Sintilimab for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

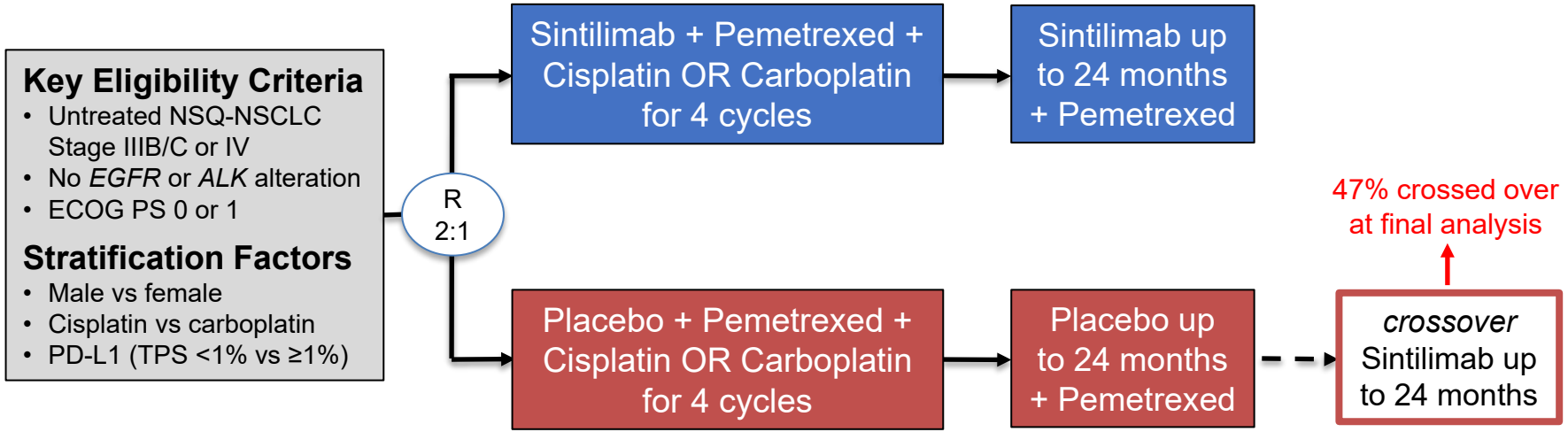
FDA Opening Remarks
Oncologic Drugs Advisory Committee (ODAC) Meeting
February 10, 2022

Harpreet Singh, MD
Director, Division of Oncology 2
Office of Oncologic Diseases

Outline

- ORIENT-11 Study Design and Results
- Regulatory Framework for Evaluation of Foreign Data
  - Code of Federal Regulations (CFR)
  - International Council of Harmonisation (ICH) Guidances E5 and E17
- Key Review Issues: Generalizability to U.S. Population
- Discussion and Voting Question for ODAC

ORIENT-11: Sintilimab + Chemotherapy for NSCLC Conducted Exclusively in China



Primary endpoints: Progression-free survival (PFS) by independent radiologic review committee (IRRC)
Descriptive secondary endpoints: OS (no α-allocation), overall response rate (ORR), duration of response (DOR)

ORIENT-11 Primary Efficacy Results: PFS by IRRC

	Sintilimab + Chemo N=266	Placebo + Chemo N=131
Events (%)	112 (42)	86 (66)
Median, mos (95% CI)[a]	8.9 (7.1, 11.3)	5.0 (4.8, 6.2)
Hazard ratio (95% CI)[b]	**0.48 (0.36, 0.64)**	
p-value[c]	<0.0001	

Data cut-off (DCO): November 15, 2019
[a] Kaplan-Meier estimate
[b] Stratified Cox proportional hazard model using Efron's method
[c] Two-sided p-value; α bound 0.01958 (interim analysis)

Overall Survival, Overall Response Rate, and Duration of Response were descriptive endpoints not formally tested.

Increasing Number of Single Country Trials

- ORIENT-11 trial design, enrollment criteria, and statistical assumptions closely resemble landmark NSCLC trials which changed treatment paradigm to include immune checkpoint inhibitors

- Reflects at least 25 oncology development programs conducted exclusively in China, many of which closely resemble prior multiregional clinal trials (MRCTs)

- Per ICH E17 guidance, MRCTs preferred approach to globally harmonized drug development

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Failure to meet any of these criteria will result in an application not being approvable based on the foreign data alone.

- FDA will apply this policy in a flexible manner according to nature of drug and data being considered

Source: 21 CFR 314.106

ICH Guidance: E5 Bridging → E17 MRCT

E5 (1998): sequential bridging from trial in one region to trial in new region

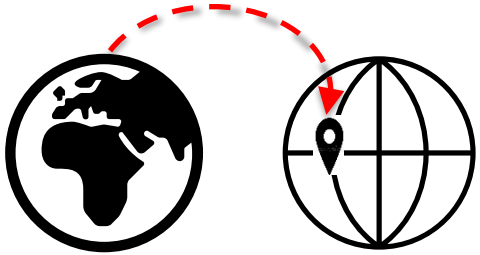
Consider intrinsic and extrinsic factors

Bridging studies fulfilled unmet need.

Inherently limited ability to demonstrate applicability.

Sequential strategy delayed access to important drugs.

E17 (2017): MRCT then evaluate regional consistency

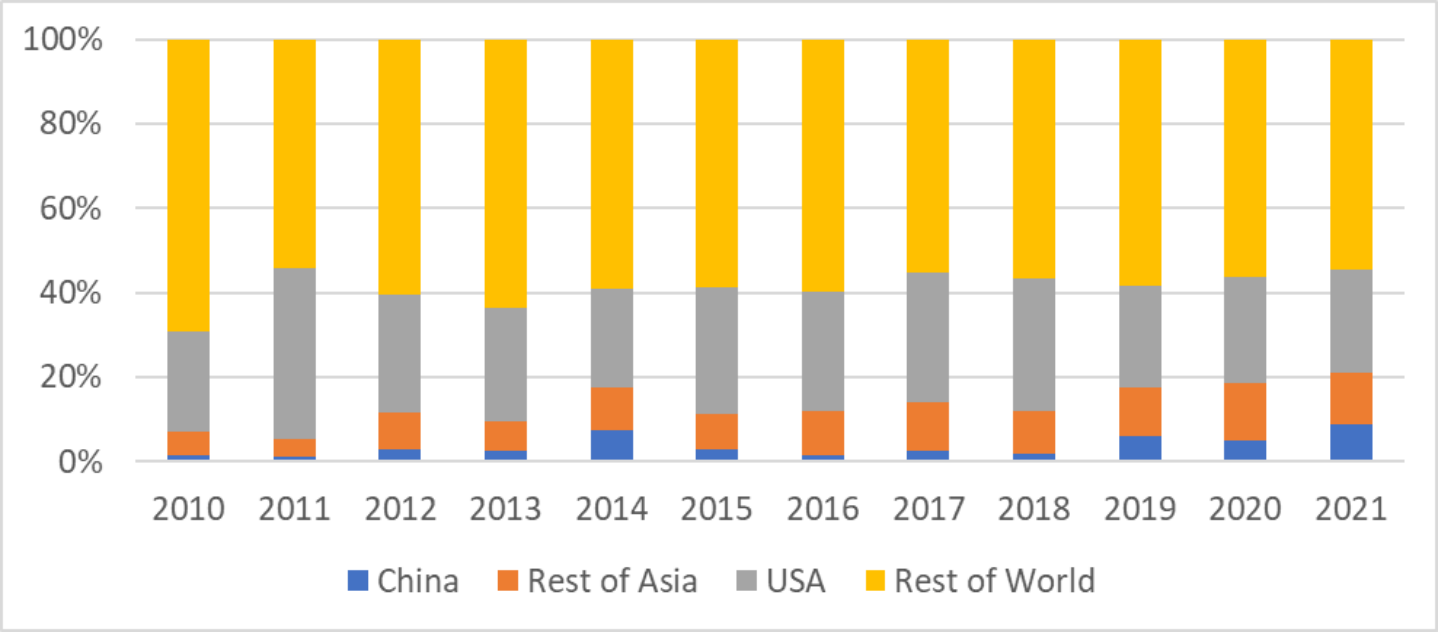


Consider regional variability during planning of MRCT

A 20-year journey from local mindset to global mindset for efficient drug development and to ensure safe and effective drugs worldwide

Asian Countries Participation in MRCTs

Oncology Submissions to the FDA: Patient Enrollment by Geographic Region



ICH E17: Multiregional Clinical Trials (MRCTs)

- Most U.S. drug applications based on international MRCTs
- Allows evaluation of **regional consistency** (i.e., safety and efficacy evaluated across geographic regions and subpopulations)
- Enables **earlier access worldwide** to therapies
- **Avoids duplication** of trials and need for bridging studies
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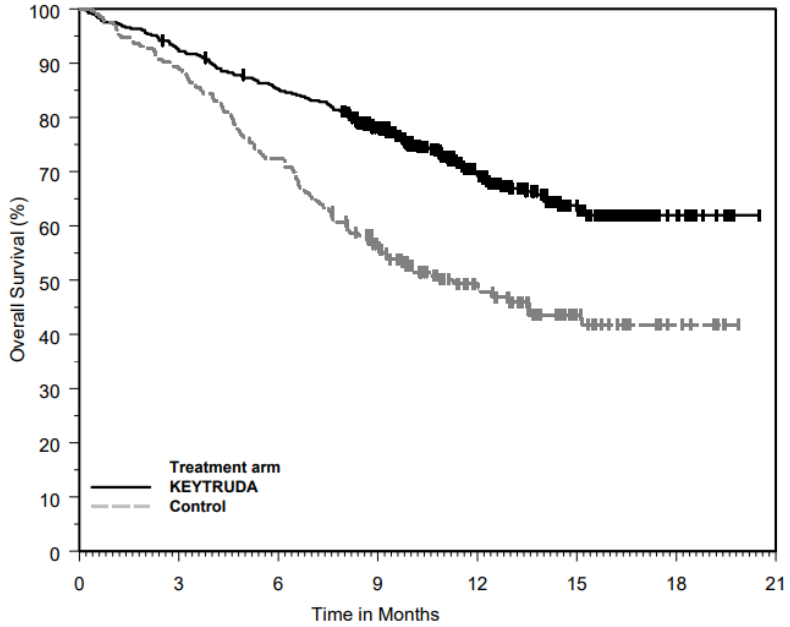
KEYNOTE-189: Landmark Approval of Pembrolizumab + Chemotherapy Based on OS



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NR – not reported

Regular approval based on statistically significant improvement in OS

Source: KEYTRUDA (Pembrolizumab) USPI

Control Arm Inapplicable to U.S. Medical Practice

- Enrollment to ORIENT-11 began after FDA approval of pembrolizumab/chemotherapy (KEYNOTE-189) which demonstrated **statistically significant OS benefit** for patients with nonsquamous NSCLC

- ORIENT-11 could not have been conducted in the United States
  - Lack of investigator support given substandard chemotherapy comparator arm
  - Available FDA approved therapies conferred survival advantage

If consulted, FDA would have likely advised direct comparison of sintilimab to an approved anti-PD-(L)1/chemotherapy regimen with OS endpoint

Study Endpoint Not Applicable to U.S. Regulatory Standards

Drug(s)	Indication*	Approval Endpoint (Year)
Pembrolizumab	NSCLC (TPS ≥50%)	OS (2016)
Pembrolizumab	NSQ-NSCLC (w/ pemetrexed and platinum chemo)	PFS (2017)[AA]; OS (2018)
Pembrolizumab	SQ-NSCLC (w/ carboplatin and paclitaxel or nab-paclitaxel)	OS (2018)
Atezolizumab	NSQ-NSCLC (w/ carboplatin, paclitaxel, & bevacizumab)	OS and PFS (2018)
Pembrolizumab	NSCLC (TPS ≥1%)	OS (2019)
Atezolizumab	NSQ-NSCLC (w/ carboplatin & nab-paclitaxel)	OS and PFS (2019)
Nivolumab/Ipilimumab	NSCLC (TPS ≥1%)	OS (2020)
Nivolumab/Ipilimumab	NSCLC (w/ platinum-doublet chemo)	OS (2020)
Atezolizumab	NSCLC (TC ≥50% or IC ≥10%)	OS (2020)
Cemiplimab-rwlc	NSCLC (TPS ≥50%)	OS (2021)

* Indicated for all NSCLC histologies unless otherwise noted
AA – Accelerated Approval
NSQ – nonsquamous; SQ – squamous

ORIENT-11 not reflective of U.S. population

- Compared to U.S. patients with NSCLC, patients in ORIENT-11 were younger, predominantly male, lower rates of smoking
- Unknown impact of concomitant (herbal) medications
- Unknown impact of differences in body weight/composition
- Fails to address persistent underrepresentation of racial and ethnic minorities in drug development

FDA Validation of Data Limited in Scope

- Few selected clinical sites unable to fully capture heterogeneity in trial conduct and data quality
- Prior participation in MRCTs, as well as previously reported challenges to data integrity are key factors
- ORIENT-11 investigators with limited MRCT experience leading to FDA registration

Woodhead M, *BMJ*, 2016

Applicability to U.S. Population: Applicant Position

1. Similar clinical practice standards between China and U.S.
   Standard of care in China at time of trial initiation (2018) not applicable to U.S. patients, who had shifted to first-line immunotherapy

2. Similar pharmacokinetics (PK) and pharmacodynamics (PD) of sintilimab between Chinese and U.S. patients
   Insufficient PK data provided to conclude similarity to diverse U.S. population, best evaluated in a MRCT

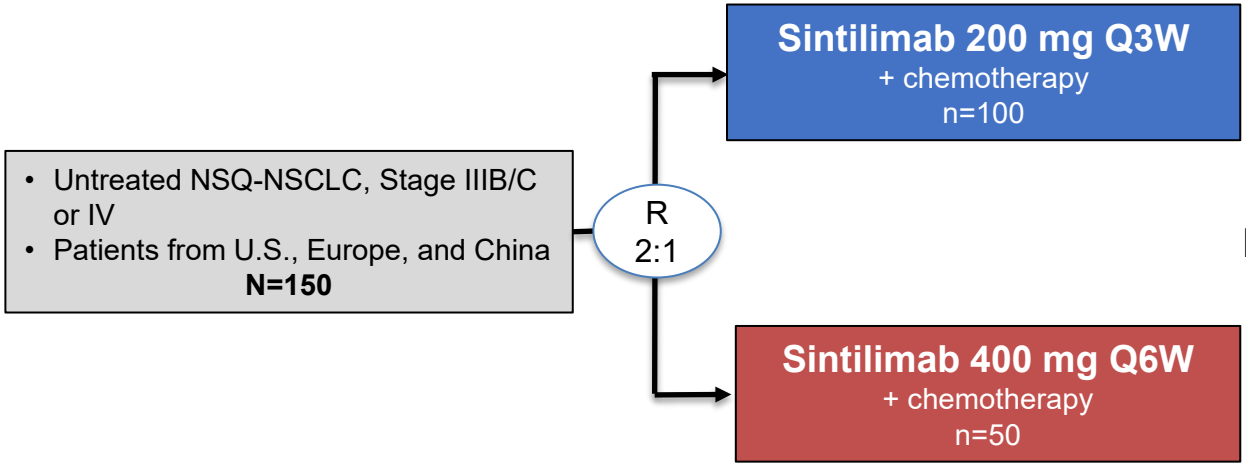
3. Similar efficacy and safety of sintilimab between Chinese and U.S. patients
   Retrospective, exploratory analyses with mixed results, best evaluated in a MRCT

ORIENT-11 Not Applicable to U.S. Population

- **Comparator arm** and **endpoint (PFS)** not consistent with U.S. medical practices and regulatory standards
  - ORIENT-11 lacked FDA consultation and oversight
- **Study population** not reflective of diverse U.S. population
- **Informed consent** not updated to reflect changing standard of care (SOC) as required per good clinical practice (GCP)
- **Inspections limited in scope** to assess trial conduct and data integrity

Therapeutic landscape does not warrant regulatory flexibility.

Applicant's Proposal for Non-Comparative Study Examining Two Doses of Sintilimab



Primary Endpoint: ORR

Does not address applicability issues → possible trial would compare sintilimab to approved anti-PD-(L) antibody with OS endpoint

ORIENT-11 Not Envisioned in ICH E5, Not Aligned with ICH E17

- ICH E5 guidance on bridging not intended for “me too” drugs
  - Does not fulfill an unmet regional need

- If designed as a well-conducted MRCT, ORIENT-11 would have:
  - Involved early communication with international regulatory authorities → selection of appropriate comparator, OS endpoint
  - Permitted structured exploration of regional consistency of results
  - Addressed concerns about applicability to U.S. population

Building Equity through MRCTs

- MRCTs strengthened by additional regional participants
- Increased diversity may address underrepresentation of ethnic minorities in drug development
- Increased global participation in MRCTs provides a framework to establish regulatory experience
- Patient centered approach expedites therapeutic advances

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Voting Question

Should additional clinical trial(s) demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Sintilimab for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

FDA Presentation
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February 10, 2022

Paz J. Vellanki, MD, PhD
Clinical Reviewer, Thoracic and Head and Neck Cancer
Division of Oncology 2, Office of Oncologic Diseases

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Shenghui Tang, Ph.D., Director, DBV
Yuan-Li Shen, Ph.D., Deputy Director, DBV
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Jana Highsmith, Regulatory Health Project Manager, DRO-ORO
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Increasing Number of Single Country Trials

- ORIENT-11 trial design, enrollment criteria, and statistical assumptions closely resemble landmark NSCLC trials which changed treatment paradigm to include immune checkpoint inhibitors

- Reflects at least 25 oncology development programs conducted exclusively in China, many of which closely resemble prior multiregional clinal trials (MRCTs)

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FDA Mission

The U.S. Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

FDA **does not** consider cost or drug pricing in regulatory decision making.

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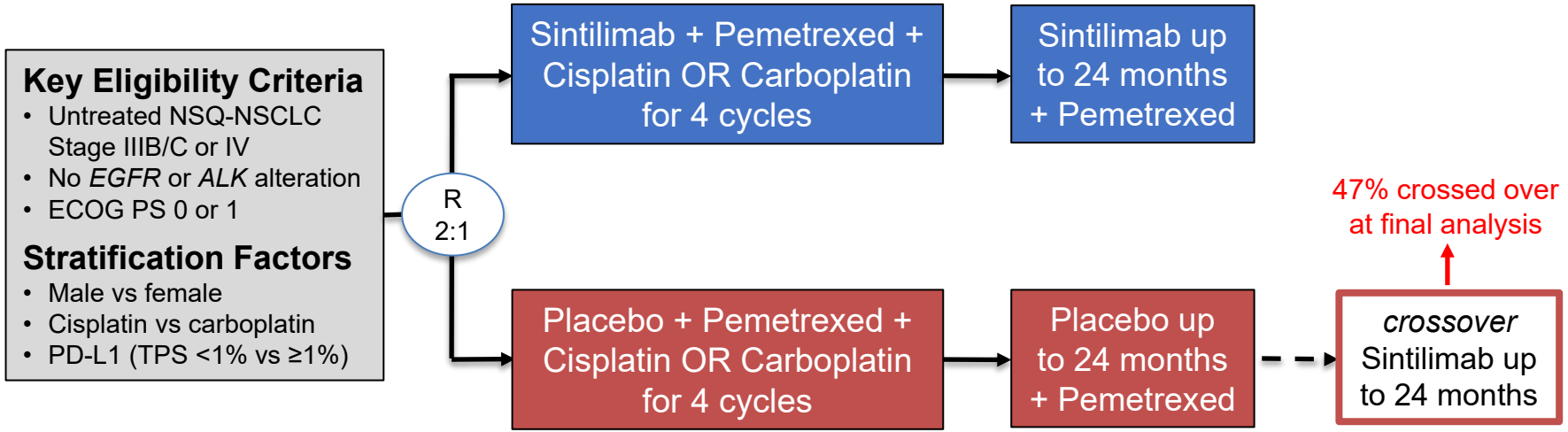

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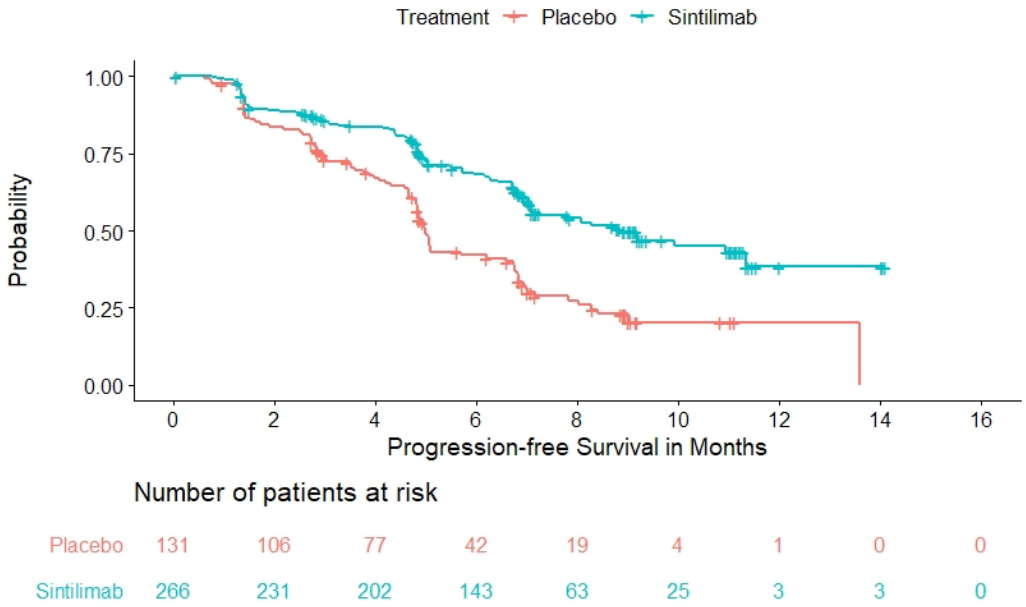
Demographics and Baseline Characteristics

	Sintilimab + Chemo N=266	Placebo + Chemo N=131
Age, median (range)	61 (30 – 75)	61 (35 – 75)
Sex, Male*	204 (77%)	99 (76%)
Race, Chinese (mainland China)	266 (100%)	131 (100%)
ECOG, PS 1	190 (71%)	97 (74%)
Disease Stage Stage IIIB/IIIC Stage IV	 21 (8%) 245 (92%)	 15 (11%) 116 (89%)
PD-L1* <1% ≥1%	 85 (32%) 181 (68%)	 44 (34%) 87 (66%)
Current/Former Smoker	171 (64%)	87 (66%)
Platinum Choice* Cisplatin Carboplatin	 71 (27%) 195 (73%)	 33 (25%) 98 (75%)
Brain Metastases	36 (14%)	22 (17%)

* Stratification Factor

Primary Efficacy Results: PFS by IRRC



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[a] Kaplan-Meier estimate

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Summary of Safety

	Sintilimab + Chemo N=266 n (%)	Placebo + Chemo N=131 n (%)
All-cause AEs		
Any Grade	265 (100%)	131 (100%)
Grade 3-4	158 (59%)	69 (53%)
Grade 5	6 (2.3%)	11 (8%)
SAEs	75 (28%)	44 (34%)
AEs Leading to Interruption	125 (47%)	63 (48%)
AEs Leading to Discontinuation	14 (5%)	12 (9%)

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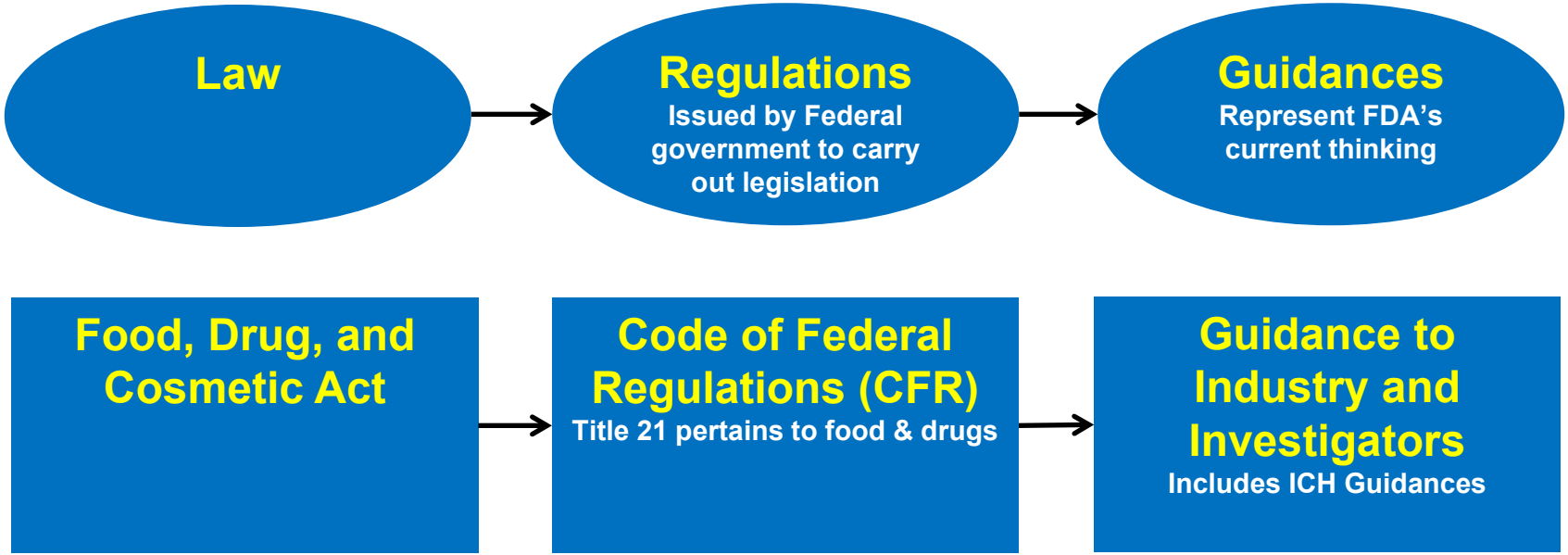
Legal Framework and FDA Guidances



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- FDA will apply this policy in a flexible manner according to nature of drug and data being considered

Source: 21 CFR 314.106

Considerations for Regulatory Flexibility

FDA will apply 21 CFR 314.106 in a flexible manner according to nature of drug and data being considered.

- **Unmet medical need**
- **Rare disease**: MRCTs difficult to conduct
- **Novel drug class**

Oncology Drug Development Harmonized by ICH Guidelines

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) established in 1990

ICH brings together global regulatory authorities and the pharmaceutical industry; China officially joined as a member in 2017

Goal of ICH to harmonize scientific and technical requirements of medicinal products to ensure safe, effective, and high-quality medicines worldwide

ICH guidances used and applied by FDA, and often incorporated into Code of Federal Regulations (CFR)

Source: ich.org

1998 ICH E5 Guidance for Acceptability of Foreign Data

Assessment of data package

- Are clinical trials applicable to **regulatory standards in new region,** including **primary endpoint and control arm?**
- Trials adequate and **well-controlled?**

Sensitivity to ethnic factors

- Extrinsic factors: associated with environment and culture
- Intrinsic factors: define/identify a subpopulation

Need for bridging study

- Based on likelihood that ethnic and extrinsic factors could affect a product's safety or efficacy

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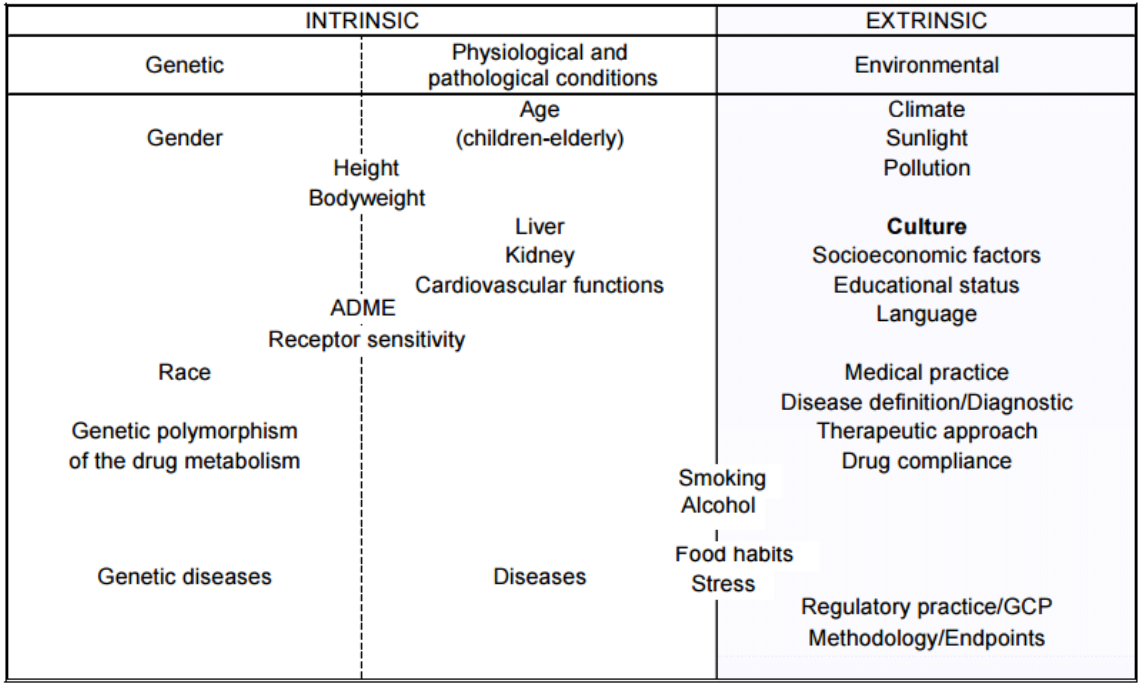
Ethnic Factors May Impact Drug Efficacy and Safety (ICH E5 and E17)



Source: ICH E5 Guidance – Ethnic Factors in the Acceptability of Foreign Clinical Data

Bridging Studies Inherently Limited

1) **Bridging studies may not address concerns regarding generalizability**
   - Often smaller, non-randomized
   - Less clinically meaningful endpoints compared to original trial
   - May provide additional pharmacodynamic and clinical data but not sufficient to support a marketing application

2) **Reliance on bridging trials resulted in delayed access**

Limitations with bridging studies → increased participation in MRCTs

ICH Guidance: E5 Bridging → E17 MRCT

E5 (1998): sequential bridging from trial in one region to trial in new region

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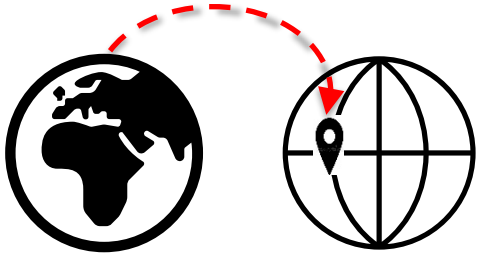

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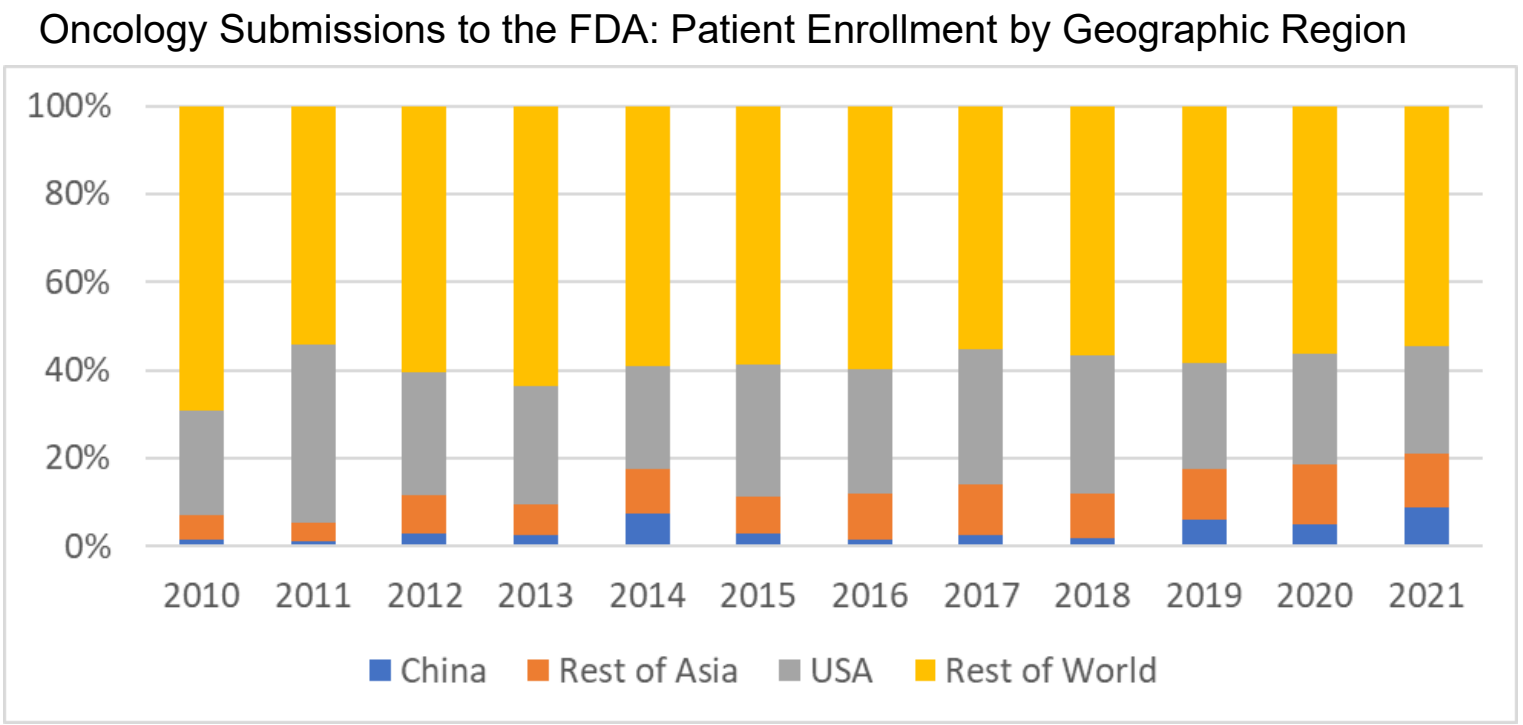
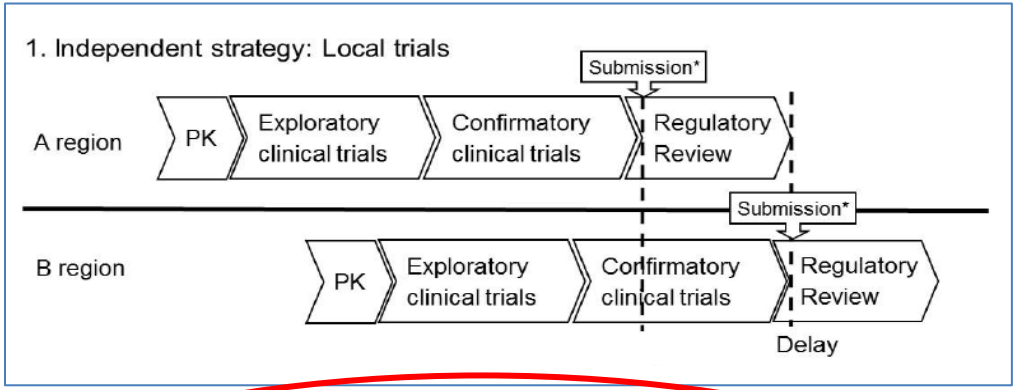
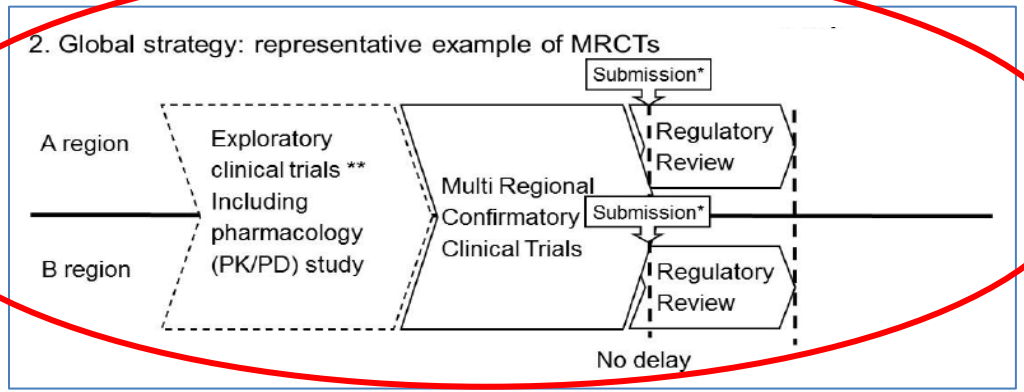


MRCT Represents Efficient Drug Development





- Earlier access to therapies across different regions
- Avoid duplication of trials and need for bridging studies
- Promote international harmonization

MRCT – multiregional clinical trial

ICH E17 Guiding Principles for MRCTs

1. Strategic use of MRCT's in drug development
2. Intrinsic/extrinsic factors identified early
3. Strategic allocation of sample size to regions
4. Pre-specified pooling of regions or subpopulations
5. **Structured exploration of consistency across regions and subpopulations**
6. Ensure high quality study design and conduct across regions (ICH E6)
7. Communication with regulatory authorities during planning of MRCTs

Inclusion of Diverse Populations in Cancer Drug Development

- Study populations should represent intended populations[1]
- Racial and ethnic minorities underrepresented in trials
- Project Equity: FDA Oncology Center of Excellence initiative to promote diversity in clinical trials and generate data in more representative patient groups
- Commitments and initiatives for inclusion and diversity across pharmaceutical industry[2], professional societies[3], and patient advocacy groups[4]

[1] Fashoyin-Aje L, Beaver JA, Pazdur R. *Jama Oncol*. 2021
[2] Quilici E, www.pharmexec.com, Driving diversity and inclusion, February 2021
[3] Clarifyhealth.com, Diversity and inclusion in oncology clinical trials, October 2021
[4] Kim ES et al., J Clin Oncol, October 2017

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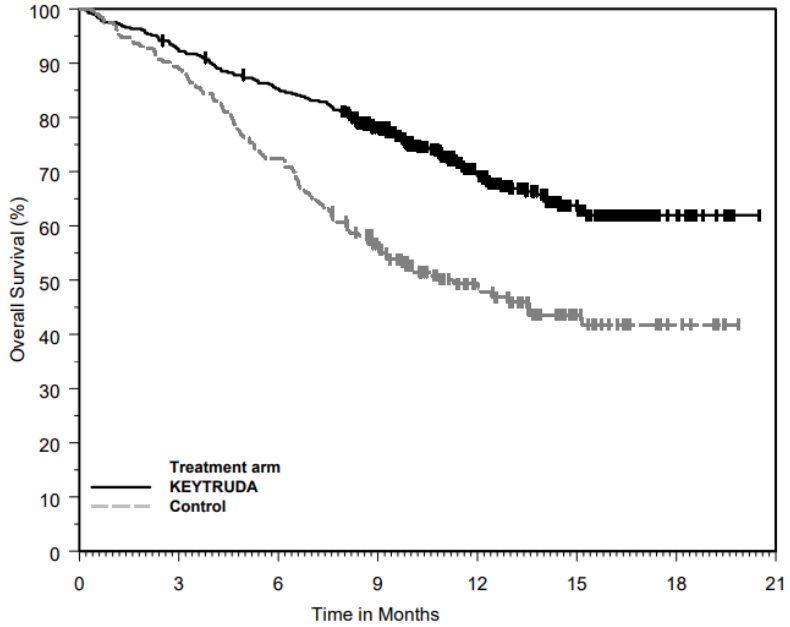

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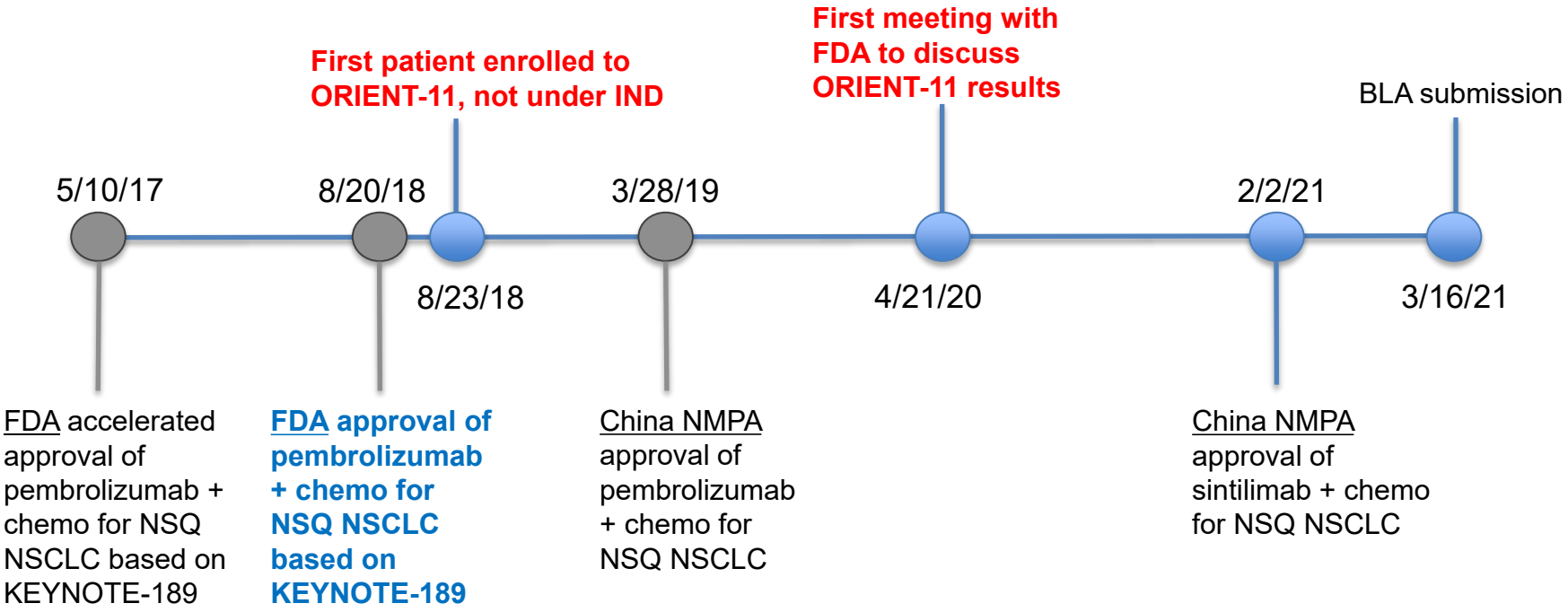

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Precedent of Overall Survival as Approval Endpoint for Immunotherapy Approvals for Metastatic NSCLC

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Pembrolizumab	NSCLC (TPS ≥1%)	OS (2019)
Atezolizumab	NSQ-NSCLC (w/ carboplatin & nab-paclitaxel)	OS and PFS (2019)
Nivolumab/Ipilimumab	NSCLC (TPS ≥1%)	OS (2020)
Nivolumab/Ipilimumab	NSCLC (w/ platinum-doublet chemo)	OS (2020)
Atezolizumab	NSCLC (TC ≥50% or IC ≥10%)	OS (2020)
Cemiplimab-rwlc	NSCLC (TPS ≥50%)	OS (2021)

* Indicated for all NSCLC histologies unless otherwise noted
AA – Accelerated Approval
NSQ – nonsquamous; SQ – squamous

ORIENT-11 Endpoint Not Applicable to U.S. Regulatory Standards

- Statistically significant benefit in PFS
- However, OS not statistically tested in ORIENT-11 despite precedent for OS endpoint for approvals in metastatic NSCLC
- For other combination therapies with anti-PD-(L)1 antibodies, OS benefit demonstrated despite crossover in trials → weakens Applicant's position that OS could not have been reasonably tested
- Acceptance of PFS risks loss of gains in OS seen with prior approvals

Applicability to U.S. Population: Applicant Position

1. Similar clinical practice standards between China and U.S.
   Standard of care in China at time of trial initiation (2018) not applicable to U.S. patients, who had shifted to first-line immunotherapy

2. Similar pharmacokinetics (PK) and pharmacodynamics (PD) of sintilimab between Chinese and U.S. patients
   Insufficient PK data provided to conclude similarity to diverse U.S. Population; best evaluated in a MRCT

3. Similar efficacy and safety of sintilimab between Chinese and U.S. patients
   Retrospective, exploratory analyses suggest potential differences; best evaluated in a MRCT

Known Differences Between Patients in U.S. and ORIENT-11

U.S. population with non-squamous NSCLC[1,2]

- Median age 70 at diagnosis
- ~ 50% male
- ~ 85% current/former smokers
- ~ 79% White
- ~ 15% Black
- ~ 6% Asian

ORIENT-11

- Median age 61
- 76% male
- 65% current/former smokers
- 100% Chinese

[1] Howlader N et al., SEER Cancer Statistics Review, 1975 - 2017
[2] United States Census Bureau: April 1, 2010 to July 1, 2019

Comparison of Baseline Characteristics

	U.S. Patients with Nonsquamous NSCLC[1,2]	KEYNOTE-189[3] Pembrolizumab N=616	ORIENT-11[4] Sintilimab N=397
Countries of Enrollment, n	N/A	16	1
Race	~ 79% White ~15% Black ~6% Asian	94% White 2.3% Black 2.9% Asian	100% Asian (all Chinese)
Sex, male	~50%	59%	76%
Current/former smokers	~85%	88%	65%
Age, median at diagnosis (range)	~70	64 (34 – 84)	61 (30 – 75)

[1] Howlader N et al., SEER Cancer Statistics Review, 1975 – 2017
[2] United States Census Bureau: April 1, 2010 to July 1, 2019
[3] KEYTRUDA (Pembrolizumab) USPI
[4] ORIENT-11 Clinical Study Report and Datasets

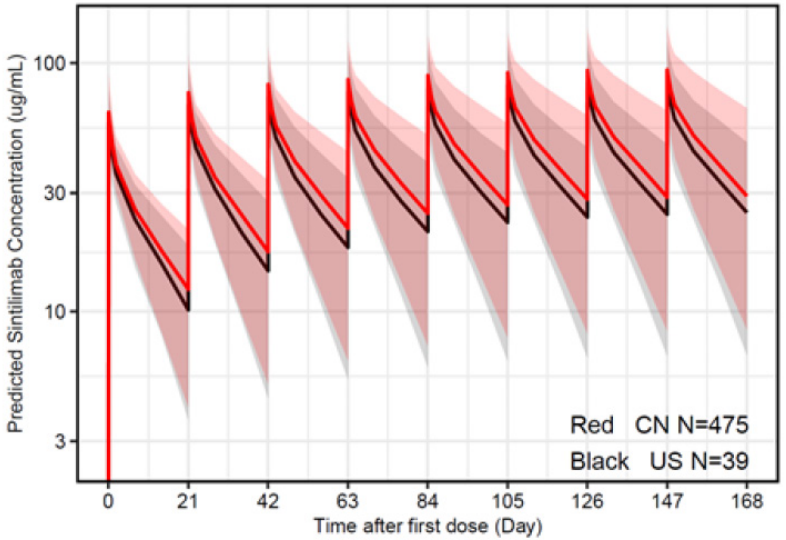
Unknown Impact of Differences Between Study Population in ORIENT-11 and U.S. Patients

- Diagnosis and management of NSCLC (e.g., decision for chemoradiation)
- Concomitant medications, including herbal medications
  - 69% of patients in ORIENT-11 received at least one herbal medication primarily for adverse events (50%) or prophylactic measures (22%)*
- Body weight and composition
- Unknown regional differences

* Applicant Analysis (data cutoff date: January 15, 2021)

Additional PK Data Needed to Support Dosage, Efficacy, and Safety for U.S. Patients

- Population pharmacokinetic (PopPK) analyses compared pharmacokinetic (PK) characteristics of Chinese (n=475) and U.S. patients (n=39)
- U.S. patients (none with NSCLC): n=30 White, n=5 Black, n=3 Asian, n=1 Native American
- Modeling and simulation data suggest no clinically significant difference in PK between White and Chinese patients, or significant effect of body weight on PK
- **However, limited U.S. patients do not represent ethnic and racial diversity of U.S.**
- FDA standard to request sparse PK collection inclusive of intent-to-treat (ITT) population (i.e., U.S. patient cohort) **→ additional PK data needed to support efficacy and safety for U.S. patients**



CN – China; US – United States

Applicant Analysis: Response to Information Request, May 24, 2021

Exploratory Analyses Suggest Differences Between Asian and Non-Asian Patients: Need MRCTs

- Epidemiologic studies suggest Asian ethnicity favorable prognostic factor for OS for NSCLC, in general[1-3]
- Exploratory studies suggest longer OS with anti-PD-(L)1 antibodies for Asians compared to non-Asians[4-7]
- Differences in clinicopathological characteristics (smoking history, driver mutations, PD-L1 expression, tumor mutation burden) may contribute to differential survival[6]
- Potential differences in safety, including increased pneumonitis in Asian patients[7]

[1] Ahn MJ, *J Thorac Oncol*, 2010
[2] Kawaguchi T, *J Thorac Oncol*, 2010
[3] Ou SH, *J Thorac Oncol,* 2009
[4] Peng L, *Oncoimmunology,* 2020
[5] Chang E et al., ASCO Abstract, 2019
[6] Qian J. *Int J Cancer,* 2020
[7] Peng L, *J Thorac Dis*, 2018

Informed Consent Not Updated to Reflect New Approvals with OS Benefit (GCP)

Version	Effective Date	Discussion of Other Treatment Options
1.0	May 11, 2018	Reliance on study doctor to discussion options
2.0	January 29, 2019	Reliance on study doctor to discussion options
March 28, 2019*: Pembrolizumab plus pemetrexed and platinum chemotherapy approved for first-line treatment of nonsquamous NSCLC in China		
3.0	August 13, 2019	Reliance on study doctor to discussion options

***Informed consent form not updated to discuss pembrolizumab approval in China, which demonstrated overall survival benefit**

FDA Site Inspections
(21 CFR 312.68, 312.120, 812.145)

- Requirement for new molecular entities
- Performed to verify accuracy and reliability of clinical trial data
- Not all clinical trial sites inspected → only a sampling of data
- 2016 report by China's State Food and Drug Administration that 80% of clinical trial data from China were "fraudulent or substandard"[1]

[1] Woodhead M, *BMJ*, 2016

Uncertain Level of Past Participation of ORIENT-11 Sites in MRCTs

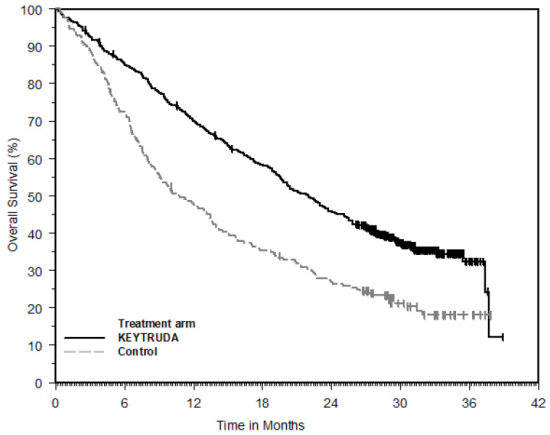
- Prior participation in MRCTs may help provide confidence in trial conduct and data integrity; however, uncertain level of prior participation for ORIENT-11 investigators

- Estimate of prior participation in MRCTs based on participation in trials conducted in both U.S. and China
  - 10 of 48 sites with prior FDA inspections (14 total inspections in Oncology or Hematology)
  - Queried Applicant but unable to indicate 1) number of patients enrolled in MRCTs per site or 2) MRCTs which led to U.S. approval

- Minimal FDA interactions and no prior FDA site inspections for Applicant

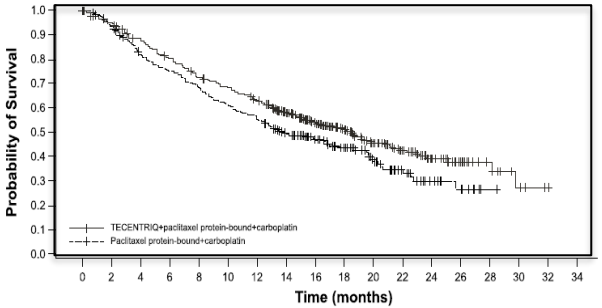
Multiple FDA Approved Anti-PD-(L)1 Antibodies with OS Benefit

Pembrolizumab



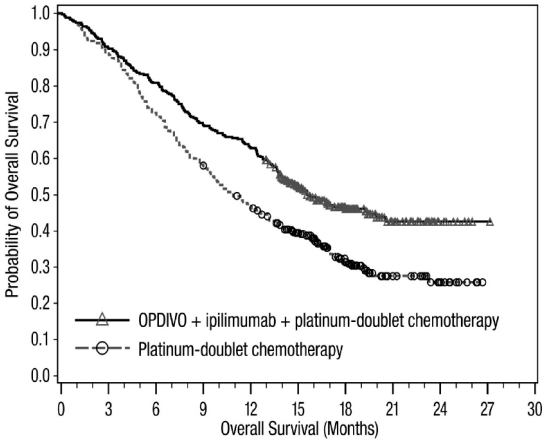
Source: KEYTRUDA (Pembrolizumab) USPI

Atezolizumab



Source: TECENTRIQ (Atezolizumab) USPI

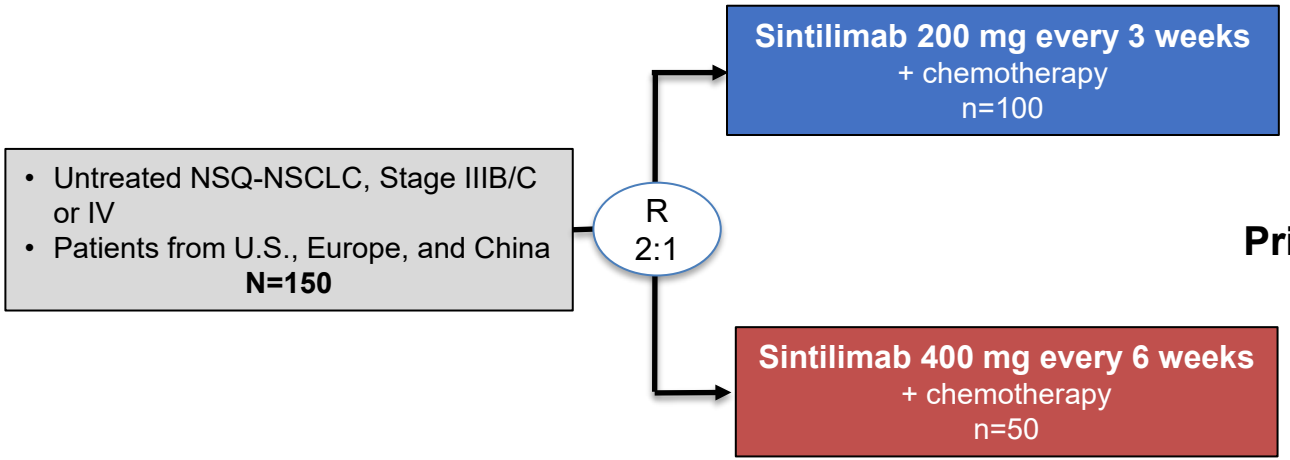
Nivolumab



Source: OPDIVO (Nivolumab) USPI

- ORIENT-11 does not fulfill unmet need
- Does not merit regulatory flexibility when considering applicability
- Approval based on PFS would diverge from current regulatory standards
- The Applicant compares sintilimab to other first-line therapies, however each must be evaluated on its own merit

Applicant's Proposal for Non-Comparative Study Examining Two Doses of Sintilimab



Primary Endpoint: ORR

Does not address applicability issues → possible trial would compare sintilimab to approved anti-PD-(L) antibody with OS endpoint

Proposed Study Does Not Address FDA Concerns

- Dose-finding study rather than study to address concerns of generalizability to U.S. population
- Small study (n=150)
- Less clinically meaningful endpoint (ORR)
- **Proposed study does not address applicability issues → alternatively, a possible trial to address FDA concerns would compare sintilimab to an approved anti-PD-(L)1 antibody with an OS endpoint**

ORIENT-11 Not Envisioned in ICH E5, Not Aligned with ICH E17

- ICH E5 guidance on bridging not intended for “me too” drugs
  - Does not fulfill an unmet regional need

- If designed as a well-conducted MRCT, ORIENT-11 would have:
  - Involved early communication with international regulatory authorities → selection of appropriate comparator, OS endpoint
  - Permitted structured exploration of regional consistency of results
  - Addressed concerns about applicability to U.S. population

ORIENT-11 Not Applicable to U.S. Population

- **Comparator arm** and **endpoint (PFS)** not consistent with U.S. medical practices and regulatory standards
  - ORIENT-11 lacked FDA consultation and oversight
- **Study population** not reflective of diverse U.S. population
- **Informed consent** not updated to reflect changing standard of care (SOC) as required per good clinical practice (GCP)
- **Inspections limited in scope** to assess trial conduct and data integrity

Therapeutic landscape does not warrant regulatory flexibility.

Building equity through multiregional clinical trials

Outline

- ORIENT-11 Study Design and Results
- Regulatory Framework for Evaluation of Foreign Data
  - Code of Federal Regulations (CFR)
  - International Council of Harmonisation (ICH) Guidances E5 and E17
- Key Review Issues: Generalizability to U.S. Population
- Discussion and Voting Question for ODAC

Discussion

- Discuss the generalizability of ORIENT-11 to a U.S. population and U.S. medical practice.

- Discuss potential clinical trials (if any) which may address issues of applicability of ORIENT-11 to a U.S. population.

Voting Question

Should additional clinical trial(s) demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?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