[a] Based on Category 1 recommendations. [b] Based on Category 1 recommendations (pembrolizumab for PD-L1 TPS 1% - 49% is Category 2).

1. https://crain-platform-genomeweb-prod.s3.amazonaws.com/s3fs-public/files_copied/nccn_nsclc_guidelines.pdf (Accessed May 10, 2021);
2. Guidelines of Chinese Society of Clinical Oncology: Non-Small Cell Lung Cancer: People's Medical Publishing House; 2021; 3. Detterbeck FC, et al. *Chest*. 2017;151(1):193-203.

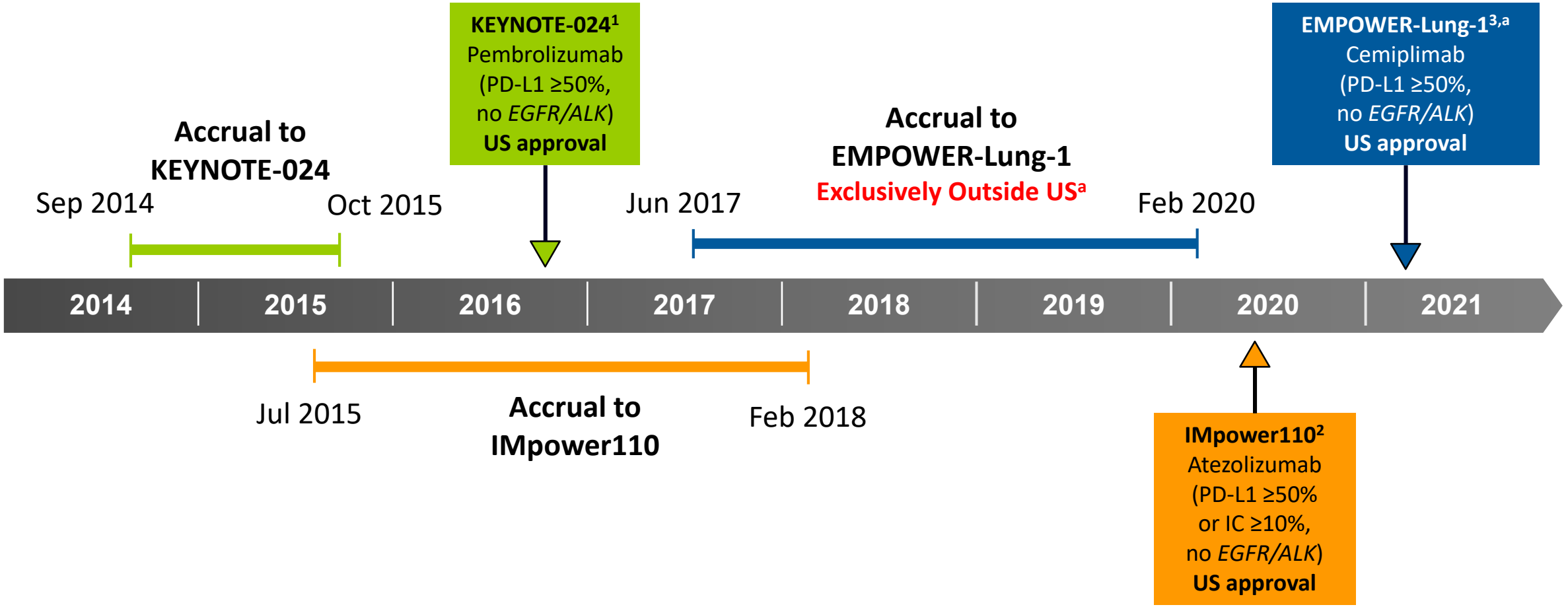
First-Line Approvals for Immunotherapy in NSCLC in the US



Data from Zhou F, et al. *Cell Mol Immunol*. 2021;18(2):279-293.

FDA Approved Drugs for PD-L1 ≥50% (All Priority Review)

All Used Chemotherapy Doublet Control Arms

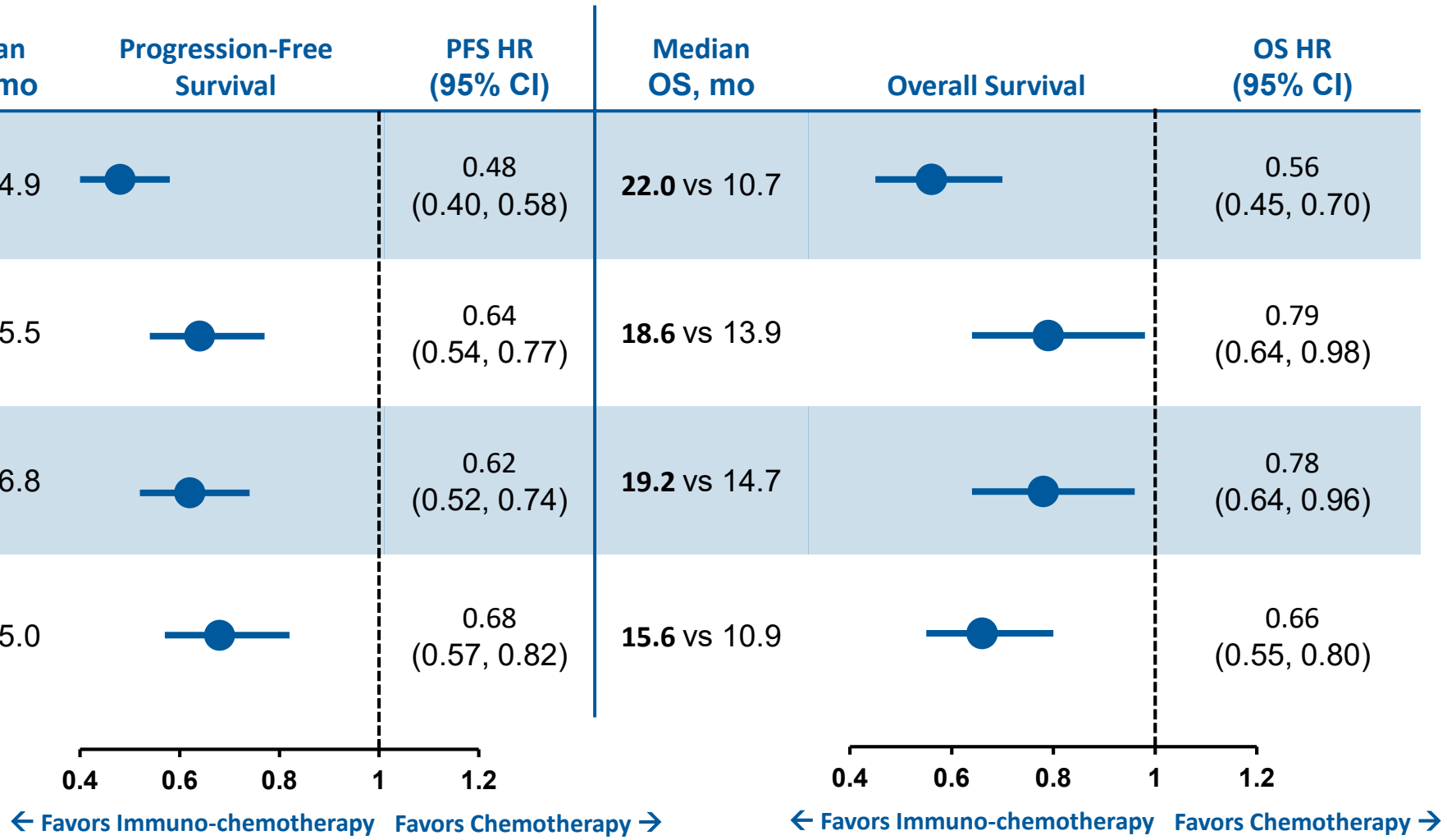


[a] Top enrolling countries: Turkey, Russia, Ukraine, Georgia.

1. Reck M, et al. *N Engl J Med*. 2016; 375:1823-1833.
2. Herbst RS, et al. *N Engl J Med.* 2020;383:1328-1339.
3. Sezer A, et al. *Lancet*. 2021;397:592-604.

Comparable Efficacy Across the PD-1/L1 Class in nsqNSCLC

Study/Regimen	N	Median PFS, mo	PFS HR (95% CI)	Median OS, mo	OS HR (95% CI)
KEYNOTE-189[1,a] Pembro + pem + platinum chemo	616	**9.0** vs 4.9	0.48 (0.40, 0.58)	**22.0** vs 10.7	0.56 (0.45, 0.70)
IMpower130[2,b] Atezo + carbo + nab-pacl	679	**7.0** vs 5.5	0.64 (0.54, 0.77)	**18.6** vs 13.9	0.79 (0.64, 0.98)
IMpower150[3,b] Atezo + bev + carbo + pacl	692	**8.3** vs 6.8	0.62 (0.52, 0.74)	**19.2** vs 14.7	0.78 (0.64, 0.96)
CheckMate 9LA[4,c] Nivo + ipi + 2 cycles platinum chemo	719	**6.7** vs 5.0	0.68 (0.57, 0.82)	**15.6** vs 10.9	0.66 (0.55, 0.80)

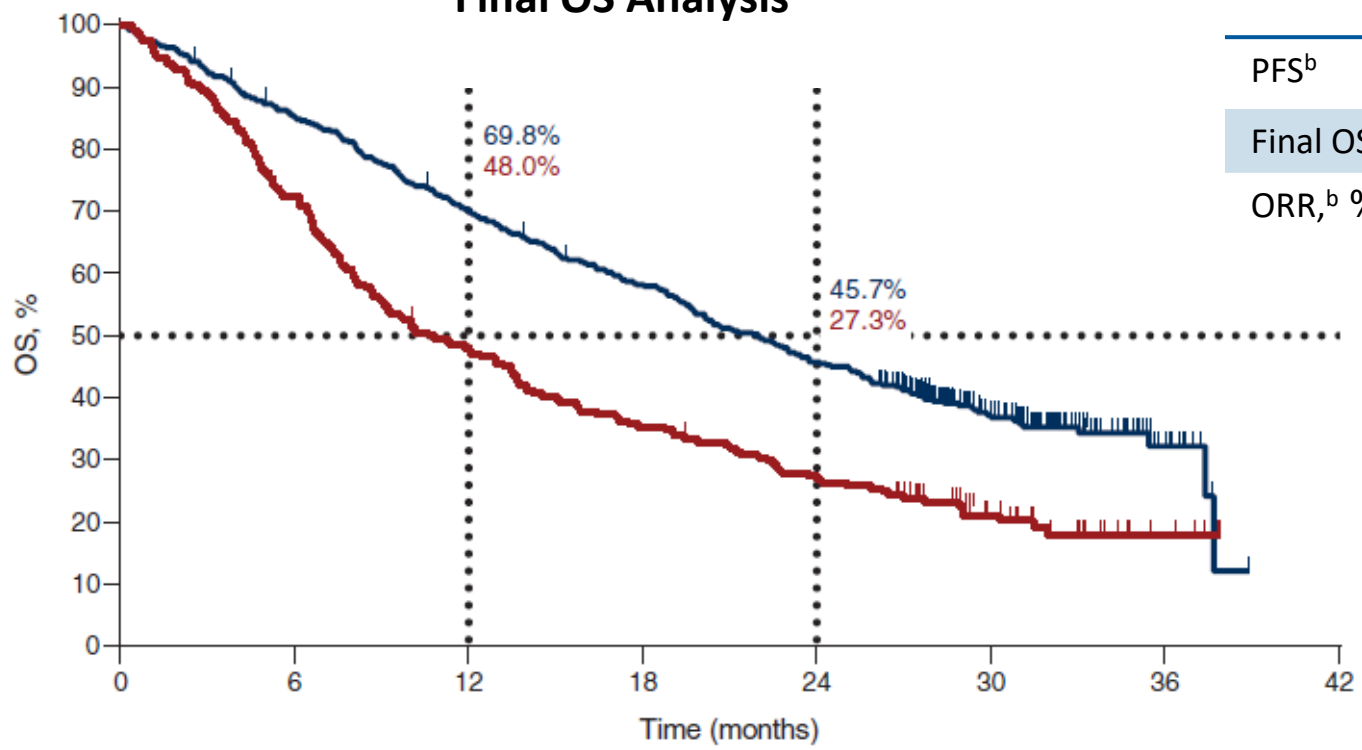


[a] Primary endpoints were OS and PFS by blinded independent central radiology review; [b] Co-primary endpoints were investigator-assessed PFS and OS; [c] Primary endpoint was OS.

1. Gadgeel S, et al. *J Clin Oncol*. 2020;38(14):1505-1517; 2. West H, et al. *Lancet Oncol*. 2019;20(7):924-937;
3. Socinski MA, et al. *N Engl J Med*. 2018;378(24):2288-2301; 4. Reck M, et al. *J Clin Oncol*. 2020;38(suppl 15):Abstract 9501.

KEYNOTE-189 Established a Standard of Care in 1L nsqNSCLC in the United States

Final OS Analysis[a]



No. at risk:							
Pembro + chemo	410	347	283	234	184	86	12	0
Placebo + chemo	206	149	98	72	55	25	5	0

	Median, mo	HR (95% CI)
PFS[b]	**9.0** vs 4.9	0.48 (0.40, 0.58)
Final OS[a]	**22.0** vs 10.6	0.56 (0.46, 0.69)
ORR,[b] %	**48.0** vs 19.4	

[a] Rodriguez-Abreu D, et al. *Ann Oncol*. 2021;32(7):881-895.
[b] Gadgeel S, et al. *J Clin Oncol*. 2020;38(14):1505-1517.
Data cutoff: May 20, 2019; Median follow-up=31.0 months (range, 26.5-38.8 mo).

Figure adapted from *Annals of Oncology*, 32(7), Rodriguez-Abreu D, et al, Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189, 881-895, Copyright 2021, with permission from Elsevier.

Conclusions

- Disease characteristics of both Chinese and US patients are similar with the exception of oncogenic alterations
- Diagnostics and treatment standards/patterns are similar in the US and China
- Immunotherapy has dramatically improved outcomes in lung cancer patients
- Pemetrexed and platinum is the most widely used chemotherapy in nsqNSCLC in both the US and China
- Only pembrolizumab is approved in the US in combination with pemetrexed and platinum for nsqNSCLC

ORIENT-11 Efficacy and Conduct

Eduard Gasal, MD
President
Innovent Biologics USA, Inc.

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ORIENT-11 Phase 3 Pivotal Study Schema

Enrollment: Aug 2018 – Jul 2019

N=397

- **1L non-squamous NSCLC (IIIB/C, IV)**
- ***EGFR/ALK* negative**
- **ECOG PS 0,1**
- **No active brain metastases**

R 2:1

n=266

Sintilimab 200 mg +
pemetrexed + cisplatin/carboplatin Q3W for 4 cycles
Followed by sintilimab + pemetrexed maintenance

n=131

Placebo +
pemetrexed + cisplatin/carboplatin Q3W for 4 cycles
Followed by placebo + pemetrexed maintenance

Sintilimab 200 mg Q3W

Conditional crossover upon confirmed PD

Randomization stratification

- Sex
- Platinum (cisplatin vs carboplatin)
- PD-L1 expression (TPS <1% vs ≥1%)

Primary endpoint: PFS by BIRRC
Secondary endpoints: OS, ORR, DCR, TTR, DOR, safety

Yang Y, et al. *J Thorac Oncol*. 2020;15(10):1636-1646.

Selection of Control Arm, Endpoints, and Study Analysis

ORIENT-11

- Pemetrexed and platinum chemotherapy was an appropriate control arm in China
  - KN189 regimen approved in China March 2019 (ORIENT-11 80% accrued)
- PFS was primary endpoint
  - PFS is clinically relevant endpoint in first-line NSCLC
  - PFS not confounded by post-progression therapy
- For an HR=0.65, 263 PFS events required to ensure 90% power at a 2-sided alpha=0.05
- Interim PFS analysis was planned when 184 (70%) events observed
- OS was a secondary endpoint
  - No alpha assigned; method of analysis was pre-specified in SAP

Experienced and Qualified Sites and Investigators

ORIENT-11

- 48 academic sites across China
  - Previous experience with multiregional clinical trials
  - 10 sites have had 17 prior FDA inspections (2 are part of current application)
  - 23 sites participated in trials that led to FDA approval

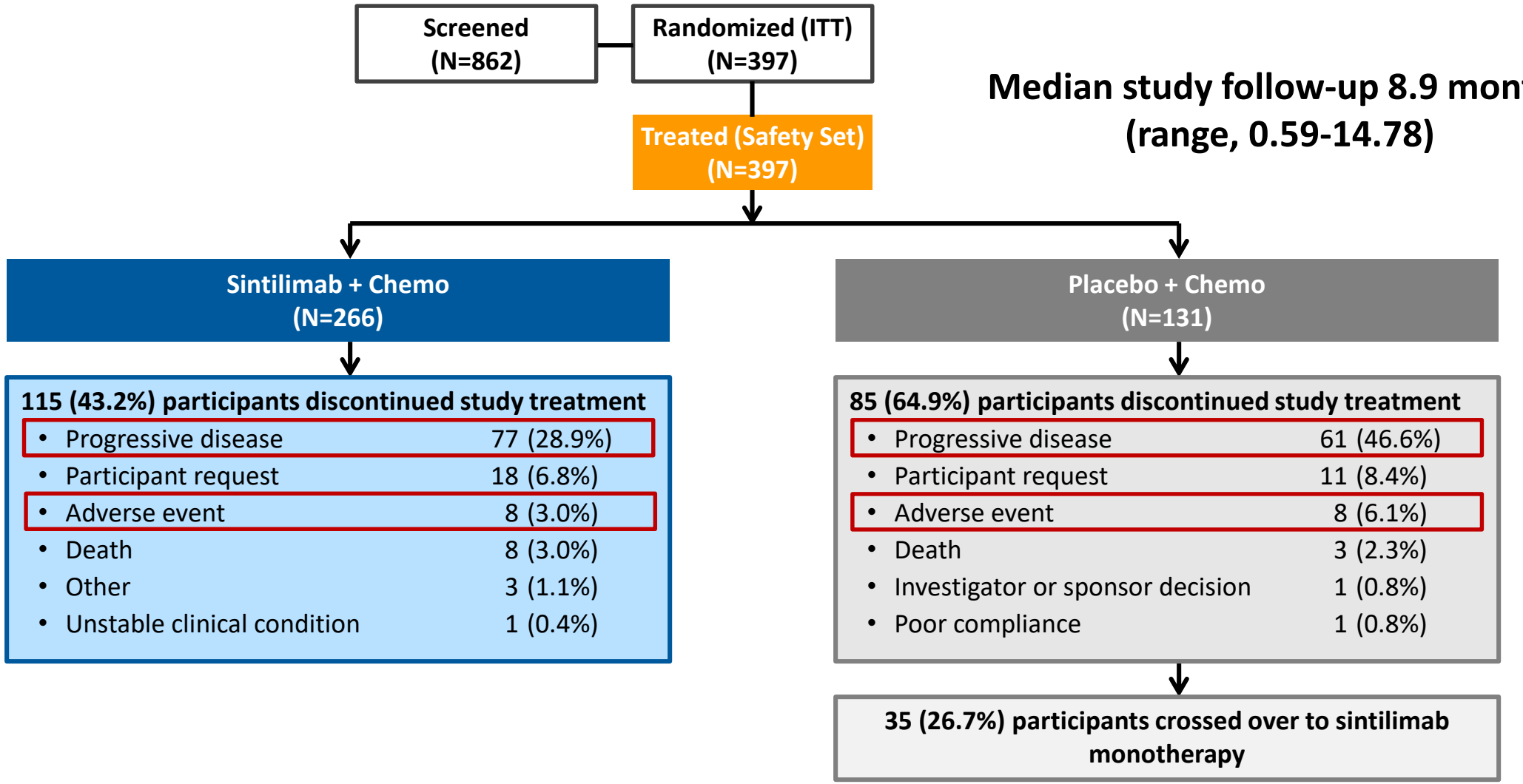
- All investigators are board-certified oncologists trained in ICH GCPs
  - 46 of 48 primary investigators previously participated in multiregional clinical trials
  - 9 participated in at least one clinical trial that ultimately led to the drug being approved by FDA

Study Conduct
ORIENT-11

- PFS assessed by blinded independent radiology review committee (BIRRC) managed through a globally recognized and validated vendor (PAREXEL)
  - Review committee was comprised of North American and European radiologists
- PD-L1 TPS (Dako 22C3), PK, and ADA assessed by central vendor (Covance)
- Independent data monitoring committee (iDMC) reviewed interim analysis
  - Efficacy boundary met; iDMC recommended to continue the study

Patient Disposition

ORIENT-11 Interim Analysis



Data cutoff date: 15 Nov 2019

Baseline Characteristics Balanced Between Treatment Groups

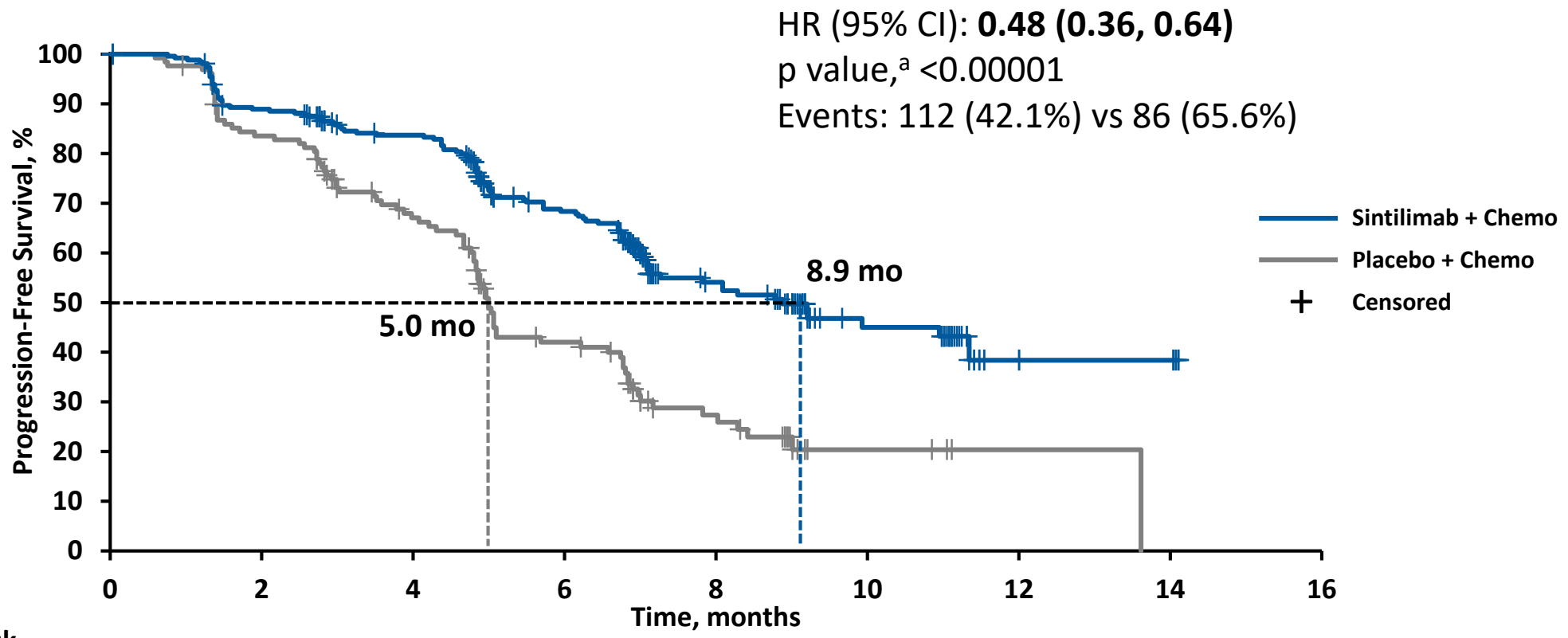
ORIENT-11

	Sintilimab + Chemo (N=266)	Placebo + Chemo (N=131)
Male, n (%)	204 (76.7)	99 (75.6)
Median age, years (range)	61.0 (30-75)	61.0 (35-75)
ECOG PS score=1, n (%)	190 (71.4)	97 (74.0)
Adenocarcinoma	253 (95.1)	123 (93.9)
Disease stage		
IIIB/C, n (%)	21 (7.9)	15 (11.5)
IV, n (%)	245 (92.1)	116 (88.5)
Brain metastasis		
Yes, n (%)	36 (13.5)	22 (16.8)
PD-L1 TPS (per CRF), n (%)[a]		
<1%	77 (28.9)	40 (30.5)
≥1%	181 (68.0)	87 (66.4)
Smoking status, n (%)		
Smoker (current/former)	171 (64.3)	87 (66.4)
Never smoker	95 (35.7)	44 (33.6)

[a] Only includes evaluable patients.

Study Met Primary Endpoint of PFS at Interim Analysis

ORIENT-11 ITT

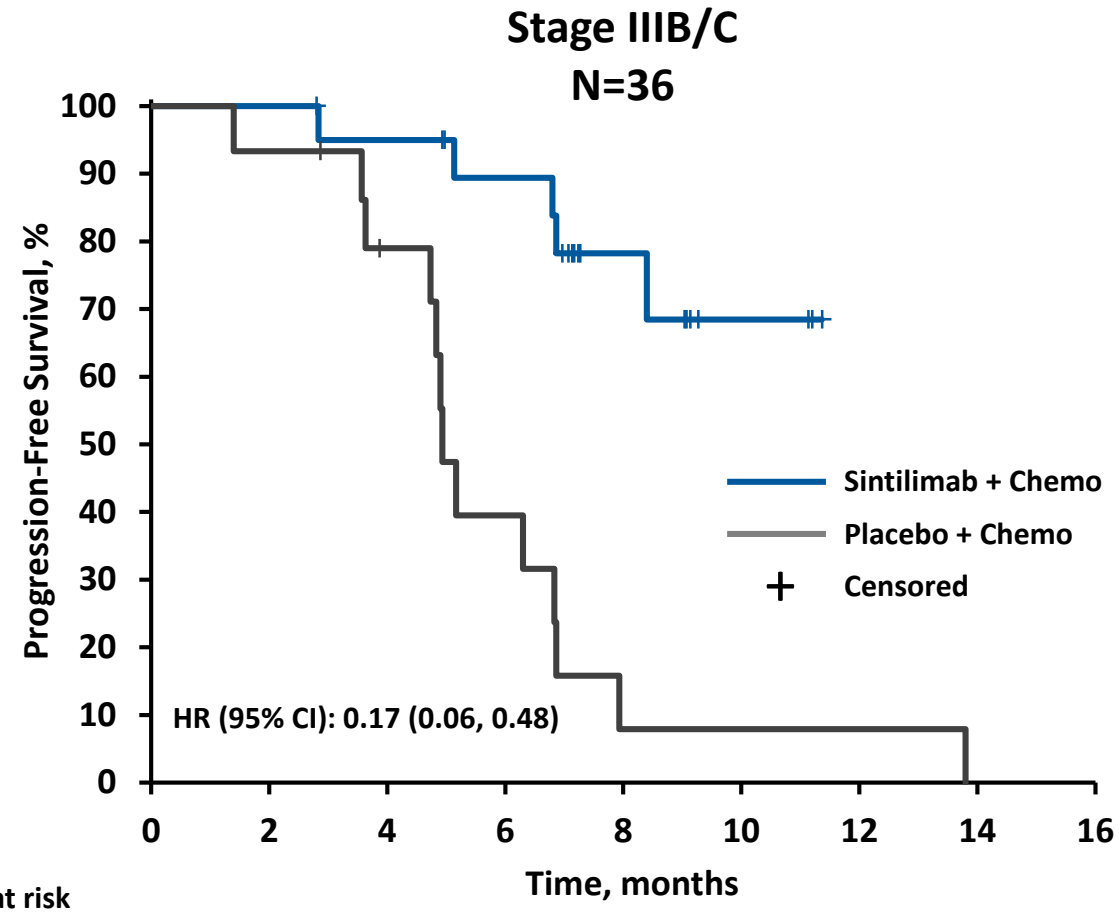


Number at risk									
Sintilimab + Chemo	266	231	202	143	63	25	3	3	0
Placebo + Chemo	131	106	77	42	19	4	1	0	

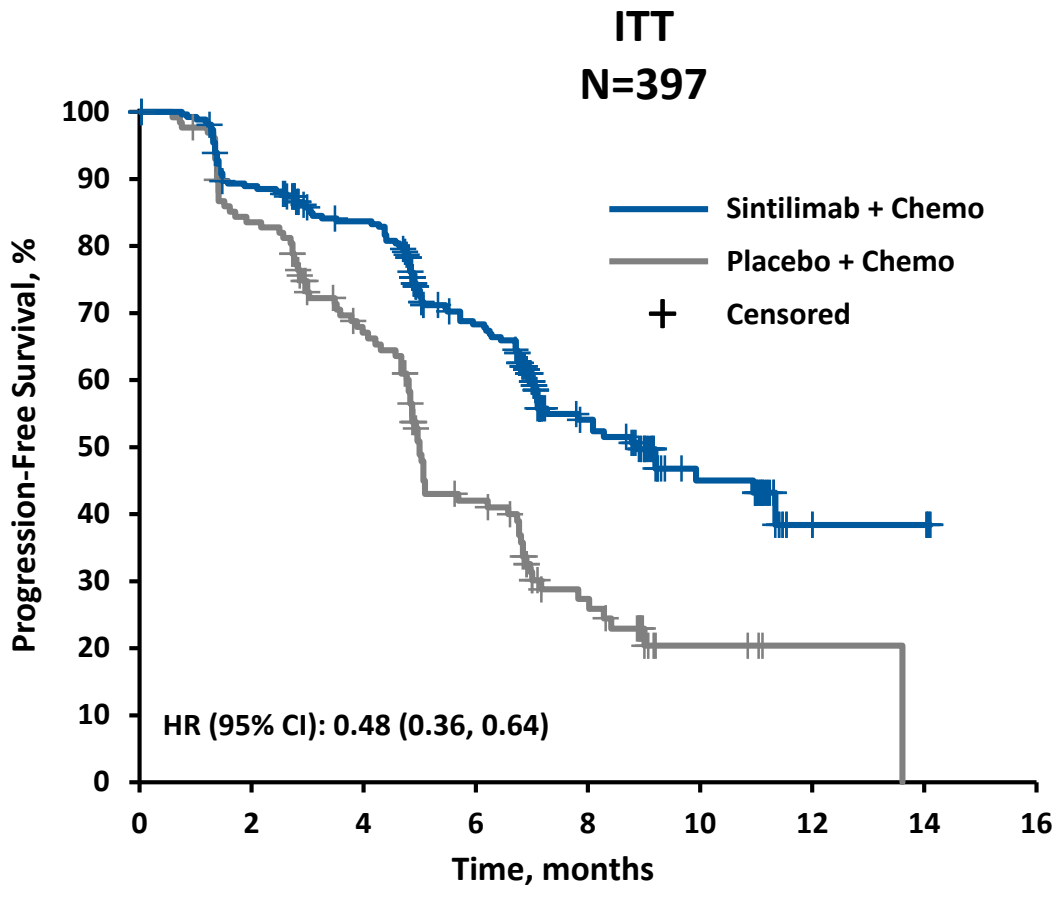
[a] Interim analysis (cut-off date - Nov 2019) α boundary based on 198 PFS events is 0.01958.

Progression-Free Survival

Stage III(B/C) vs ITT



Number at risk								
Sintilimab + Chemo	21	21	19	16	8	3	0	
Placebo + Chemo	15	14	10	5	1	1	1	0



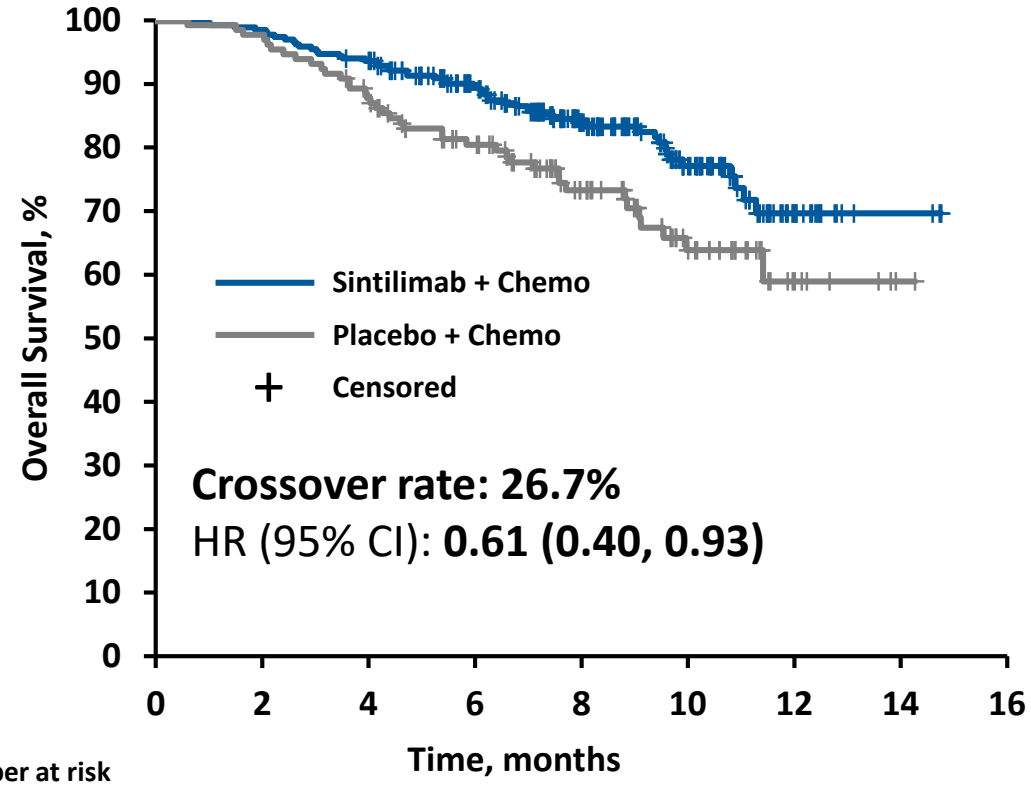
	266	231	202	143	63	25	3	3	0
	131	106	77	42	19	4	1	0	

Data cutoff date - Nov 2019

Consistent Overall Survival Benefit With Longer Follow-up

ORIENT-11 ITT

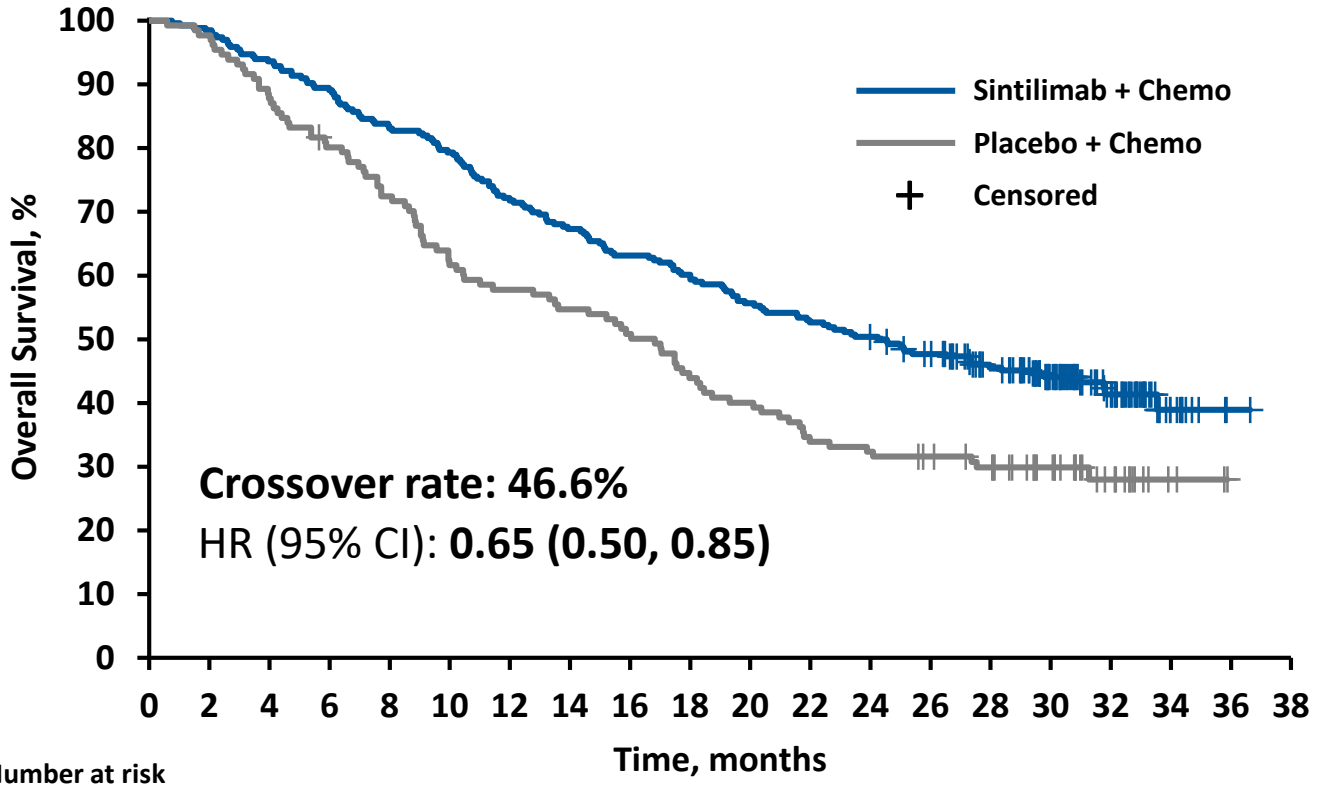
Interim Analysis (15 Nov 2019)[a]
90 events



Number at risk									
Sintilimab +Chemo	266	262	248	206	134	72	18	3	0
Placebo +Chemo	131	128	113	92	61	33	8	1	0

+ 22 months F/U

Final Analysis (15 Sept 2021)[b]
243 events



Number at risk																				
Sintilimab +Chemo	266	262	249	237	221	211	191	179	168	160	148	140	133	123	102	73	42	10	1	0
Placebo +Chemo	131	128	115	104	94	80	75	71	66	57	52	44	42	39	35	25	13	3	0	

[a] Yang Y, et al. *J Thorac Oncol*. 2020;15(10):1636-1646.

[b] After the interim PFS, a protocol amendment defined the final analysis to occur when approximately 65% of deaths observed or 2 years after last patient randomized.

Results of Sequential OS Analyses Indicate the Statistical Boundary Adjusted for Multiplicity Would Have Been Crossed

Analysis	PFS Interim (15 Nov 2019)	FDA Agreement (15 May 2020)	120-day Safety Update (15 Jan 2021)	Final Analysis (15 Sept 2021)
OS events	90	149	207	243
HR (95% CI)	0.61 (0.40, 0.93)	0.61 (0.44, 0.84)	0.60 (0.45, 0.79)	0.65 (0.50, 0.85)
OBF boundary[a]	0.00046	0.00826	0.02770	0.04058
Bonferroni boundary[a]	0.01250	0.01250	0.01250	0.01250
Observed p value	**0.01921**	**0.00250**	**0.00027**	**0.00135**

Had OS been tested hierarchically after meeting the primary endpoint, it would have met conventional statistical significance

[a] Post-hoc adjustment for multiplicity.

Summary
ORIENT-11

- High quality study conducted by competent investigators and experienced sites
- Sintilimab in combination with pemetrexed and platinum-based chemotherapy demonstrated clinically meaningful treatment effect across all endpoints
  - PFS HR (95% CI): 0.48 (0.36, 0.64); p<0.00001
- Overall survival consistently favored sintilimab despite high crossover rate
  - Interim OS analysis: HR (95% CI): 0.61 (0.40, 0.93)
  - Final OS analysis: HR (95% CI): 0.65 (0.50, 0.85)

Safety

Maria Fernandes, MD
Senior Medical Advisor, Global Patient Safety
Eli Lilly and Company

Overview of Safety Profile During Double-Blind Period[a]

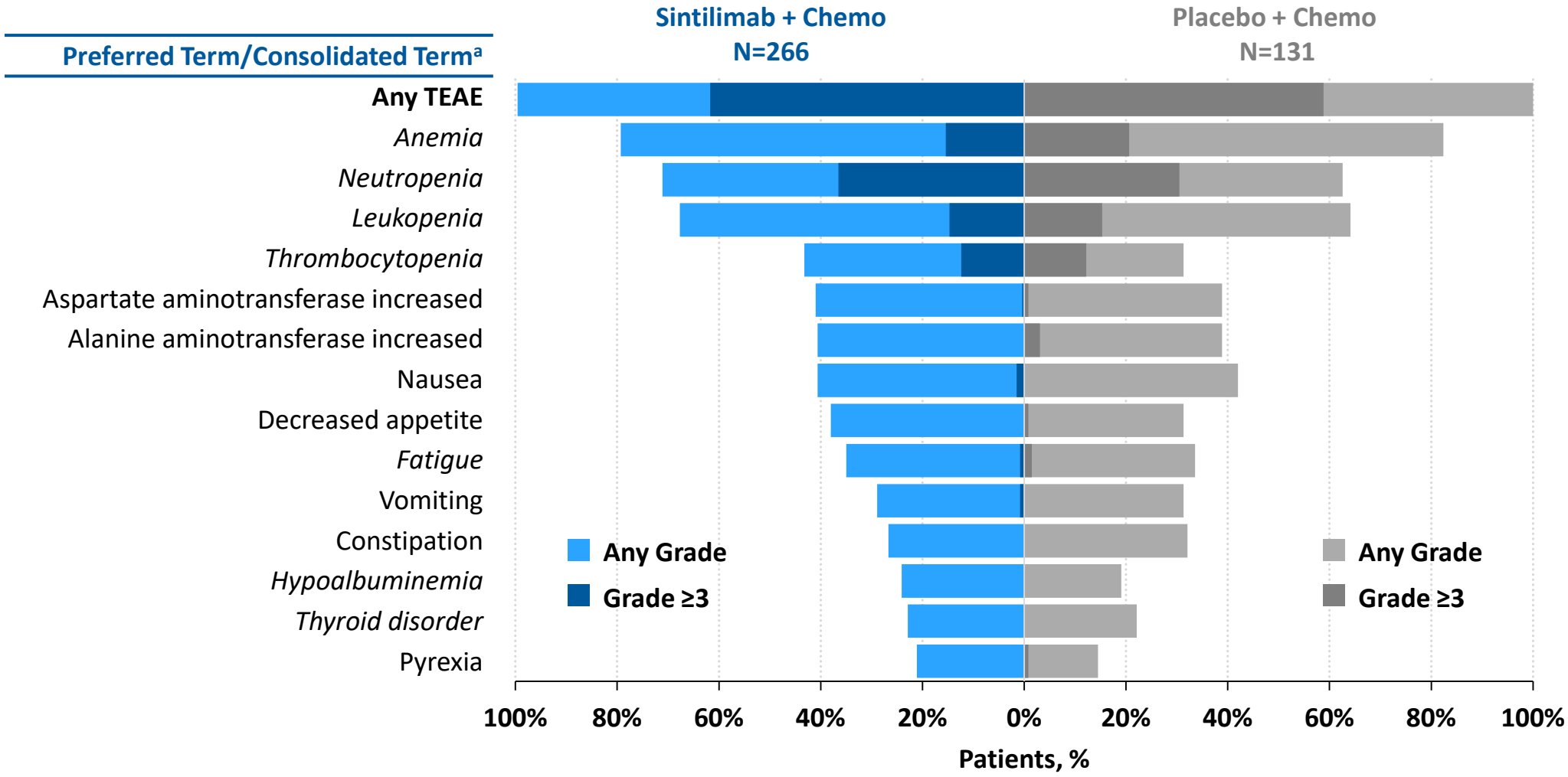
ORIENT-11

	Patients, %	
	Sintilimab + Chemo (N=266)	Placebo + Chemo (N=131)
TEAE	99.6	100.0
Grade ≥3	61.7	58.8
TEAE related to sintilimab or placebo	82.7	80.9
Grade ≥3	23.7	20.6
SAE	28.2	29.8
Grade ≥3	16.9	17.6
TEAE leading to discontinuation to all study treatment	3.0	6.1
TEAE leading to discontinuation of sintilimab or placebo	5.3	6.9
TEAE leading to death	2.3	6.9
Related to sintilimab or placebo	0.8	2.3

[a] Does not include data from crossover.
Data cutoff: 15 Nov 2019.

Comparable Incidence of TEAEs Across Treatment Groups

ORIENT-11 (≥20% in Sintilimab Arm)



[a] Terms in italics are consolidated terms.
Data cutoff: 15 Nov 2019.

Immune-Related Adverse Events[a]

ORIENT-11 & All Sintilimab (>1% Patients)

	Patients, %			
	ORIENT-11 N=266		All Sintilimab Treated N=1045	
	All Grades	Grade ≥3	All Grades	Grade ≥3
At least one irAE	**33.1**	**5.6**	**39.6**	**9.2**
Endocrinopathy	20.3	0	25.3	0.7
Hypothyroidism	12.0	0	16.7	0.2
Hyperthyroidism	10.2	0	9.7	0
Thyroid disorders	3.0	0	4.9	0
Pancreatitis and elevation of amylase/lipase	7.1	1.9	7.7	3.2
Elevation of amylase	6.8	1.9	5.1	1.6
Elevation of lipase	0.4	0	3.5	1.8
Pneumonitis	7.1	1.5	6.3	2.7
Skin adverse reaction	4.9	1.1	7.3	1.4
Hepatitis and hepatotoxicity	0.4	0.4	1.0	0.7

[a] Sponsor adjudicated.
Data cutoff: 15 Nov 2019.

Overall Safety Conclusions

- Safety profile of sintilimab in combination with pemetrexed + platinum chemotherapy in ORIENT-11 is acceptable and consistent with the known safety profile of PD-1/L1 inhibitors in combination with chemotherapy for the same indication
- Post-marketing safety data available on ~170,000 patients treated with sintilimab with no new safety signal
- Risks will be appropriately managed through product labeling

Applicability to US Population

David Ferry, MD, PhD
Vice President, Oncology Medical Strategy
Eli Lilly and Company

Foreign Data as the Sole Basis for Marketing Approval

- The studies have been performed by clinical investigators of recognized competence *21CFR314.106(b)(2)*
- The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means *21CFR314.106(b)(3)*
- The foreign data are applicable to the U.S. population and U.S. medical practice *21CFR314.106(b)(1)*

Framework for Applicability of Sintilimab Data to the US Population

Clinical Practice Standards in China vs US

Factors Affecting PK/PD

Efficacy and Safety

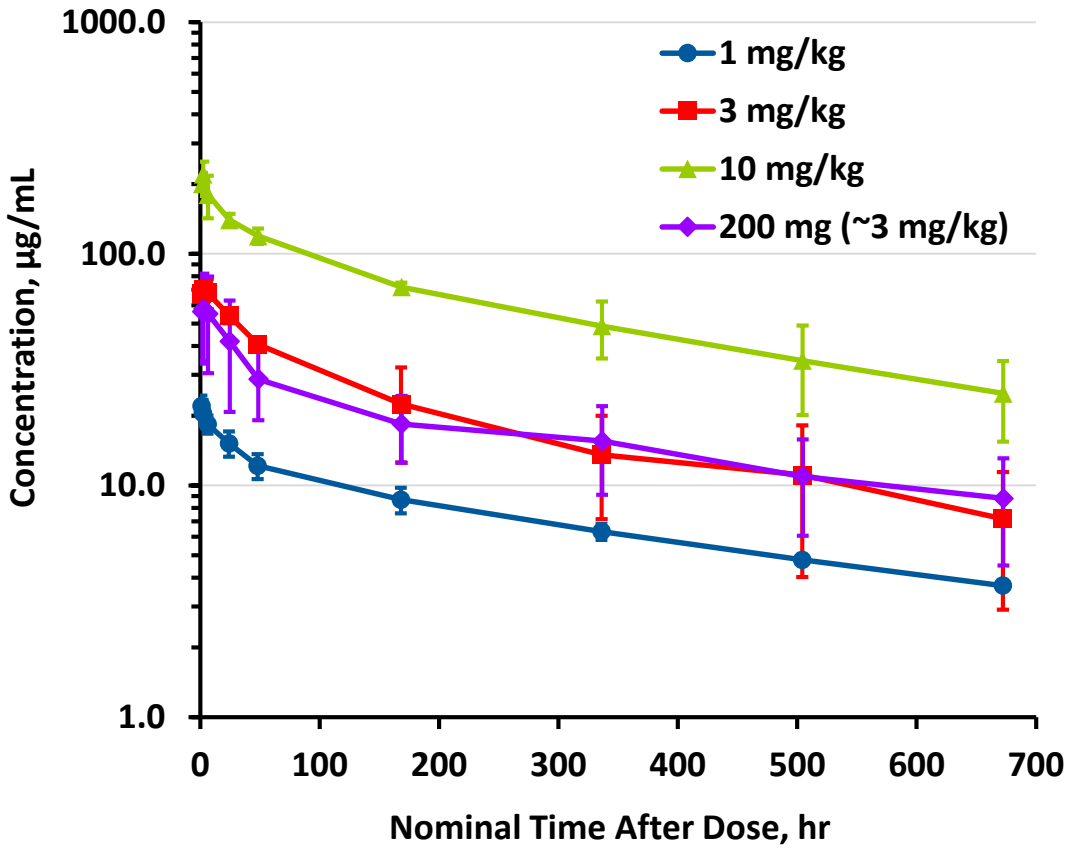
Diagnostic and Treatment Standards in US and China Are Similar

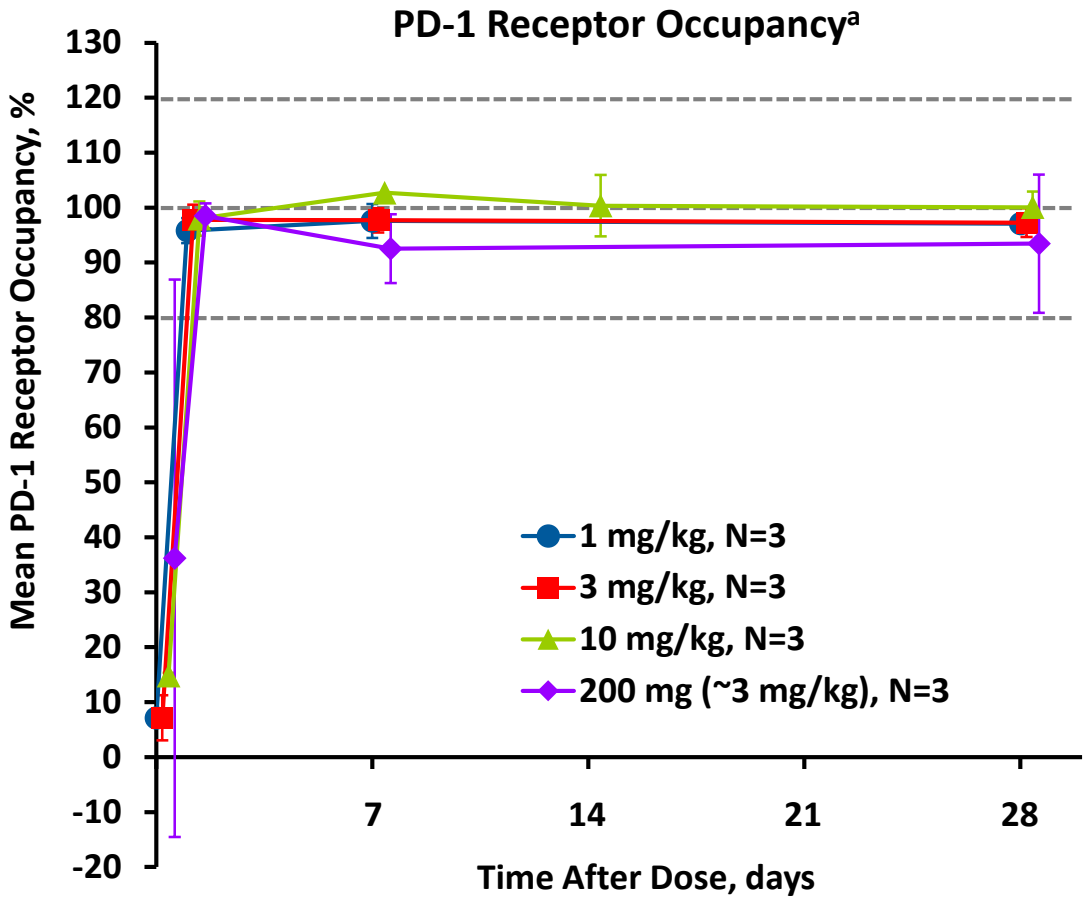
Factor	United States	China
Treatment guidelines	NCCN 2021 version 4[1]	CSCO 2021[2]
Staging system	AJCC Cancer Staging Manual, 8th edition[3]	
Pathology	2015 WHO classification	
Standard genomic testing[a]	*EGFR, ALK*	
PD-L1 biomarker testing	PD-L1 CDx per product label	
1L immunotherapy options for patients without driver mutations[b]	Pembrolizumab + chemo Pembrolizumab for PD-L1 ≥1% or atezolizumab for PD-L1 ≥50% Atezolizumab + bevacizumab + chemo Nivolumab + ipilimumab + chemo Nivolumab + ipilimumab for PD-L1 TPS ≥1% Cemiplimab for PD-L1 ≥50%	Sintilimab, atezolizumab, camrelizumab, or tislelizumab + chemo
SoC chemotherapy backbone	Platinum-based chemo: cisplatin or carboplatin with Pemetrexed/Bevacizumab/Gemcitabine/Docetaxel/Paclitaxel/Vinorelbine	

[a] Based on Category 1 recommendations. [b] Based on Category 1 recommendations (pembrolizumab for PD-L1 TPS 1% - 49% is Category 2).

1. https://crain-platform-genomeweb-prod.s3.amazonaws.com/s3fs-public/files_copied/nccn_nsclc_guidelines.pdf (Accessed May 10, 2021);
2. Guidelines of Chinese Society of Clinical Oncology: Non-Small Cell Lung Cancer: People's Medical Publishing House; 2021; 3. Detterbeck FC, et al. *Chest*. 2017;151(1):193-203.

Sintilimab Demonstrated Linear PK and Receptor Saturation Across 1-10 mg/kg Dose Range in Patients (Study A101)

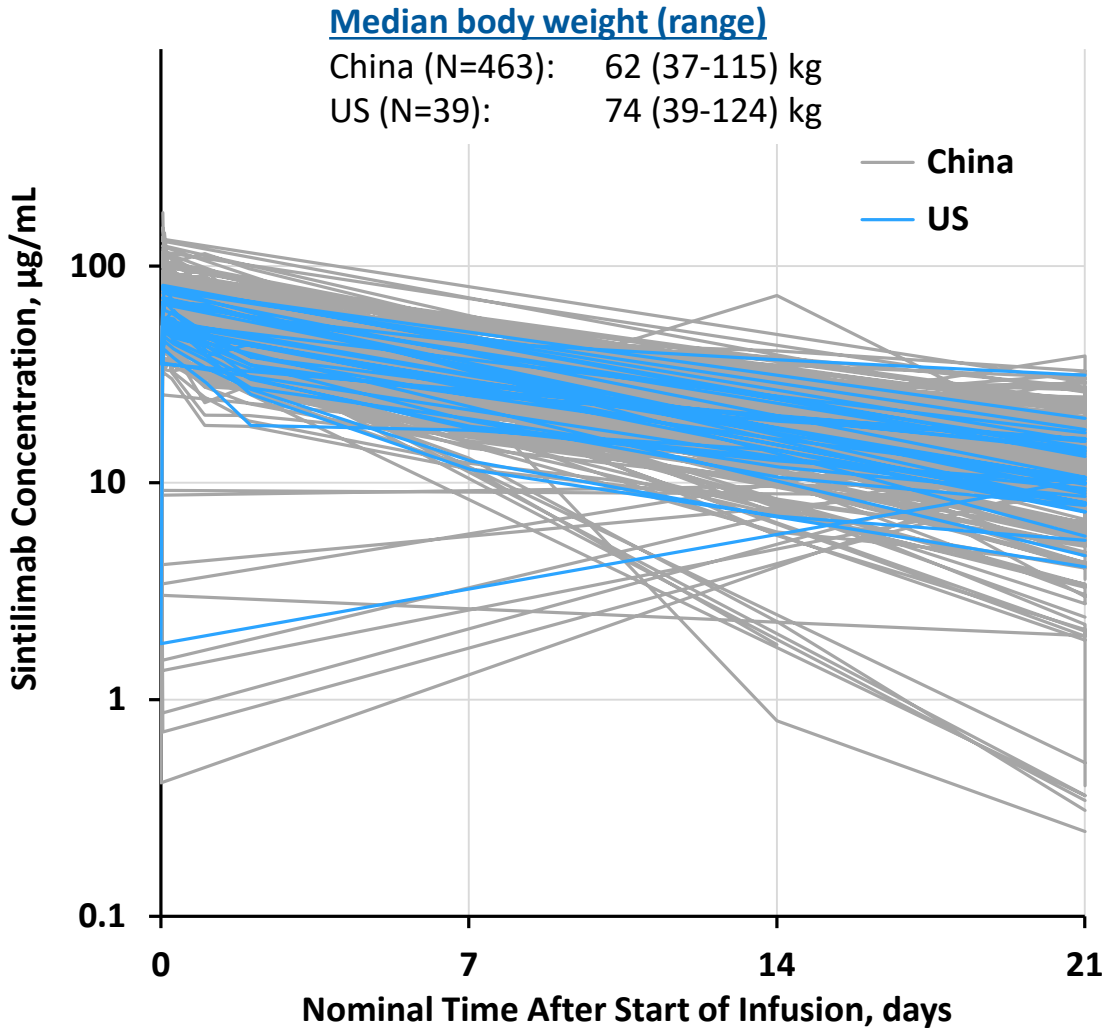


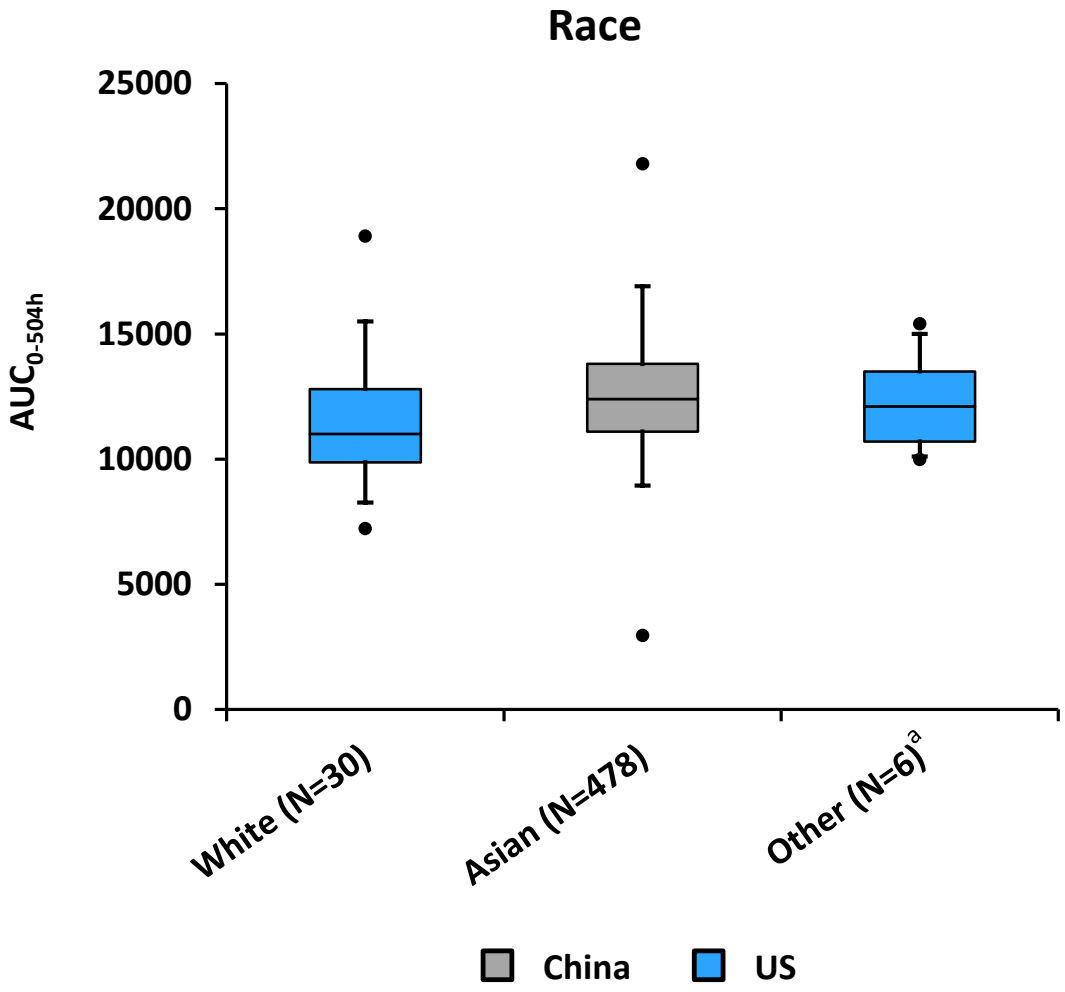


[a] Measured on circulating CD3 T cells.

Right image adapted from Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit, Wang J, et al, *mAbs*, 2019, by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd, http://www.tandfonline.com.

Intrinsic Factors: Weight and Race Had No Clinically Important Effect on PK of Sintilimab





[a] Other race included 5 Black or African American and 1 American Indian or Alaska Native.

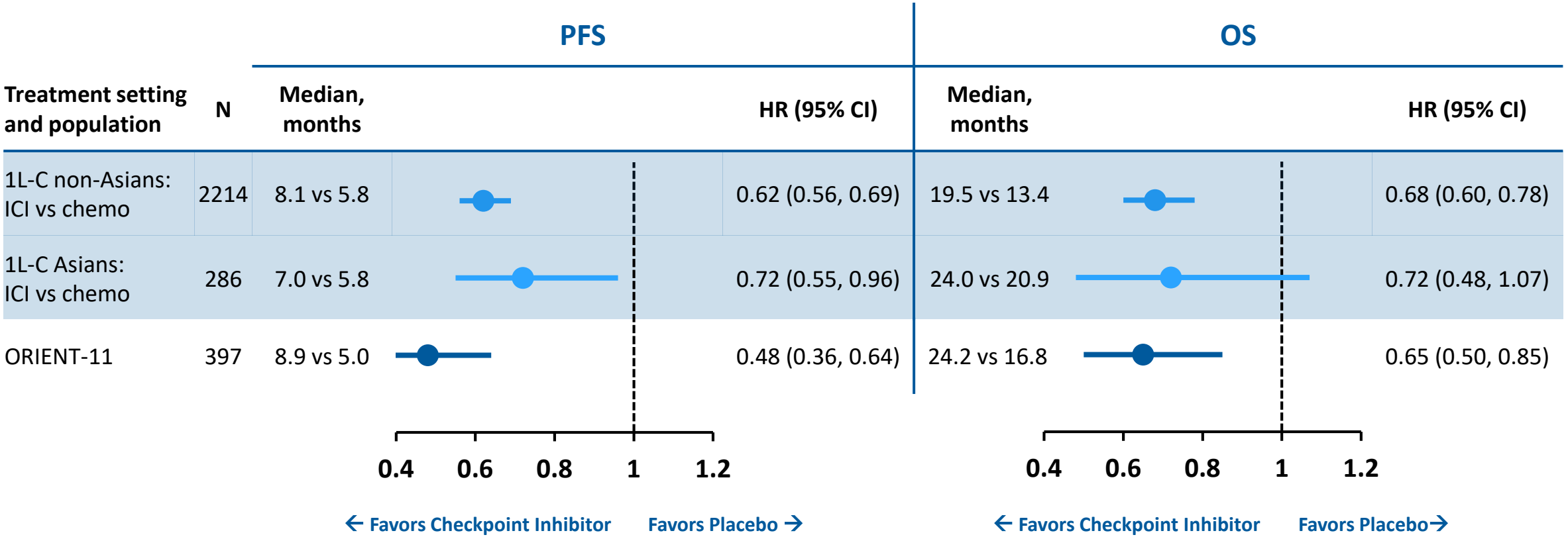
Dosing Schedule of Approved PD-1/L1 Inhibitors Is Consistent Between China and the US

ICH E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

"The clinical experience with other members of the drug class in the new region will also contribute to the assessment of the medicine's sensitivity to ethnic factors. It may be easier to conclude that the pharmacodynamic and clinical behavior of a medicine will be similar in the foreign and new regions if other members of the pharmacologic class have been studied and approved in the new region with dosing regimens similar to those used in the original region."

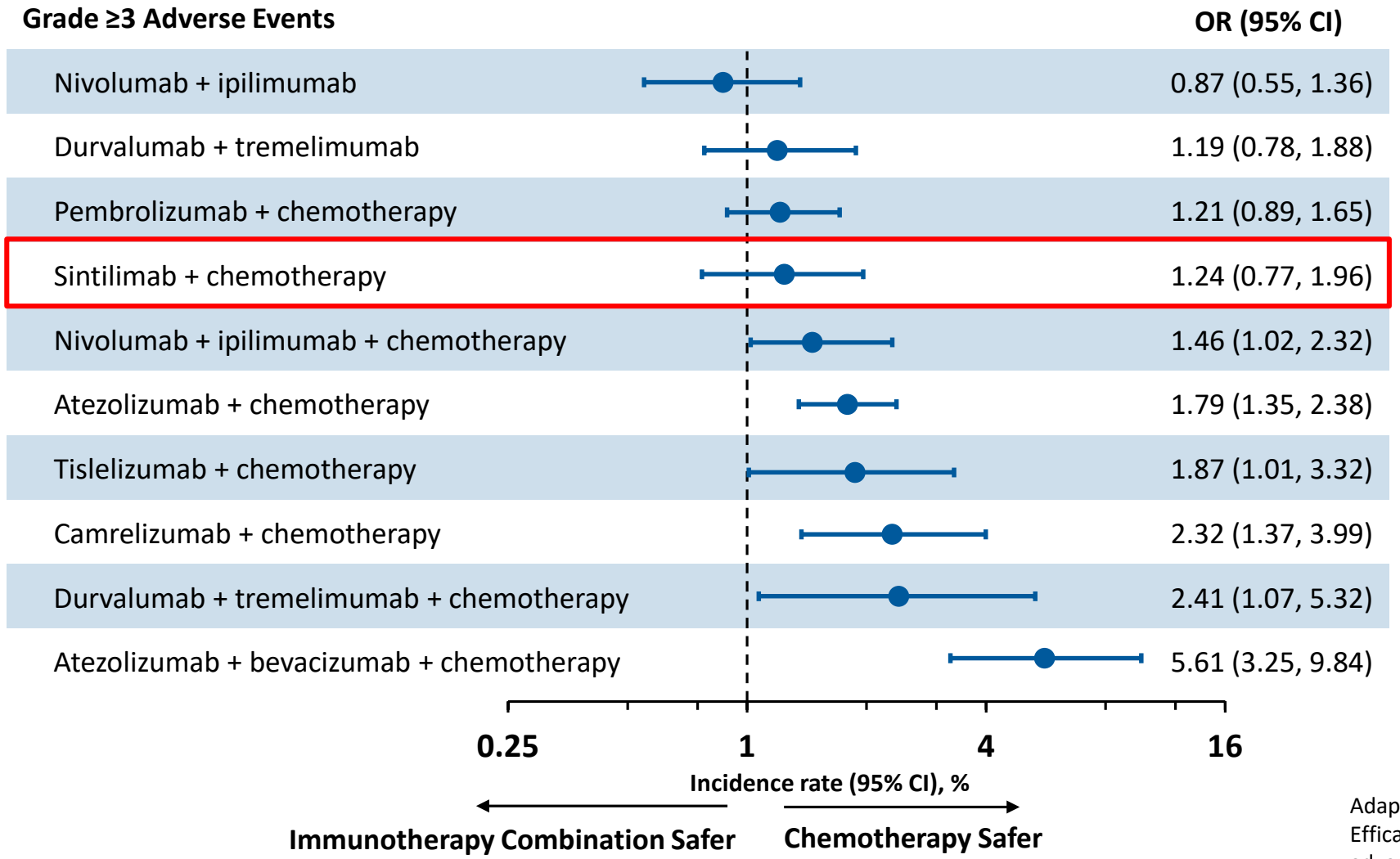
		Region	
Type	**Study/Regimen**	**United States**	**China**
Chemotherapy combinations	**KEYNOTE-189** Pembrolizumab + pemetrexed + platinum chemotherapy (non-squamous, no *EGFR/ALK*)	200 mg every 3 weeks or 400 mg every 6 weeks	200 mg every 3 weeks or 400 mg every 6 weeks
	KEYNOTE-407 Pembrolizumab + nab-paclitaxel + carboplatin (squamous)	200 mg every 3 weeks or 400 mg every 6 weeks	200 mg every 3 weeks or 400 mg every 6 weeks
Monotherapy	**KEYNOTE-042** Pembrolizumab (PD-L1 ≥1%, no *EGFR/ALK*)	200 mg every 3 weeks or 400 mg every 6 weeks	200 mg every 3 weeks or 400 mg every 6 weeks
	IMpower110 Atezolizumab (PD-L1 ≥50% or IC ≥10%, no *EGFR/ALK*)	840 mg every 2 weeks or 1200 mg every 3 weeks or 1680 mg every 4 weeks	1200 mg every 3 weeks

FDA Meta-Analysis of NSCLC Trials Demonstrates Similar OS and PFS Benefits in Asian and Western Populations



Data cutoff for ORIENT-11 OS was 15 September 2021 and for PFS was 15 November 2019.
1L-C=First-line combination with chemotherapy; ICI=immune checkpoint inhibitor.
Chang E, et al. *J Clin Oncol*. 2019;37(15 suppl):e20690.

Sintilimab Demonstrates a Comparable Safety Profile to Other Checkpoint Inhibitors in NSCLC



- 16 studies – 8278 patients
- Quality of included studies studied by Cochrane risk of bias
- Preferred reporting items for systematic reviews for meta-analysis

Adapted from *J Thorac Oncol*. 2021;16(7):1099-1117. Liu L, et al. Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: a systematic review and network meta-analysis. Copyright 2021 with permission from Elsevier.

ORIENT-11 Data Are Applicable to the US Population

Clinical Practice	PK/PD	Efficacy & Safety
Similar clinical practice standards in United States and China	No clinically important difference; PK/PD profile is insensitive to ethnicity	Efficacy and safety of sintilimab are anticipated to be similar in the US population as they were in ORIENT-11

FDA's Key Review Issues

ICH E17 Guidance on Planning and Design of Multiregional Clinical Trials Is Not Applicable

- Intent of study was only for registration in China
- Consideration of foreign data governed by US regulation *21CFR314.106(b)*

Foreign Data as the Sole Basis for Marketing Approval

- The studies have been performed by clinical investigators of recognized competence *21CFR314.106(b)(2)*
- The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means *21CFR314.106(b)(3)*
- The foreign data are applicable to the U.S. population and U.S. medical practice *21CFR314.106(b)(1)*

Applicability of Comparator Arm to US Standard of Care

- Control arm was standard of care in China
- Agreement with China Health Authority and approved by IRBs
- Same comparator used to establish the US standard of care

Sintilimab 200 mg +

pemetrexed + cisplatin/carboplatin Q3W for 4 cycles

Followed by sintilimab + pemetrexed maintenance

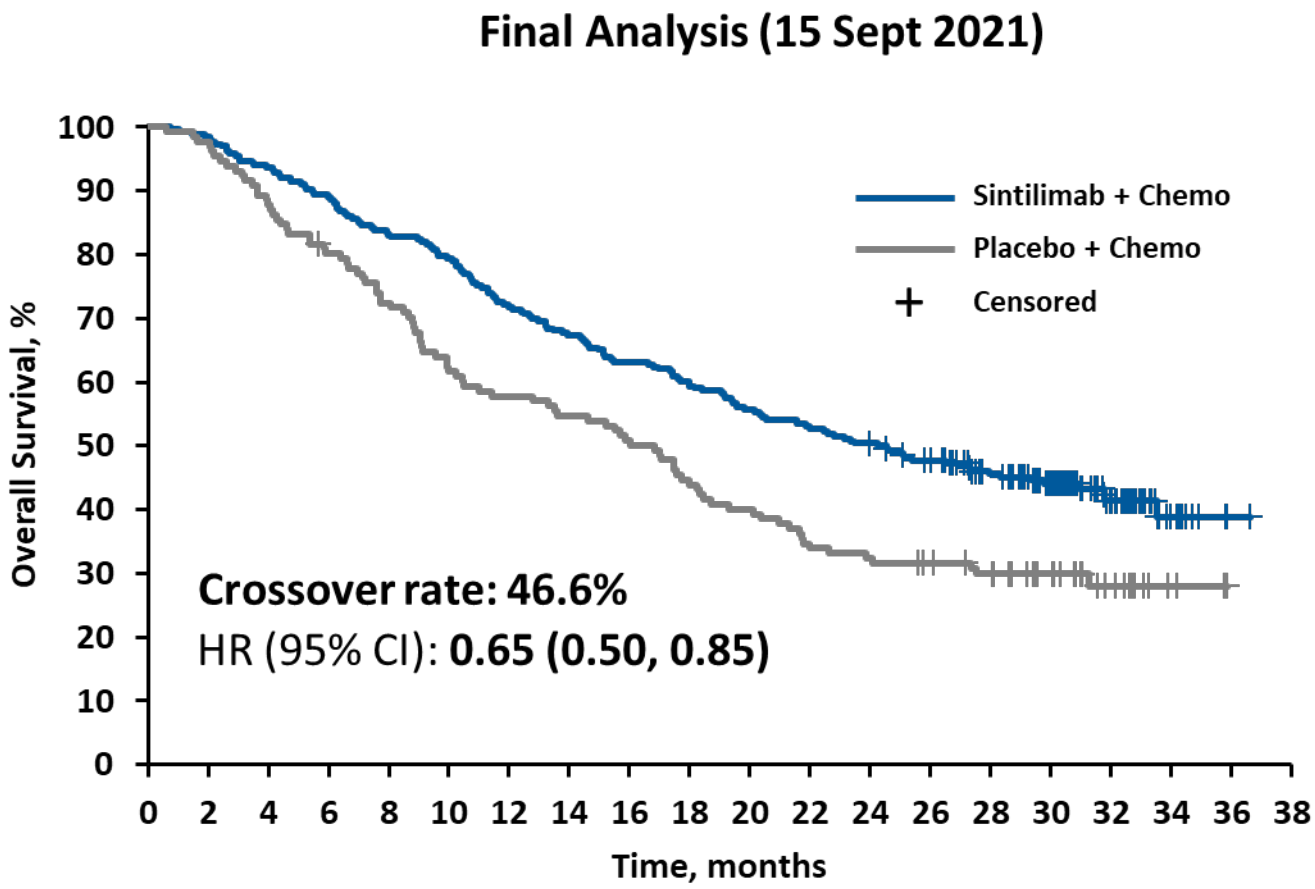
Placebo +

pemetrexed + cisplatin/carboplatin Q3W for 4 cycles

Followed by placebo + pemetrexed maintenance

Precedent for OS Endpoint to Support Approval

- PFS may be appropriate with large magnitude of treatment effect
- Although no alpha assigned for OS, result is compelling and reassuring
- PFS and OS results consistent with class



Known and Unknown Differences in Intrinsic and Extrinsic Factors

- Efficacy and safety data from ORIENT-11 are compelling and consistent with similar studies of PD-1/L1 inhibitors
- No clinically important PK differences between White and Asian or based on body weight
- Available data for sintilimab and other PD-1/L1 inhibitors demonstrate lack of sensitivity to ethnic differences across regions, consistent with ICH E5
- We are committed to collecting additional PK data in diverse patients in the post-market setting

ICH E5 Appendix D

The following properties of a compound make it less likely to be sensitive to ethnic factors:

- Linear pharmacokinetics (pK)
- A flat pharmacodynamic (PD) (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen (this may mean that the medicine is well-tolerated)
- A wide therapeutic dose range* (again, possibly an indicator of good tolerability)
- Minimal metabolism or metabolism distributed among multiple pathways
- High bioavailability, thus less susceptibility to dietary absorption effects
- Low potential for protein binding
- Little potential for drug-drug, drug-diet and drug-disease interactions
- Non-systemic mode of action
- Little potential for inappropriate use

ICH. Ethnic Factors in the Acceptability of Foreign Clinical Data, E5(R1). Last updated: March 11, 1998. Available at: https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf

Data in Patients Representative of US NSCLC Population

- The data from ORIENT-11 are applicable to the diverse US population
- We support increasing diversity in clinical trials
- We are committed to ongoing discussions with FDA regarding a post-marketing study in a diverse population

Data in Patients Representative of US NSCLC Population

Noninferiority Study Is Not Recommended

Study population

Key Eligibility Criteria

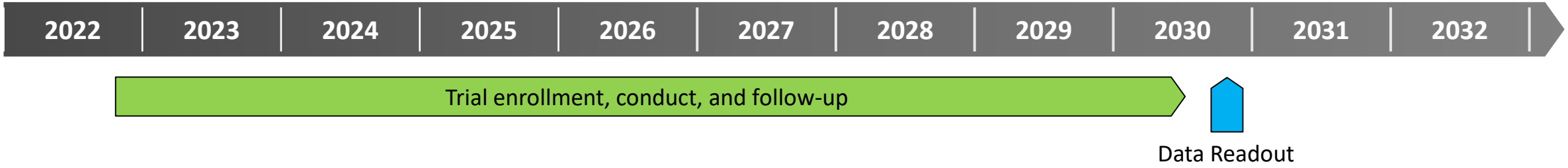
- Untreated nsqNSCLC
- Stage IV or IIIB/C ineligible for surgery or local therapy
- No *EGFR* or *ALK* genetic alteration
- Measurable disease
- ECOG PS 0 or 1

1:1

Sintilimab + chemo
N=1019

Pembrolizumab + chemo
N=1019

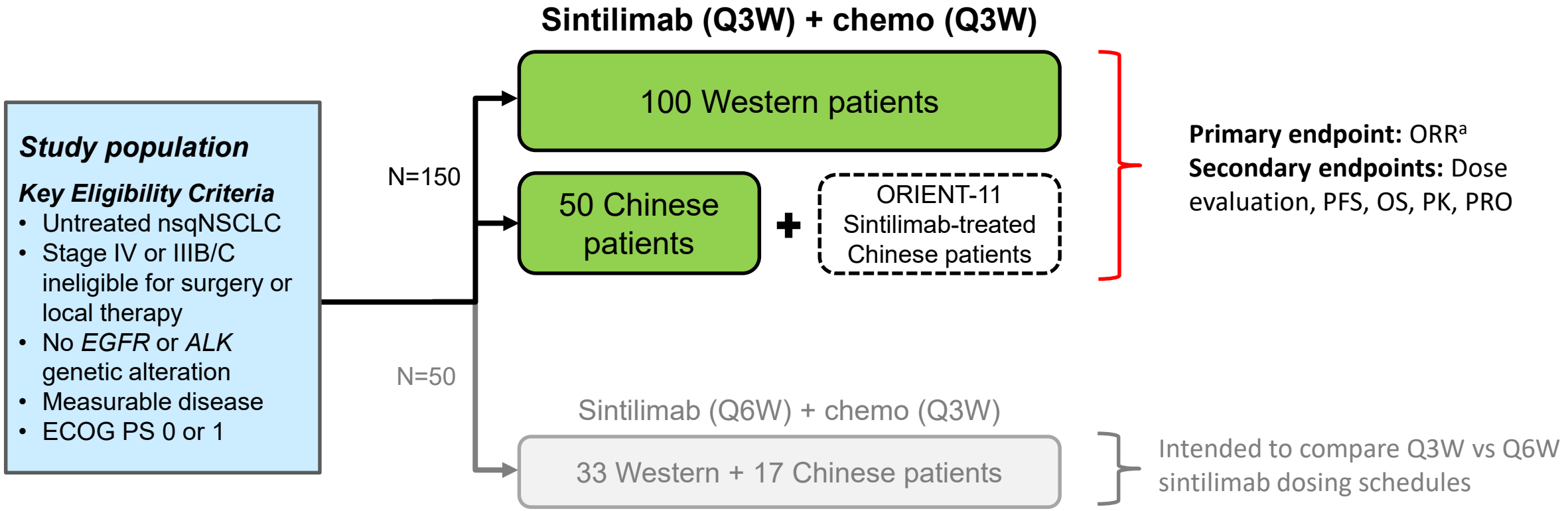
Primary Endpoint: Compare OS between sintilimab + chemo vs pembrolizumab + chemo
Secondary Endpoints: PFS, ORR, Safety
Statistical Assumptions: Non-inferiority margin of HR=1.15, 1632 events will yield 80% power to detect the noninferiority of sintilimab combination therapy at a 2-sided alpha level of 0.05



Data in Patients Representative of US NSCLC Population

Post-marketing Concept Based on Preliminary Feedback From FDA

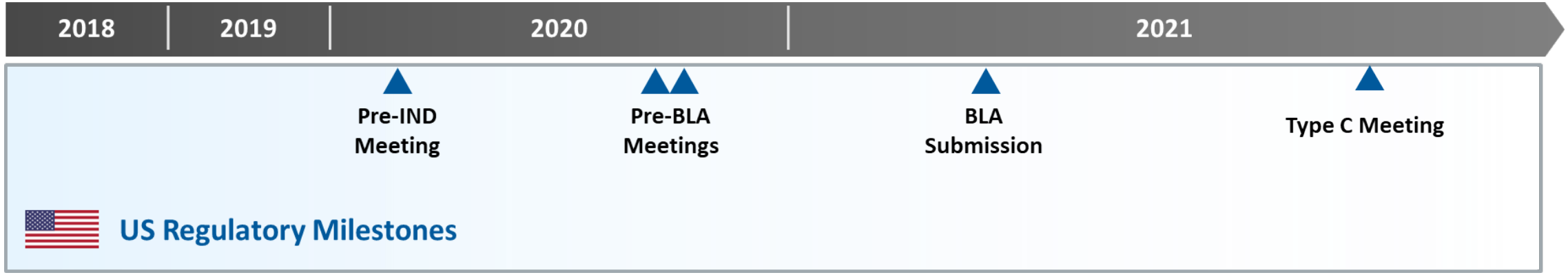
Objective: Compare PK/efficacy/safety of sintilimab + chemotherapy in Western patients vs Chinese patients



[a] sensitivity analysis that leverages additional Chinese patients from ORIENT-11 will be conducted.
Patients would be randomized between sintilimab Q3W and Q6W dosing arms.

FDA Consultation and Oversight

- Study was intended for registration in China
- Study conducted under GCP and applicable US regulations
- Met with FDA on 3 occasions in 2020



Updating Informed Consent Form

- At the time of study initiation, the informed consent form was reasonable and appropriate

Excerpts from the trial level ICF

Your study doctor will discuss with you if there are any other approaches that can be used to treat your disease. If you decide not to participate in this study, please consult your study doctor about other treatment options.

If there is a release of new information that may affect your decision to continue participating in this study, your study doctor will inform you as soon as possible.

- The Sponsor should have updated the trial level ICF, giving the sites the opportunity to update the local ICF according to their policies and procedures

Clinical Inspections and Experience of Investigators With Multiregional Clinical Trials

- Full access given to FDA for inspections
  - 2 inspections conducted as part of this application
- 10 of 48 sites previously inspected by FDA (17 inspections)
  - 12 resulted in no action indicated
  - 4 resulted in voluntary action indicated
  - 1 action pending
- 48% of sites have participated in a study that led to FDA approval

- Investigators were board-certified oncologists trained on ICH GCP
- 95% of investigators had previously participated in multiregional clinical trials

Regulatory Flexibility

- Substantial evidence of efficacy and safety provided by ORIENT-11
- Additional treatment options warranted

Innovent | Lilly Conclusion: Data From Sintilimab BLA Support Approvability

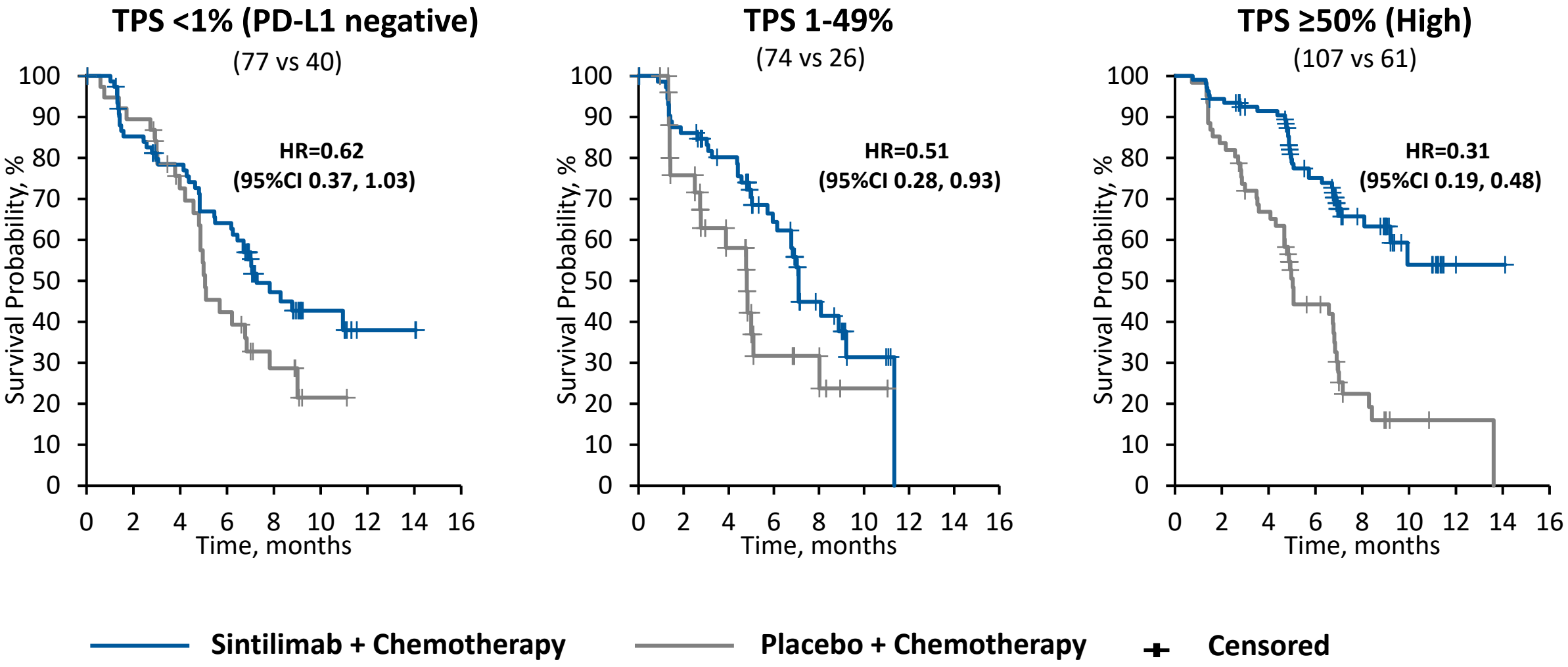
- Positive benefit/risk profile established
- Data are applicable and support US regulatory approval of sintilimab for the proposed indication
  - Sintilimab can provide another important option for nsqNSCLC
- Committed to working collaboratively with FDA to provide additional post-marketing data in US patients

Supportive Slides

Innovent | Lilly

PFS in PD-L1 Subgroups Tested

ORIENT-11



Data cutoff date: 15 Nov 2019

Pre-BLA Meeting Minutes - August 21, 2020

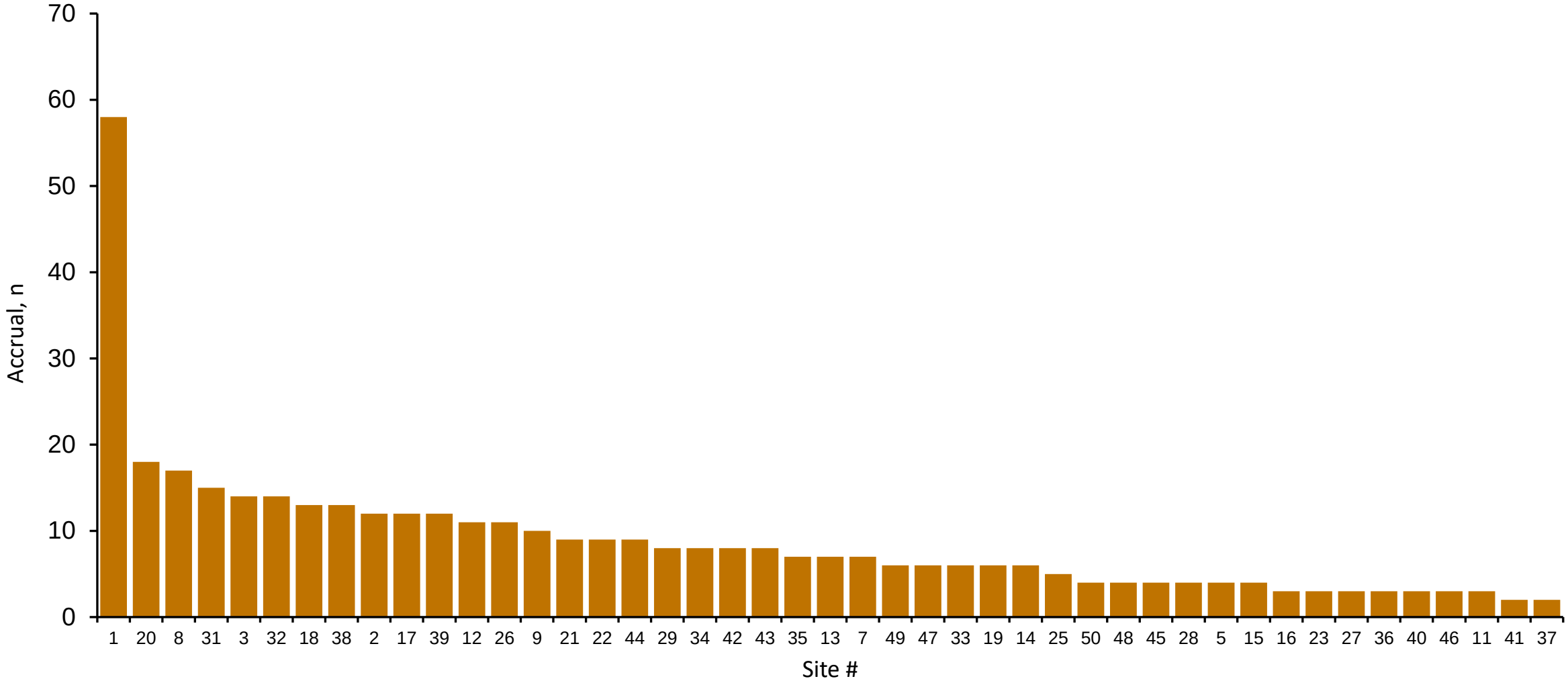
Does the Agency agree with the proposed safety database and the cutoff date of each study?

FDA Response: Overall, the proposed safety database and the cutoff date of each study are acceptable. However, FDA does not agree with your proposal to present safety data from patients in the US separately from safety data from patients in China. These data should be included in Pool 3 with other patients who received sintilimab as a single agent with a flag in the dataset identifying the 39 patients enrolled in Study CIBI308A102.

In addition, please note that FDA may make a request for post-marketing data in a population representative of the US population as a post-marketing commitment (PMC).

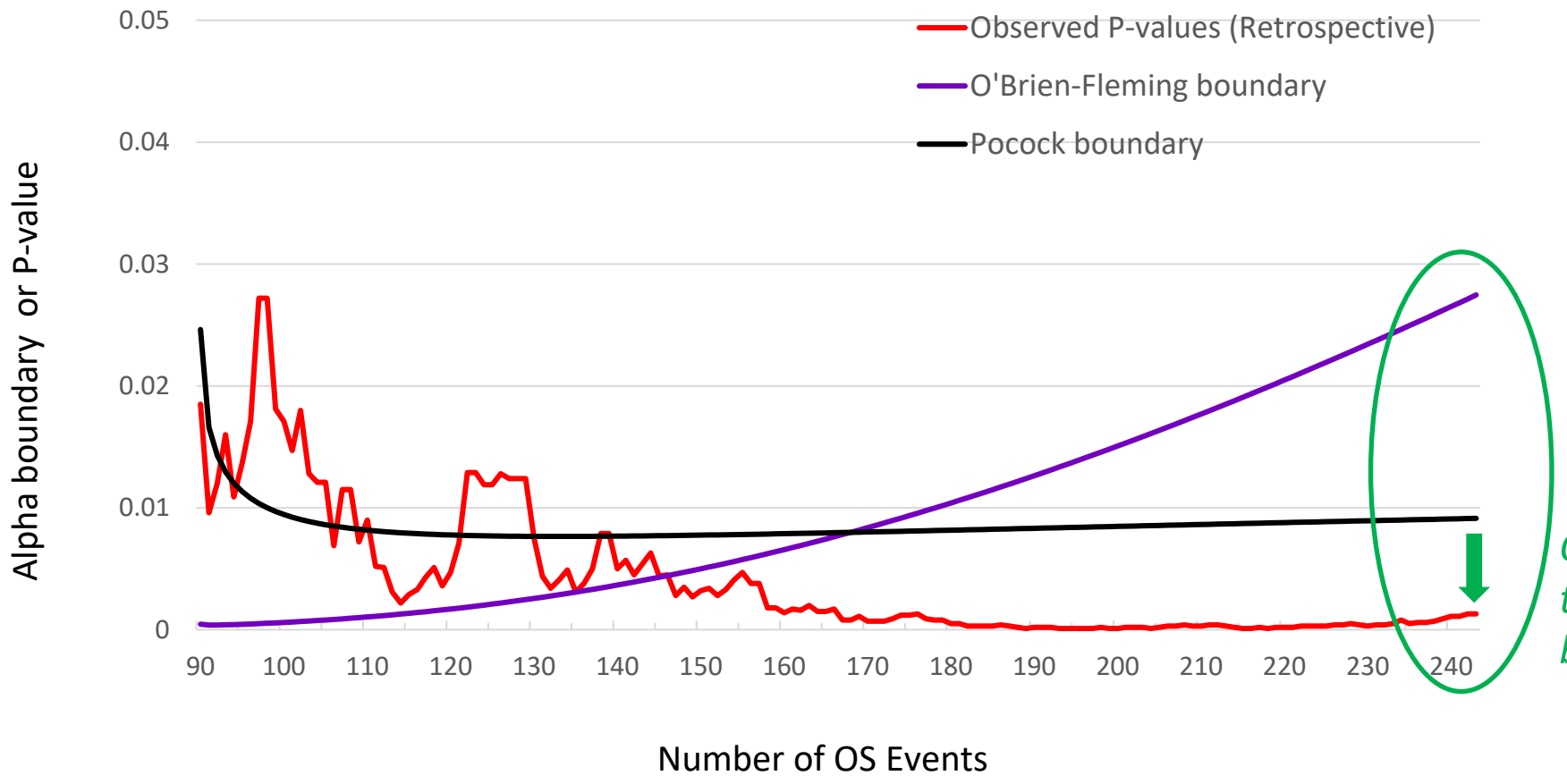
Innovent's 8/20/2020 E-mail Response: Innovent acknowledges the Agency's

Accrual by Study Site



Notes: 3 sites only enrolled 1 patient each are not included (site 24, site 30, site 10)

P Value Boundary Assuming Continue Look by the Time of Final Analysis



Observed P-value is lower than the most conservative boundaries at final analysis

23(48%) Sites and 9(18%) Investigators in ORIENT-11

Participated in Trials that Led to FDA Approval

Approval	Trial Title	NCT Code	Site Numbers	Investigators
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer	A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer	NCT02486718	02, 03, 08, 17, 25, 27	02, 08
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20	A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer	NCT02716116	08, 09, 26	08, 09, 26
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma	A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma	NCT01761266	01, 05, 07, 08,10, 12, 18, 25, 29, 35, 49	10, 49
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-first-line-treatment-metastatic-nsclc-high-pd-l1-expression	A Phase III, Open Label, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Compared With a Platinum Agent (Cisplatin or Carboplatin) in Combination With Either Pemetrexed or Gemcitabine for PD-L1-Selected, Chemotherapy-Naive Patients With Stage IV Non-Squamous Or Squamous Non-Small Cell Lung Cancer	NCT02409342	18	18
https://www.fda.gov/drugs/fda-approves-pembrolizumab-combination-chemotherapy-first-line-treatment-metastatic-squamous-nsclc	A Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in Adults With First Line Metastatic Squamous Non-small Cell Lung Cancer (MK-3475-407/KEYNOTE-407)	NCT02775435	08, 11, 17, 26, 33, 35, 36, 38, 49, 50	11, 26, 49, 50
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-esophageal-squamous-cell-cancer	A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects With Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus That Have Progressed After First-Line Standard Therapy (KEYNOTE-181)	NCT02564263	05, 08, 18, 22, 29	

History of Improvement on Data Integrity in China

Accrual in ORIENT-11

FPFV Aug 2018

LPFV July 2019

2015

2016

2017

2018

2019

2015.7 China Healthy Authorities released announcement to require all applicants completing clinical trial data self-check before submission to ensure data integrity.

2015.11 China Healthy Authorities released regulations/legislations to ensure data integrity of clinical trials

2016.1 The State Council of Peoples Republic of China announced that self-checks were completed for all clinical trials to be submitted. Furthermore, on-site inspections were also carried out to evaluate data integrity as prerequisite before NDA approval.

2017.6, China joined the ICH;

2017.8 The Supreme People's Court of The People's Republic of China released regulations/legislations to ensure data integrity of clinical trials. Data fraud is considered as a crime by criminal law

2018.6 “Due to strict regulatory supervision and high cost of breaking the law, deliberate data fraud is almost impossible”