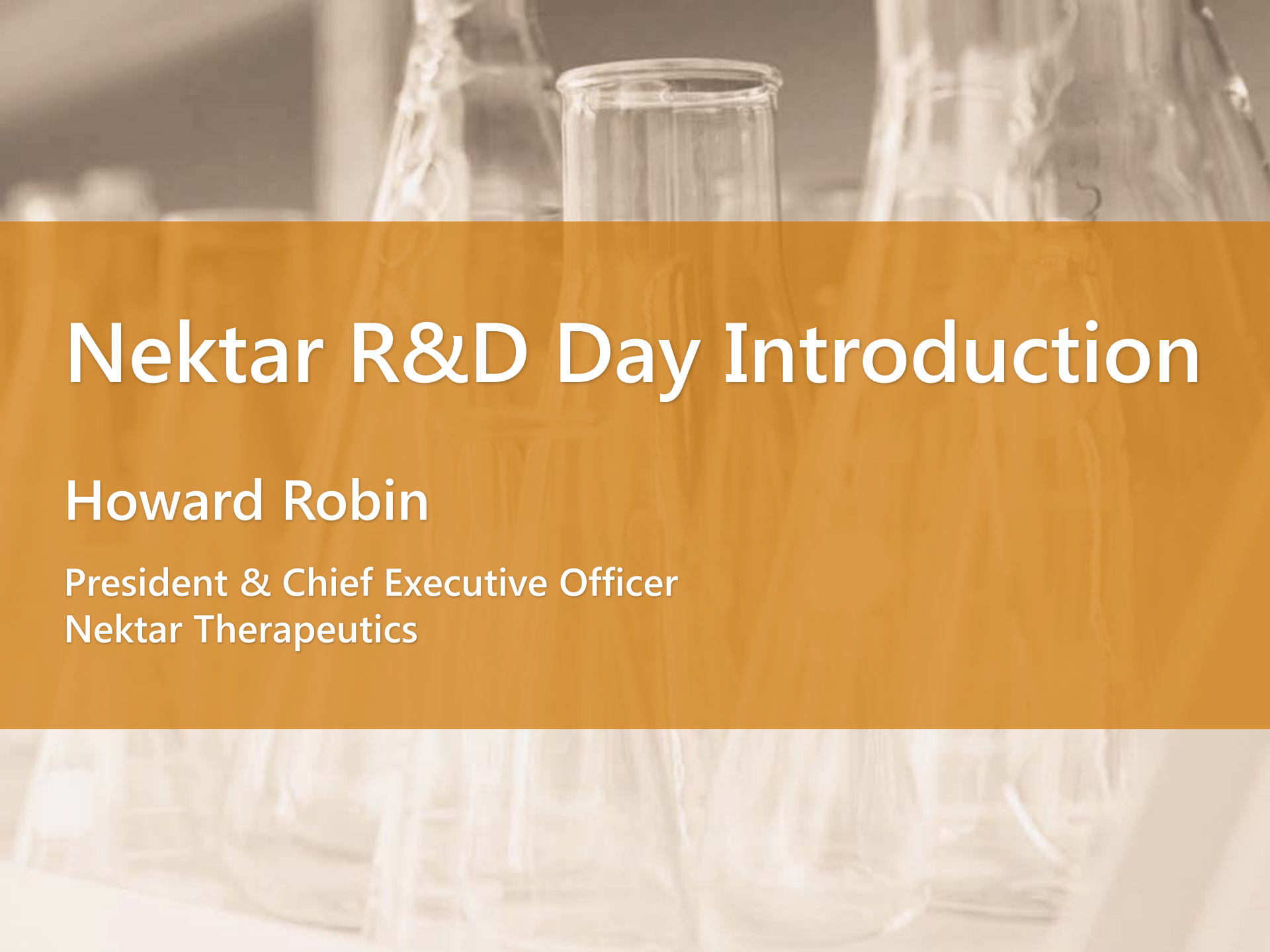
NEKTAR®

Products and Platforms for Growth

2015 Investor and Analyst R&D Day
St. Regis Hotel, New York City

October 8, 2015

This presentation includes forward-looking statements regarding Nektar's technology platform, drug candidates, clinical and regulatory objectives, market opportunity estimates, and royalty and milestone payment potential. Actual results could differ materially and these statements are subject to important risks detailed in Nektar's filings with the SEC, including the Form 10-K filed on February 26, 2015 and Form 10-Q filed on August 6, 2015. Nektar undertakes no obligation to update forward-looking statements as a result of new information or otherwise.



Nektar R&D Day Introduction

Howard Robin

President & Chief Executive Officer
Nektar Therapeutics

Nektar Therapeutics: Building a Sustainable Biopharma Company

Partnered Portfolio

Two Key Products Approved or Filed

AstraZeneca
Movantik™
Approved & launched

Baxter
Adynovate™
Filed (US)

Four Phase 3 Candidates

Bayer
Amikacin Inhale

Bayer
Cipro DPI

OPHTHOTECH
Fovista®

Halozyme THERAPEUTICS
PEGPH20

Could Generate >$750M/yr Royalty Income

Wholly-Owned Drug Candidates

Nine Clinical and Preclinical Drug Candidates

NKTR-181
Abuse-deterrent Opioid NCE

NKTR-102
Metastatic Breast Cancer

NKTR-171
Neuropathic Pain

NKTR-214
Cancer Immunotherapy

NKTR-195
Kappa Agonist

NKTR-255
IL-15 Cancer Immunotherapy

NKTR-218
IDO inhibitor

NKTR-173
Neuropathic Pain

NKTR-223
Peptide Antibiotic

Focus in Pain and Oncology

Today's Presenters - Nektar

Stephen Doberstein, Ph.D.

Senior Vice President, Research & Chief Scientific Officer

- Over 20 years of experience in biotechnology research and development
- Former head of research at Five Prime, XOMA, Xencor

Ivan Gergel, M.D.

Senior Vice President, Drug Development & Chief Medical Officer

- Over 25 years of pharmaceutical leadership and drug development experience
- Head of R&D at Endo and Forest, 10 years at SmithKline Beecham
- 14 NDAs resulting in drug approvals

Jonathan Zalevsky, Ph.D.

Vice President, Biology & Preclinical Development

- Over 15 years of drug development experience in immunology and cancer
- Former global head of immunology research at Takeda Pharmaceuticals

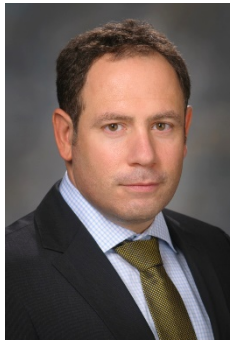
Today's Presenters

Martin Hale, M.D.
Medical Director
Gold Coast Research, LLC

Jack Henningfield, Ph.D.
Vice President, Research, Health Policy, & Abuse Liability
PinneyAssociates

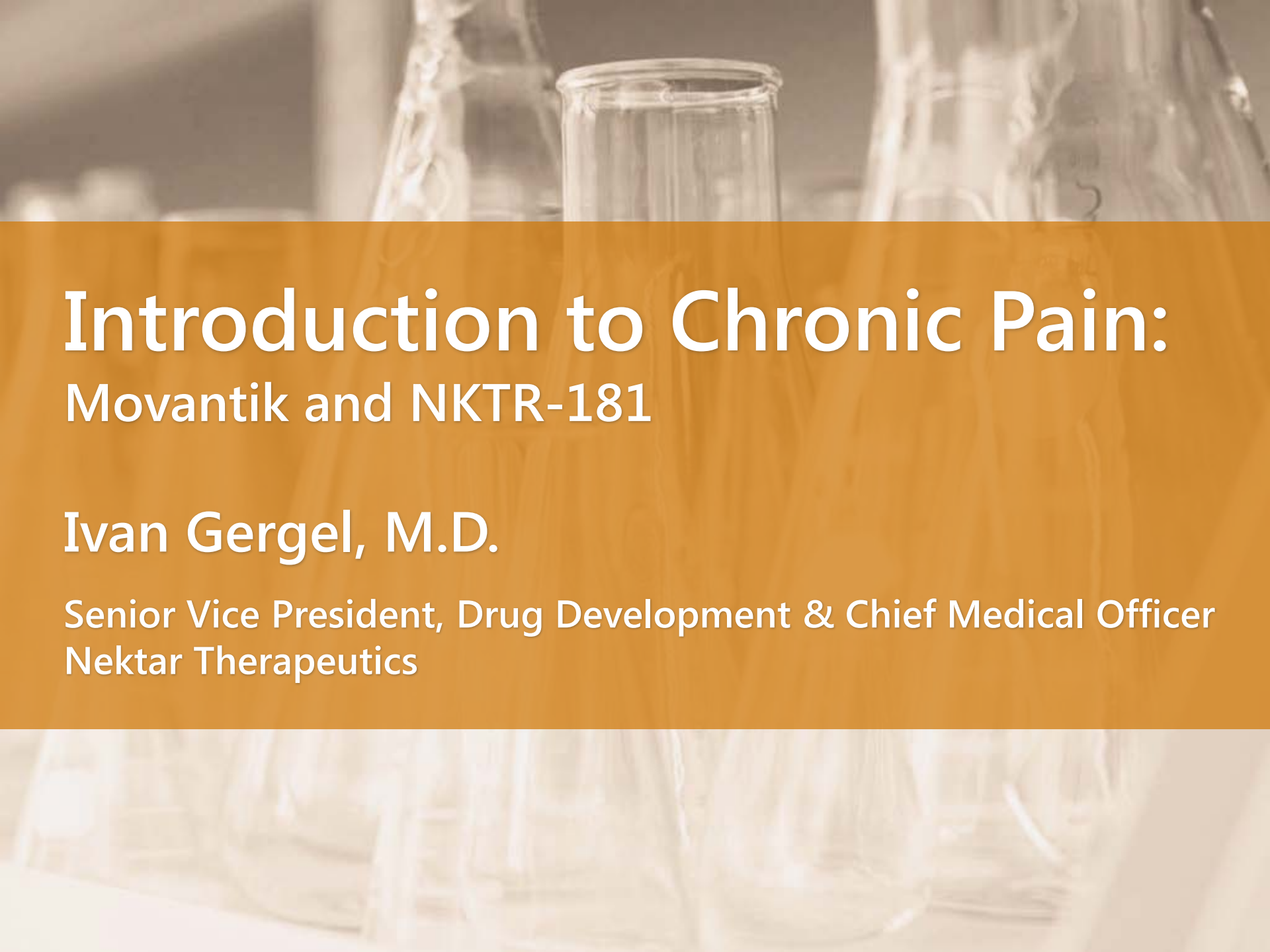
Today's Presenters

Michael Atkins, M.D.
Deputy Director of the Georgetown-Lombardi Comprehensive Cancer Center
Washington, DC
Professor of Oncology and Medicine (Hematology/Oncology)
Georgetown University School of Medicine



Adi Diab, M.D.
Assistant Professor, Department of Melanoma Medical Oncology,
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

Naiyer Rizvi, M.D.
Director of Thoracic Oncology and Director of Immunotherapeutics
Columbia University Medical Center



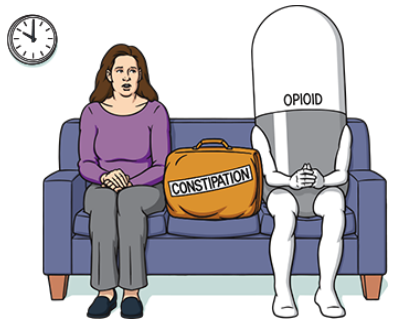
Introduction to Chronic Pain:
Movantik and NKTR-181

Ivan Gergel, M.D.

Senior Vice President, Drug Development & Chief Medical Officer
Nektar Therapeutics

U.S. Launch of Movantik™ (naloxegol) by AstraZeneca & Daiichi Sankyo

- First once-daily oral PAMORA tablet to treat opioid-induced constipation
  - 12.5 mg and 25 mg tablets priced at $8.32/day
- Significant sales efforts underway with positive physician reception
  - AstraZeneca and Daiichi Sankyo co-promoting in U.S. with AZ recording all revenues
  - 1000+ sales reps (primary care and specialty care)
- Product sampling began with launch
- Direct-to-consumer (DTC) campaigns designed to reach high number of OIC patients
  - First unbranded campaign began in May
  - Branded DTC advertising campaign began in August



"The doctor said you might come with baggage, but this is a bit much."

FOR ADULTS WITH CHRONIC NON-CANCER PAIN
WHEN OPIOIDS COME WITH
CONSTIPATION
ASK YOUR DOCTOR
ABOUT MOVANTIK

AstraZeneca

Daiichi-Sankyo

Significant Economics to Nektar on Global Sales of Movantik/Moventig

- **EU launch in Q3 2015**
  - Approval for treatment of adult patients with OIC who have had an inadequate response to laxative(s)
- **AstraZeneca responsible for all development, regulatory and commercial activities**
- **Economics to Nektar**
  - $100 million milestone for U.S. launch (received Q1)
  - $40 million milestone for first major EU country launch (received Q3)
  - U.S. tiered escalating royalty on net sales starting at 20%
  - EU and ROW tiered escalating royalty on net sales starting at 18%
  - Plus an additional $375 million in sales milestones at various annual sales levels

moventig®
naloxegol
www.moventig.com
AstraZeneca

Pain:
Expert Panel

Martin Hale, M.D.

Medical Director, Gold Coast Research, LLC

Assistant Professor of Surgery at Nova Southeastern University in Fort Lauderdale-Davie, Florida

Jack Henningfield, Ph.D.

VP, Research, Health Policy & Abuse Liability PinneyAssociates

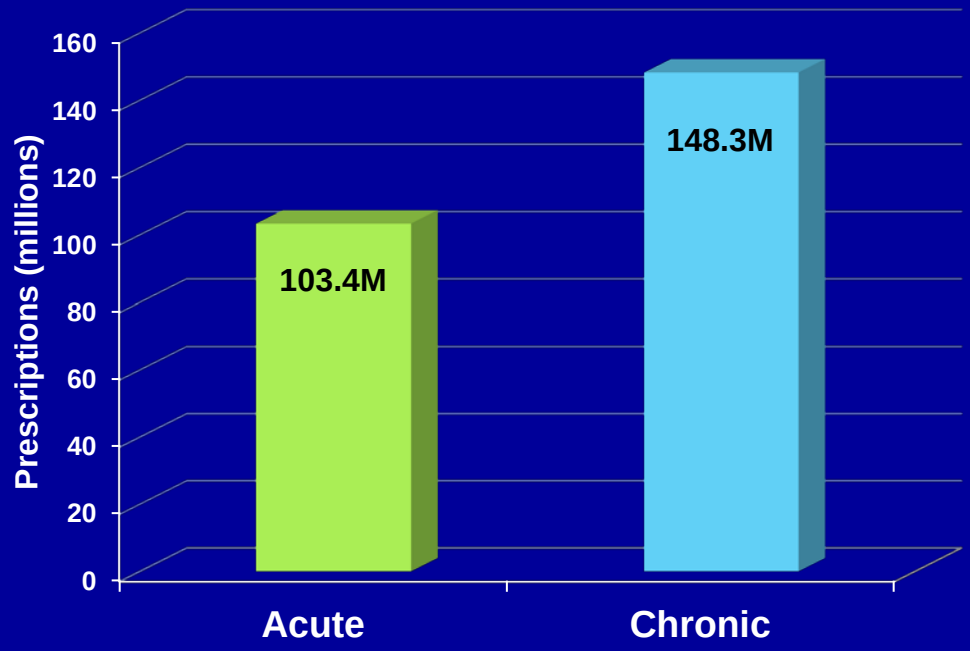
Opioid-Induced Constipation in Chronic Pain Patients

Martin Hale, MD
Gold Coast Research, LLC

38 Million Chronic, Non-Cancer Pain Patients on Opioid Regimens

- In the United States, more than 240 million opioid prescriptions are dispensed per year
- Chronic non-cancer pain conditions include:
  - Chronic back pain
  - Musculoskeletal ailments
  - Osteoarthritis
  - Fibromyalgia
  - Neuropathic pain

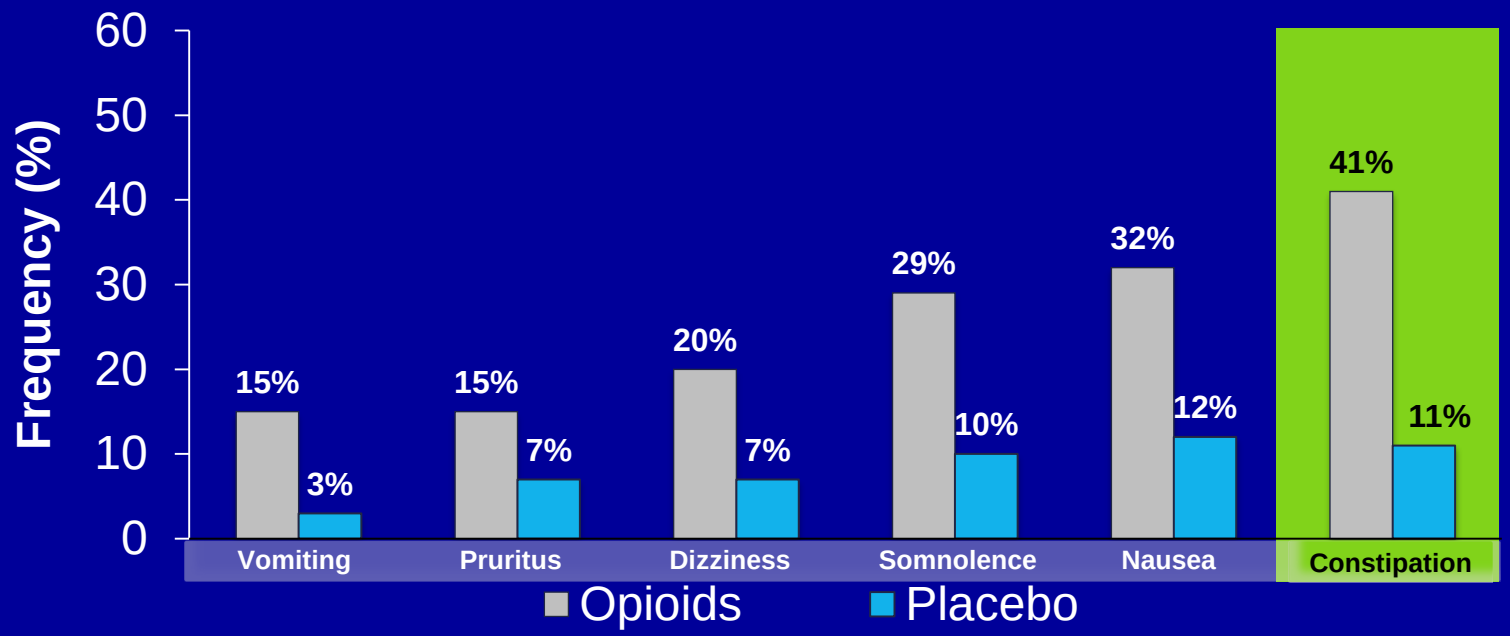
Total U.S. Opioid Prescriptions



Source: IMS LRx Database

Opioids Are Associated With Various Common Side Effects

In a meta-analysis that included randomized controlled trials of opioid therapy in patients with chronic non-cancer pain, OIC was identified as the most common side effect[1]:

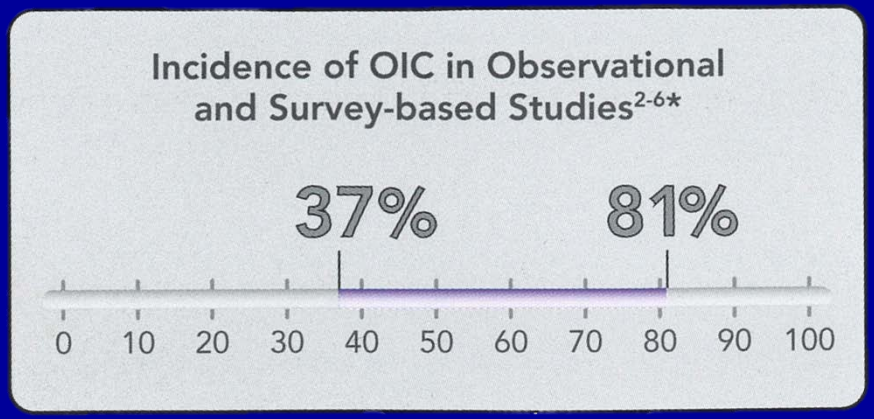


OIC can occur with initiation of opioid therapy and may persist for the duration of treatment[2,3]

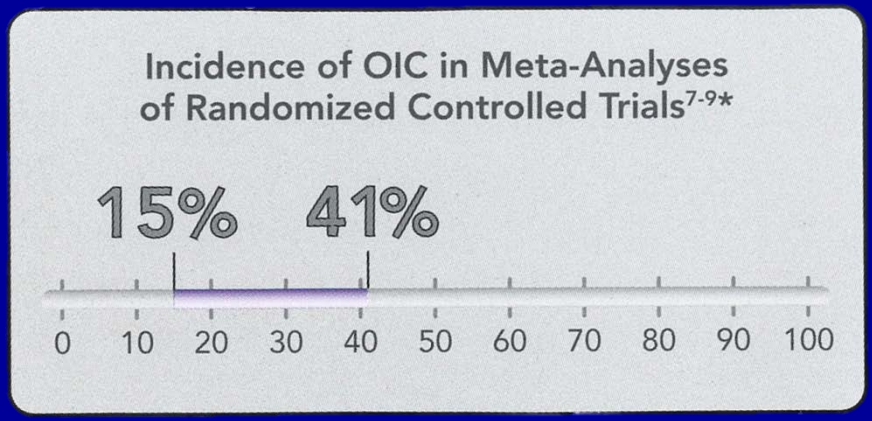
1. Kalso E et al. *Pain*. 2004;112:372-380.
2. Panchal SJ et al. *Int J Clin Pract*. 2007;61:1181-1187.
3. Becker G et al. *Lancet*. 2009;373:1198-1206.

Opioid-Induced Constipation is a Common Side Effect of Opioid Therapy

- The incidence of OIC varies and has been reported to be as high as 81%



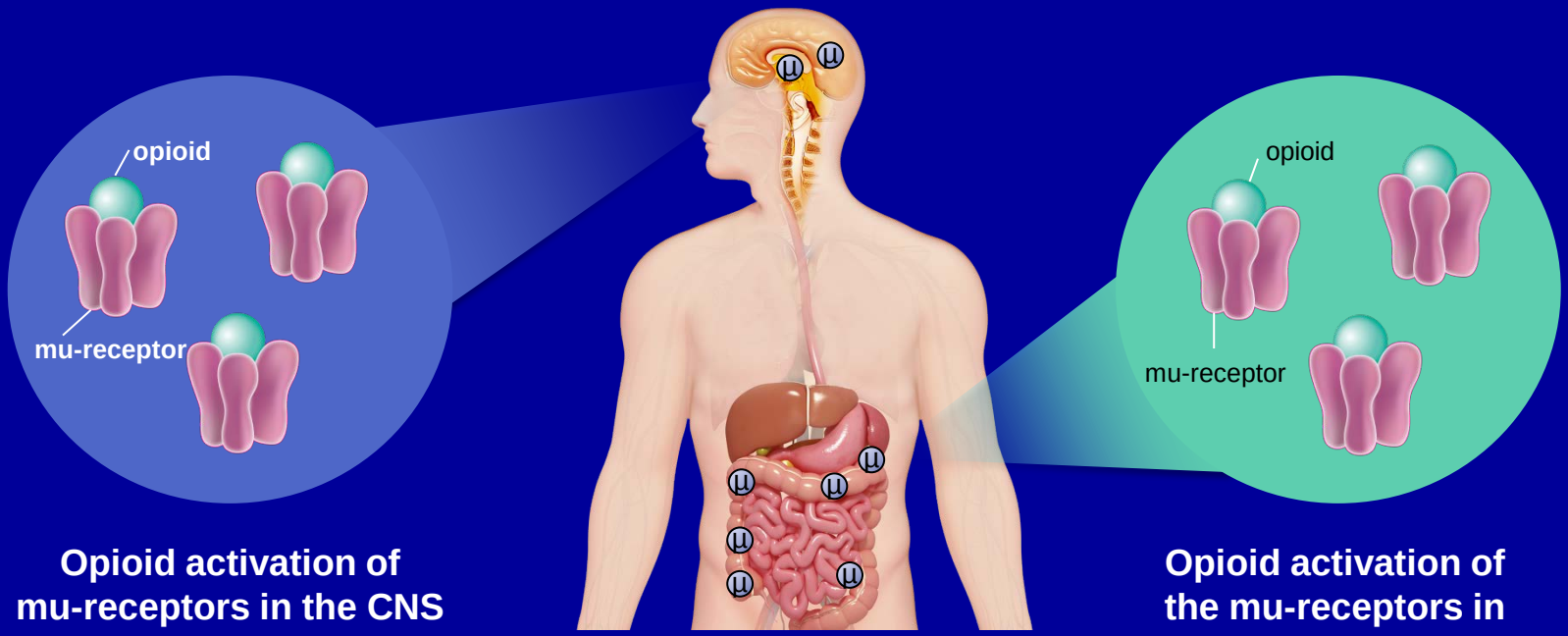
- Unlike some other opioid side effects, OIC usually persists throughout use



[2] Bell TJ, *Pain Med*. 2009;10(1):35-42; [3] Anastassopoulos KP, et al., *J Manage Care Pharm.* 2012;18(8):615-626; [4] Tuteja AK, et al., *Neurogastroenterol. Motil.* 2010;22(4):424-430, e-96; [5] Cook SF, et al., *Aliment Pharmacol Ther.* 2008;27(12):1224-1232; [6] Mahowald ML, *Arthritis Rheum.* 2005;52(1):312-321; [7] Kalso E, et al., *Pain* 2004;112(3):372-380; [8] Papaleontiou M, *J Am Geriatr Soc.* 2010;58(7):1353-1369; [9] Moore RA, et al., *Arthritis Res Ther.* 2005;7(5):R1046-R1051.

OIC is Caused by Activation of Mu-Opioid Receptors in the GI Tract

Mu-opioid receptors are widely distributed throughout the CNS (including the brain), PNS, the GI tract, and other tissues[1]



Opioid activation of mu-receptors in the CNS primarily mediates analgesia[2]

Opioid activation of the mu-receptors in the GI tract may lead to OIC[2]

CNS=central nervous system; GI=gastrointestinal; PNS=peripheral nervous system.

1. Camilleri M. *Am J Gastroenterol*. 2011;106:835-842.
2. Brock C et al. *Drugs*. 2012;72:1847-1865.

OIC Consists of 4 Primary Effects

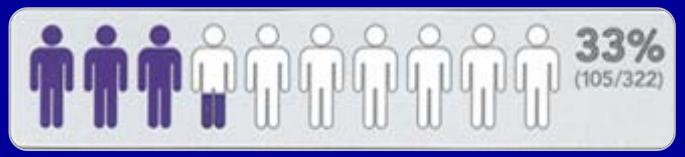
Activation of mu-receptors in the GI tract may lead to[1,2]:

Altered GI motility	• Disruption of peristalsis and GI spasm
Increased fluid absorption	• Increased passive absorption of fluids
Reduced intestinal secretions	• Overall decreased bowel secretions
Sphincter dysfunction	• Increased pyloric and anal sphincter tone

1. Brock C et al. *Drugs*. 2012;72:1847-1865.
2. Holzer P. *Am J Gastroenterol Suppl*. 2014;2:9-16.

OIC Burden to Patients

- In a survey of 322 patients taking daily opioids for chronic pain[1]:
  - One third of patients reported missing, decreasing or stopping opioids in order to make it easier to have a bowel movement



- In a survey of 2430 patients receiving opioid therapy for chronic pain, patients with OIC experience significantly[2]:
  - More frequent physician visits in the previous 6 months
  - More time missed from work
  - Greater overall work impairment
  - Greater activity impairment

[1] Bell TJ, *Pain Med.* 2009;10(1):35-42;
[2] Bell TJ, et al., *J Opioid Manag.* 2009;5(3):137-144

Patients May Be Reluctant to Discuss OIC With Their Health Care Provider

The baseline analysis of an ongoing multinational, longitudinal study of patients with chronic non-cancer pain and clinician-identified, patient-confirmed OIC found that of patients who saw their HCP in the past month, 37% did not discuss OIC.[1,2]

Why did you not talk to your doctor about your problems with constipation? n (%)	n=153
Discussed with doctor in past	90 (59%)
Concerned about need to change/reduce pain medication	20 (13%)
Embarrassed	14 (9%)
Constipation not a problem	7 (5%)
Ran out of time	7 (5%)
Other	15 (10%)

HCP=health care provider.

1. Coyne KS et al. *Clinicoecon Outcomes Res*. 2014;6:269-281.
2. Datto C et al. Poster 194. Presented at: American Academy of Pain Medicine Annual Meeting; March 6-9, 2014.

A Number of Common Approaches for Managing OIC

Some of the common methods of managing OIC include[1-3]:

- Lifestyle Modifications
  (eg, increase fluids, encourage mobility)

- Bulking Agents
- Stimulant Laxatives
- Stool Softeners
- Osmotic Laxatives

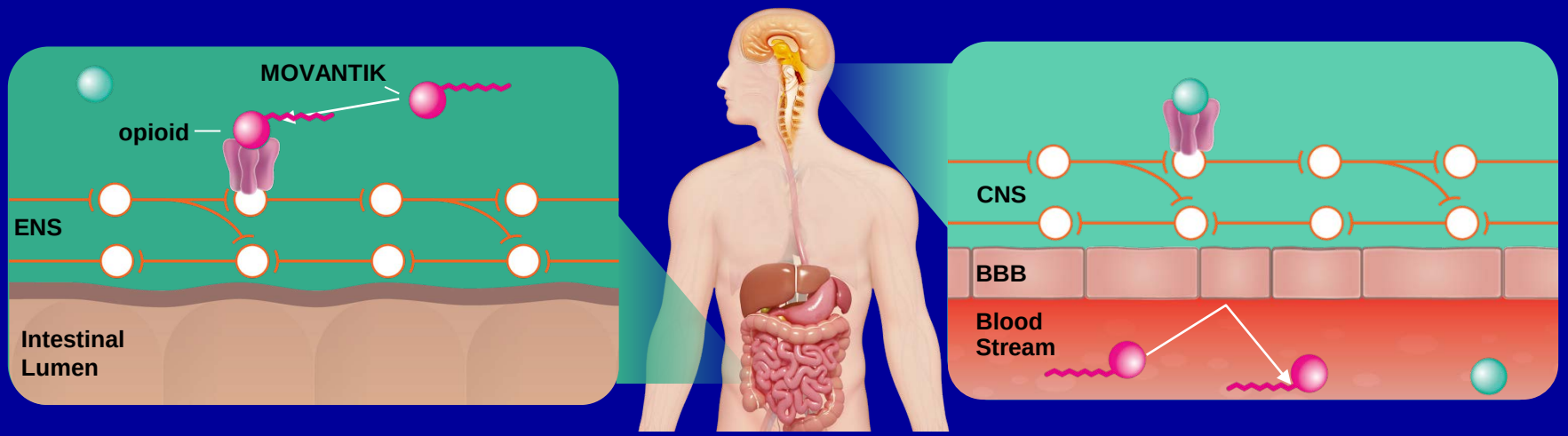
- Chloride Channel Activators
- Peripherally acting mu-opioid receptor antagonists (PAMORAs)

1. Brock C et al. *Drugs*. 2012;72:1847-1865.
2. Camilleri M et al. *Neurogastroenterol Motil*. 2014;26:1386-1395.
3. Dorn S et al. *Am J Gastorenterol Suppl*. 2014;2:31-37.

Clinical Pharmacology

Mechanism of Action[1-3]

When administered at the recommended dose levels, MOVANTIK functions as a PAMORA in tissues such as the GI tract, thereby decreasing the constipating effect of opioids, while limiting the potential for interference with centrally mediated opioid analgesia



MOVANTIK antagonizes opioid binding at the mu-receptor

The CNS penetration of MOVANTIK is expected to be negligible at the recommended dose levels

1. Prescribing Information for MOVANTIK. AstraZeneca Pharmaceuticals LP, Wilmington, DE.
2. Brock C et al. *Drugs*. 2012;72:1847-1865.
3. Poulsen JL. *Clin Exp Gastroenterol*. 2014;7:345-358.

Adverse Reactions
Clinical Trials Experience

Adverse reactions in KODIAC-04 and KODIAC-05, which occurred in ≥3% of patients receiving either MOVANTIK 12.5 mg or 25 mg, and at an incidence greater than placebo:

	Placebo (n=444)	MOVANTIK 12.5 mg (n=441)	MOVANTIK 25 mg (n=446)
Abdominal pain	7%	12%	21%
Diarrhea	5%	6%	9%
Nausea	5%	7%	8%
Flatulence	3%	3%	6%
Vomiting	4%	3%	5%
Headache	3%	4%	4%
Hyperhidrosis	<1%	<1%	3%

Summary

- OIC is one of the most common side effects associated with the use of opioids for the treatment of chronic non-cancer pain
- MOVANTIK is the only oral, once-daily PAMORA specifically designed for the treatment of OIC in adult patients with chronic non-cancer pain
- CNS penetration of MOVANTIK is expected to be negligible at the recommended dose levels, limiting the potential for interference with centrally mediated opioid analgesia
- In the KODIAC-04 and KODIAC-05 trials,
  - Response rates at 12 weeks were significantly higher with MOVANTIK 25 mg compared with placebo
  - The most common adverse reactions with MOVANTIK were abdominal pain, diarrhea, nausea, flatulence, vomiting, headache, and hyperhidrosis
- Results from two safety and tolerability trials (one 12-week extension study and a 52-week, open-label trial) were similar to the KODIAC-04 and KODIAC-05 trials

Adverse Reactions (cont'd)
Clinical Trials Experience

- **KODIAC-07 (N=302)** was a safety extension study that allowed patients from KODIAC-04 to continue the same blinded treatment for an additional 12 weeks

- **KODIAC-08 (N=844)** was a 52-week, multicenter, open-label, randomized, parallel group safety and tolerability study of MOVANTIK 25 mg vs usual care treatment* for OIC in patients with chronic non-cancer pain

Safety data for KODIAC-07 and KODIAC-08 were similar to that observed in KODIAC-04 and KODIAC-05

*Usual care treatment was determined by the investigator and excluded peripheral opioid antagonists.

Prescribing Information for MOVANTIK. AstraZeneca Pharmaceuticals LP, Wilmington, DE.

Additional Adverse Reactions
Symptoms Related to Possible Opioid Withdrawal

- In KODIAC-04 and KODIAC-05, possible opioid withdrawal was defined as at least 3 adverse reactions potentially related to opioid withdrawal that occurred on the same day and were not all related to the GI system
  - Symptoms included, but were not limited to: hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, yawning
- In KODIAC-04 and KODIAC-05, possible opioid withdrawal occurred in:
  - <1% (1/444) of placebo subjects
  - 1% (5/441) receiving MOVANTIK 12.5 mg
  - 3% (14/446) receiving MOVANTIK 25 mg

Prescribing Information for MOVANTIK. AstraZeneca Pharmaceuticals LP, Wilmington, DE.

Important Safety Information

- MOVANTIK is contraindicated in:
  - Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction due to the potential for GI perforation
  - Patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms
  - Patients with a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients
- Cases of GI perforation have been reported with the use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if this symptom develops

Important Safety Information (cont'd)

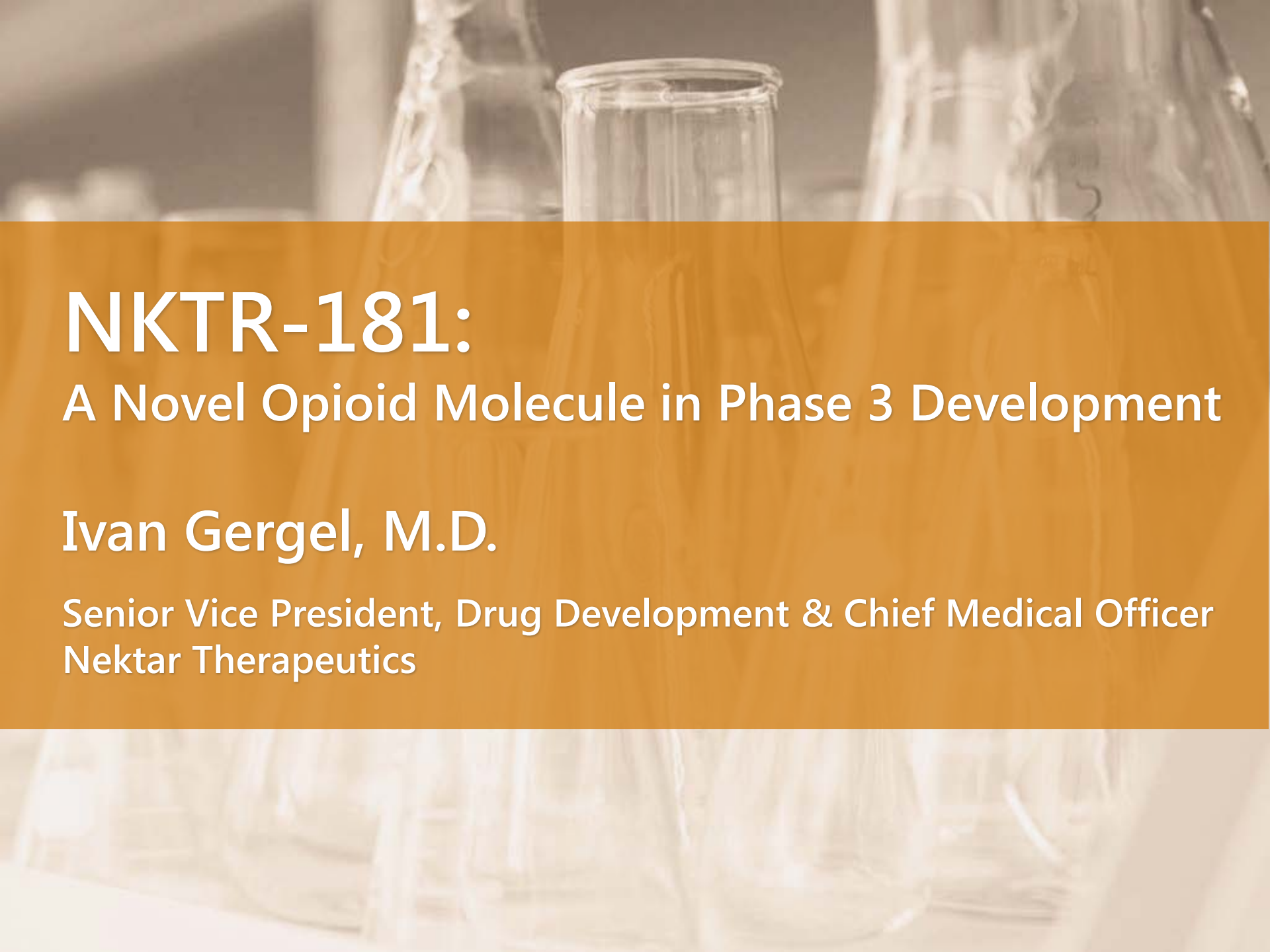
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning, occurred in patients treated with MOVANTIK. Patients receiving methadone in the clinical trials were observed to have a higher frequency of GI adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids. Patients with disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Monitor for symptoms of opioid withdrawal when using MOVANTIK in such patients

- The most common adverse reactions with MOVANTIK in clinical trials were abdominal pain (21%), diarrhea (9%), nausea (8%), flatulence (6%), vomiting (5%), headache (4%), and hyperhidrosis (3%)

Indication

MOVANTIK® (naloxegol) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

Please see full Prescribing Information available at this program.



NKTR-181:

A Novel Opioid Molecule in Phase 3 Development

Ivan Gergel, M.D.

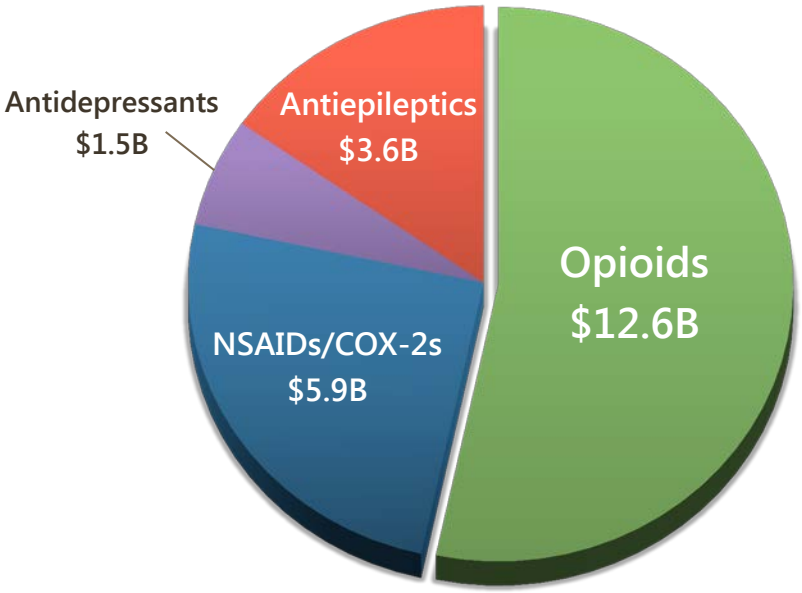
Senior Vice President, Drug Development & Chief Medical Officer
Nektar Therapeutics

NKTR-181: New Opioid Molecule for Chronic Pain in Phase 3

NKTR-181 designed to target chronic pain market with a novel opioid:

- Slow rate of entry into CNS designed to reduce abuse liability
- Plasma PK profile supports BID dosing
- Properties inherent to molecule
- Received Fast Track Status from FDA

Global Chronic Pain Therapy Market



Chronic pain market includes:

Chronic back pain
Osteoarthritis
Fibromyalgia
Neuropathic pain

Source: IMS MIDAS; Decision Resources

NKTR-181 Shows Improved Separation of Analgesia From Side Effects Compared With Oxycodone

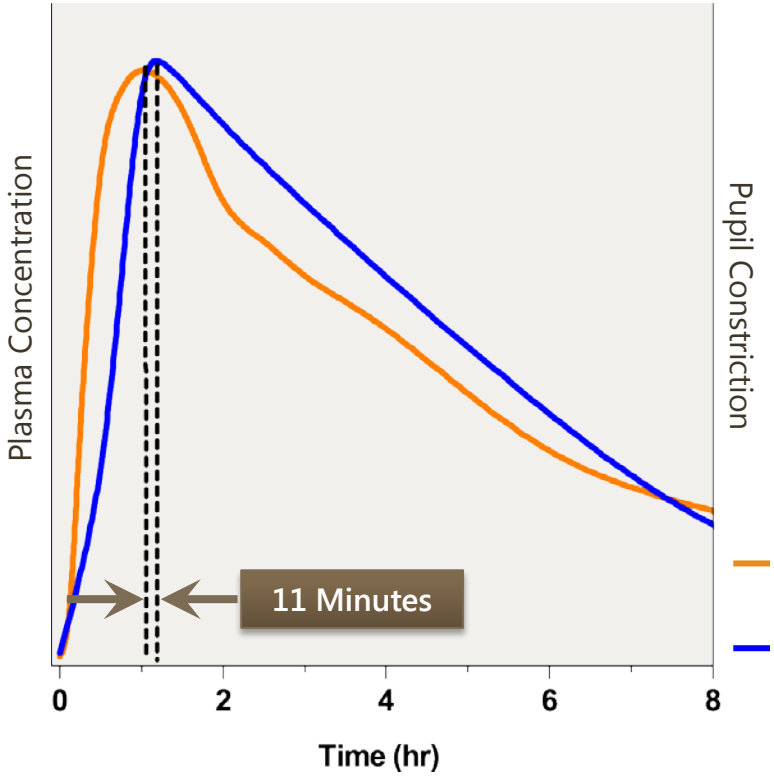
	ANALGESIA Acetic Acid Writhing (m)	ABUSE POTENTIAL Drug Discrimination (r)	RATIO Abuse Potential : Analgesia
	ED_{50} (µmol/kg)	Min AE Dose (µmol/kg)	
NKTR-181	14	790	**56**
Oxycodone	7.6	28.4	**4**
Ratio NKTR-181: Oxycodone	**1.8**	**28**	

	ANALGESIA Acetic Acid Writhing (m)	SEDATION Rotarod (r)	RATIO Sedation : Analgesia
	ED_{50} (µmol/kg)	ED_{50} (µmol/kg)	
NKTR-181	14	652	**47**
Oxycodone	7.6	94	**12**
Ratio NKTR-181: Oxycodone	**1.8**	**5.6**	

Human Studies Demonstrate That NKTR-181 Enters the Brain Slowly

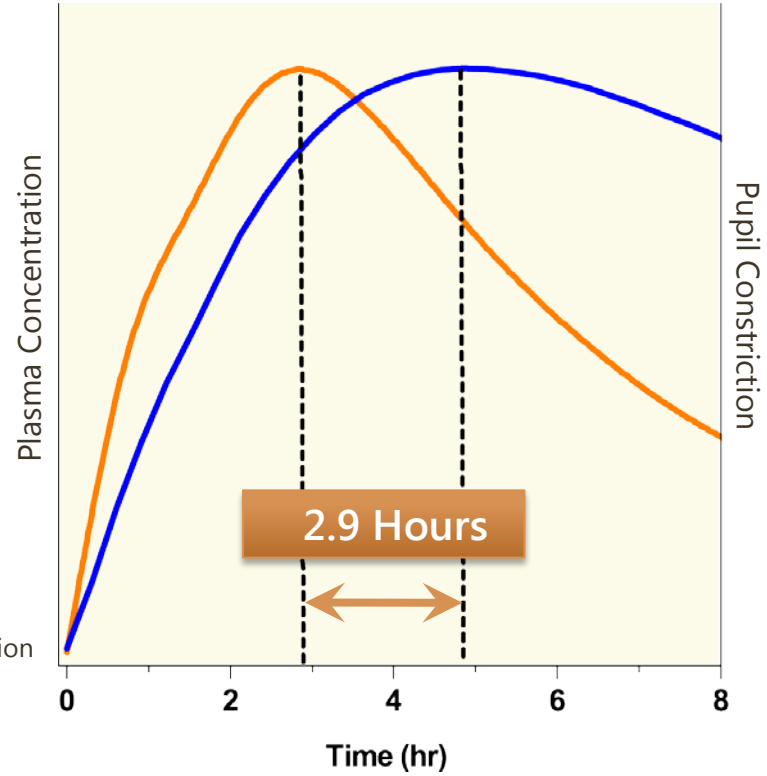
Oxycodone

Plasma to CNS Equilibration[1]



NKTR-181

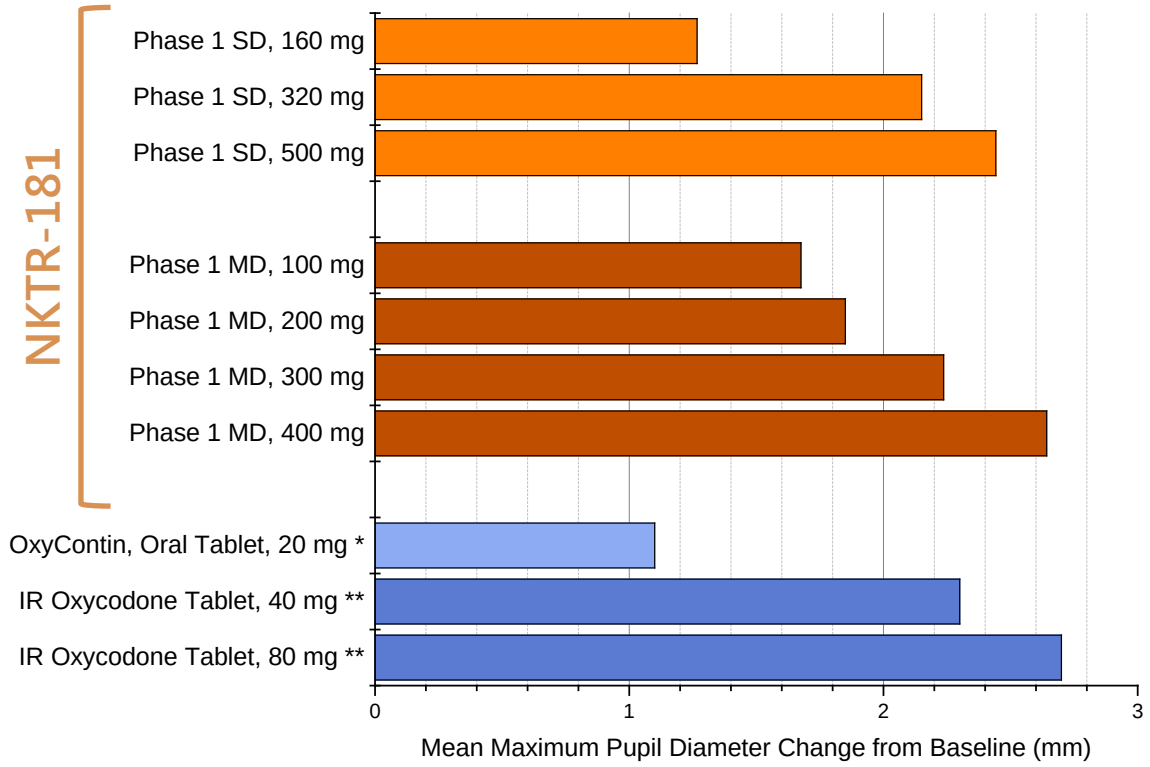
Plasma to CNS Equilibration[2]



Slow brain entry inherent to molecular structure, and not a result of a formulation approach

Source: 1) Kharash et. al, *Clinical Pharmacology and Therapeutics*, 2006 (Table IV - t1/2 eO, effect site equilibration half-life);
2) Nektar Therapeutics, Data from Phase 1 Multiple Ascending Dose Study of NKTR-181 (t1/2 eO, effect site equilibration half-life)

NKTR-181 Achieves Maximum Pupil Diameter Reduction Comparable to Oxycodone



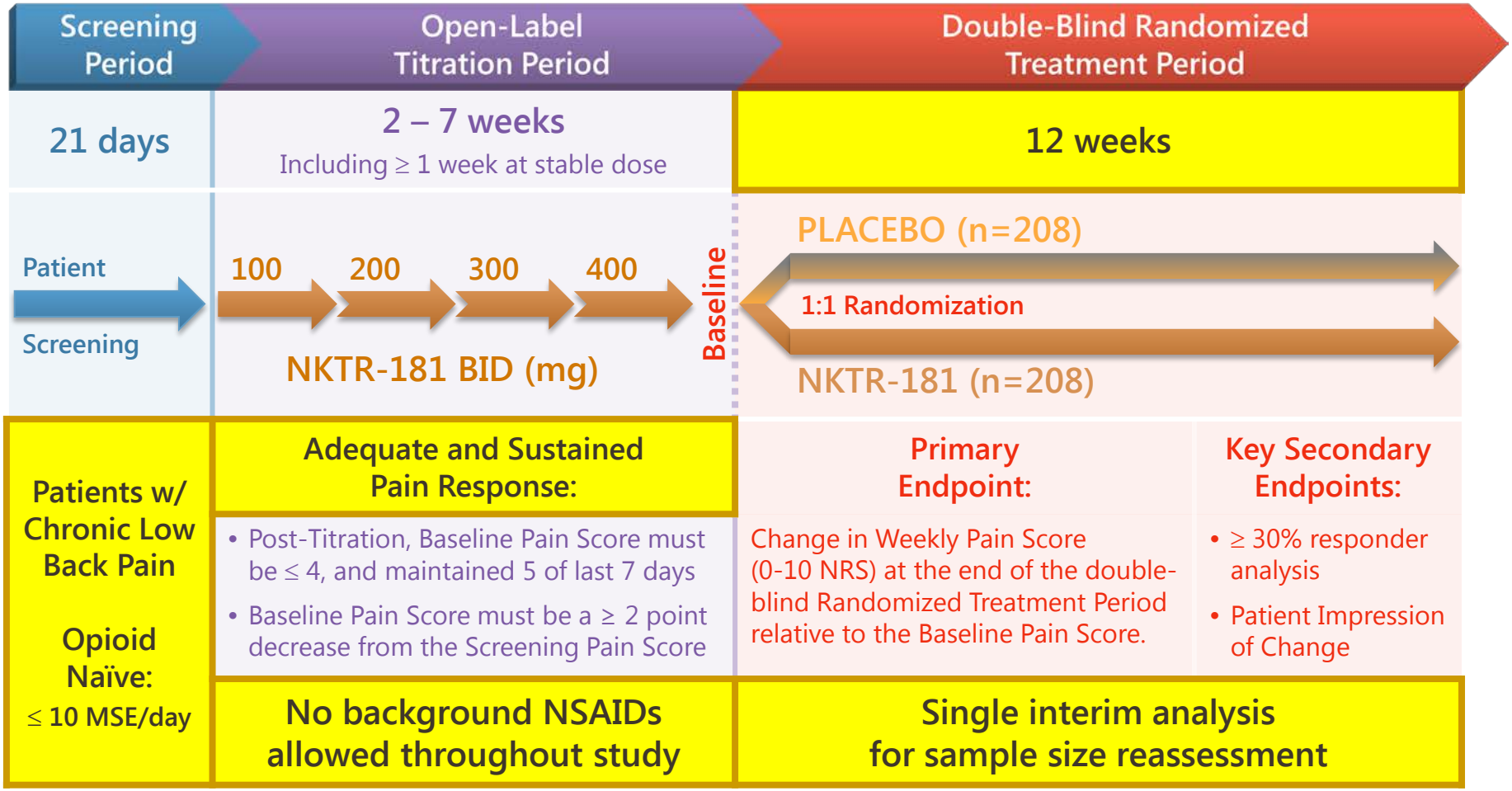
- Maximum CNS opioid responses are comparable to those reported for oxycodone
- Indicates that NKTR-181 can elicit substantial CNS opioid effect

* Benzinger et al, *J Pain Symptom Management,* (1997) 13;75
** Webster et al, Substance Abuse and Rehabilitation, (2012) 3;101

Clinical Results for NKTR-181 To-Date

- **Demonstrated slow rate of entry into the CNS as shown by pupillometry**
- **Magnitude of pupil constriction consistent with efficacious doses of long-acting opioids**
- **Results of Phase 2 EERW efficacy study**
  - Most patients in the study were on background NSAIDs
  - During randomized phase, no placebo rebound and study did not meet primary endpoint
  - In the subset analysis of the 25 patients that did not take background NSAIDs, a rebound was observed in placebo patients
- **Phase 3 EERW study is designed to overcome study design issues in Phase 2**

SUMMIT-07: First Phase 3 EERW Study in Patients with Chronic Lower Back Pain



NKTR-181: Phase 3 Registrational Program Underway

- First efficacy study underway in opioid-naïve patients with chronic low back pain (SUMMIT-07)
- Second efficacy study planned in opioid-experienced patients with chronic low back pain (SUMMIT-12)
- Long-term (52-week) safety study (SUMMIT-LTS) initiated
- Human abuse liability studies planned to support scheduling and labeling

FDA and Abuse-Deterrent Opioids:
The Regulatory Landscape and Scheduling Considerations

October 8, 2015

Jack E. Henningfield, Ph.D.
Vice President, Research & Health Policy

Pinney Associates

Objectives

- The regulatory landscape for new analgesics
- Opportunities for differentiated labeling
- Abuse-deterrent labeling for opioids
- Scheduling process and opportunities
- NKTR-181 as a fast-track new opioid entity
  - *Potential for less-restrictive scheduling*
  - *Potential for abuse-deterrent labeling*

FDA Priority: Incentivize Less-Abusable and Abuse-Deterrent Opioids

March 2015: FDA Commissioner Hamburg's final testimony to Congress highlighted FDA's efforts to "incentivize" less-abusable opioid analgesics:

"In 2014, FDA approved three new opioids with abuse-deterrent features to give physicians effective new treatment options with less risk of abuse."

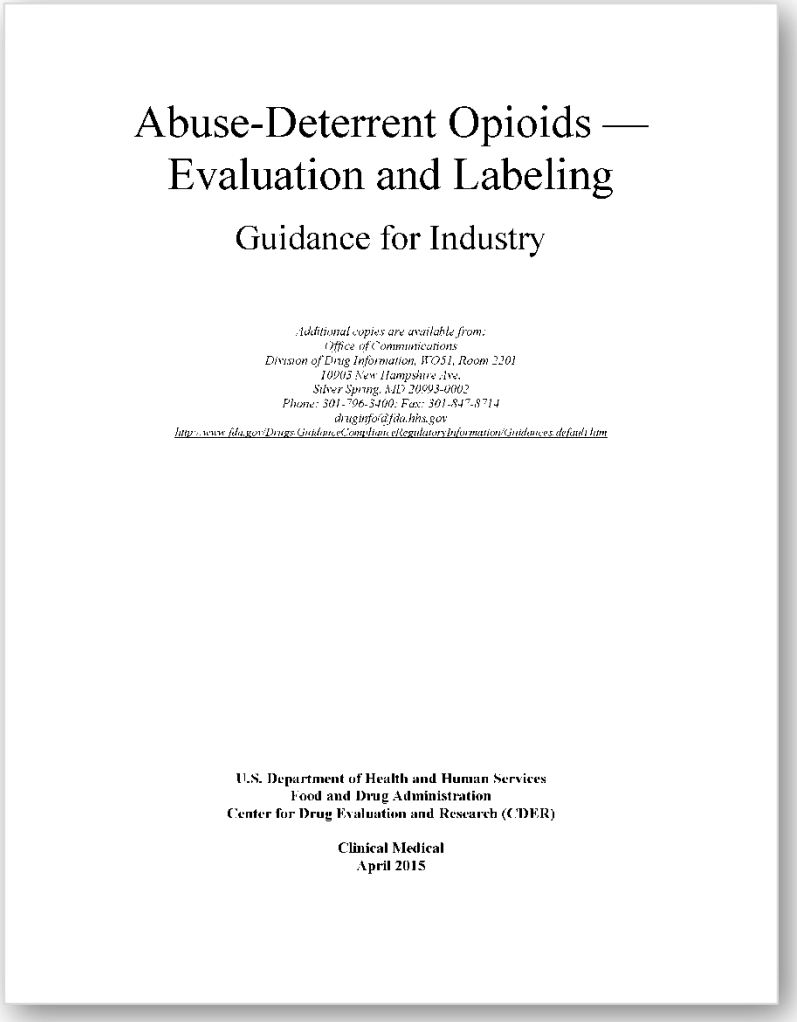
High-Risk Opioid Analgesic

- Schedule II (“CII”) of the Controlled Substances Act (CSA)
- Effective pain relief
- Highly addictive
- Substantial overdose risk
  - Examples: fentanyl, hydrocodone, morphine, methadone and oxycodone
- Readily tampered or used by off-label routes of administration so as to produce a faster delivery to the brain and stronger effects
  - Examples: injection, smoking, snorting, chewing or crushing to a powder before swallowing

NKTR-181 Goals: Compared to Prototypic CII Opioid Analgesics

- Scheduled less restrictively than CII
- Effective pain relief
- Lower addiction risk
- Lower overdose risk
- Deters tampering and conversion to routes of administration that produce faster and stronger effects than when used according to labeling

New 2015 Guidance: Path for NKTR-181 to Receive AD Labeling



Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Clinical Medical
April 2015

"New molecular entities and prodrugs– ***The properties of a new molecular entity (NME)*** *or prodrug could include the need for enzymatic activation, different receptor binding profiles,* ***slower penetration into the central nervous system, or other novel effects."***

Plus *an opening to lower scheduling:*

"New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA)."

Pre-Market Studies Required for Abuse-Deterrent Claims: NKTR-181 Status

Pre-market studies increasingly required regardless of whether AD claims are sought

FDA Study Category	Status of NKTR-181
Category 1: **Laboratory-Based *In Vitro* Manipulation & Extraction**	Findings are highly supportive of AD Claim
Category 2: **Pharmacokinetic**	Findings are highly supportive: Need to discuss with FDA if further study is needed
Category 3: **Human Abuse Potential (HAP)**	Exploratory study data highly supportive: Pivotal study planned

Abuse-Deterrent Testing: Category 1 New *In Vitro* Data ("Kitchen Chemistry")

Smoking *Negative*	Decomposition of API (NKTR-181) occurs
Enzymatic Hydrolysis *Negative*	NKTR-181 unchanged by enzyme library
Chemical Hydrolysis *Negative*	22 chemicals and 39 conditions tested. No morphinan derivatives generated, decomposition of API (NKTR-181) occurs

Comprehensive battery of *in vitro* studies show no formation of morphinan derivatives from NKTR-181

These data support approval and a potential abuse-deterrent claim

PK & HAP provide additional support

Examples of New Opioid Therapies with Abuse-Deterrent Labeling

All in CSA Schedule II (CII)

- Oxycontin
  - Oxycodone
- Targiniq ER
  - Oxycodone/Naloxone
- Embeda
  - Morphine Sulfate/Naltrexone Hydrochloride
- Hysingla ER
  - Hydrocodone Bitartrate

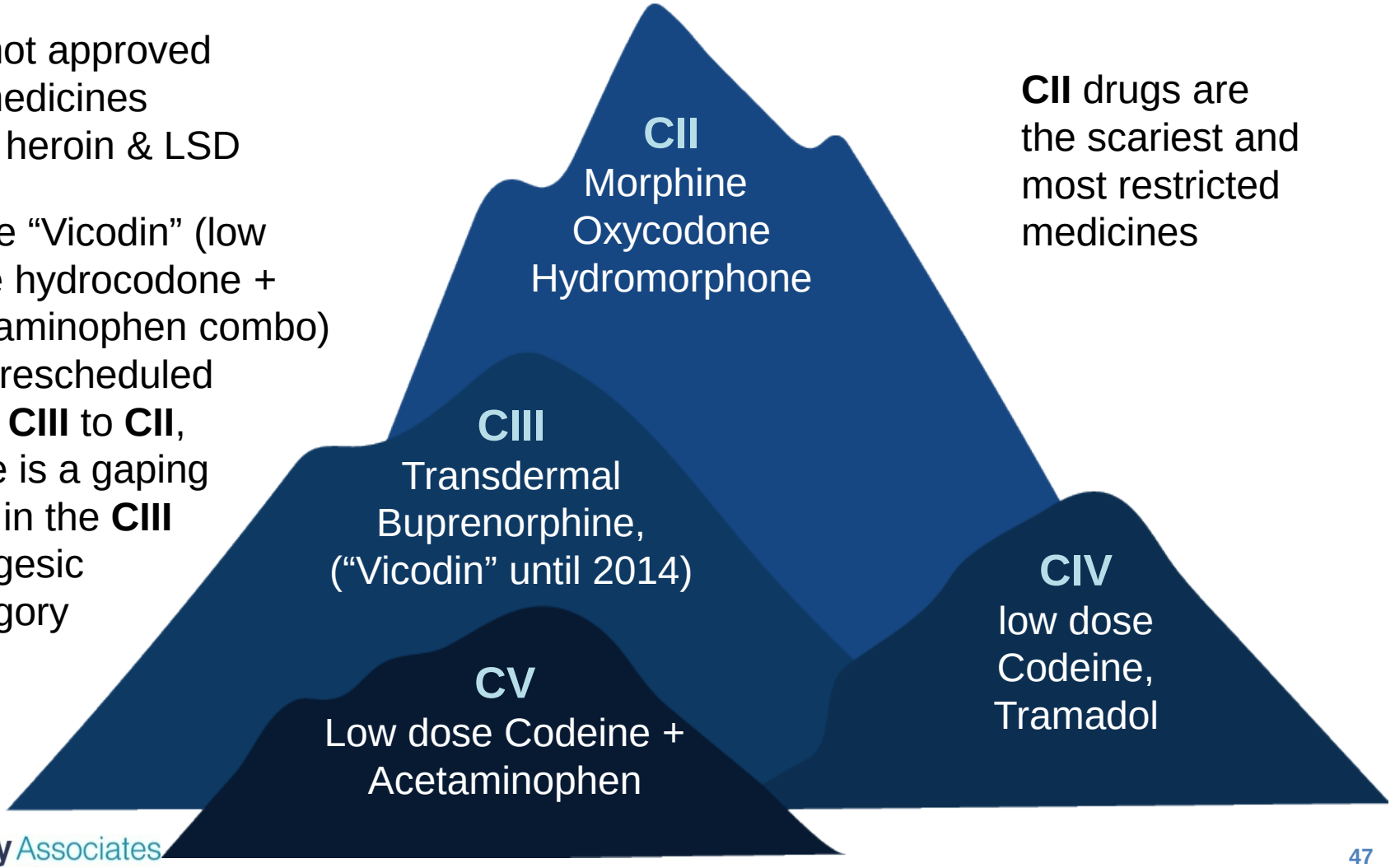
Recently Approved Therapies that Seem Candidates for AD Labeling

All in CSA Schedule II (CII)

- Opana ER (Oxymorphone HCl)
- Exalgo (Hydromorphone)
- Nucynta (Tapentadol)
- Oxecta/Oxaydo (Oxycodone HCl/Niacin)

Need for Effective Intermediately Scheduled Analgesic Medicines

- **CI:** not approved as medicines e.g., heroin & LSD
- Since “Vicodin” (low dose hydrocodone + acetaminophen combo) was rescheduled from **CIII** to **CII**, there is a gaping hole in the **CIII** analgesic category



CII drugs are the scariest and most restricted medicines

Understanding Scheduling: The 1970 Controlled Substances Act (CSA)

- FDA is the focal point for the sponsor's scheduling recommendation for Dept. Health & Human Services (DHHS)
- FDA (and NIDA) consider sponsor recommendation but base recommendation on FDA's 8 Factor analysis
- Assistant Secretary, DHHS makes recommendation to Dept. of Justice (DOJ) – typically 2-6 months after drug approval
- At DOJ, the Drug Enforcement Administration (DEA) places its recommendation for comment in the Federal Register
- Final Schedule placement by DEA/DOJ typically 6 months or more after receiving DHHS recommendation

Scheduling Process for New Opioids (including NKTR-181)

- The law (CSA) requires “administrative” placement in CII while in development
- Schedule changes can be initiated by DEA, FDA, sponsor or others, ideally with FDA concurrence upon approval of the New Drug Application (NDA)
- For NDAs, FDA develops recommendation for DEA
- DEA generally schedules according to FDA recommendation, e.g., Nektar’s naloxegol (MOVANTIK®) which was licensed to AstraZeneca, was descheduled from initial CII placement

Prescribing Barriers are Less Onerous for CIII Opioids as Compared to CIIs

Examples of Prescribing Requirements & Barriers

CII	CIII
Requires written prescription signed by practitioner	May be faxed
No refills	Up to 5 times in 6 months
Not transferrable between pharmacies	May transfer for 1 refill (if allowed by state law)
No electronic transfer for chains	May transfer up to max number of prescriptions
Rx expires 7 days after issuance	Rx expires 6 months after issuance

Scheduling Placement Based on Analysis of 8 Factors

1. Actual or relative potential for abuse
2. Scientific evidence of its pharmacological effect, if known
3. The state of current scientific knowledge regarding the drug or other substance
4. History and current pattern of abuse
5. Scope, duration and significance of abuse
6. Risk, if any, to the public health
7. Psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

Key Factors Opening Door to Less Restrictive Scheduling for NKTR-181

#1 “Actual abuse potential”
#2 “Pharmacology” and
#3 “Current knowledge”

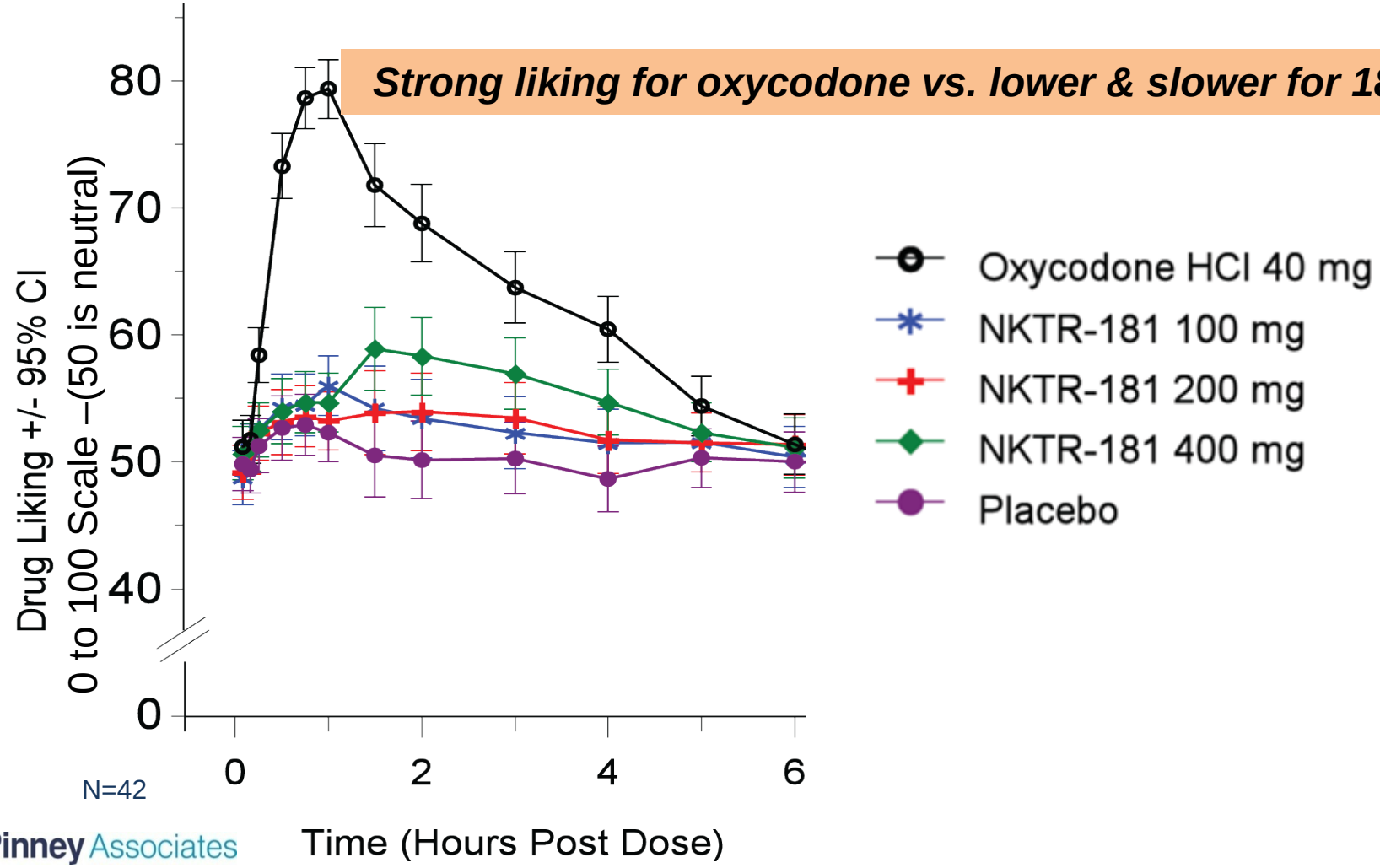
#8 Whether the substance is an approved and already scheduled drug or an immediate precursor of an already scheduled drug

These 3 factors provide the hard science supporting less restrictive scheduling AND abuse-deterrent labeling

NKTR-181 is a new chemical entity (NCE) that had never before been scheduled

It is therefore a candidate for rescheduling from its current legal CII status

NKTR-181: Primary Human Abuse Potential Finding: Drug Liking Profile



Exemplary Human Findings Supporting Scheduling Less Restrictive than CII

- Human Abuse Potential study findings are consistent with other findings:
  - Gradual onset physiological effects (over approximately 1-2 hours) as opposed to 10-20 minutes for oral oxycodone
  - Low reinforcing effects in animal drug self-administration compared to CII opioids
  - Low signs of physical dependence and withdrawal in chronically dosed human volunteers

NKTR-181: Potential Label Claims and Scheduling Differentiation

A unique candidate for both abuse-deterrent labeling and less restrictive scheduling than CII analgesics:

1. NKTR-181 is a new chemical entity
2. The molecule prevents rapid brain entry regardless of route of administration
3. The overall abuse potential is low compared to CII opioids
4. Will deter abuse by smoking, injecting, snorting & crushing

NKTR-181 has the potential to fill the need for an effective Schedule III (CIII) analgesic

Pain:
Expert Panel

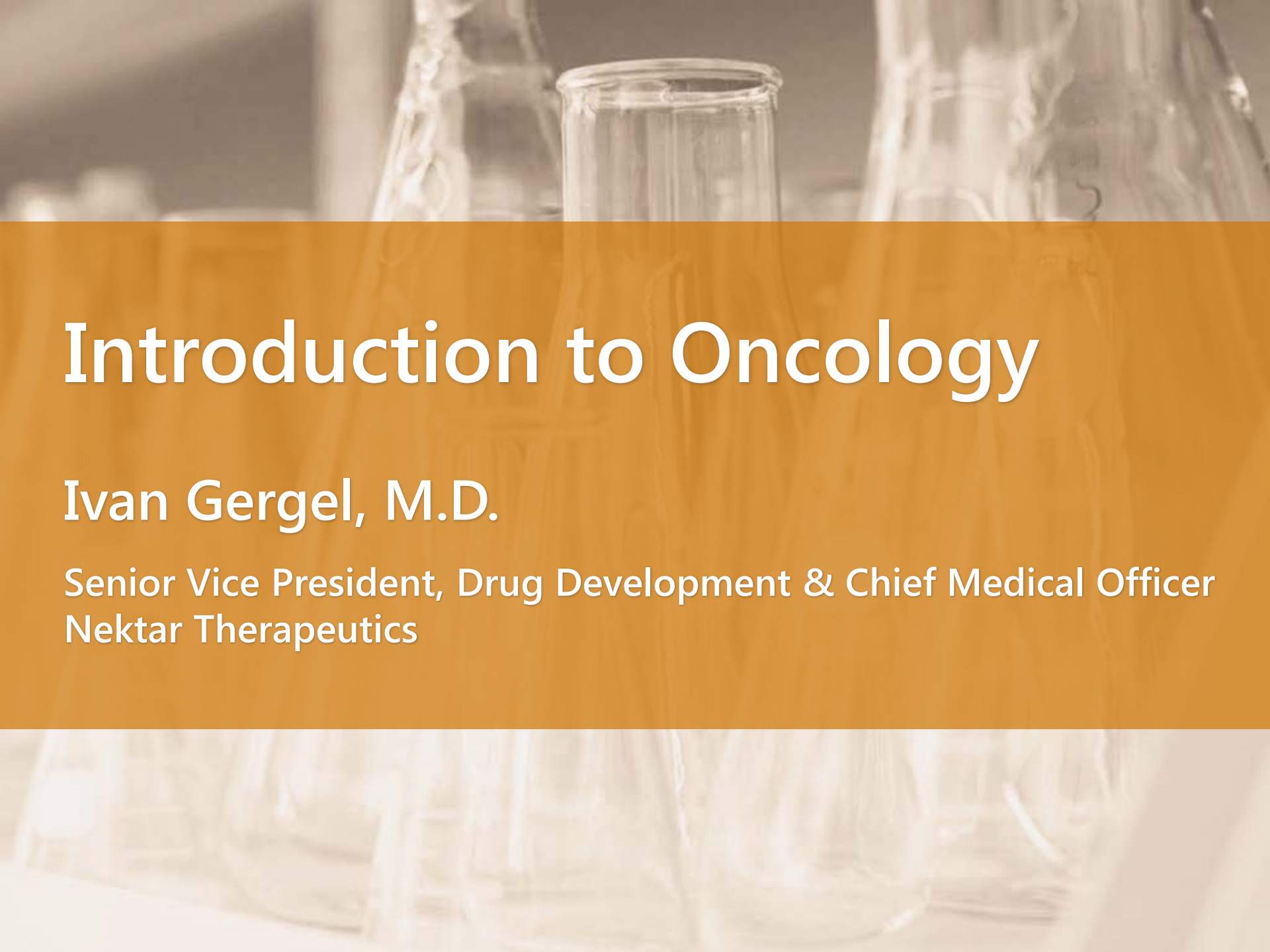
Martin Hale, M.D.

Medical Director, Gold Coast Research, LLC

Assistant Professor of Surgery at Nova Southeastern University in Fort Lauderdale-Davie, Florida

Jack Henningfield, Ph.D.

VP, Research, Health Policy & Abuse Liability PinneyAssociates



Introduction to Oncology

Ivan Gergel, M.D.

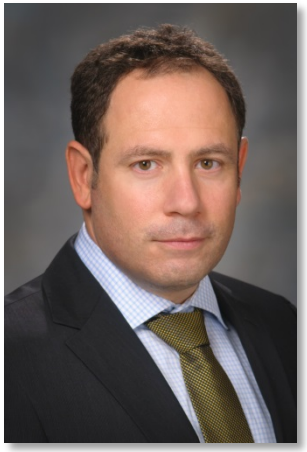
Senior Vice President, Drug Development & Chief Medical Officer
Nektar Therapeutics

Oncology:
Expert Panel

Michael Atkins, M.D.

Deputy Director of the Georgetown-Lombardi Comprehensive Cancer Center in Washington, DC and Professor of Oncology and Medicine

(Hematology/Oncology) at Georgetown University School of Medicine



Adi Diab, M.D.

Assistant Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Naiyer Rizvi, M.D.

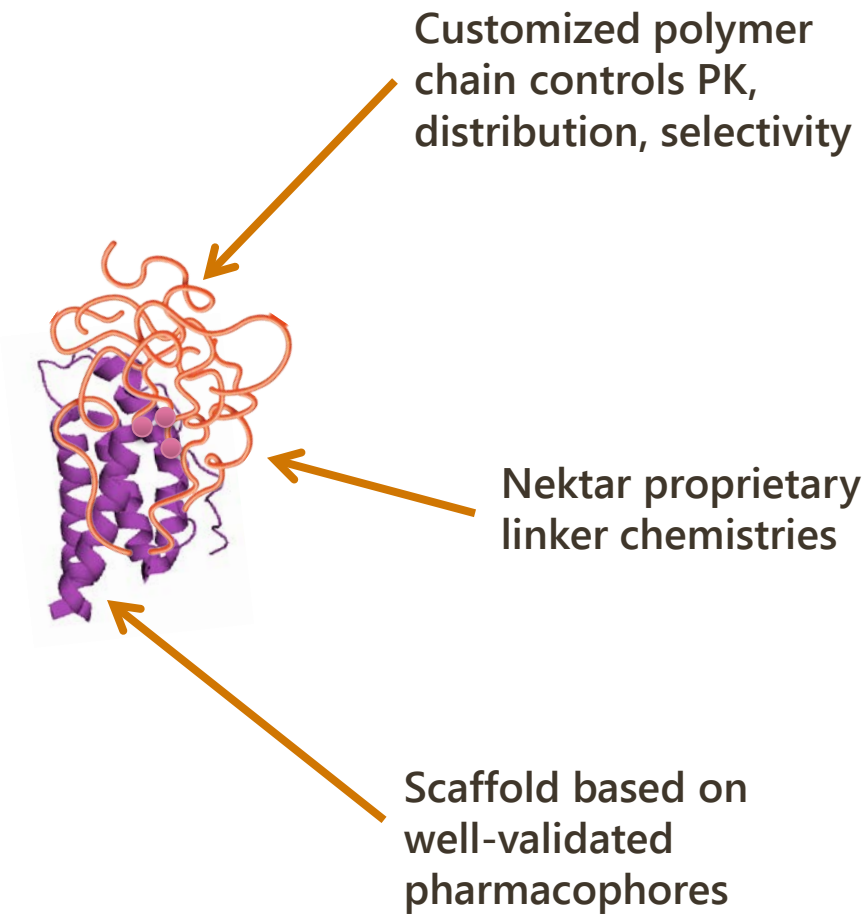
Director of Thoracic Oncology and Director of Immunotherapeutics, Columbia University Medical Center

Nektar in Immuno-Oncology:
Accessing Cytokines as New Medicines

Stephen Doberstein, Ph.D.

Senior Vice President, Research & Chief Scientific Officer
Nektar Therapeutics

Nektar's Innovative Technology Drives Our Drug Discovery



- Platform creates innovative NCEs based on well-understood biology
- NCE pipeline includes both small molecule and biologic drugs
- Technology capabilities expanded to unlock breakthrough biology
- Immuno-oncology (IO) and Pain are current focus areas in Research

Evolution of Nektar's Polymer Conjugation Technology

2001

2001

PegIntron (Peginterferon alfa-2b) — Schering-Plough

Hepatitis C

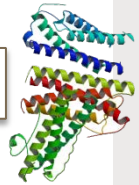
2002

Neulasta (pegfilgrastym) — AMGEN

Neutropenia

PEGASYS (Peginterferon alfa-2a) — Roche

Hepatitis C



2003

SOMAVERT (pegvisomant for injection) — Pfizer

Acromegaly

2004

MACUGEN (pegaptanib sodium injection) — Pfizer Ophthalmics

Wet macular degeneration

2007

MIRCERA — Roche

Chronic kidney disease anemia

2008

cimzia (certolizumab pegol) — UCB Pharma

Crohn's

Movantik: First Approved Small Molecule PEGylated Drug

2001

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PegIntron Peginterferon alfa-2b

Schering-Plough

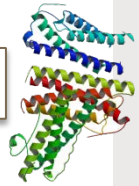
Hepatitis C

2002

Neulasta (pegfilgrastym)

AMGEN

Neutropenia



PEGASYS (Peginterferon alfa-2a)

Roche

Hepatitis C

2003

SOMAVERT (pegvisomant for injection)

Pfizer

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2004

MACUGEN PEGAPTANIB SODIUM INJECTION

Pfizer Ophthalmics

Wet macular degeneration

2007

MIRCERA

Roche

Chronic kidney disease anemia

2008

cimzia (certolizumab pegol)

ucb Pharma

Crohn's

2014

movantik naloxegol tablets

AstraZeneca

Opioid induced constipation

ADYNOVATE® Approval Anticipated in 2015

2001

PegIntron (Peginterferon alfa-2b)

Schering-Plough

Hepatitis C

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Neulasta® (pegfilgrastym)

AMGEN

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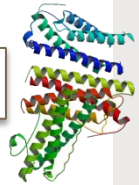
Roche

Hepatitis C



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MACUGEN® PEGAPTANIB SODIUM INJECTION

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Wet macular degeneration

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Roche

Chronic kidney disease anemia

2008

cimzia® (certolizumab pegol)

ucb Pharma

Crohn's

2014

movantik™ naloxegol tablets

AstraZeneca

Opioid induced constipation

Expected 2015

ADYNOVATE [Antihemophilic Factor (Recombinant), Pegylated]

Baxalta

Hemophilia A

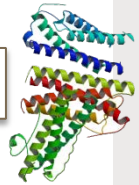
Evolution of Nektar's Polymer Conjugation Technology

R&D

2001
PegIntron (Peginterferon alfa-2b) — Schering-Plough
Hepatitis C

2002
Neulasta (pegfilgrastym) — AMGEN
Neutropenia

PEGASYS (Peginterferon alfa-2a) — Roche
Hepatitis C



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Chronic kidney disease anemia

2008
cimzia (certolizumab pegol) — ucb Pharma
Crohn's

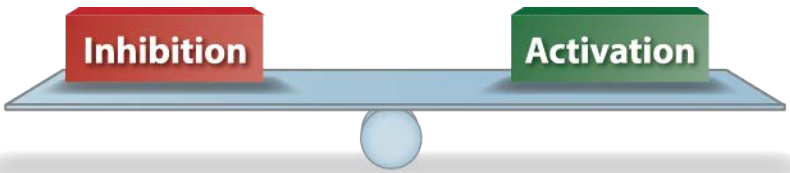
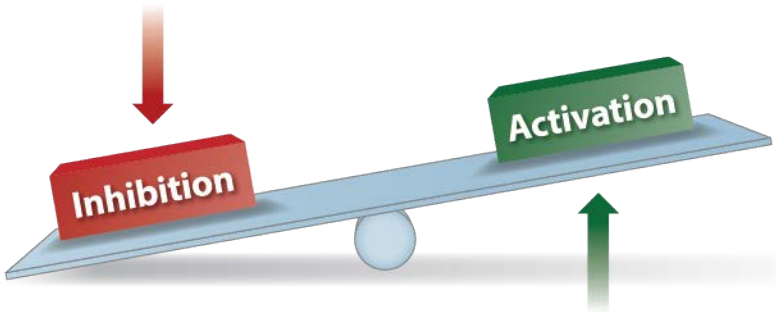
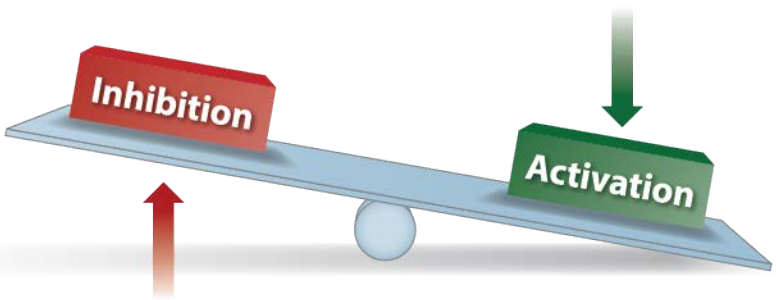
2014
movantik (naloxegol tablets) — AstraZeneca
Opioid induced constipation

Expected 2015
ADYNOVATE [Antihemophilic Factor (Recombinant), Pegylated] — Baxalta
Hemophilia A

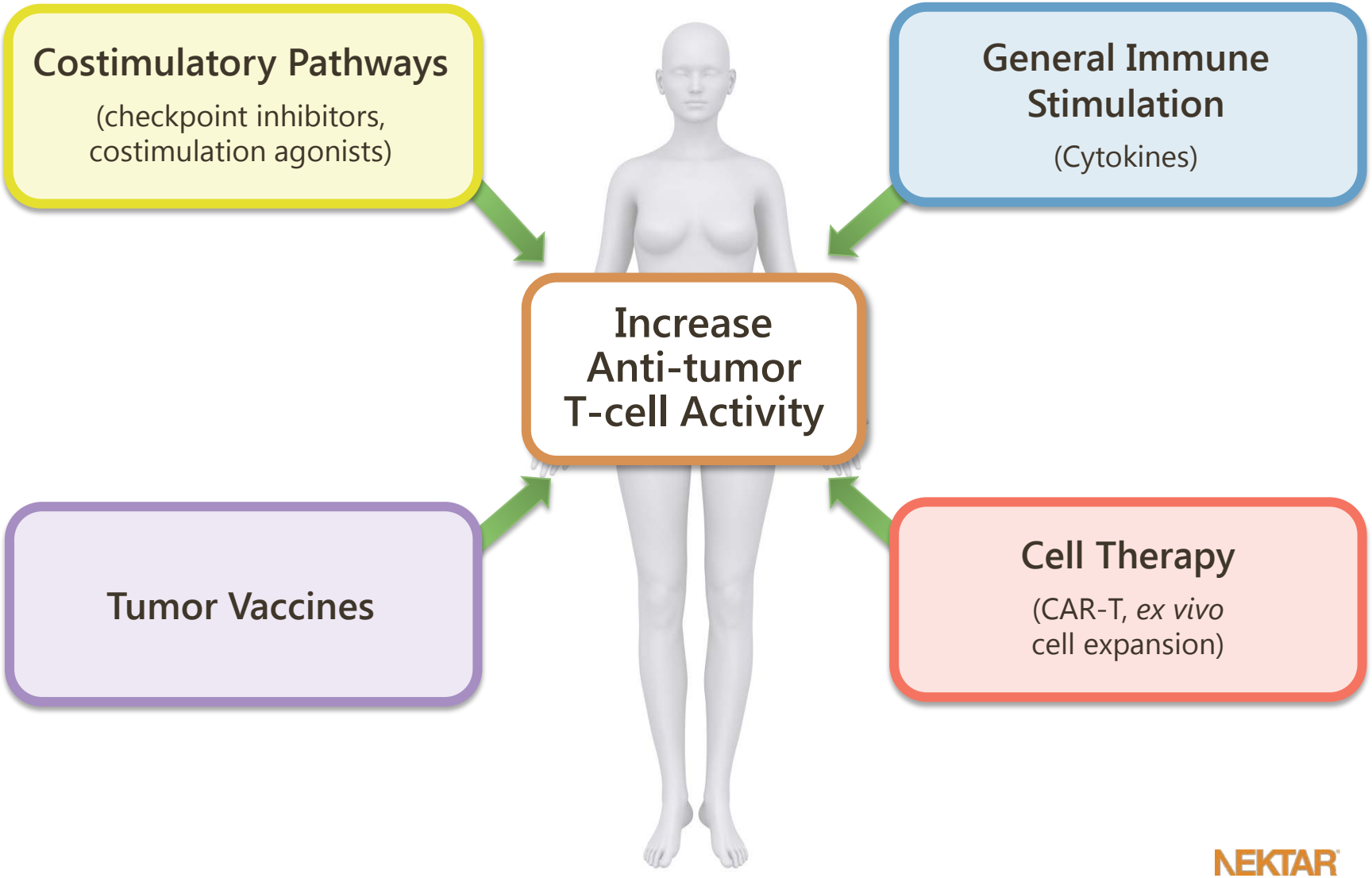
Small molecule
- NKTR-181
- NKTR-218

Biologics
- NKTR-214
- NKTR-255

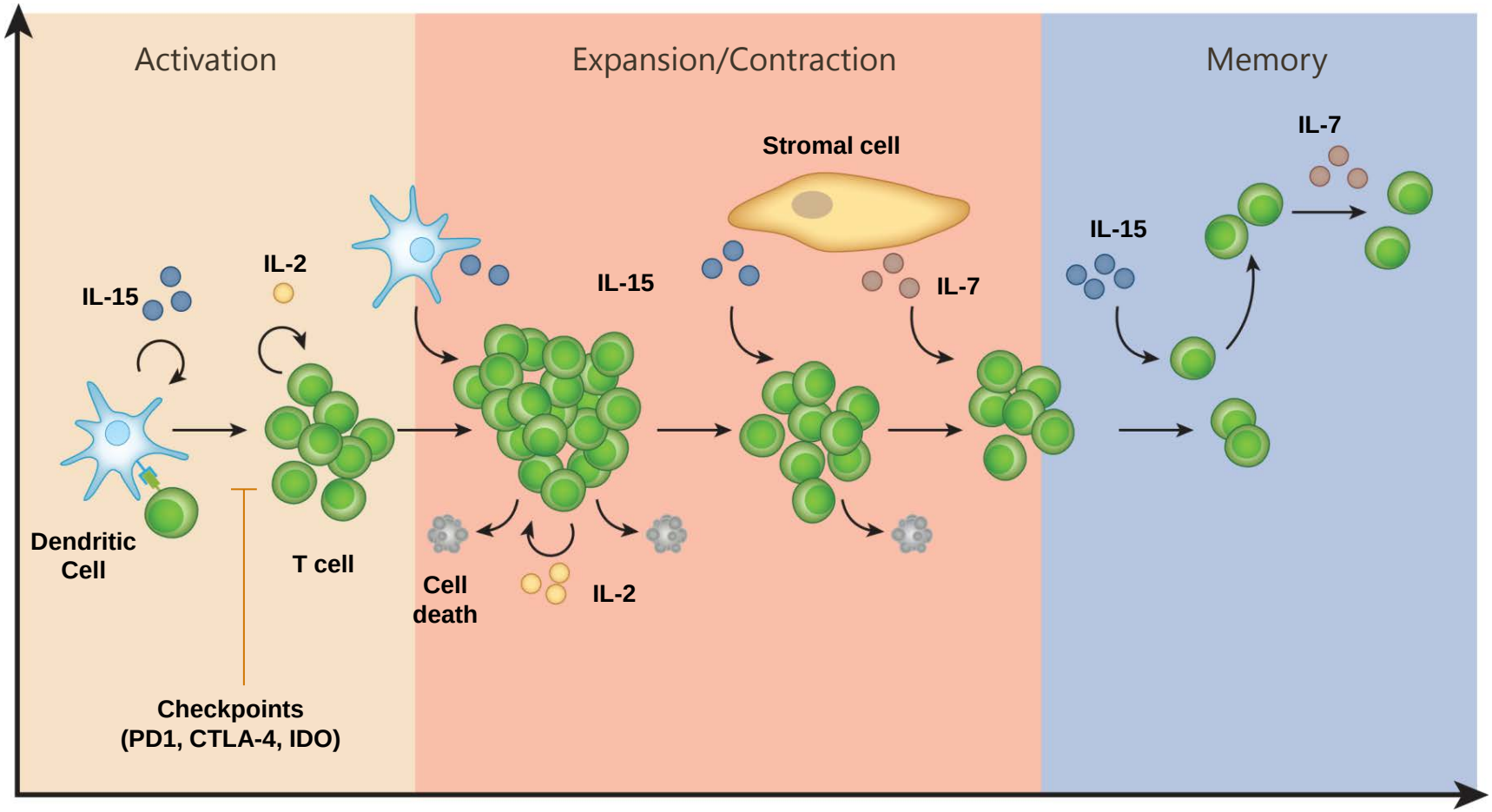
Loss of Immune Balance and Disease

Immune System	Health Outcome
	Healthy
	Inhibition of immune system promotes tumor escape
	Systemic activation of immune system promotes autoimmunity

The Four Major Classes of Immunotherapy Drugs All Increase T-Cell Activity



Cytokines Control T-Cell Growth and Survival



Differentiated Strategy in IO: Accessing Cytokines as New Medicines

Cytokines are the master regulators of growth and activity of the immune system

HOWEVER

Most native cytokines make suboptimal drugs

Nektar technology is well-suited to give cytokines drug-like properties

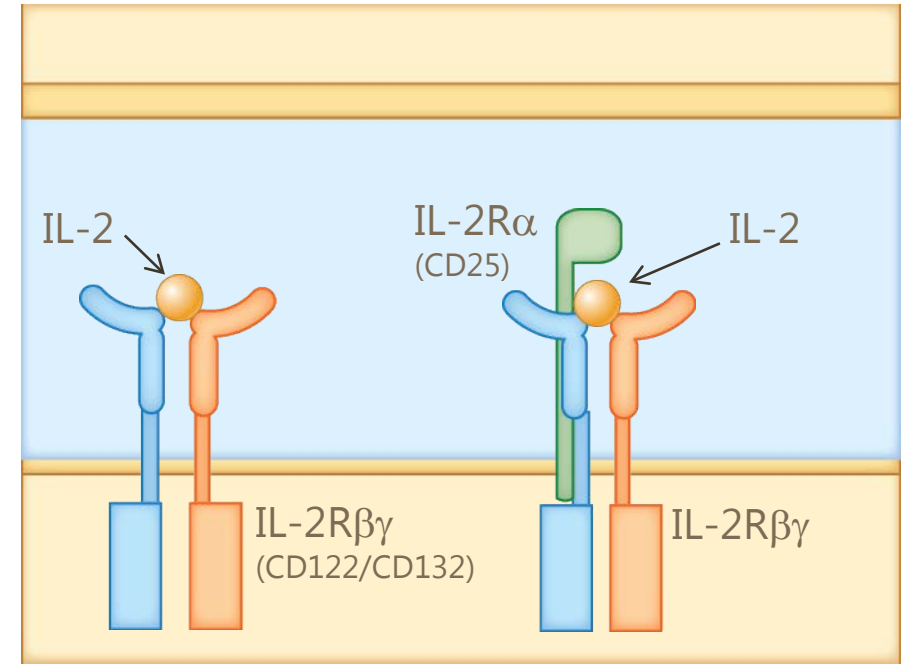
→

Advances in our technology allow us to access new cytokine biology

→

These mechanisms represent opportunities for differentiated drugs in IO

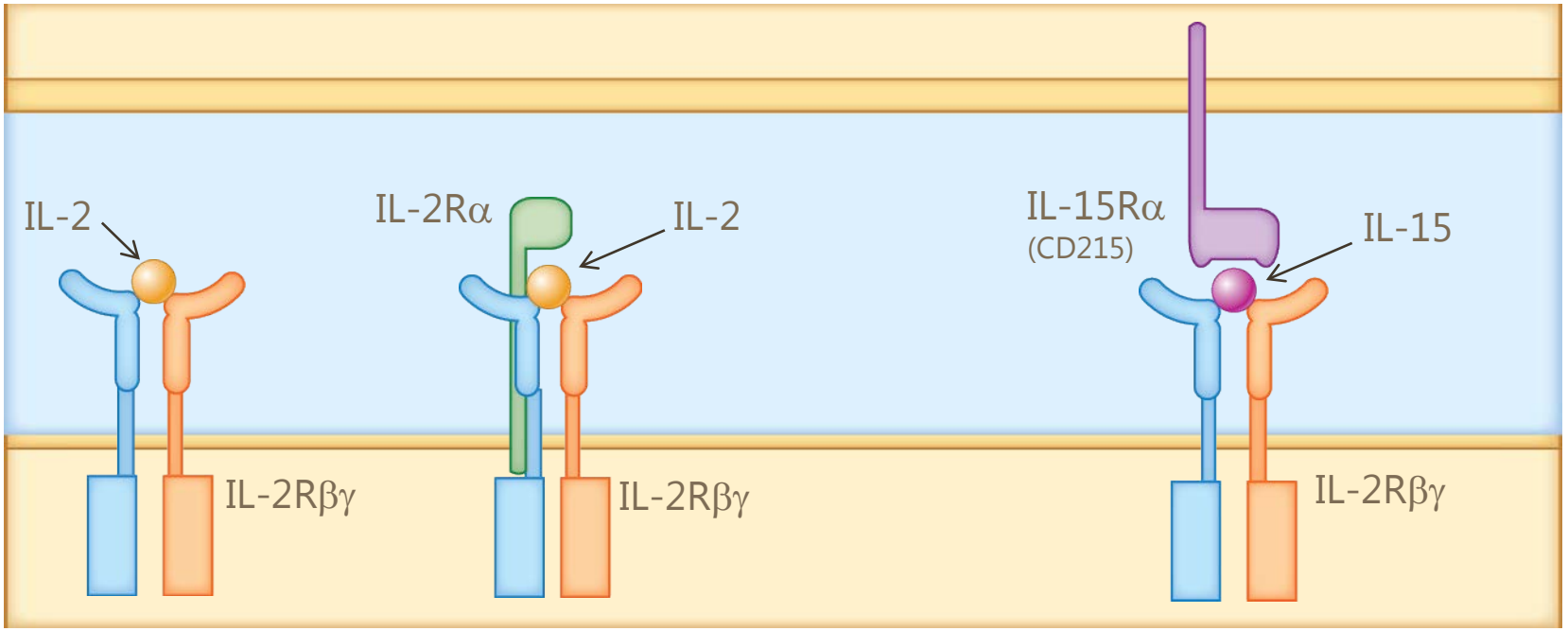
Cytokine Signaling Is Context-Dependent



CD8+ effector T-cell expansion

Regulatory T-cell expansion

Cytokine Signaling Is Context-Dependent

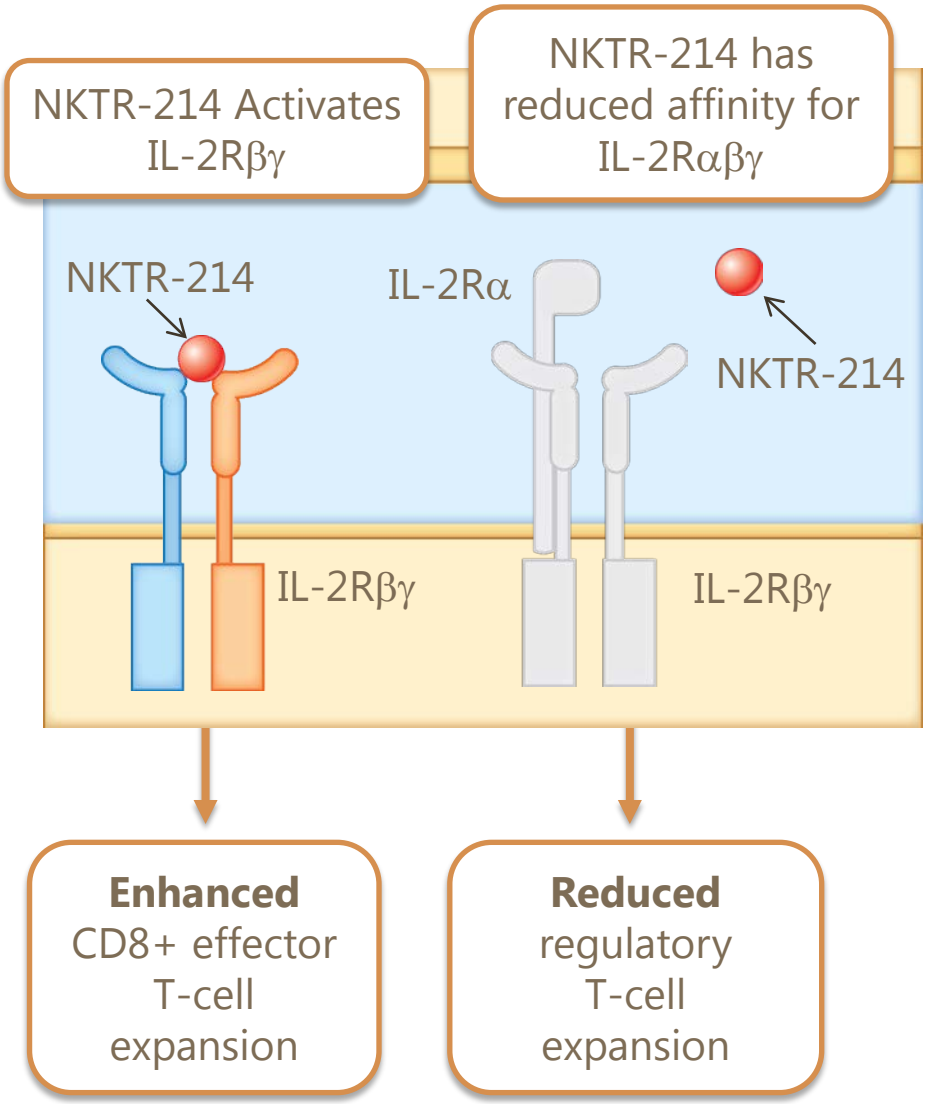


CD8+ effector T-cell expansion

Regulatory T-cell expansion

Memory T-cell maintenance

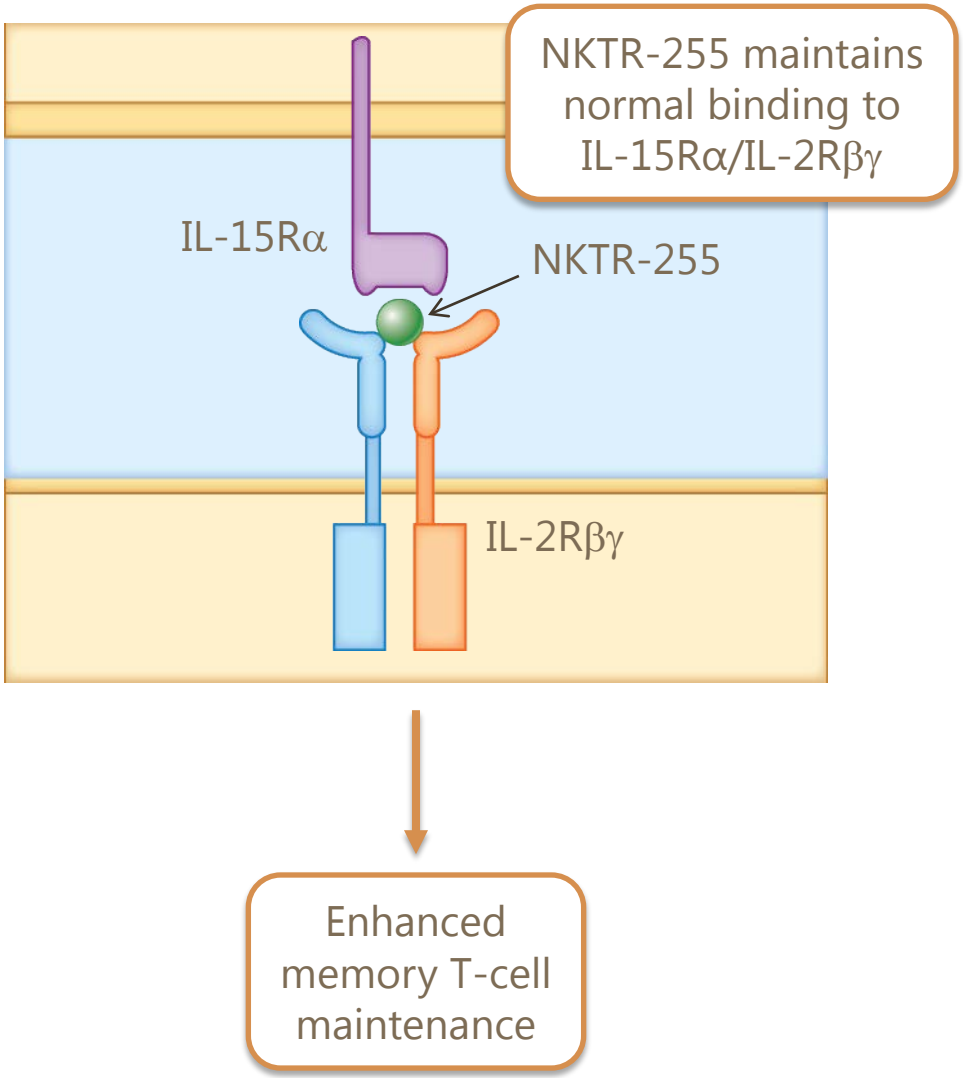
NKTR-214: Biased IL-2 Receptor Agonist



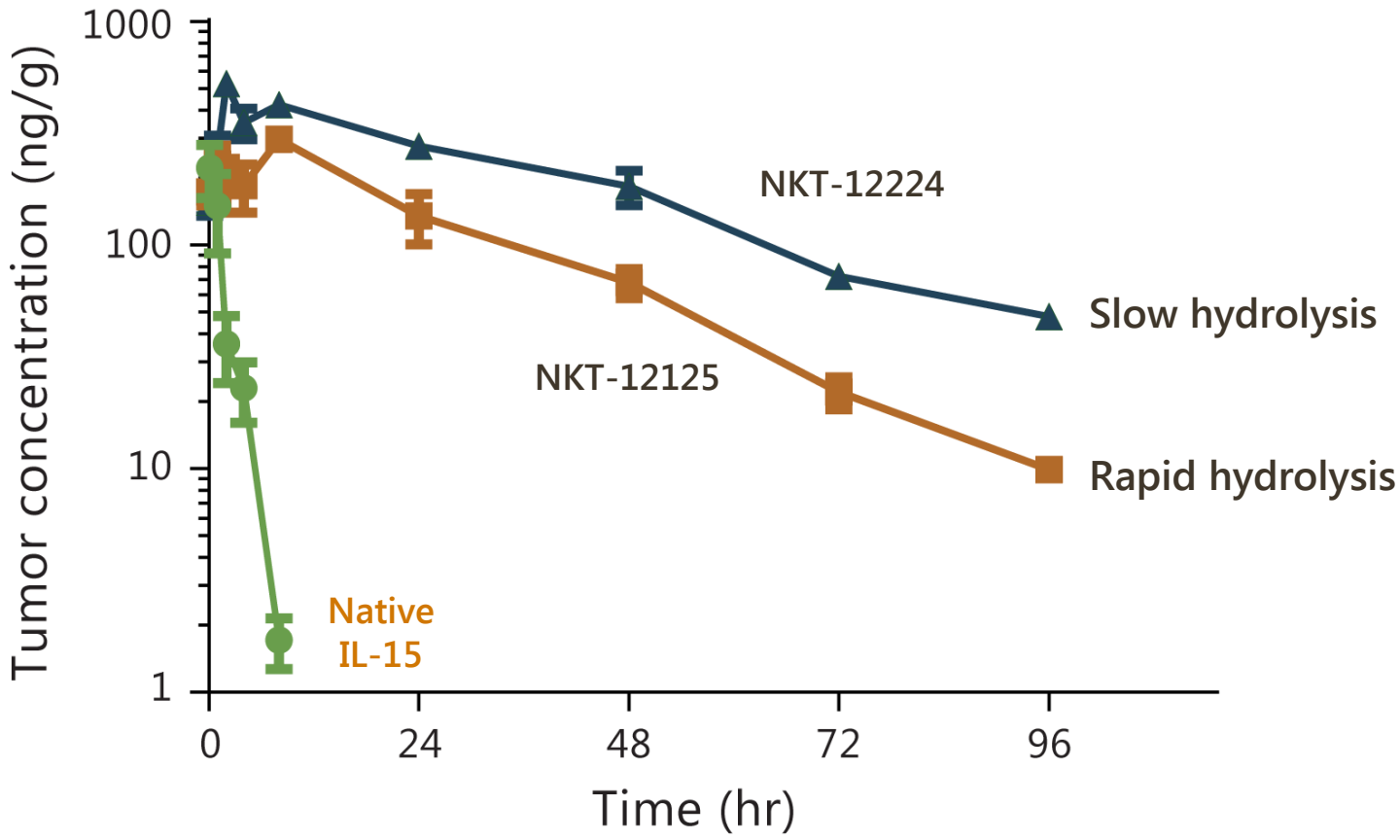
- CD122 (IL-2Rβ) bias causes dramatic expansion of effector cells without increase in Tregs
- Tunable PEG allows precise control of receptor affinity and cytokine exposure
- Breakthrough biology uniquely enabled by Nektar technology

NKTR-255: Preserve Unique Biology of IL-15 in a Long-Acting Cytokine

- Highly active, long-exposure cytokine to improve T-cell memory
- Optimal drug must maintain the unique binding of IL-15 to IL-15Rα
- Eliminate spikes in exposure that cause increased side effects in rhIL-15 dosing

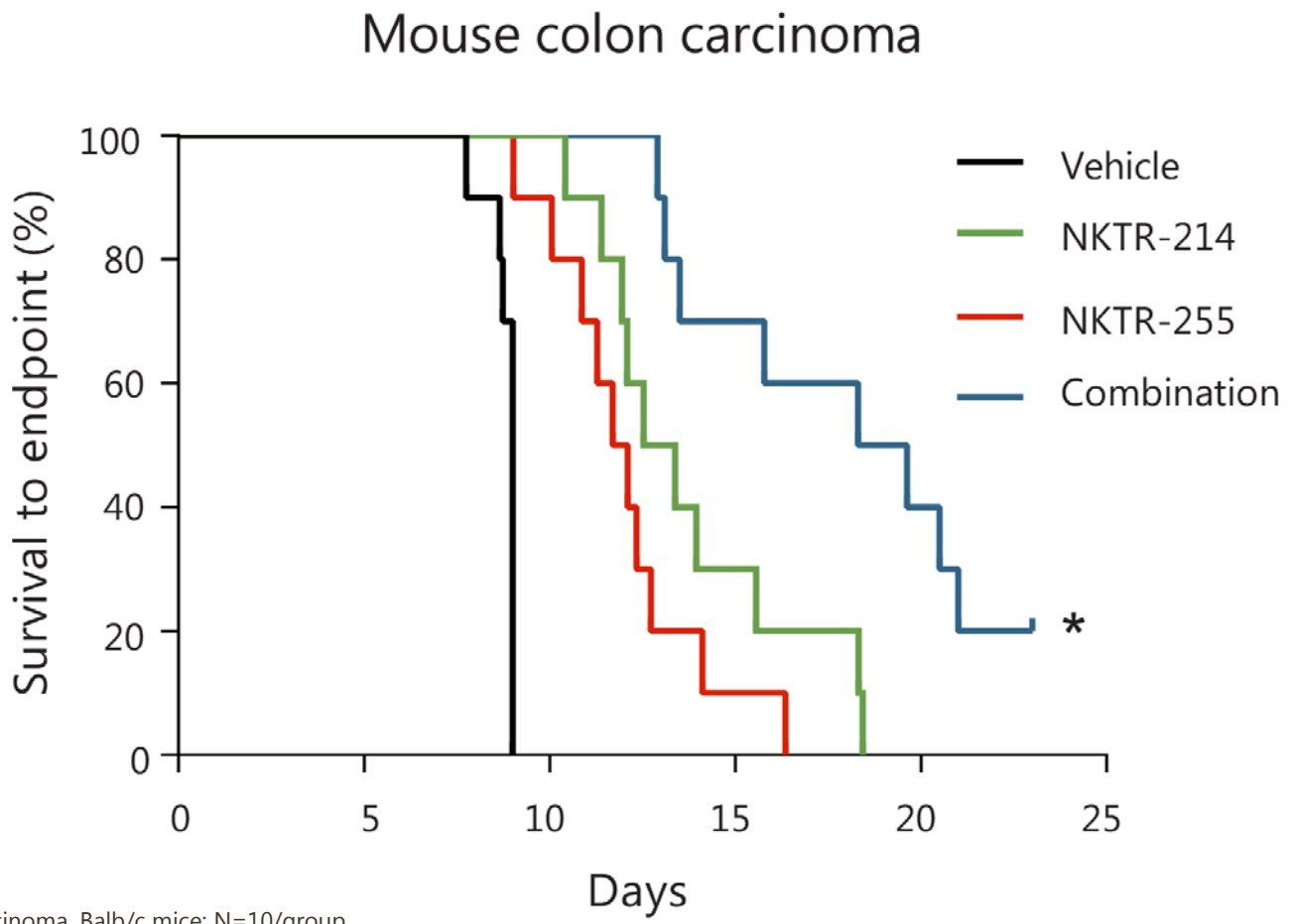


Nektar Tunable Linkers Increase Tumor Exposure of IL-15 Conjugates



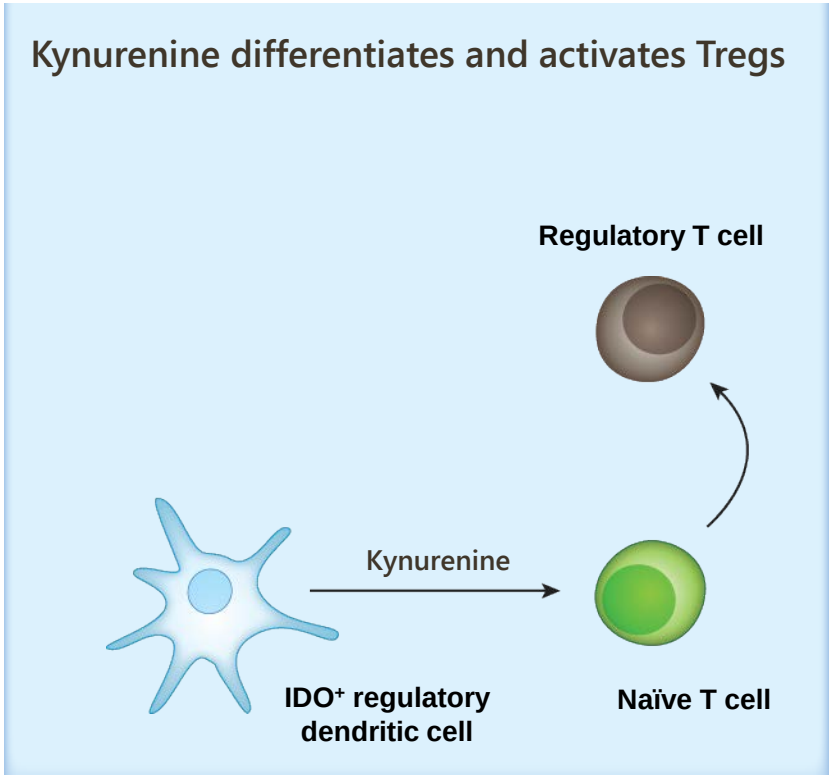
C57Bl/6 mice
N=10 per group

NKTR-255 Candidate Improves Efficacy of NKTR-214 in a Mouse Colon Carcinoma Model



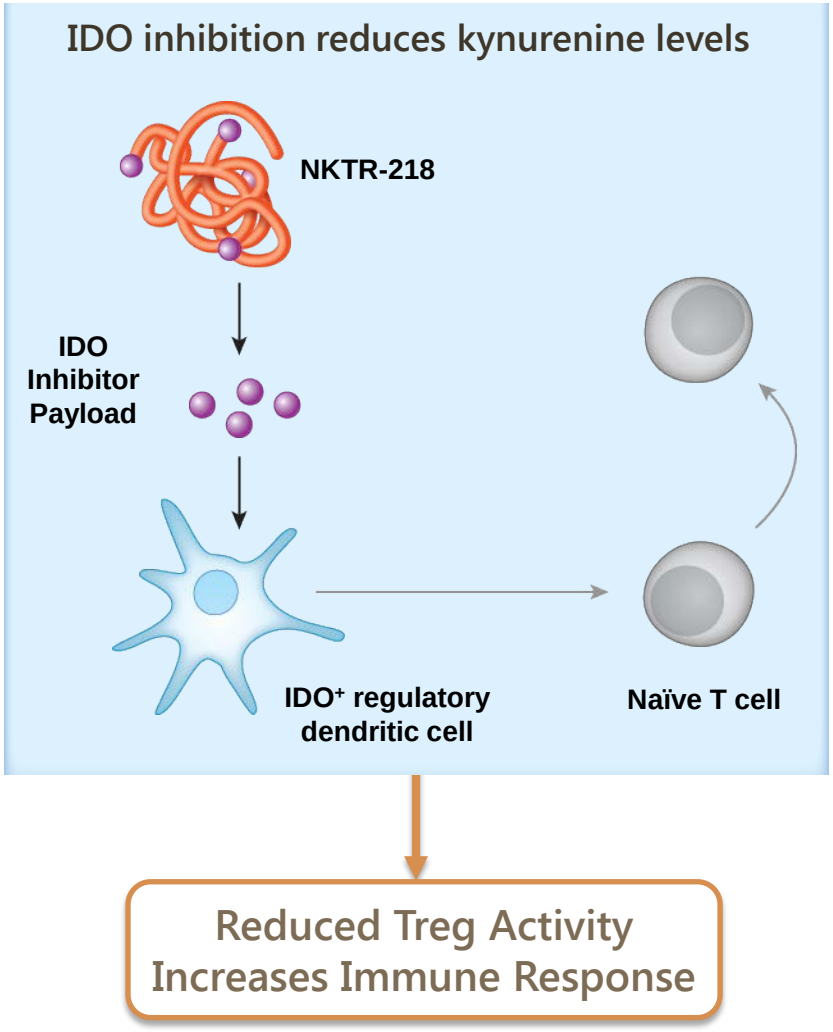
CT26 colon carcinoma, Balb/c mice; N=10/group
NKTR-214, 0.8mg/kg; NKTR-255, 0.3mg/kg q5dx3
Log-rank (Mantel-Cox) test
*=p<0.05 vs individual treatment of each single agent

Beyond Cytokines: NKTR-218



- IDO is an enzyme that controls synthesis of kynurenine from tryptophan
- Kynurenine is a potent activator of regulatory T cells
- Inhibition of kynurenine production will promote immune activation in the tumor microenvironment

Beyond Cytokines: NKTR-218

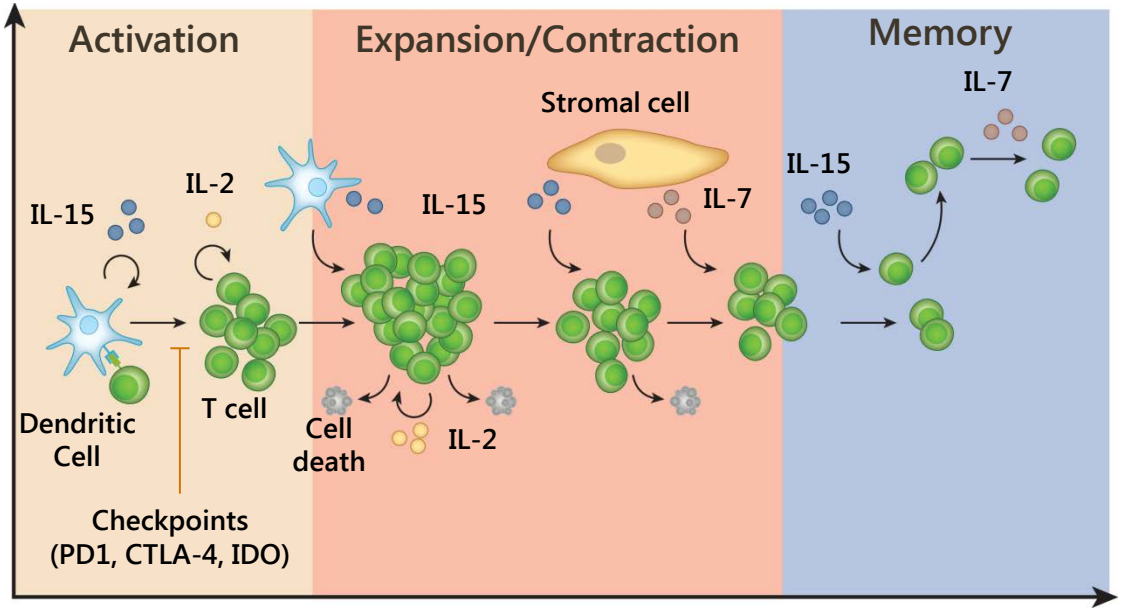


- Highly active, long-lasting exposure to tumor IDO inhibition
- Allows for IV dosing
- Eliminates the compromises in potency and specificity required to permit oral dosing of short-acting candidates in development

Nektar IO Strategy: Focus on the T cell

NKTR-214

Grow the T cell population



NKTR-218 (IDO)

Release the checkpoint

NKTR-255 (IL-15)

Sustain the response

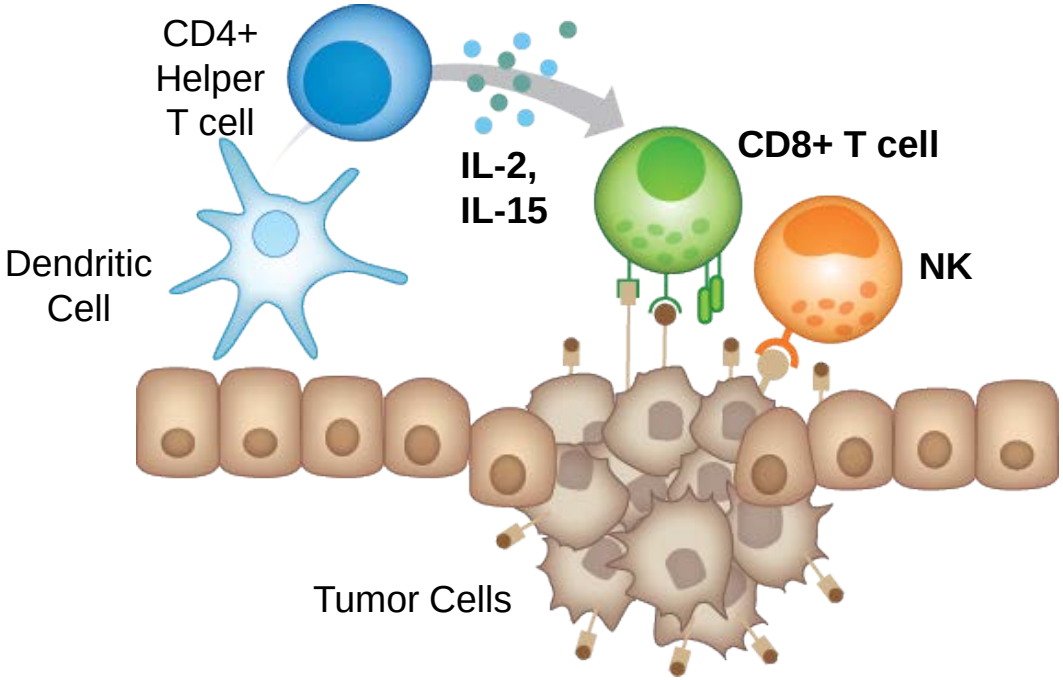
NKTR-214:

A T-Cell Growth Engine in Immuno-Oncology

Jonathan Zalevsky, Ph.D.

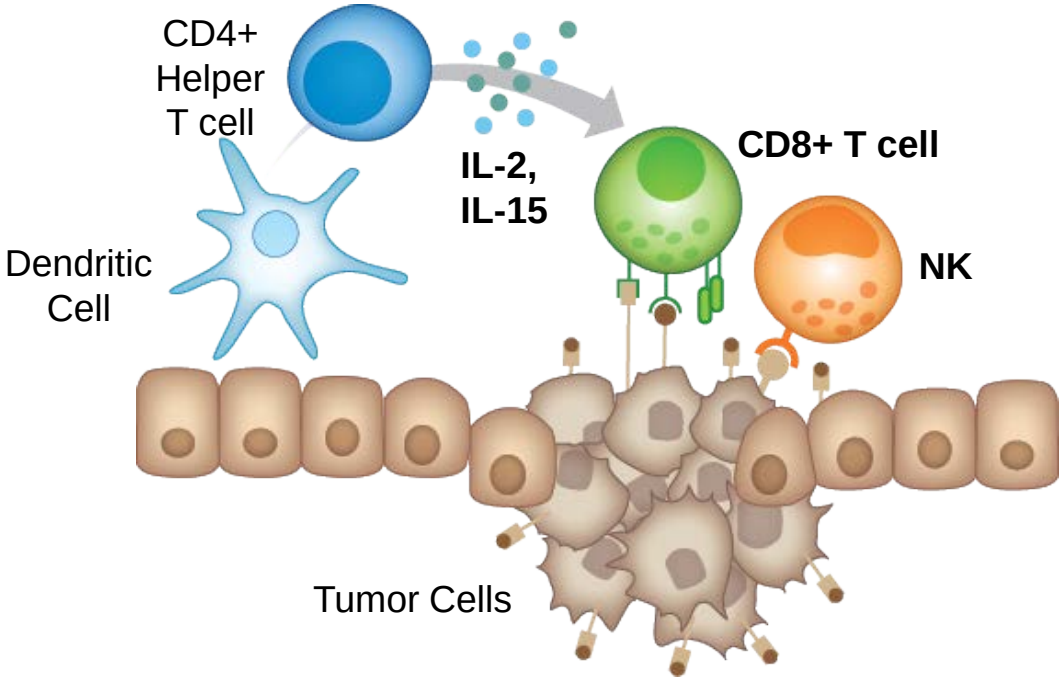
Vice President, Biology & Preclinical Development
Nektar Therapeutics

The Immune System Is The Primary Defense Against Development Of Cancer



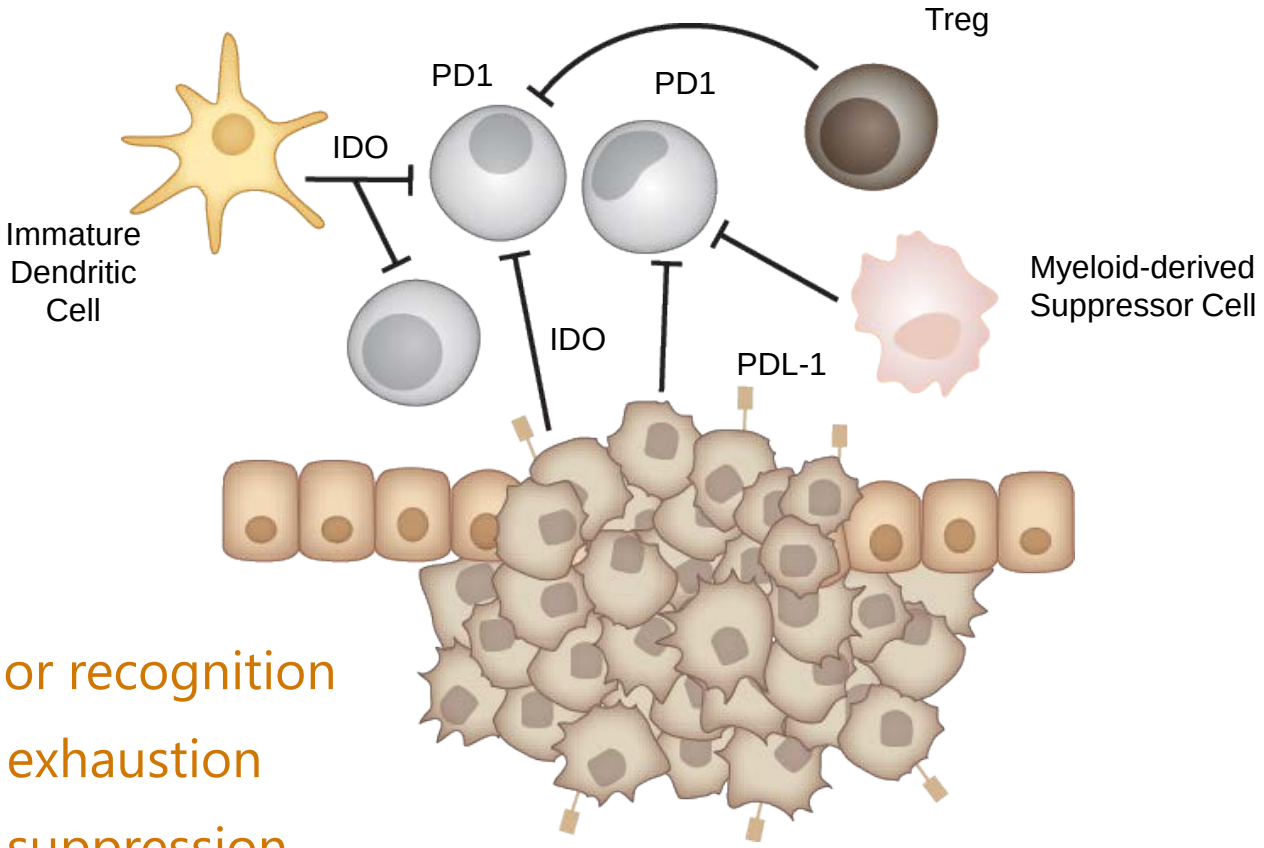
- Almost all microtumors are recognized as non-self and destroyed
- Immune surveillance eliminates tumor cells and prevents emergence of detectable tumors
- Immune system must be 100% effective

Selective Advantage To Tumors That Can Evade Surveillance



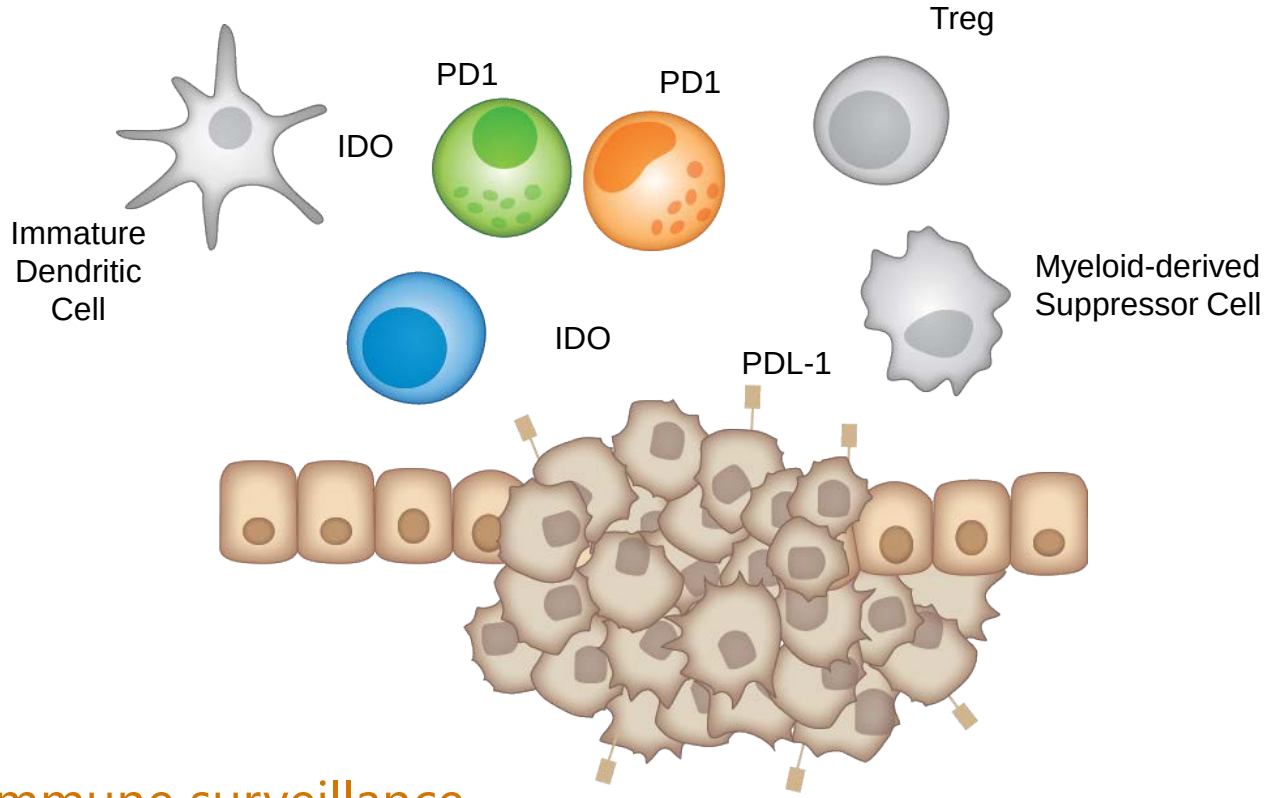
- Constant rounds of elimination select for evading cells
- Mutations distort self/non-self recognition
- Microenvironment remodeling promotes tumor survival

Tumor Growth Dramatically Increases When Tumor Evolves To Escape Surveillance



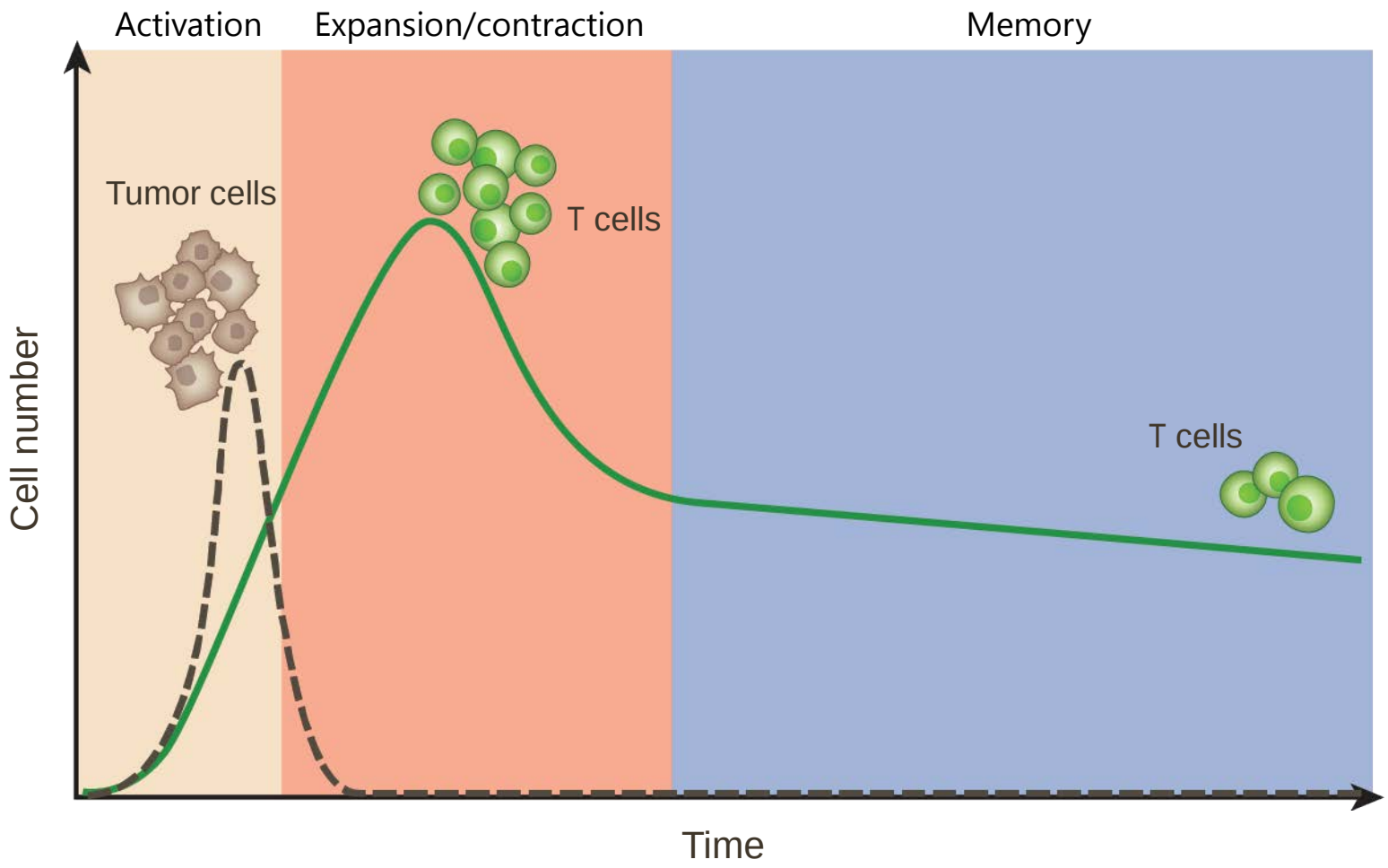
- Lost tumor recognition
- Immune exhaustion
- Immune suppression

Goal of IO: Reactivate Immune Surveillance and Restore Homeostasis

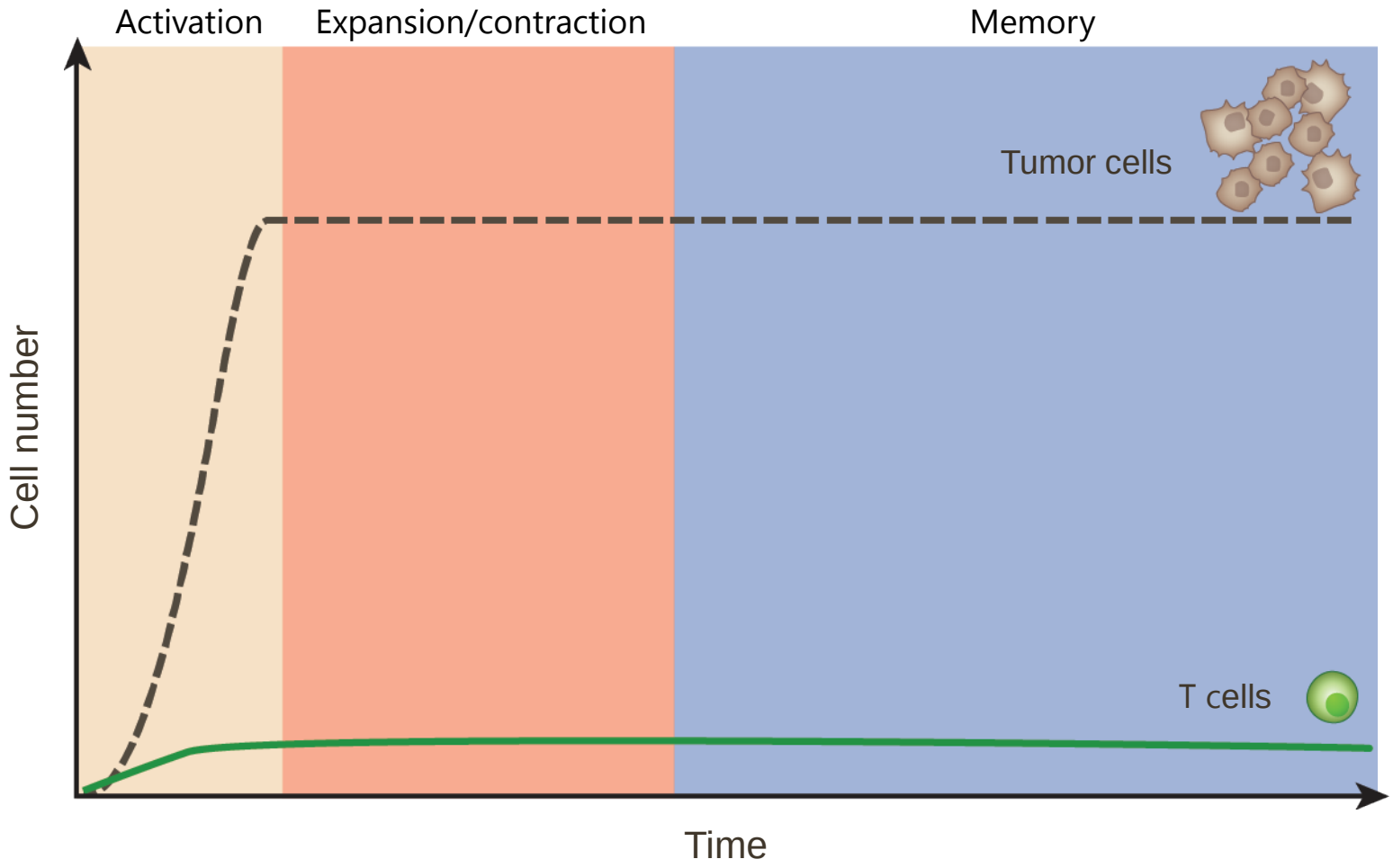


- Robust immune surveillance
- Immune activation in the tumor microenvironment

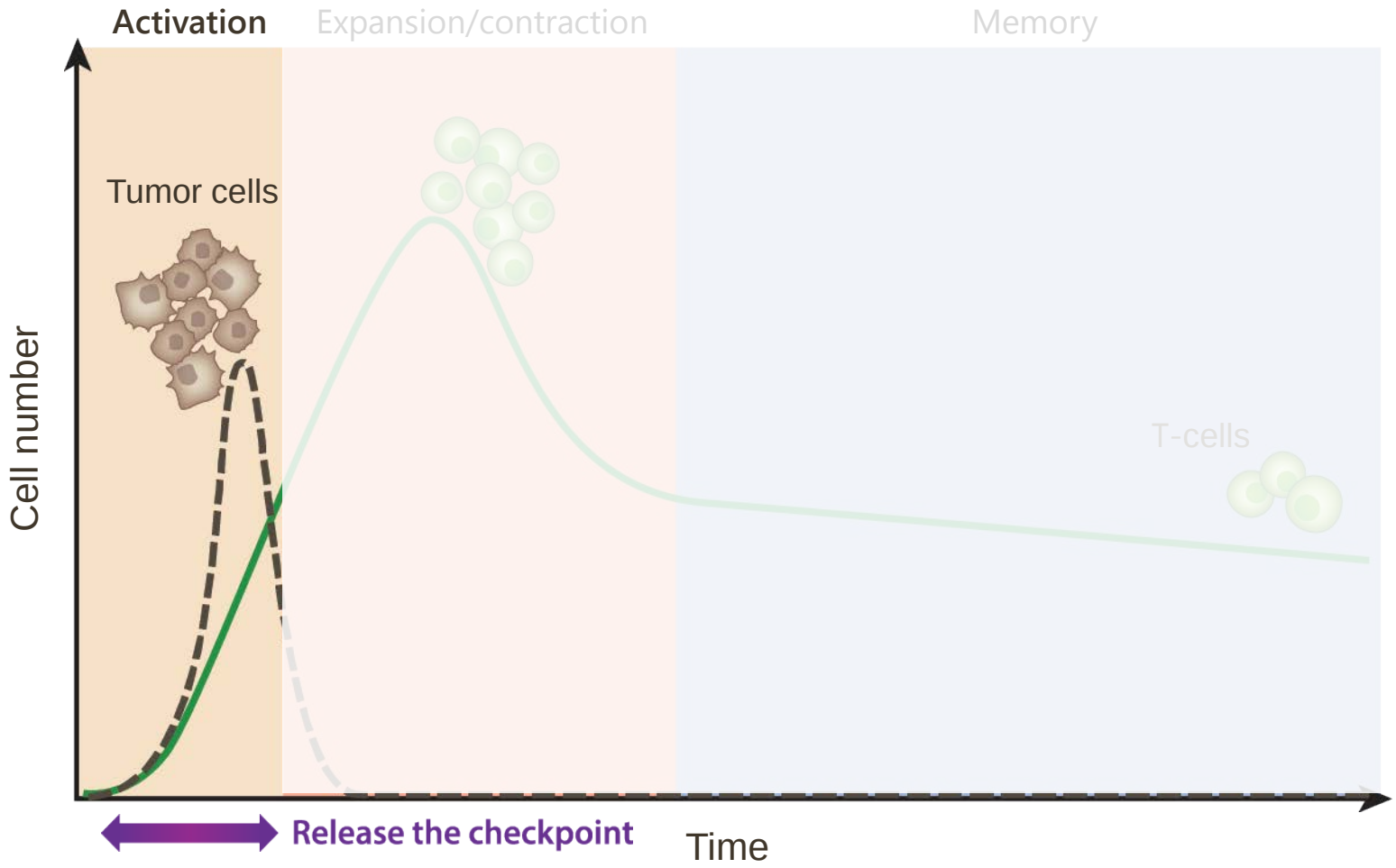
Time Course Of Normal T-Cell Responses



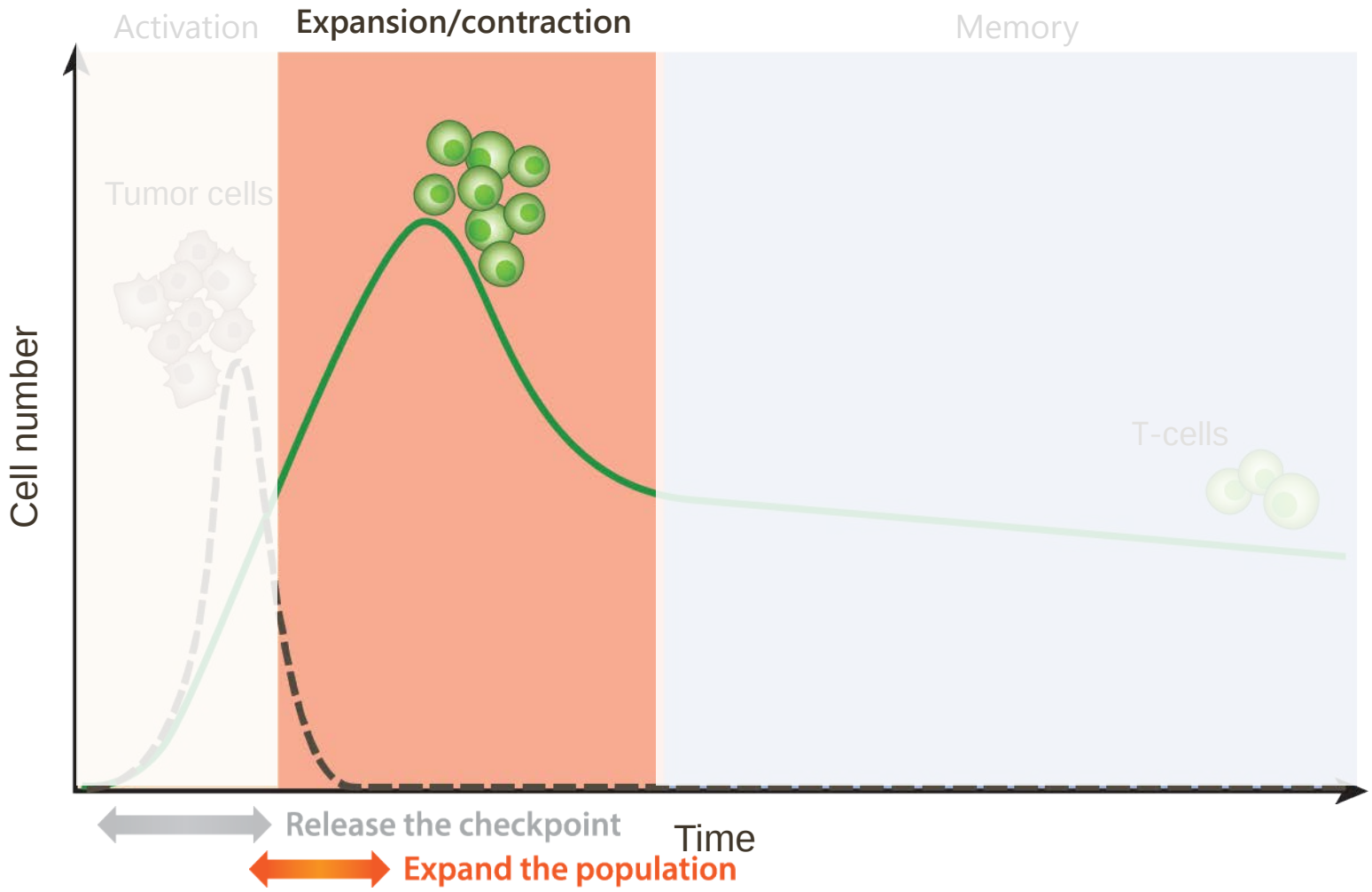
Tumors Inhibit T-Cell Growth And Differentiation



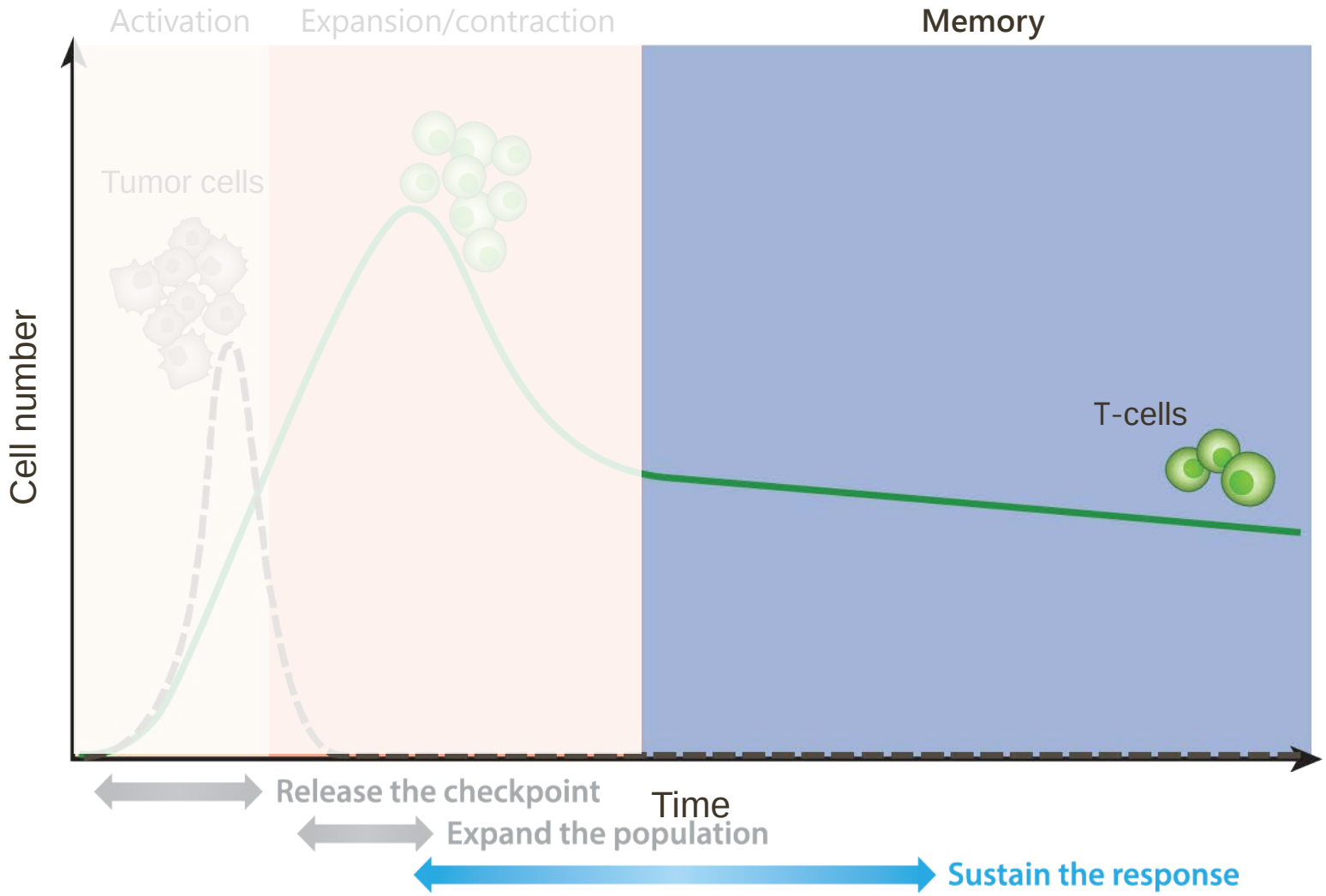
Immunotherapies Increase Anti-tumor T-Cell Activity



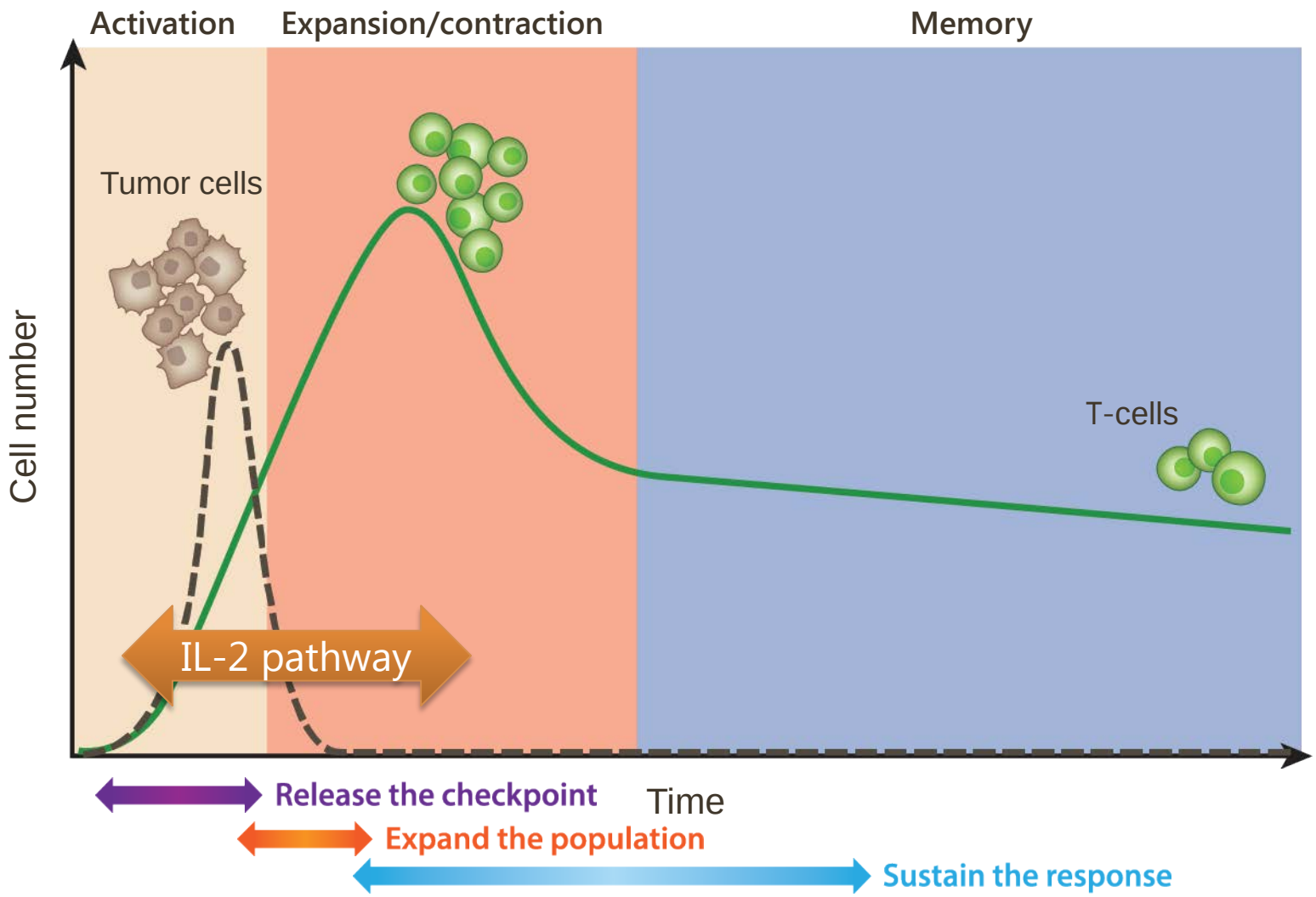
Immunotherapies Increase Anti-tumor T-Cell Activity



Immunotherapies Increase Anti-tumor T-Cell Activity



Immunotherapies Increase Anti-tumor T-Cell Activity

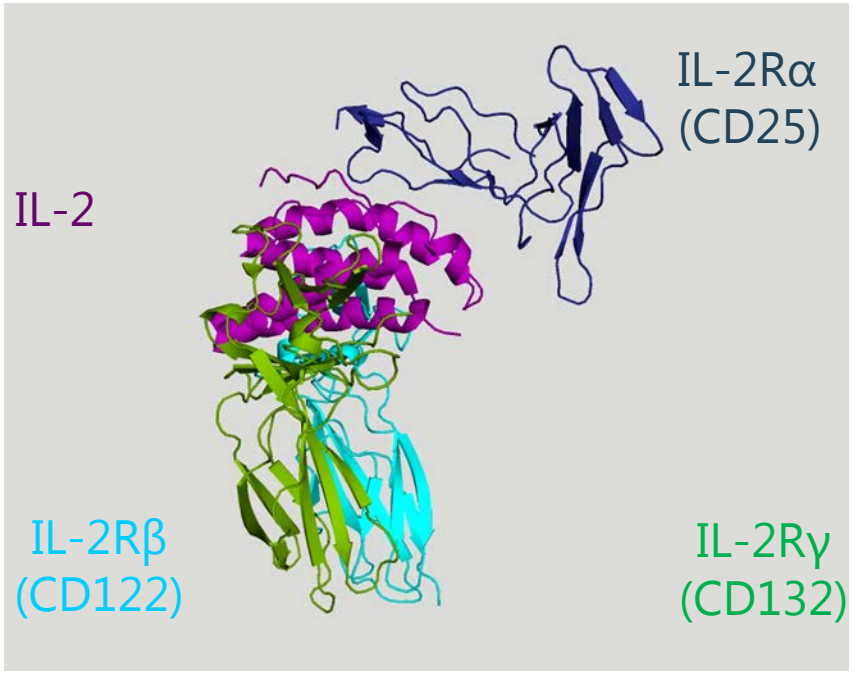


The IL-2 Pathway Regulates T-Cell Response

- First discovered cytokine
- Regulates T-cell and NK-cell activation and expansion
- Signals through multiple receptor complexes
  - IL-2Rαβγ and IL-2Rβγ
- First approved immunotherapy
  - High promise of the therapeutic potential of the IL-2 pathway
  - Overall tolerability and side-effect profile limit utility
  - High opportunity to deliver an optimized drug to effectively target the IL-2 pathway

Design Goals For Targeting The IL-2 Pathway

Structural model of IL-2 docked with IL-2Rαβγ

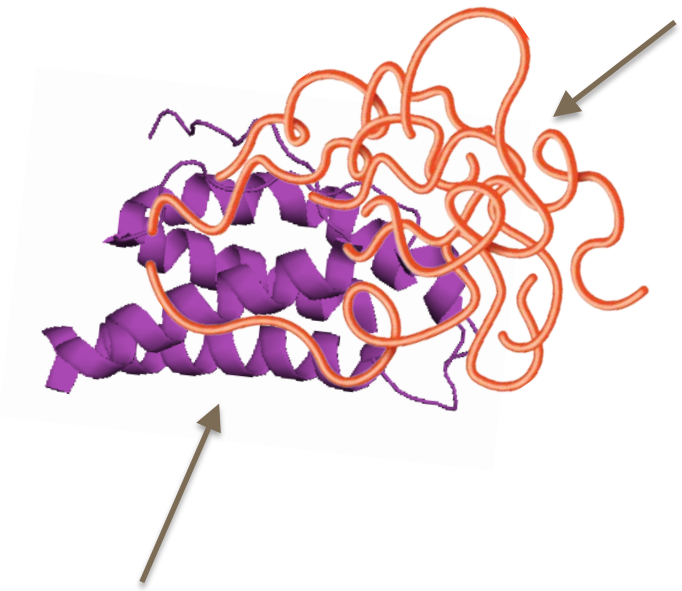


IL-2: purple
IL-2Rβ: cyan

IL-2Rα: blue
IL-2Rγ: green

- Bias signaling to favor the IL-2Rβγ complex
- Deliver a sustained and controlled signal to the IL-2 pathway
- Enhance CD8+ T-cell and NK-cell anti-tumor function and minimize Treg expansion
- Improve on the benefit/risk profile of IL-2

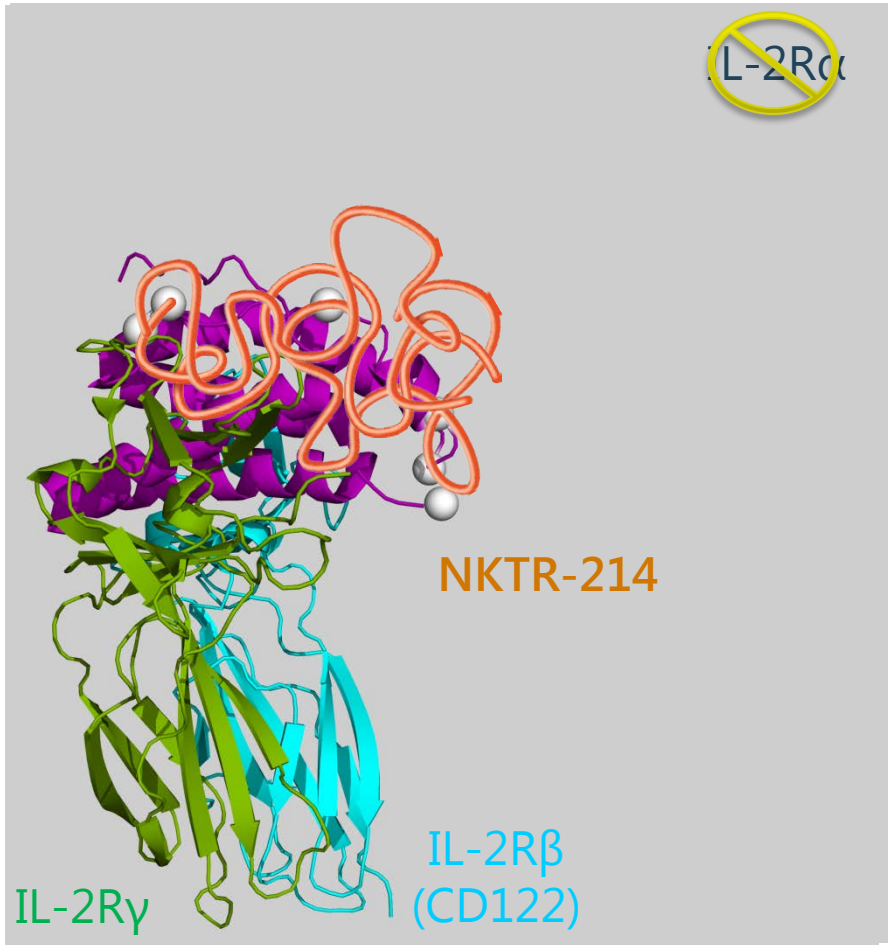
NKTR-214 Is A CD122-biased Cytokine, Designed To Improve Efficacy And Mitigate Toxicity



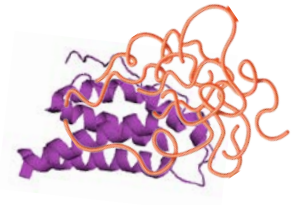
IL-2 cytokine core

- rhIL-2, same amino acid sequence as clinically validated molecule (aldesleukin)

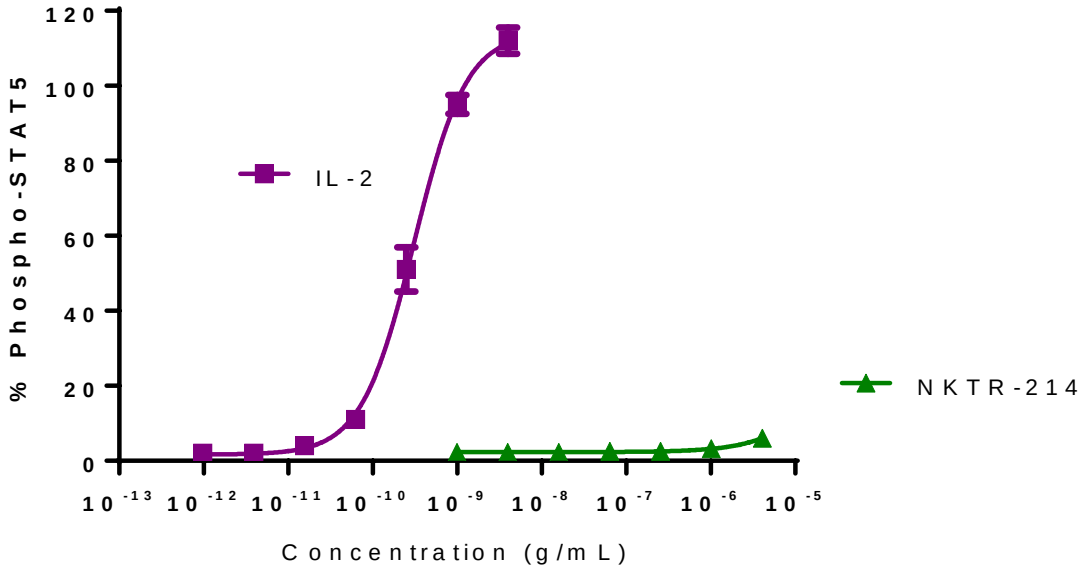
High molecular weight hydrolyzable polymers located at strategic sites



NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile

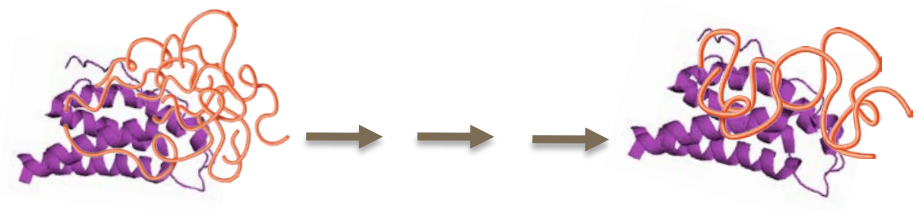


NKTR-214
(essentially inactive)



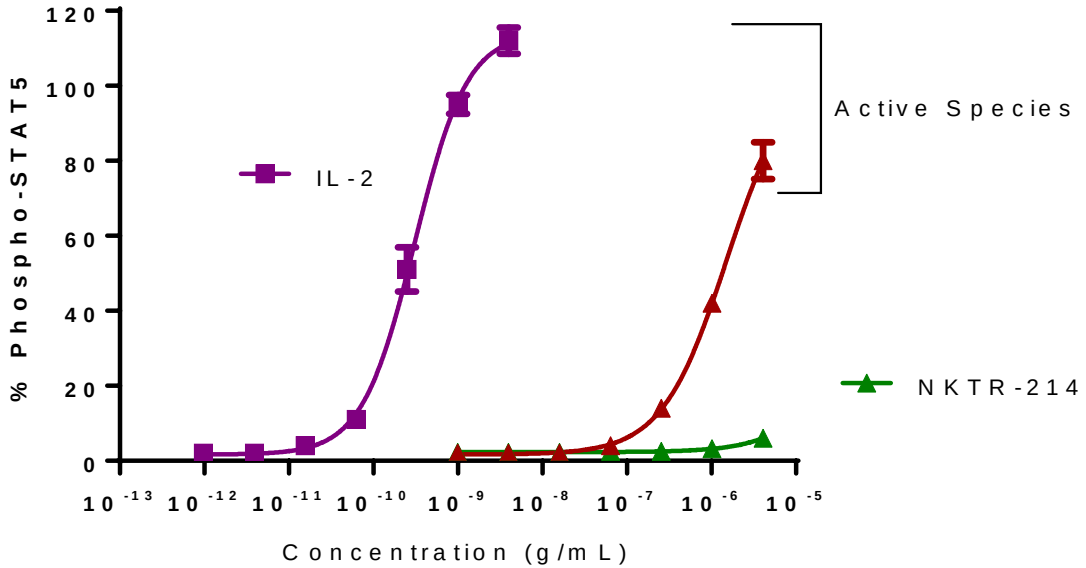
Charych, D., et al. AACR 2013, Abstract #482

NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile



NKTR-214
(essentially inactive)

Active Species
(Biased signaling, increased potency with fewer PEGs)



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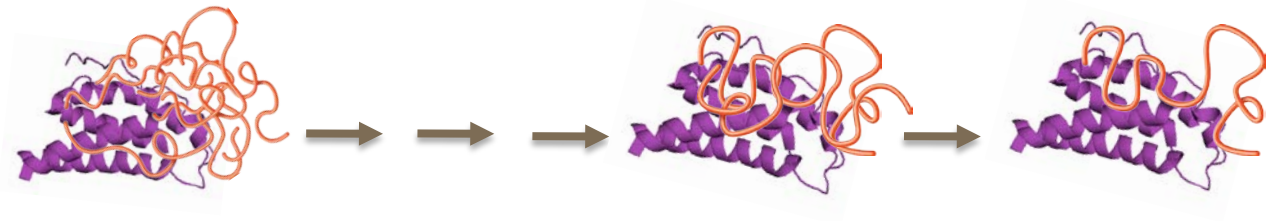
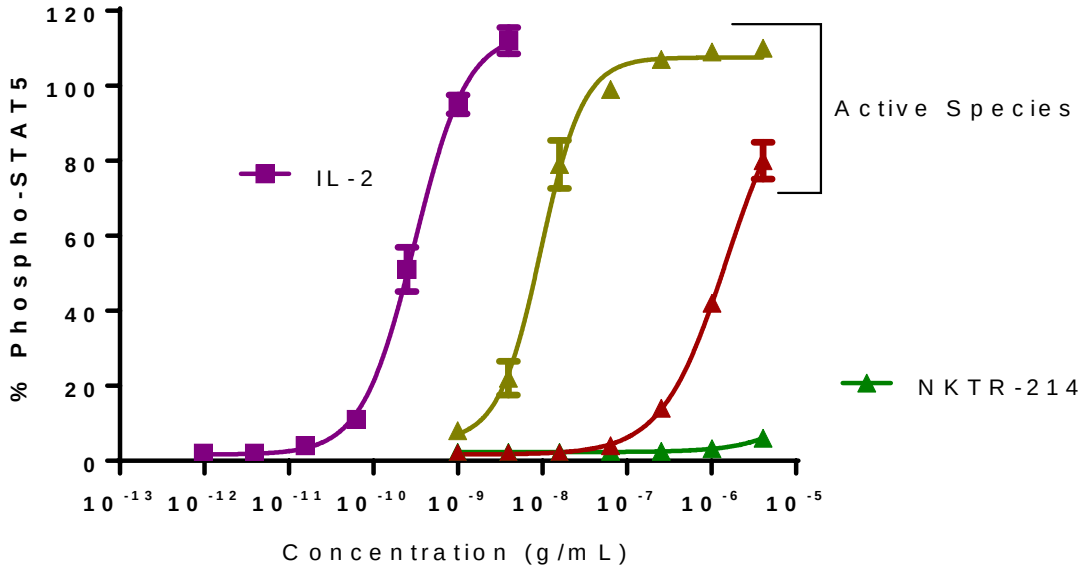
NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile



NKTR-214
(essentially inactive)

Active Species
(Biased signaling, increased potency with fewer PEGs)



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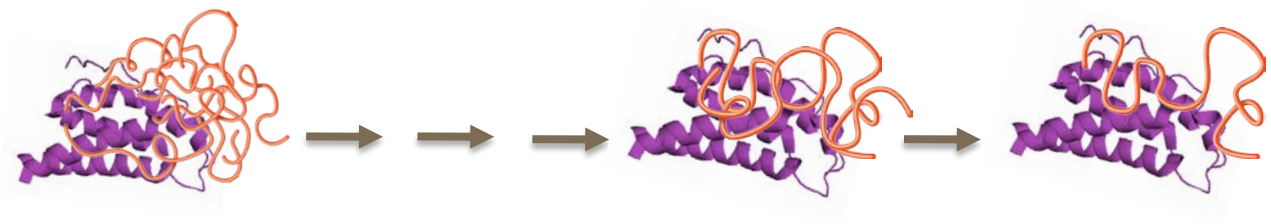
NKTR-214: Biased Signaling And Prodrug Design To Improve Risk/Benefit Profile



NKTR-214
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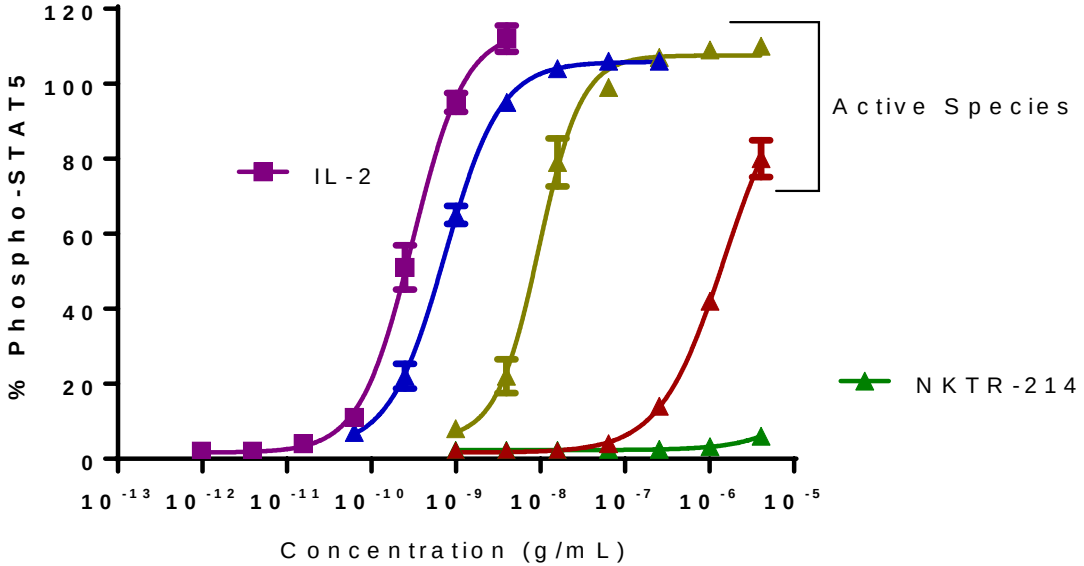
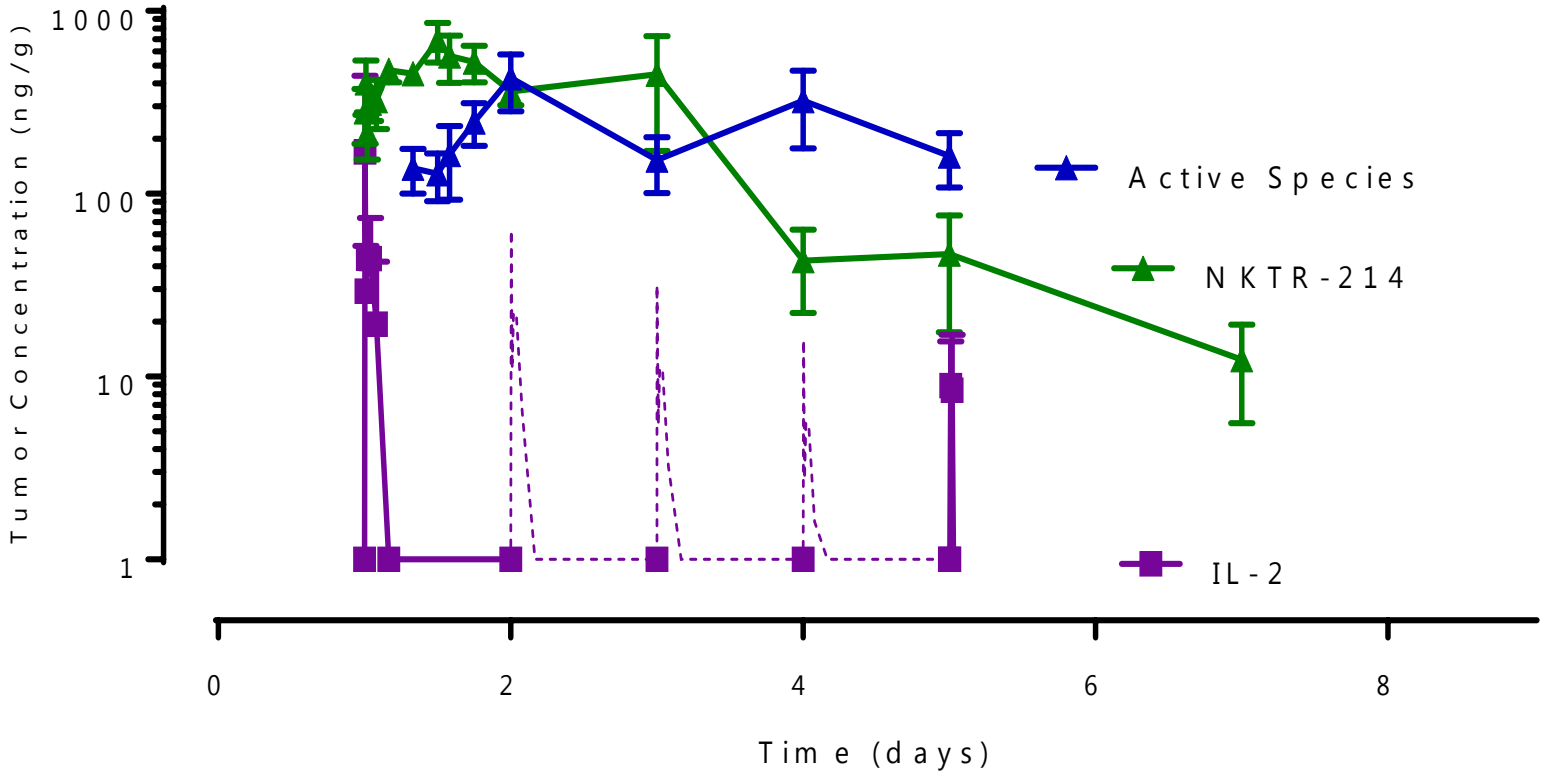


Charych, D., et al. AACR 2013, Abstract #482

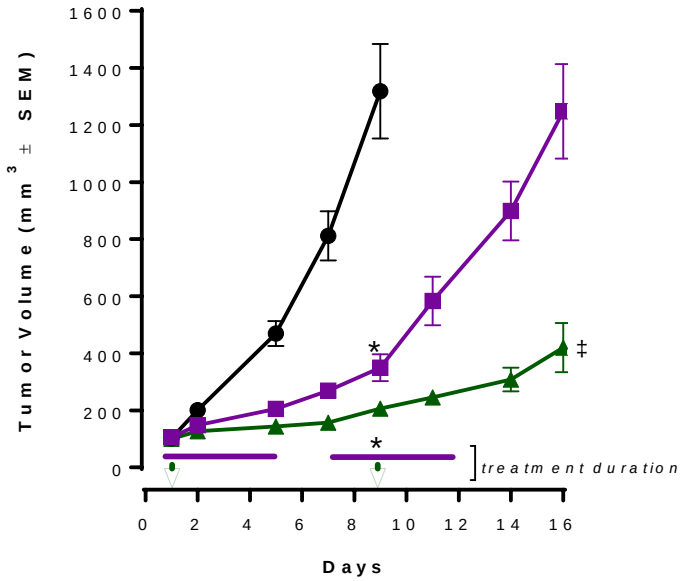
NKTR-214: Sustained Exposure Of Biased Cytokine Activity In Tumor Microenvironment



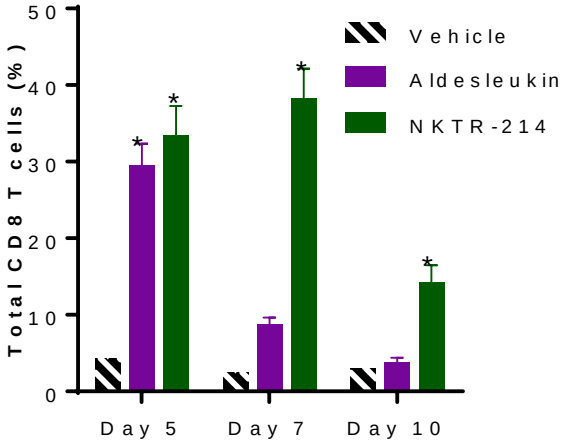
Multiple doses of IL-2 (3mg/kg, I.P.) or single dose of NKTR-214 (2mg/kg, I.V.) was given to tumor-bearing mice (N=4 mice/timepoint).
Concentrations of IL-2, Active cytokine (PEG-IL-2 derived from NKTR-214 hydrolysis), and NKTR-214 were measured using immunoassay methods

NKTR-214 Increases The Quality And Quantity Of The T-cell Response

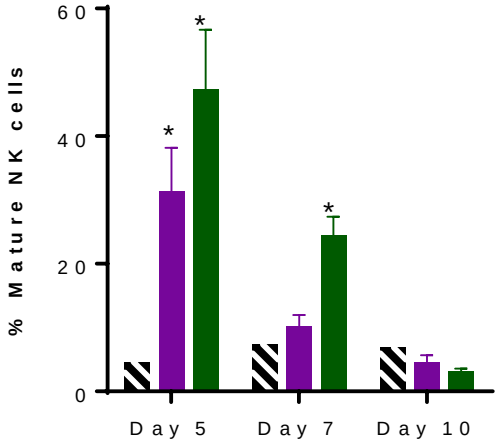
Mouse melanoma model



CD8 T cells



NK cells

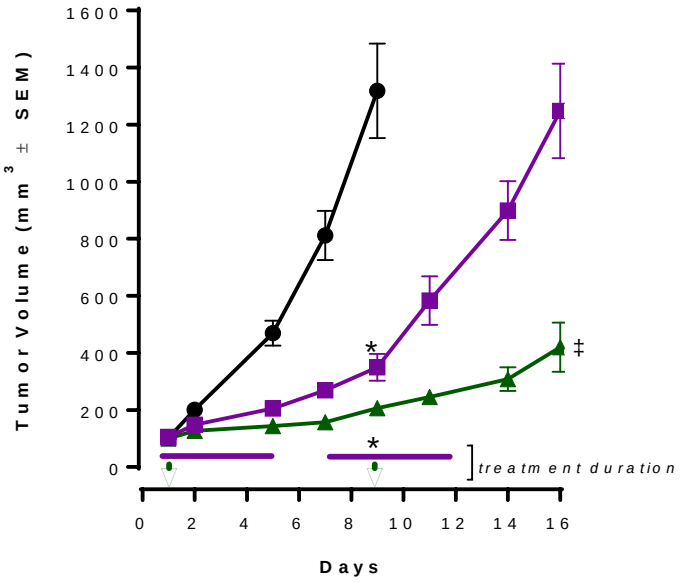


- Single agent efficacy in aggressive mouse melanoma
- Strong and sustained elevation of anti-tumor T and NK cells

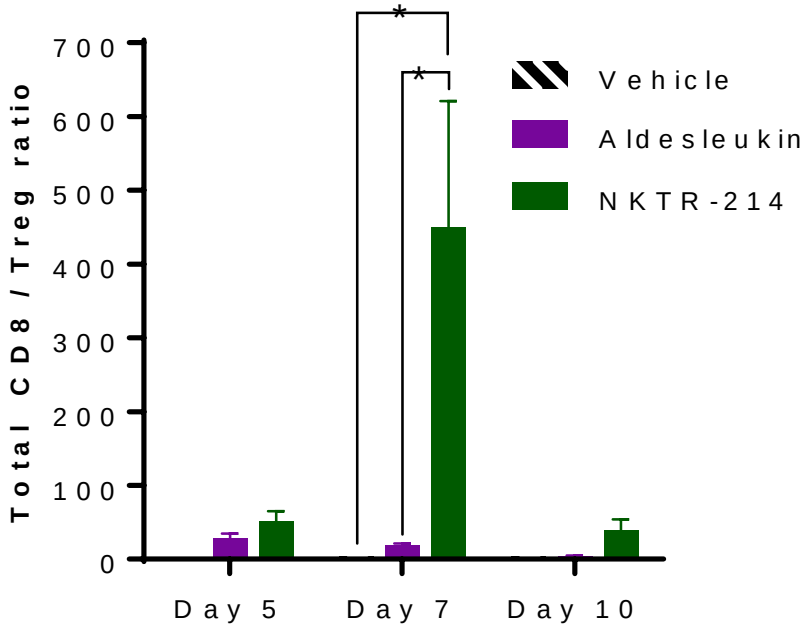
B16F10 melanoma, C57Bl/6 mice; N=9-12/group
NKTR-214, 2mg/kg i.v. q9dx3; Aldesleukin, 3mg/kg i.p. bidx5, 2 cycles
*, $p<0.05$, ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle
‡, $p<0.05$, Student's T-test (left) or Log-Rank (right) w.r.t. Aldesleukin

NKTR-214 Increases The Quality And Quantity Of The T-cell Response

Mouse melanoma model



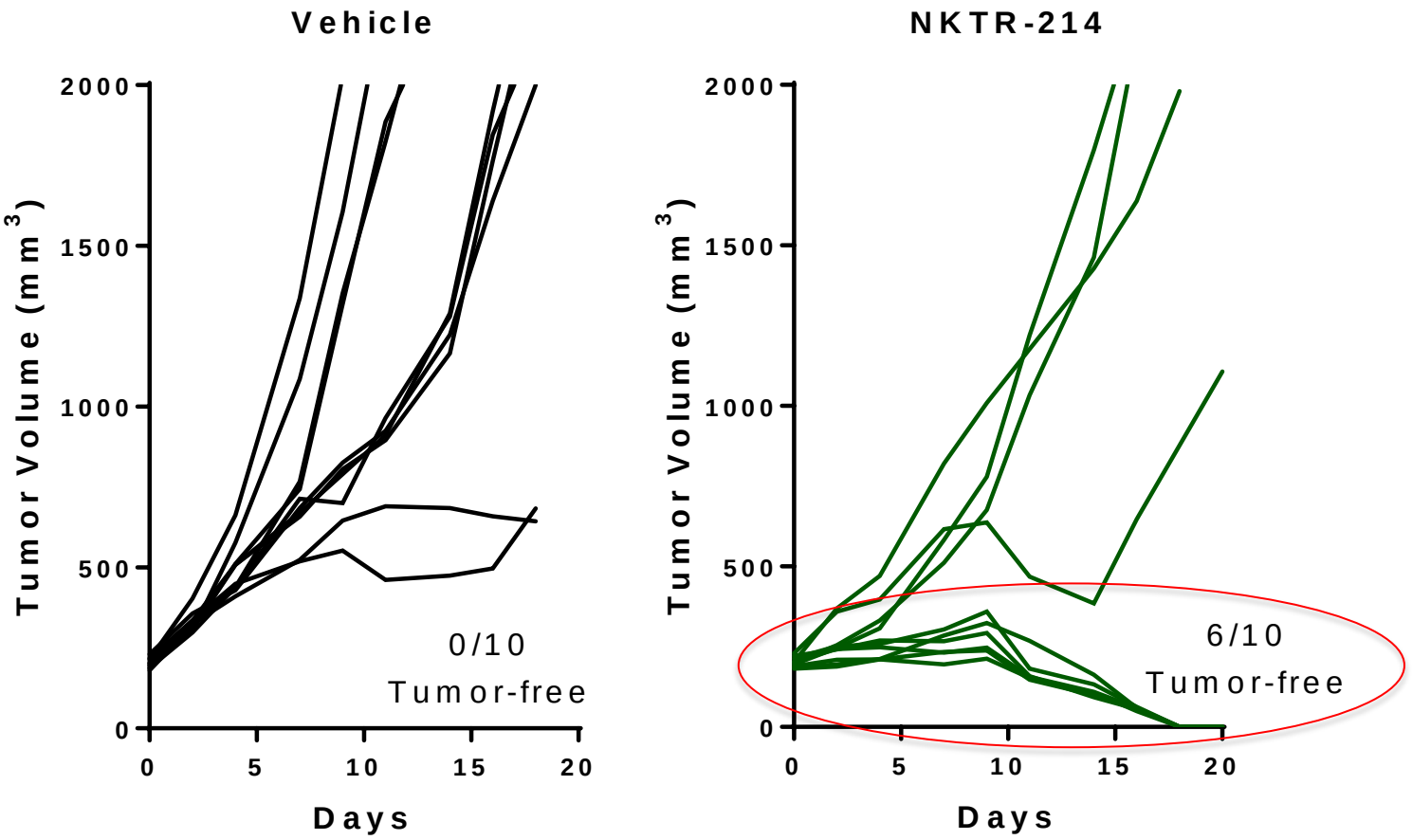
CD8/Treg ratio



> 400-fold increased ratio of CD8 to Treg cells

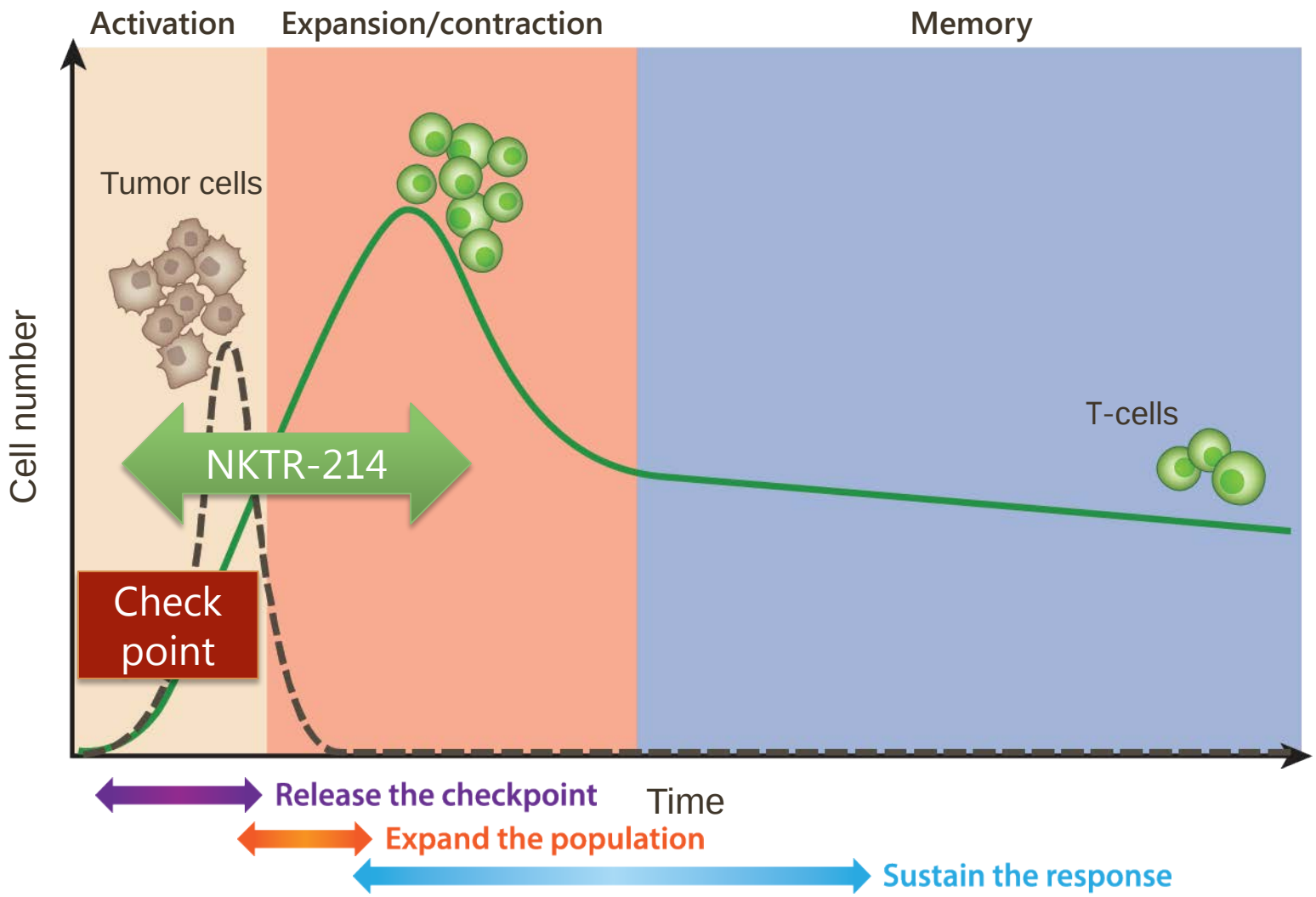
B16F10 melanoma, C57Bl/6 mice; N=9-12/group
NKTR-214, 2mg/kg i.v. q9dx3; Aldesleukin, 3mg/kg i.p. bidx5, 2 cycles
*, $p<0.05$, ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle
‡, $p<0.05$, Student's T-test (left) or Log-Rank (right) w.r.t. Aldesleukin

NKTR-214 Produced Complete Responses In Lewis Lung Carcinoma As Single-Agent



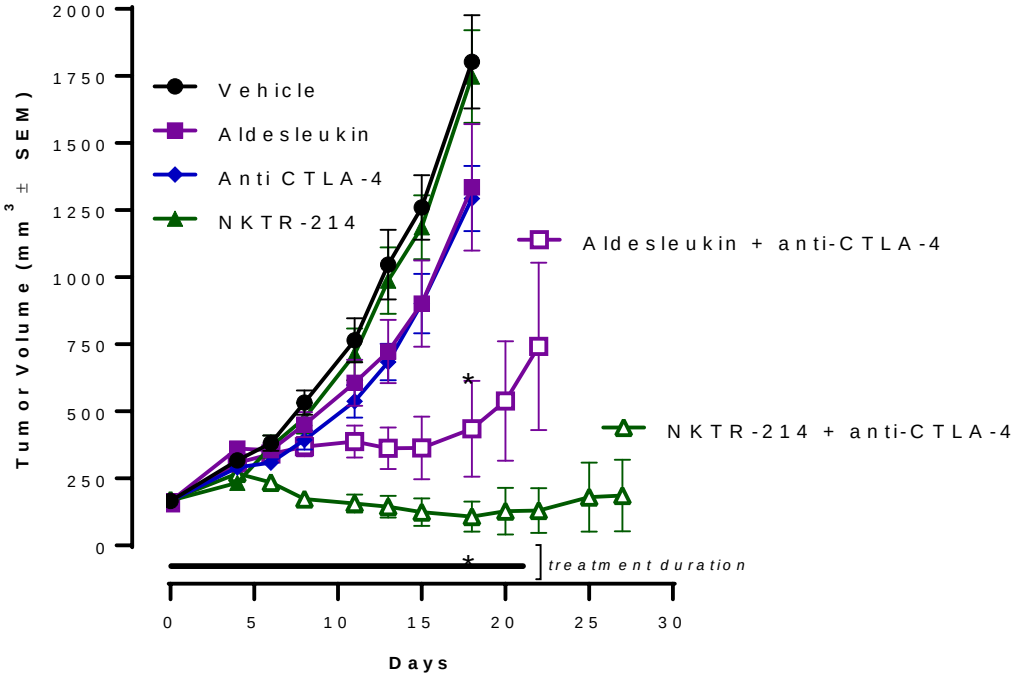
LLC lung carcinoma, C57Bl/6 mice
NKTR-214, 0.7mg/kg i.v. q9dx3
N=10/group

NKTR-214: Combination With Checkpoint Inhibitors Can Optimize Anti-tumor Activity

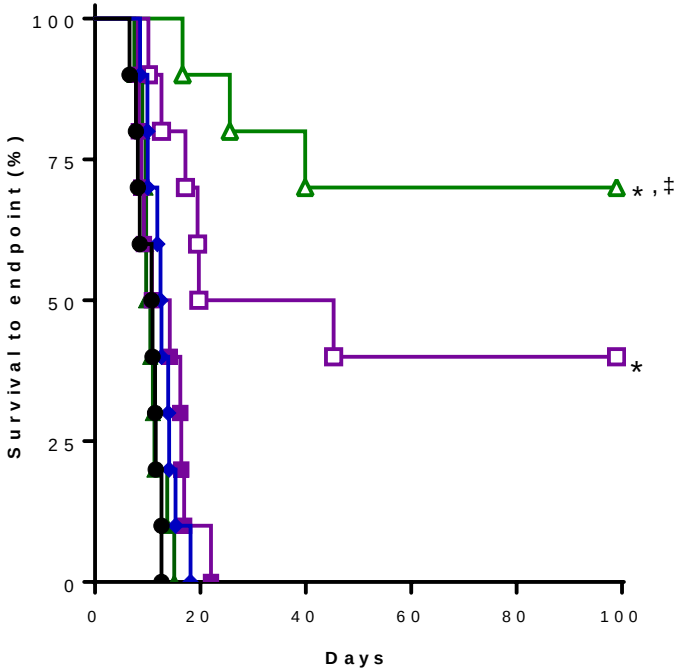


NKTR-214: Combination With Anti-CTLA-4 Produces Durable Responses

Tumor growth Breast



Long-term survival Breast

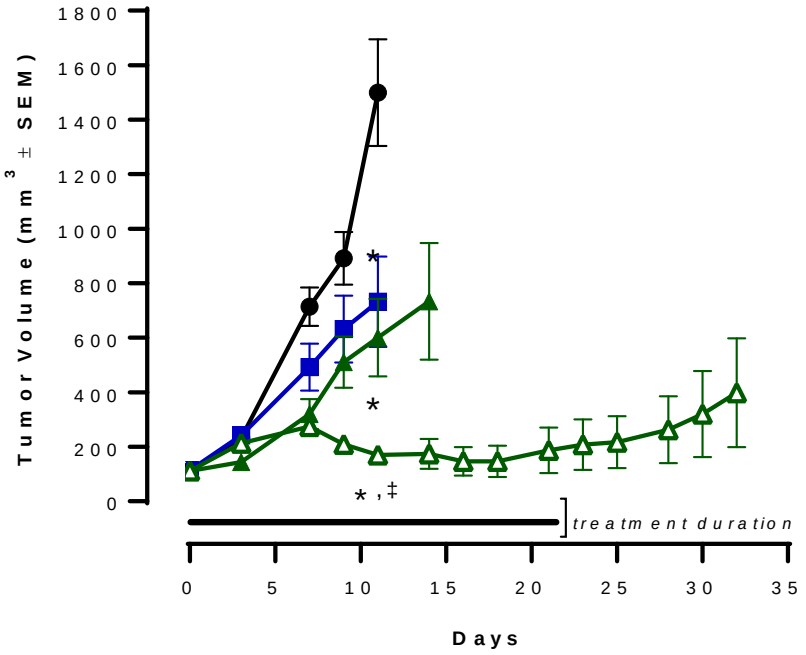


NKTR-214 superior to aldesleukin in head to head study

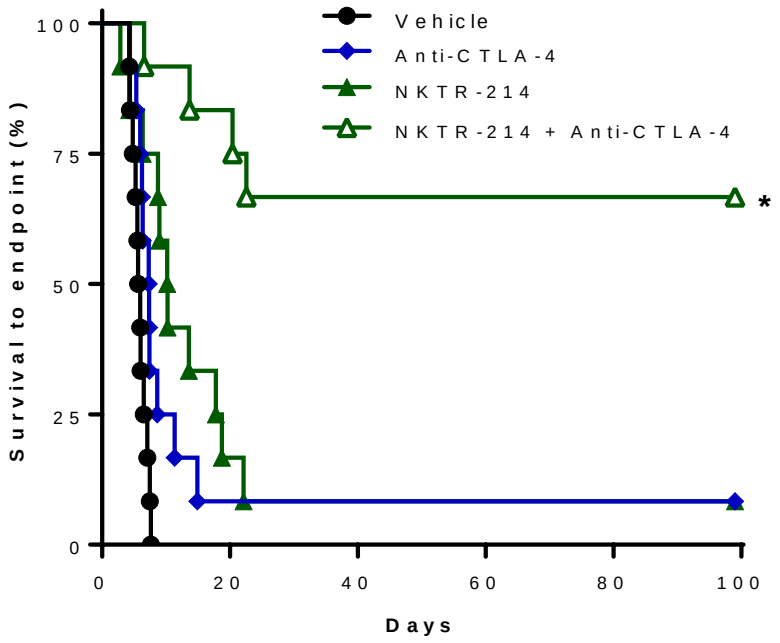
EMT6 mammary carcinoma, Balb/c mice; N=10/group
Anti-CTLA-4, 100µg i.p., twice-weekly ; Aldesleukin 0.5mg/kg qdx5, 2 cycles; NKTR-214, 0.8mg/kg i.v. q9dx3
*, $p<0.05$, ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle
‡, $p<0.05$, Log-Rank (right) w.r.t. Aldesleukin + anti-CTLA-4

NKTR-214: Combination With Anti-CTLA-4 Produces Durable Responses

Tumor growth
Colon



Long-term survival
Colon

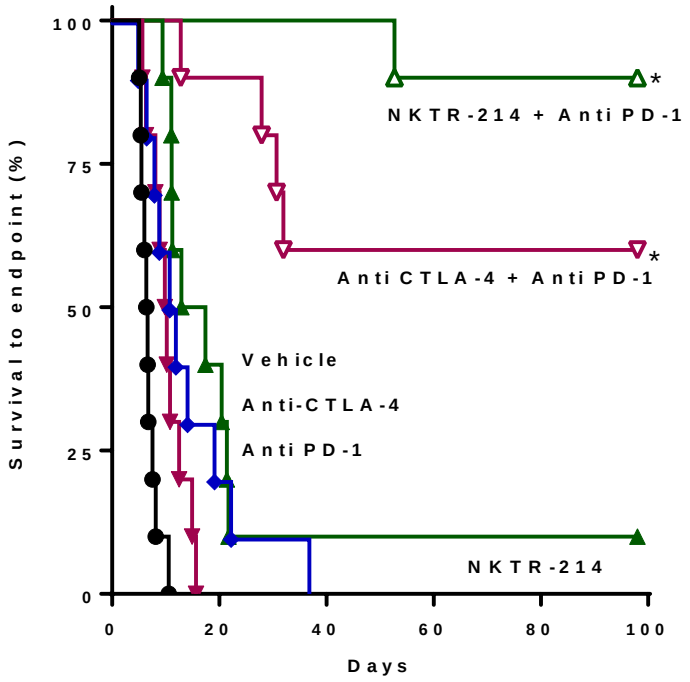


NKTR-214 + anti-CTLA-4 is superior to single agent

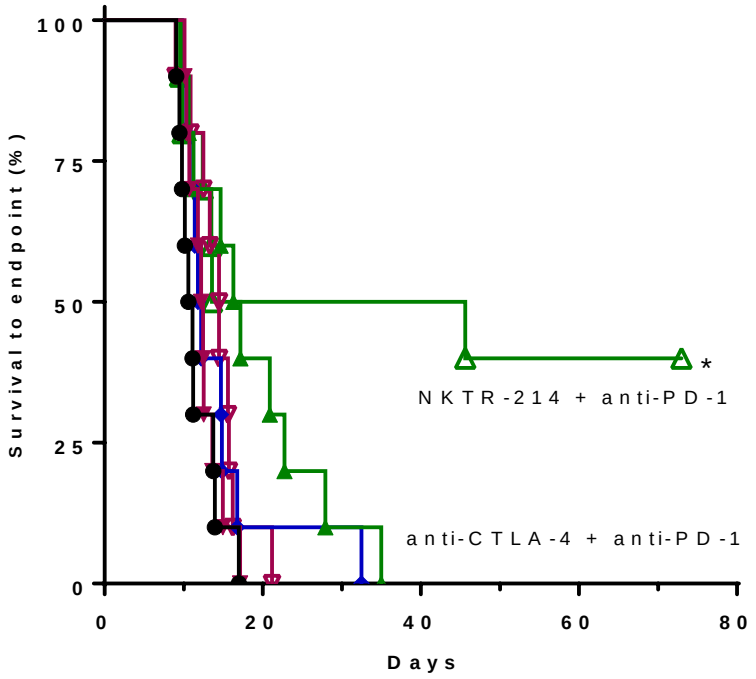
CT26 colon carcinoma, Balb/c mice; N=12/group
Anti-CTLA-4, 100µg i.p., twice-weekly; NKTR-214, 0.8mg/kg i.v. q9dx3
*, $p<0.05$, ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle
‡, $p<0.05$, Student's T-test (left) w.r.t. anti-CTLA-4

NKTR-214: Combination With Anti-PD-1 Consistently Produces Durable Responses

Long-term survival Colon



Long-term survival Breast

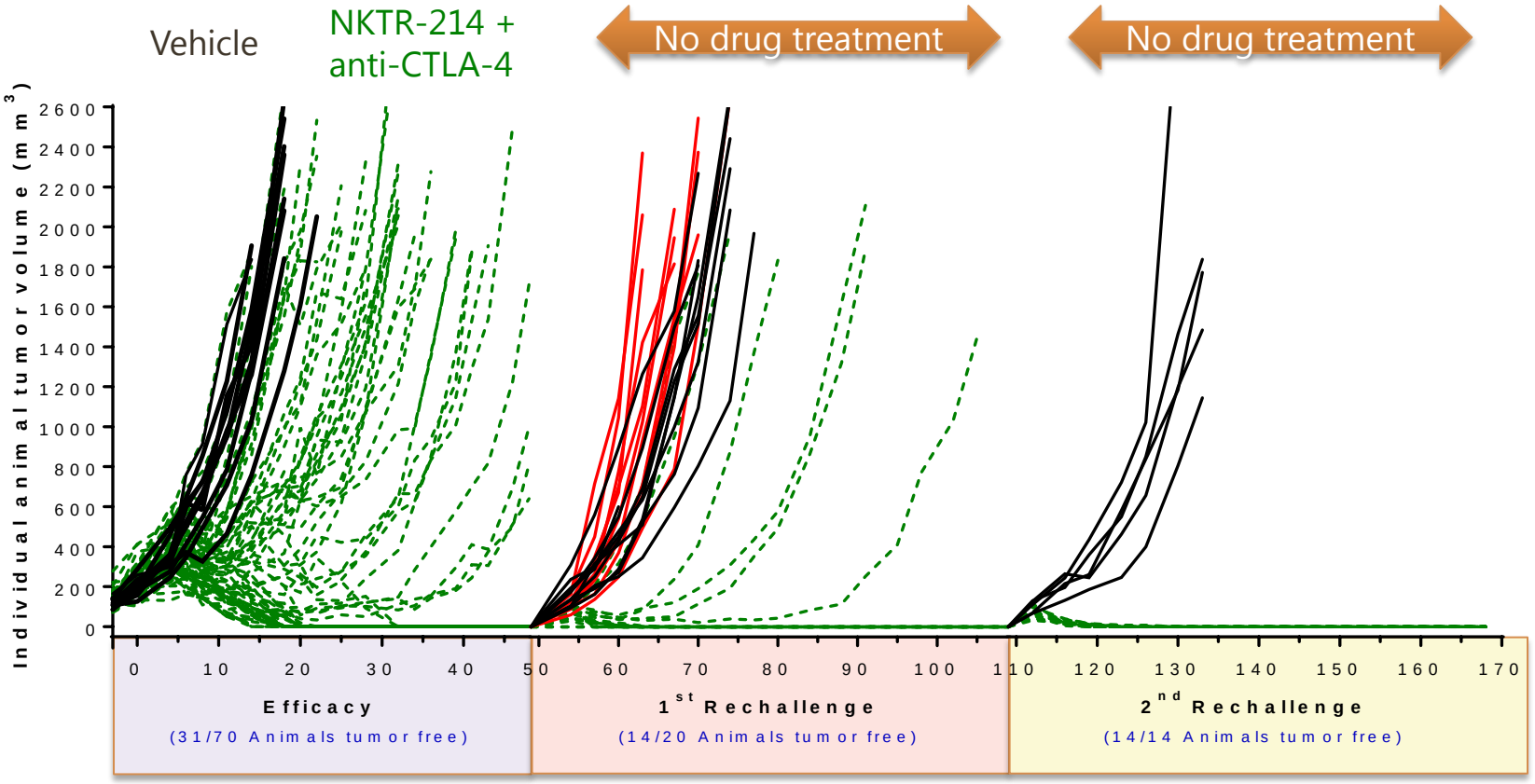


NKTR-214 + anti-PD-1 is superior to anti-CTLA-4 + anti-PD-1

CT26 colon carcinoma, Balb/c mice, N=10/group
Anti-CTLA-4, 100µg i.p., twice-weekly; Anti-PD-1, 200µg i.p., twice weekly
NKTR-214, 0.8mg/kg i.v. q9dx3
*, $p<0.05$, ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle

EMT6 breast carcinoma, Balb/c mice, N=10/group
Anti-CTLA-4, 100µg i.p., twice-weekly; Anti-PD-1, 200µg i.p., twice weekly
NKTR-214, 0.8mg/kg i.v. q9dx3
*, $p<0.05$, ANOVA with Tukey's post-test (left) or Log-Rank (right) w.r.t. vehicle

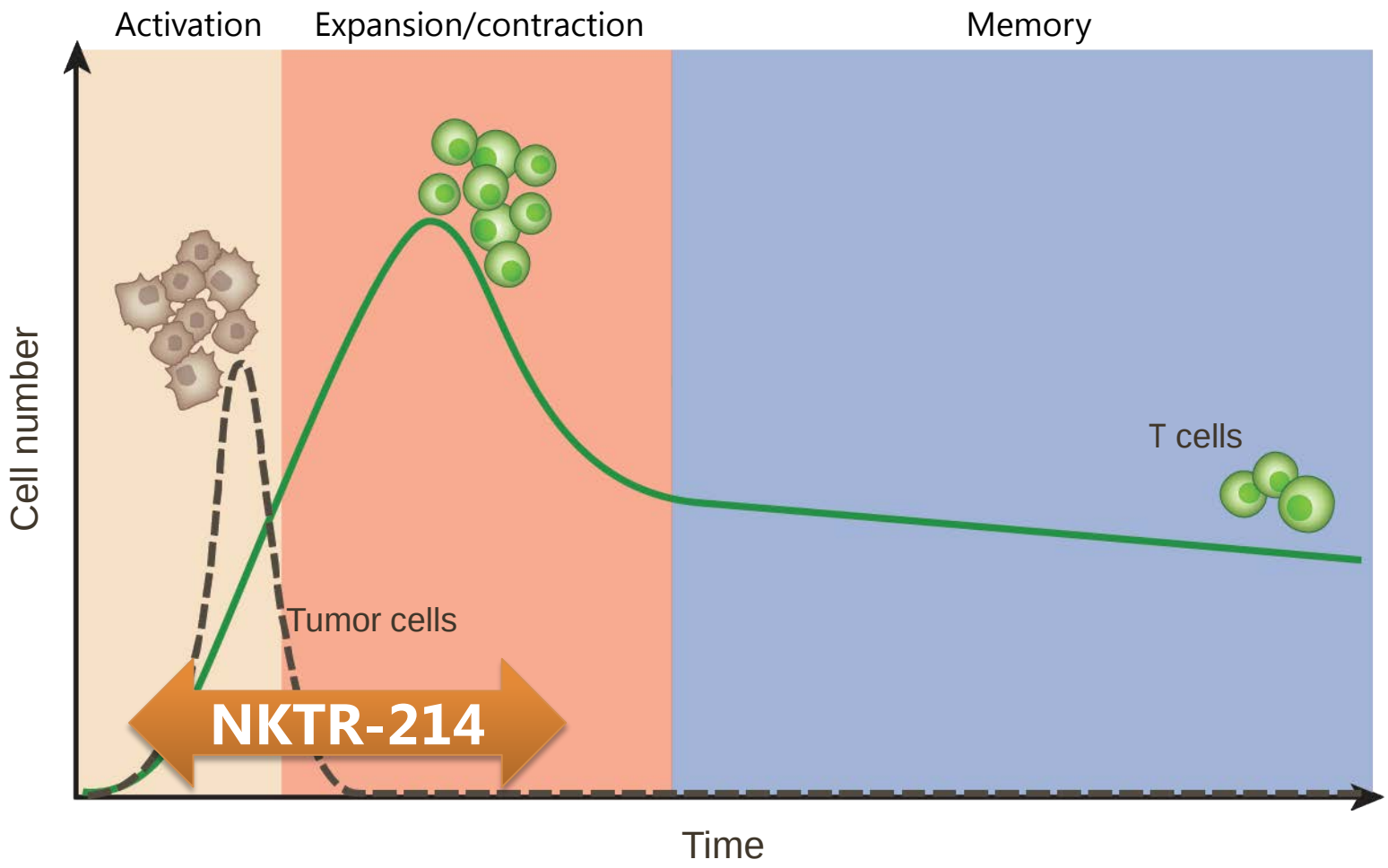
NKTR-214: Vaccine-like Tumor Resistance In Combination With Anti-CTLA-4 In Breast



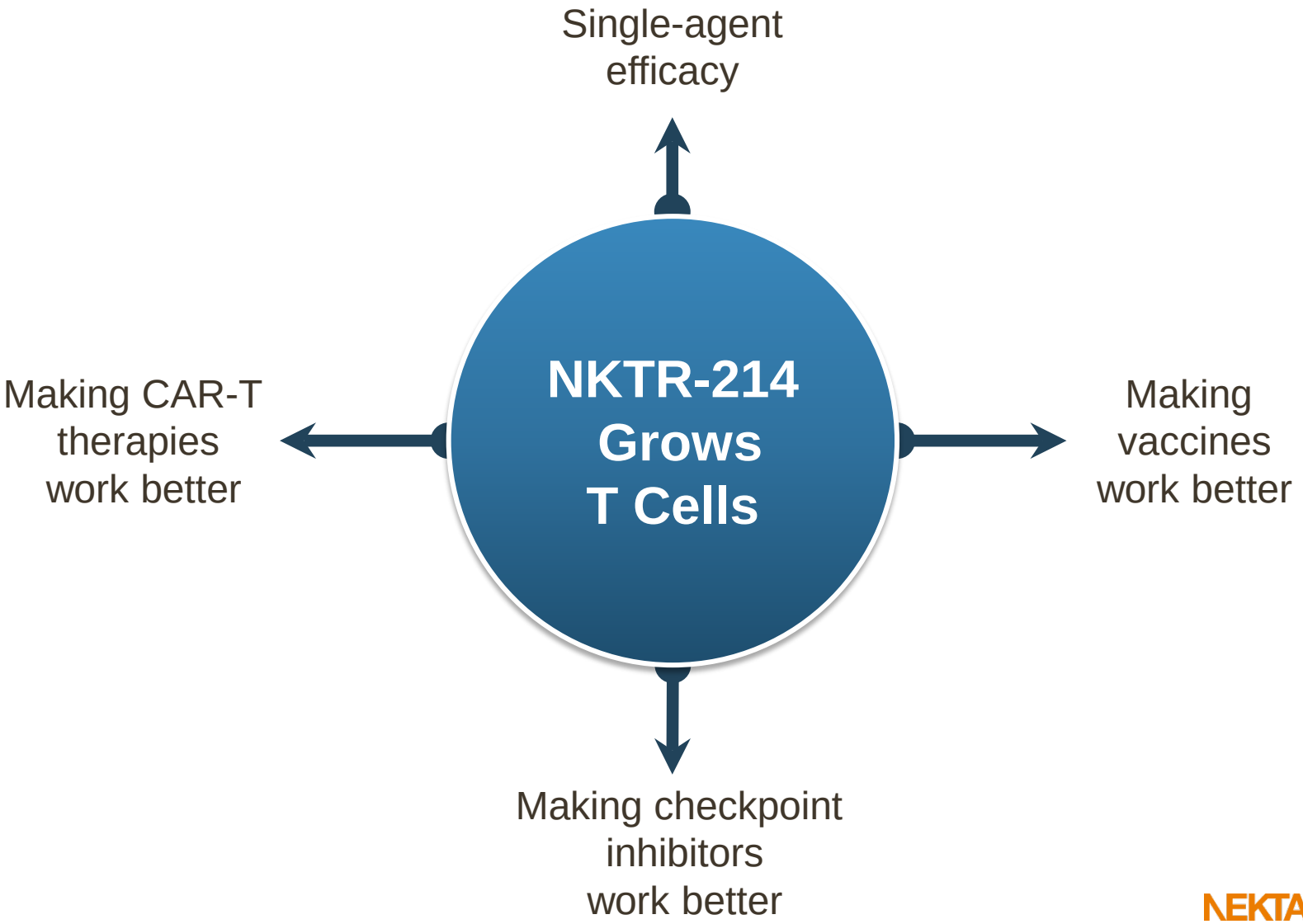
NKTR-214 + anti-CTLA-4 re-educated the immune system to provide long-term vaccine-like tumor resistance

Primary model : EMT6 mammary carcinoma (green),
Non-related rechallenge model : CT26 colon carcinoma (red)
Balb/c mice; N=70 for primary efficacy; N=20 for EMT6 rechallenge and N=10 for CT26 challenge; N=14 for second EMT6 rechallenge
Anti-CTLA-4, 100µg i.p., twice-weekly; NKTR-214, 0.8mg/kg i.v. q9dx3

NKTR-214 Unlocks the IL-2 Pathway to Improve the Quality of IO Therapy



NKTR-214: A Differentiated IO Opportunity

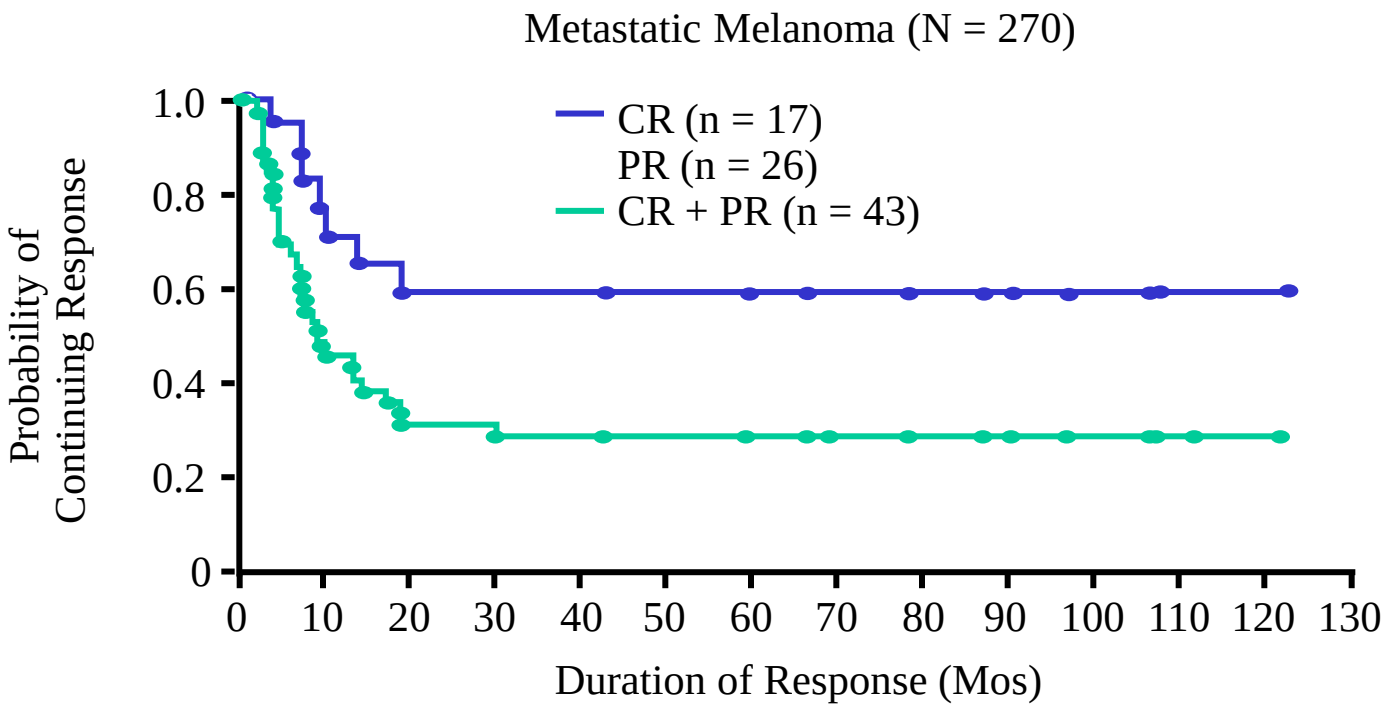


Systemic Immunotherapy for Metastatic Melanoma

Michael B. Atkins, M.D.
Deputy Director
Lombardi Comprehensive Cancer Center
Professor of Medicine and Oncology
Georgetown University Medical Center
Washington, DC

High-Dose IL-2 Therapy: Durable Responses Seen

- High-dose IL-2 produces durable responses in 16% of pts with advanced melanoma
- Few relapses in pts responding for over 2.5 yrs (likely cured)
- FDA approval in 1998 for melanoma

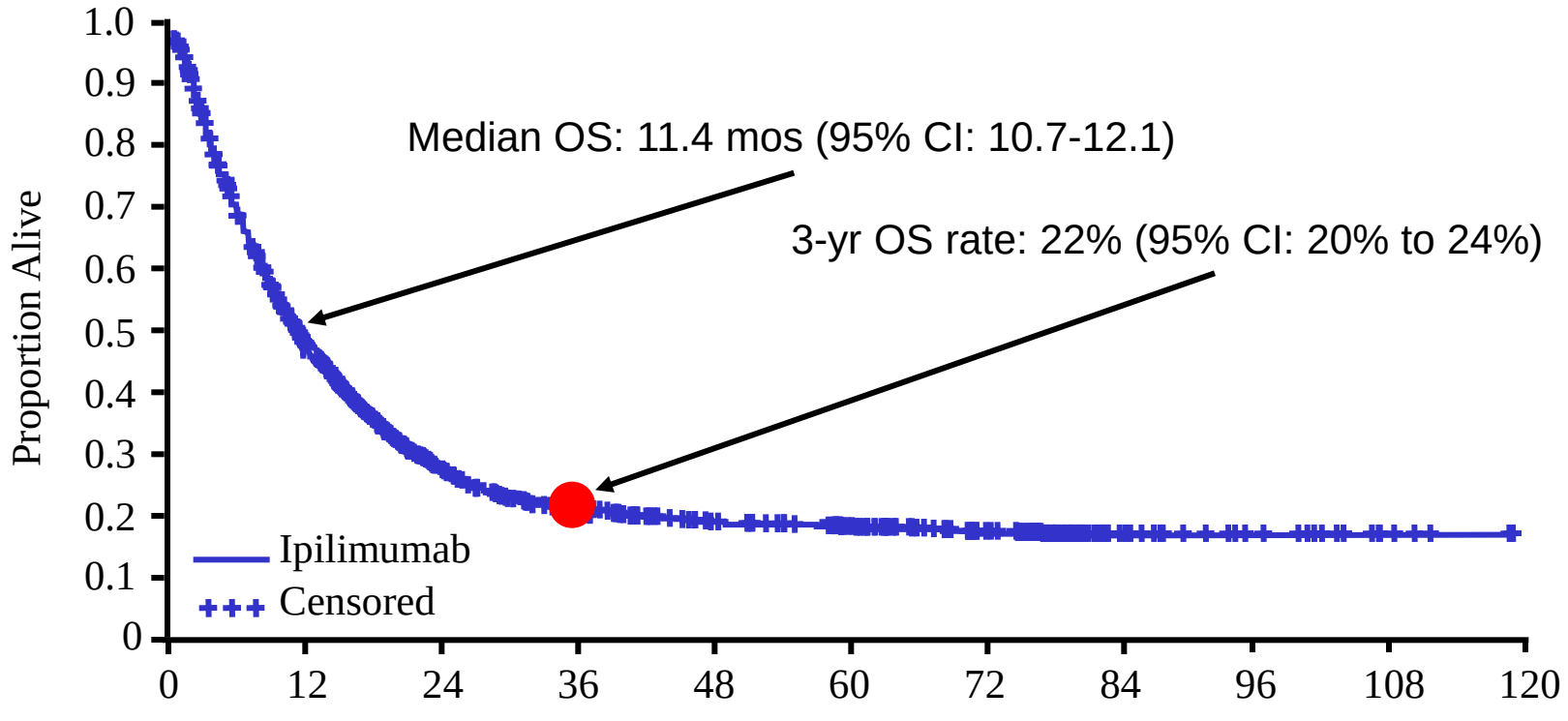


Atkins MB, et al. *J Clin Oncol*. 1999;17:2105-2116.

High-Dose IL-2 Therapy in Melanoma-30 year history

- High-dose IL-2 appears to benefit pts, but:
  - Toxic, complex; must be delivered as an inpatient regimen
- Use remained limited to selected pts treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select pts who might benefit from high-dose IL-2 therapy produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in pts with cancer, but newer immunotherapies are needed

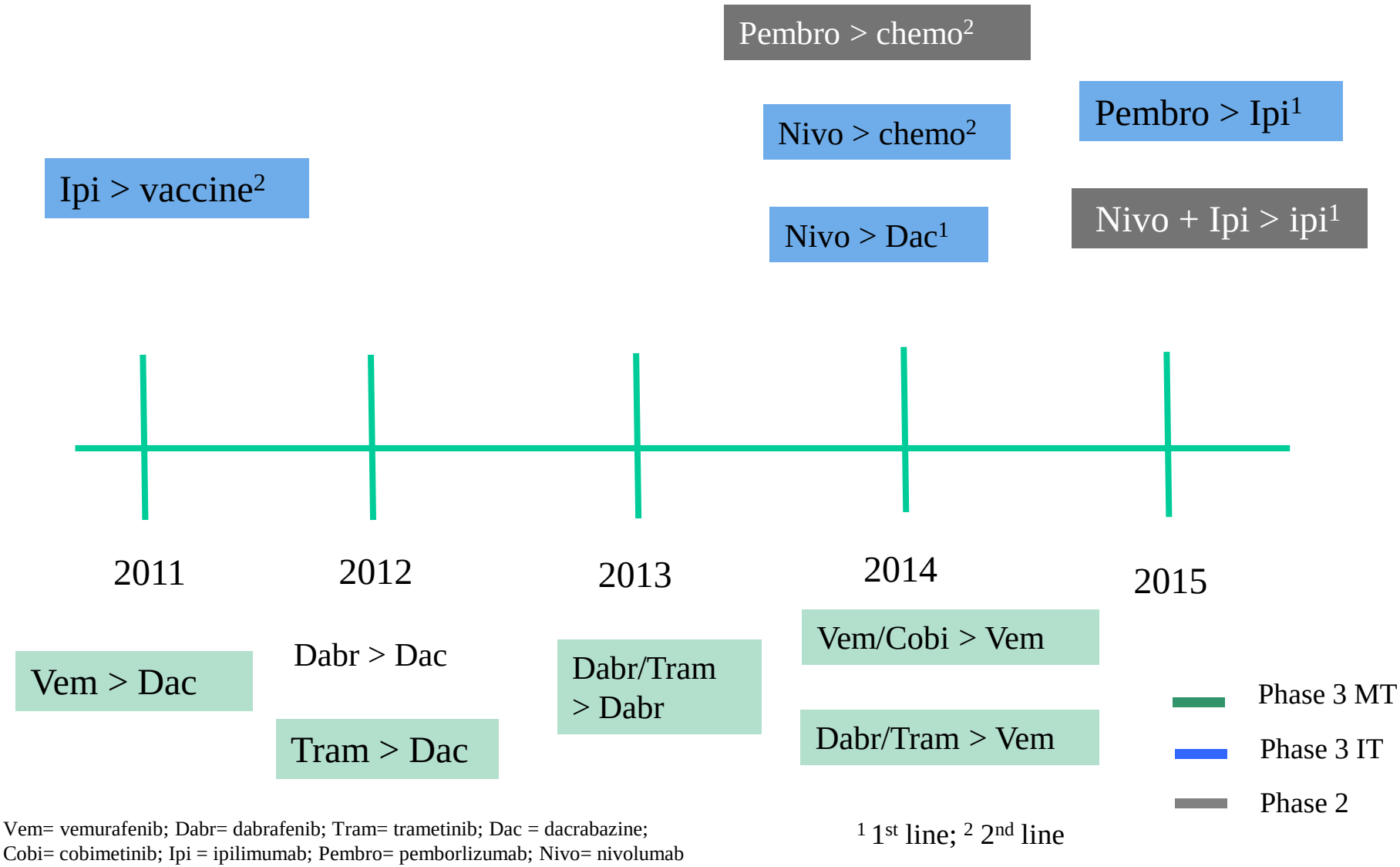
Analysis From Phase II and Phase III Trials of Ipilimumab Show OS Plateau at 3 Years



Pts at Risk, n											
Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.
Schadendorf D, et al. J Clin Oncol. 2015 [Epub ahead of print].

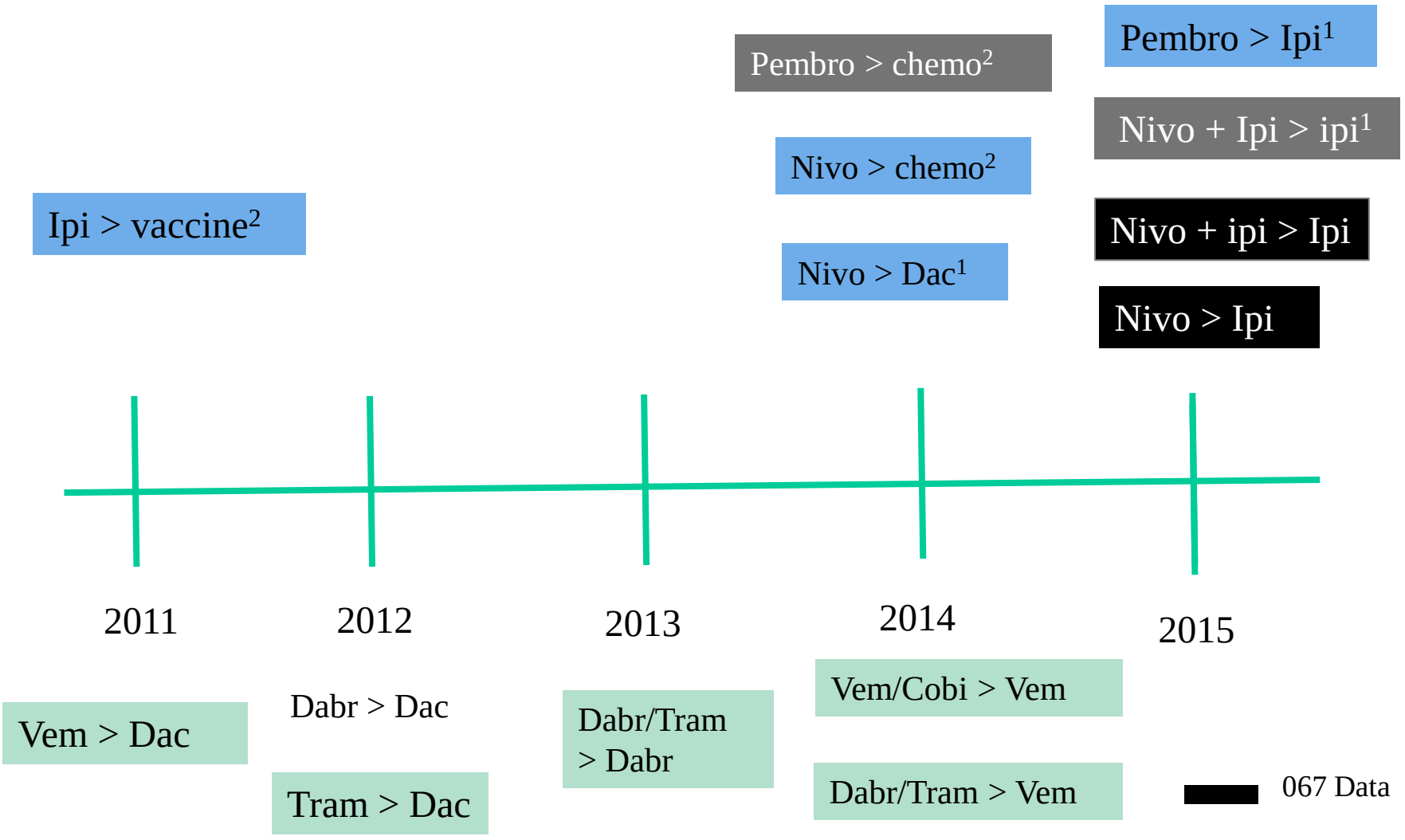
Major Treatment Advances For Metastatic Melanoma



Vem= vemurafenib; Dabr= dabrafenib; Tram= trametinib; Dac = dacrabazine;
Cobi= cobimetinib; Ipi = ipilimumab; Pembro= pemborlizumab; Nivo= nivolumab

[1] 1st line; [2] 2nd line

Major Treatment Advances For Metastatic Melanoma



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Cobi= cobimetinib; Ipi = ipilimumab; Pembro= pemborlizumab; Nivo= nivolumab

[1] 1st line; [2] 2nd line

Principal Take Home Message From AACR/ASCO 2015

Ipilimumab can no longer be considered a standard first line immunotherapy for patients with advanced melanoma

Single Agent Anti-PD1 Blockade: Future Directions

- Determine when to stop
  - Our current approach
- Adjuvant protocols
- Biomarker refinement
- Treatment of resistance
- Combinations:
  - Immunotherapy, targeted therapy, RT, Vaccines

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Company	Development stage
PD-1	Nivolumab	Fully human IgG4	Bristol-Myers Squibb	Approved in Melanoma, NSCLCa Phase III in RCC, HNSCC etc
	Pembrolizumab	Humanized IgG4	Merck	Approved in Melanoma, Phase III in Lung, bladder etc
	Pidilizumab	Humanized IgG1	Curetech Medivation	Phase II Melanoma, Heme Malignancies
PD-L1	MEDI-4736 (Durvalumab)	Engineered human IgG1	MedImmune	Phase I-II multiple tumors
	MPDL-3280A* (Atezolizumab)	Engineered human IgG1	Genentech	Phase III in bladder, RCC, NSCLC
	MSB0010718C (Avelumab)	Fully human IgG1	EMD Serono (Pfizer)	Phase II in ovarian, Phase I in multiple solid tumors

Role of anti-PD-L1 Antibodies in Melanoma

- Activity appears equivalent to nivo or pembro in many diseases including melanoma
- Limited data in melanoma, to date
- Don’t see a role for single agent anti-PDL1 antibodies in melanoma
- May find a role in combinations particularly with BRAF/MEK inhibitors (or other proprietary drugs)

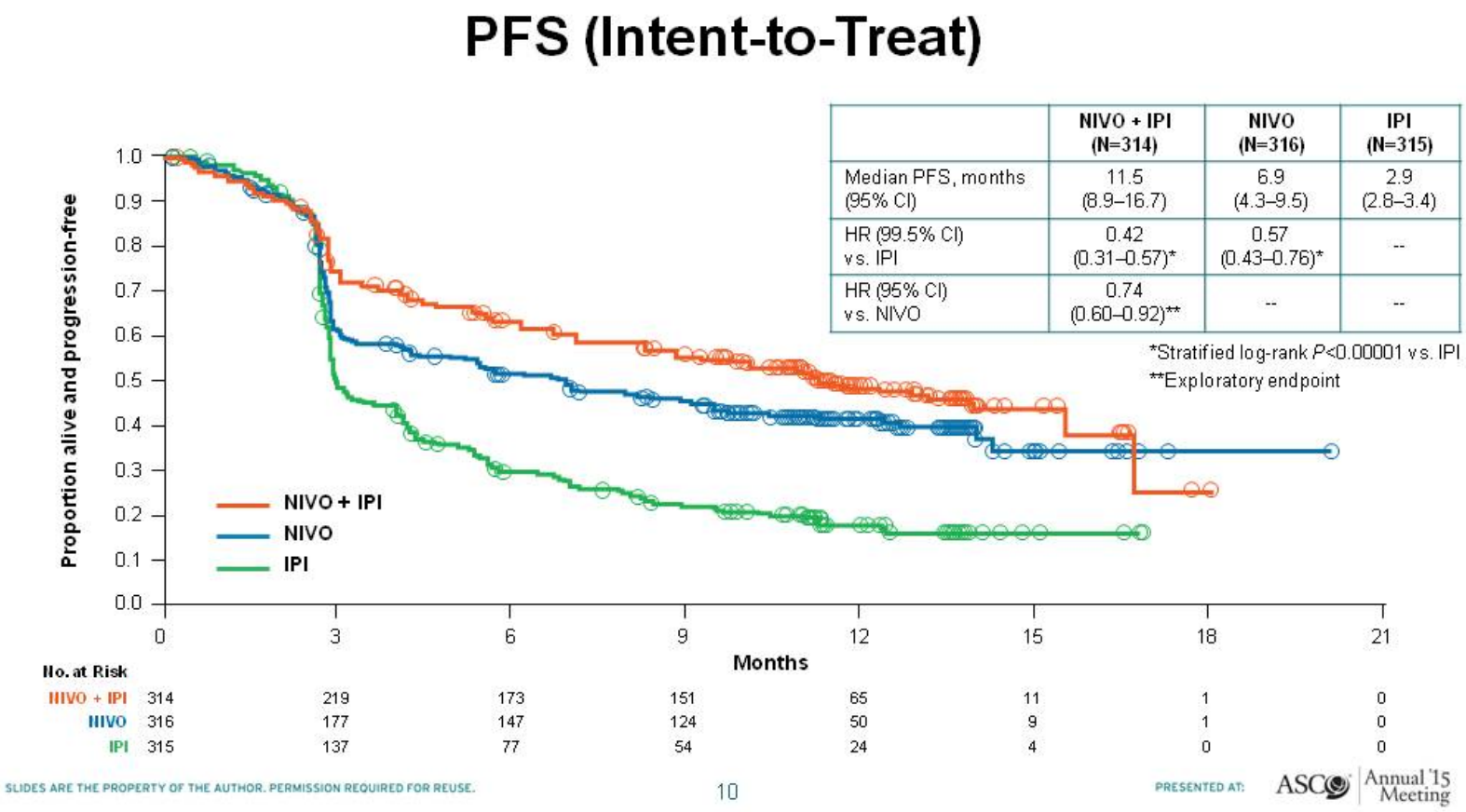
Nivo vs Nivo + Ipi: Topline data

	Nivo	Nivo + Ipi
Med PFS (months)	**6.9** (4.3-9.5)	**11.5** (8.9-16.7)
ORR, % (95% CI)	**43.7** (38.1-49.3)	**57.6** (52.0-63.2)
CR %	8.9	11.5
Tumor Burden change	- 34.5%	- 51.9%
Response Duration	NR	NR
Med OS	NR	NR
Grade 3-4 SAEs	16%	55%

Proof of principle that combination immunotherapy can produce greater activity than anti-PD1 alone

Melanoma Clinical Opportunities

Combination therapy improves PFS but at 1 year 50% of patients have progressed

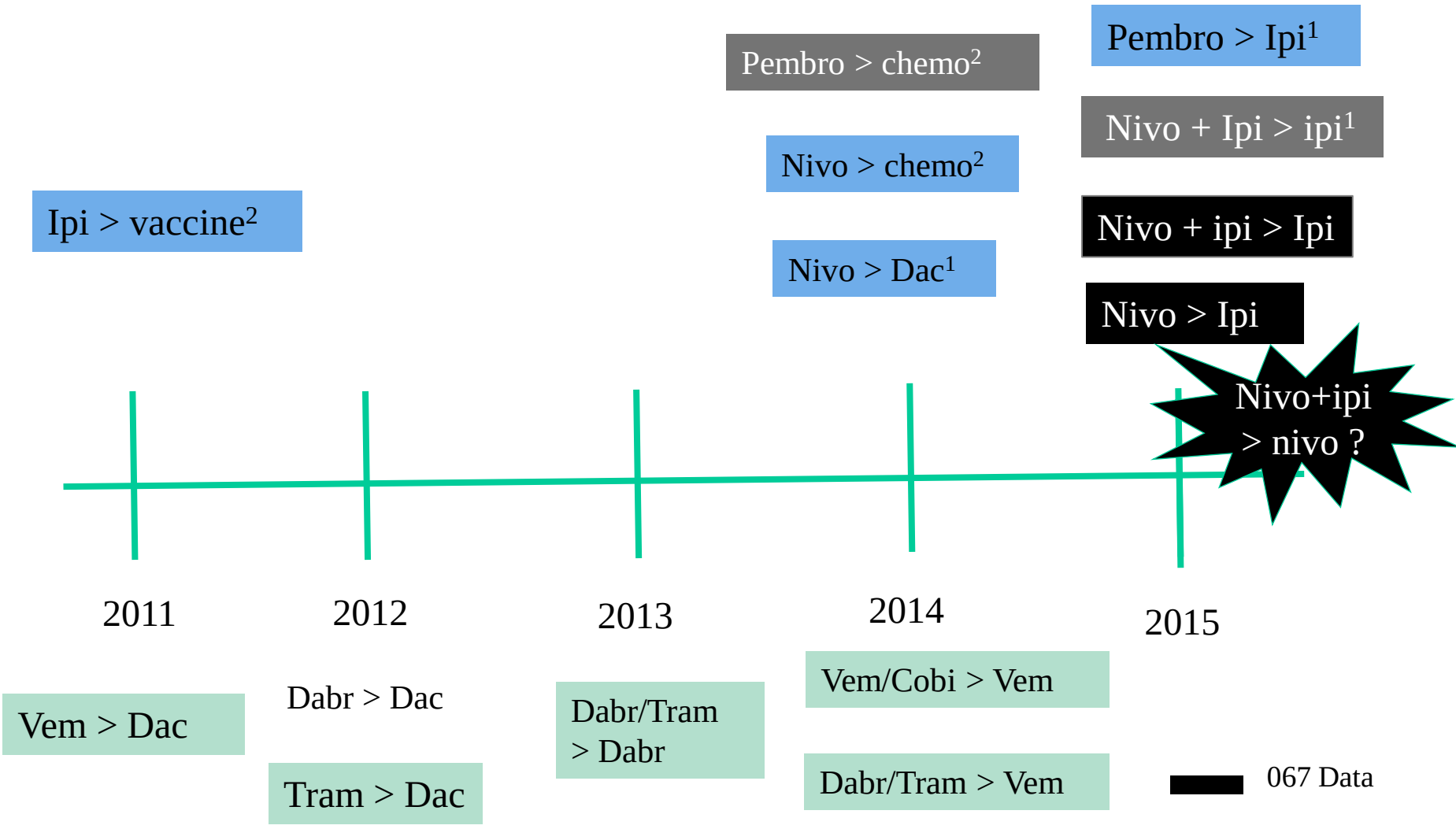


	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

Nivo + Ipi Toxicity

- Toxicity is severe
  - Mostly immune related AEs (irAEs)
  - 55% of patients have G3-4 SAEs
  - ~36% of patients had treatment discontinuation
- Manageable with immune modulatory drugs
  - No treatment related deaths
- irAE treatment doesn’t prevent tumor response
  - 67% (81/120) developed a response
  - 50% of responses appeared after treatment stopped

Major Treatment Advances For Metastatic Melanoma



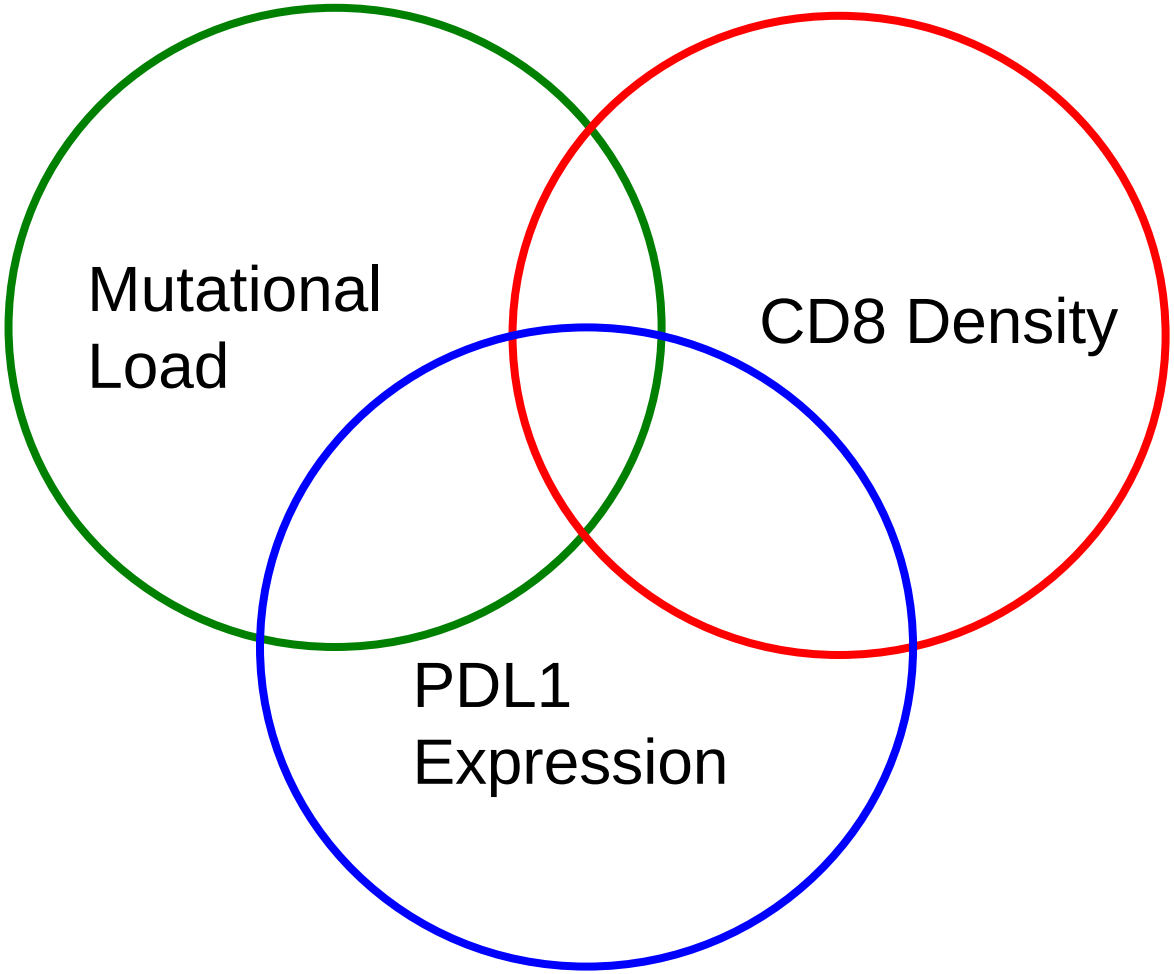
Vem= vemurafenib; Dabr= dabrafenib; Tram= trametinib; Dac = dacrabazine;
Cobi= cobimetinib; Ipi = ipilimumab; Pembro= pemborlizumab; Nivo= nivolumab

[1] 1st line; [2] 2nd line

PD-L1 Expression is a Weak Biomarker in Melanoma

- Assays are technically difficult and imperfect
  - Low expression, Tumor heterogeneity, Inducible gene expression ➡ sampling errors
  - ~ 2/3rd of responders to nivo alone were PDL1 negative
- Variable assay conditions
  - Antibody/assay (tumor vs immune cells)
  - Specimen used (archived vs fresh, primary vs met)
  - Threshold **(067- 27% PDL1+ vs. Keynote 006 study - 80% PDL1+)**
- **Biomarker refinement and standardization needed for clinical decision making- (yet to be validated subset analysis)**
- Even with a high threshold for positivity, the utility of biomarker for selection of nivo monotherapy is unconvincing

Biomarker Model



All inter-related

Melanoma may have a larger sweet spot

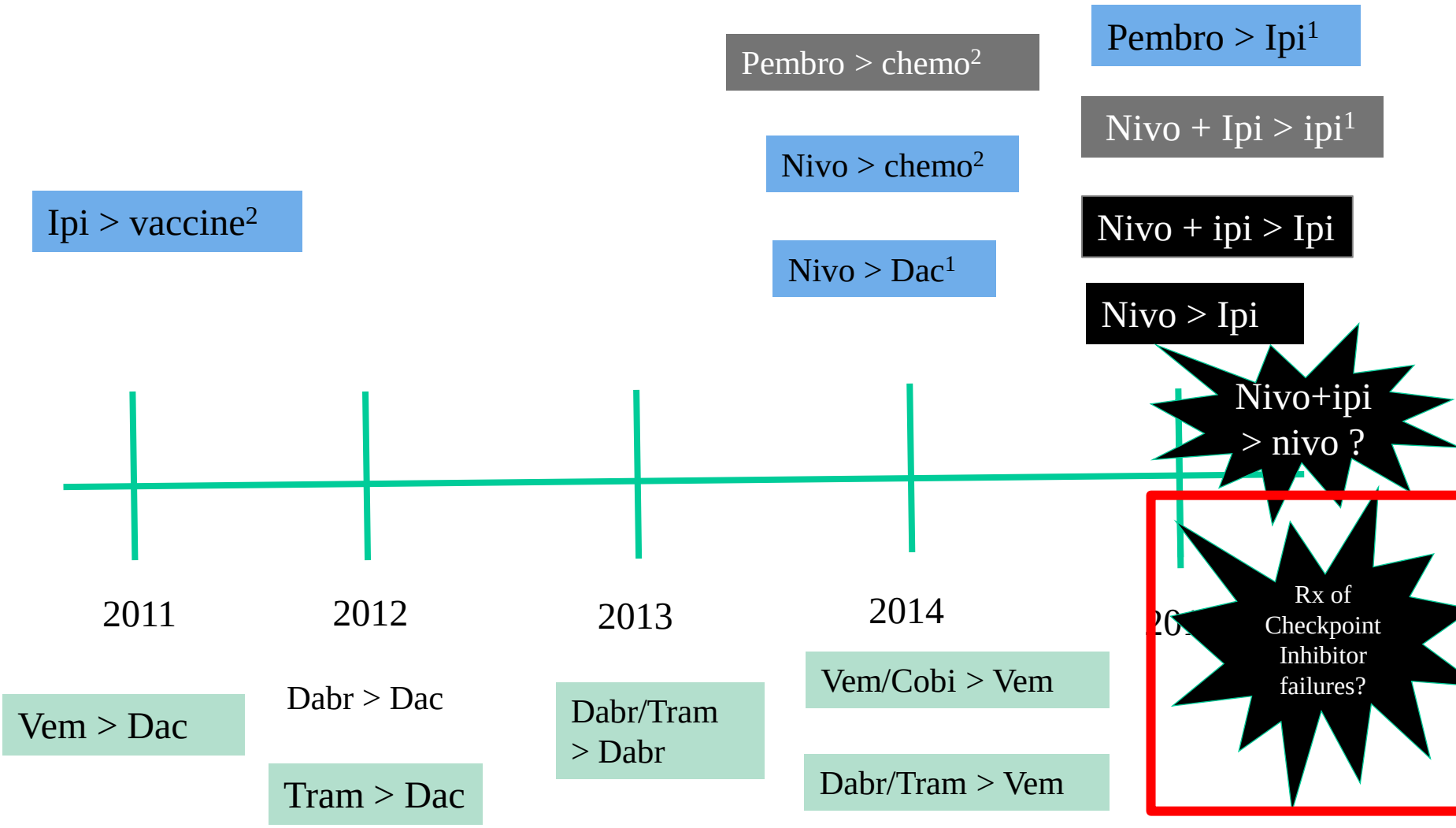
Treatment of Anti-PD1 Failures

- 60-70% of patients on anti-PD1 monotherapy and 40-50% of patients Nivo + Ipi will eventually exhibit disease progression

- The mechanism of disease progression after response is unclear, but likely involves either upregulation of other checkpoints, lack of diversity of T cell response or insufficient T cells.

- The major unmet need in the future will be restoring anti-tumor immunity in patients with time limited response to anti-PD1 therapy

Major Treatment Advances For Metastatic Melanoma- Future



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Cobi= cobimetinib; Ipi = ipilimumab; Pembro= pemborlizumab; Nivo= nivolumab

[1] 1st line; [2] 2nd line

Conclusions

- Nivo and pembro are new standards for advanced melanoma therapy
- Nivo + Ipi is likely more effective than anti-PD1 monotherapy
- Biomarker-based selection is not ready for Prime Time
- Combination immunotherapy has been established as a platform on which to explore- many options
- Treatment of anti-PD1 failures represents a new challenge/opportunity
- Much work remains to be done

Mutational Profiles and Immuno-Oncology Therapies in NSCLC

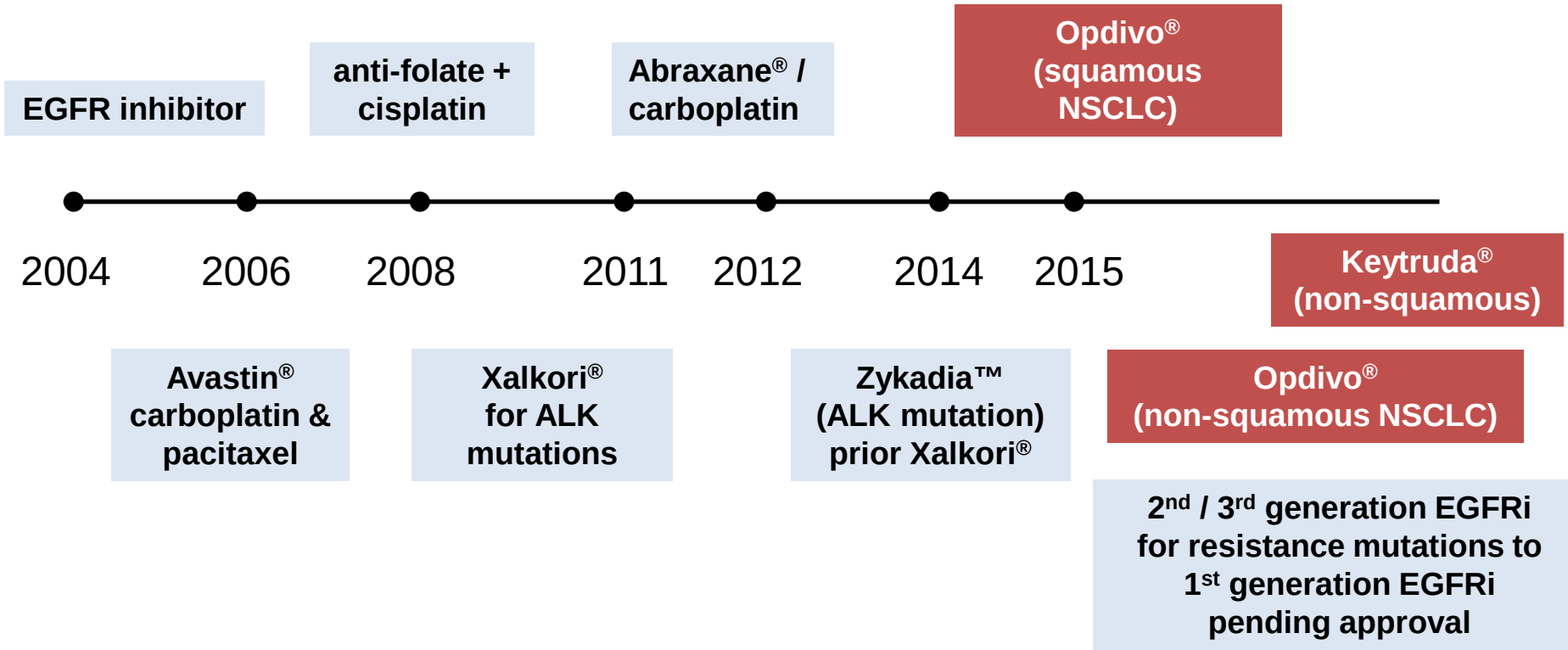
Naiyer Rizvi, M.D.

Columbia University Medical Center

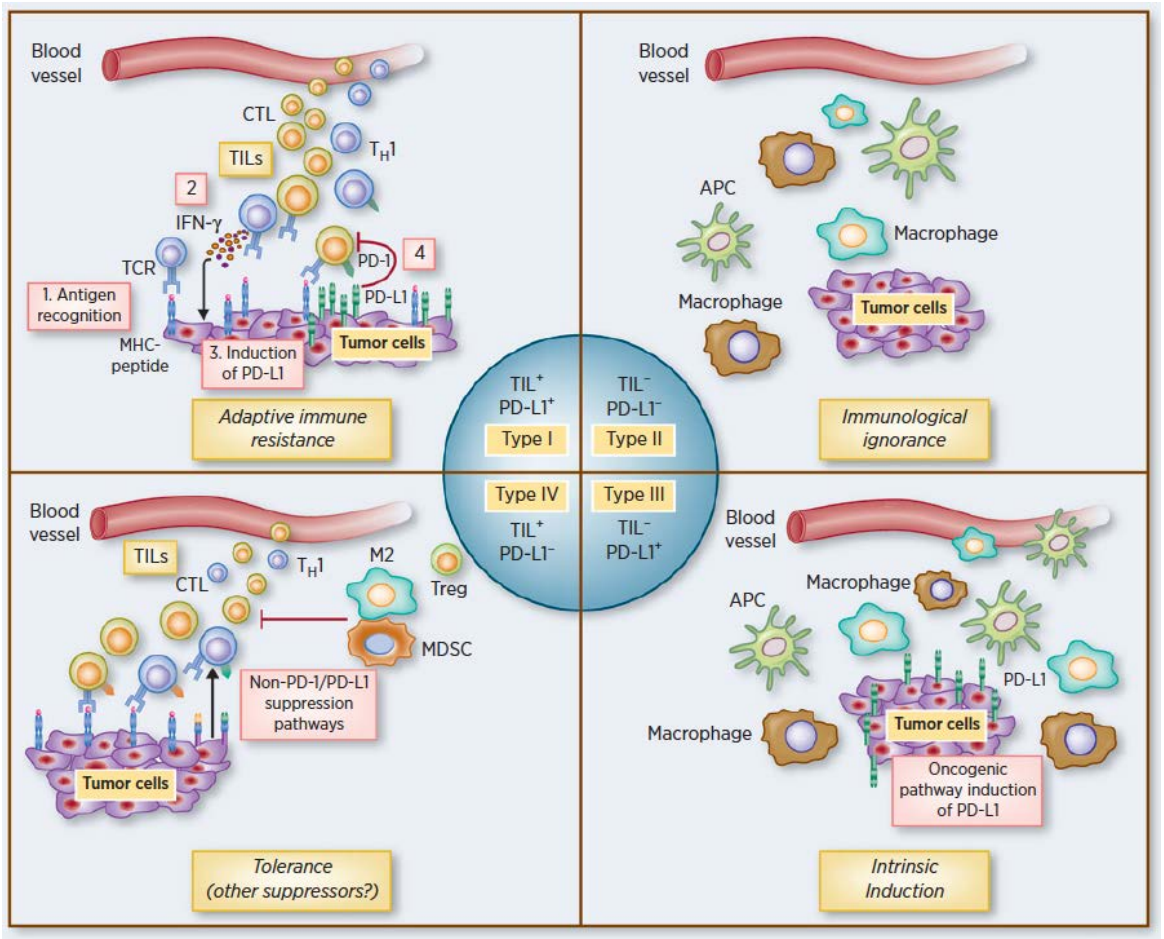
Major Treatment Advances for Non-Small Cell Lung Cancer Mostly Focused on Targeting Driver Mutations

Non-squamous wild-type (wt):
Avastin, gemcitabine, cisplatin, docetaxel

Squamous wt:
Carboplatin + paclitaxel, Abraxane or gemcitabine are the most common therapies



Immunosuppressive Tumor Phenotypes



Teng et al *Cancer Res* 2015

CheckMate 017:
Nivo in Squamous (SQ) NSCLC

- Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit versus standard-of-care docetaxel in previously-treated patients with advanced SQ NSCLC
  - 41% reduction in risk of death (HR 0.59; *P*=0.00025)
  - 1-year OS: 42% vs 24%
  - mOS: 9.2 vs. 6.0 mo
- Nivolumab received FDA approval in the U.S. on March 4, 2015 for metastatic SQ NSCLC with progression on or after platinum-based chemotherapy
- Nivolumab benefit was independent of PD-L1 expression

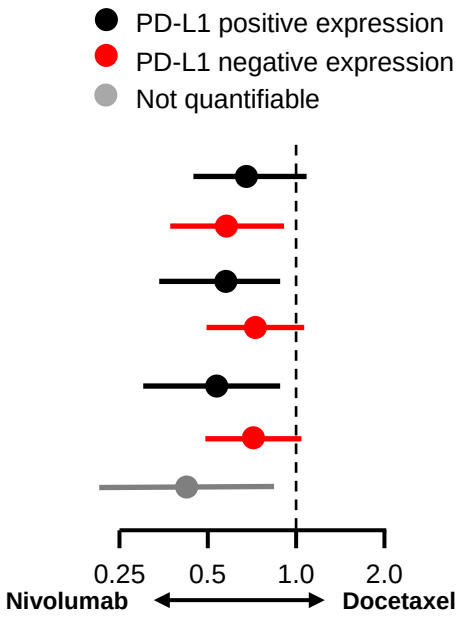
CheckMate 057: Nivo in Non-SQ NSCLC

- Nivolumab is the first PD-1 inhibitor to significantly improve OS and ORR vs. docetaxel in previously treated patients with advanced non-SQ NSCLC
  - 27% reduction in risk of death (HR = 0.73; *P* = 0.0015)
- CheckMate 057 is the second phase 3 trial to demonstrate superior survival of nivolumab over docetaxel in advanced NSCLC
- PD-L1 expression is predictive of benefit with nivolumab, starting at the lowest expression level (1%)
  - Median OS nearly doubled with nivolumab vs. docetaxel across PD-L1 expression continuum
  - ORR nearly tripled in PD-L1 expressors

CheckMate 017 and 057: Nivo Benefit +/- PD-L1 Expression

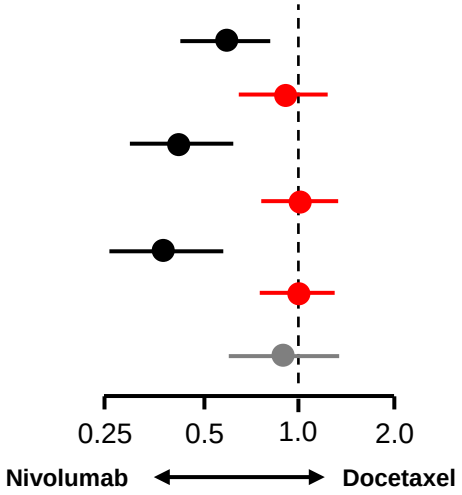
CheckMate 017

PD-L1 Expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	63	56	0.69 (0.45, 1.05)	**0.56**
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	**0.47**
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	**0.41**
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	



CheckMate 057

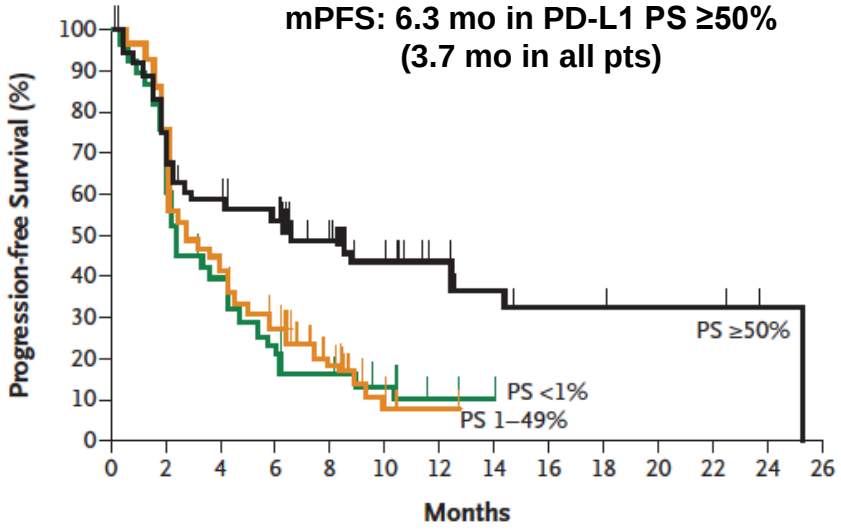
PD-L1 Expression	Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	**0.0646**
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	**0.0004**
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	**0.0002**
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable	61	66	0.91 (0.61, 1.35)	



ASCO 2015

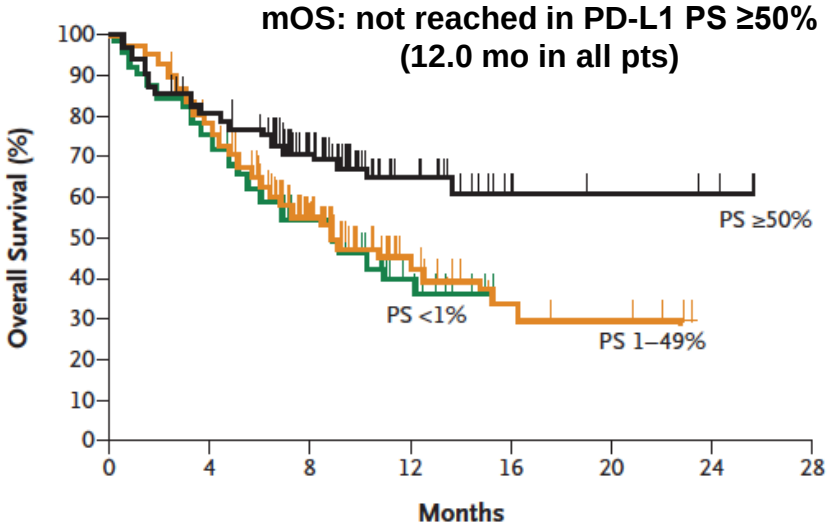
KEYNOTE-001: PFS and OS by PD-L1 Expression in Tumor Cells in NSCLC

PFS



No. at Risk														
PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1–49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0

OS



No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon EB, et al. *N Engl J Med*. 2015;372:2018-2028.

Pembrolizumab Monotherapy for NSCLC: Efficacy Data Supporting the Approved Indication

KEYTRUDA is indicated for the treatment of:

- Patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA

Efficacy Results

Endpoint	N=61
Overall Response Rate	
ORR%, (95% CI)	41% (29, 54)
Complete Response	0%
Partial Response	41%

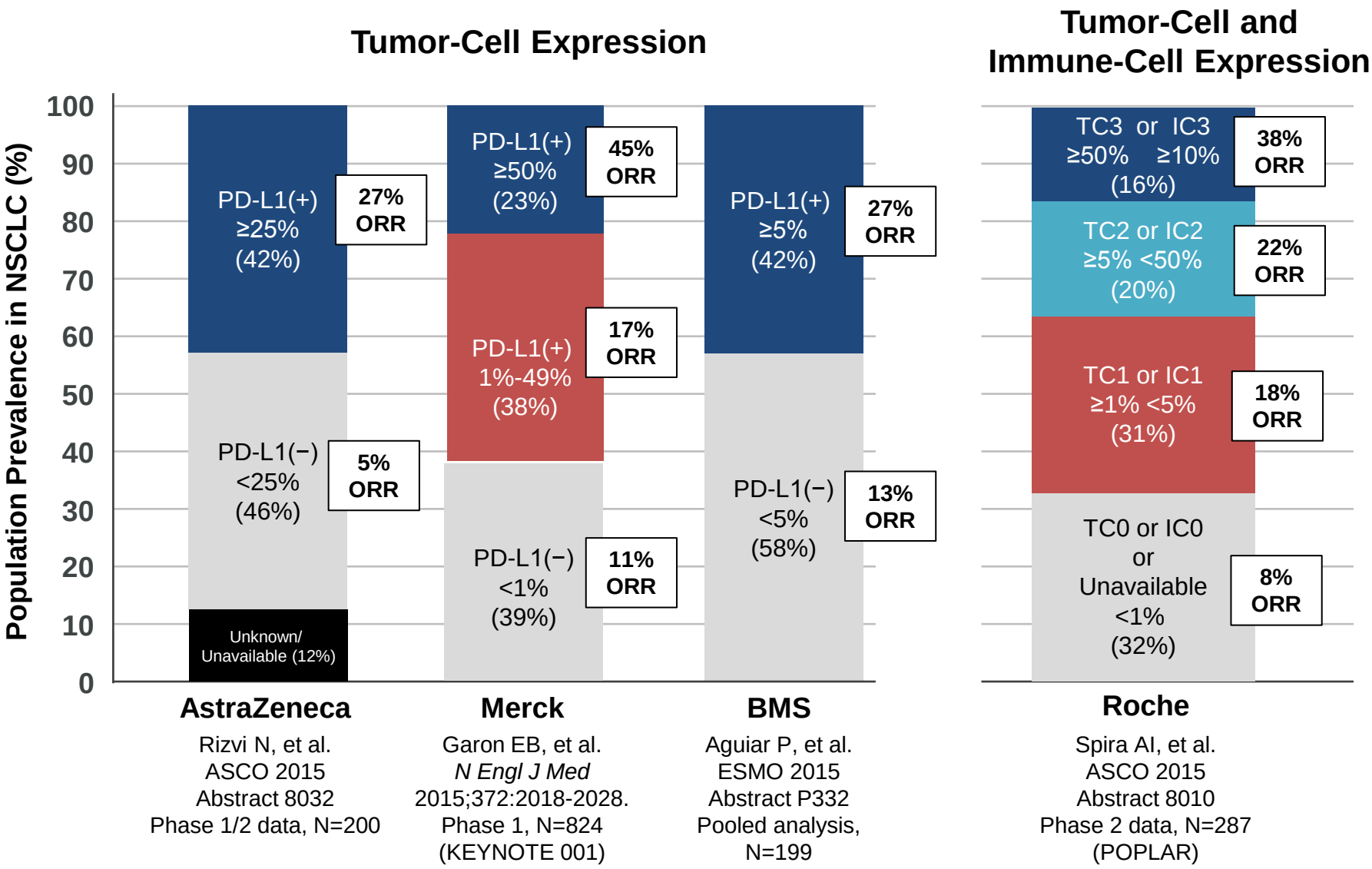
Keytruda (pembrolizumab) Prescribing Information. Whitehouse Station, NJ: Merck & Co, Inc; October 2015.

Comparison of Companion Diagnostics in Development

	MERCK	Bristol-Myers Squibb	AstraZeneca / MedImmune (A member of the AstraZeneca Group)	Roche	Pfizer / MERCK
Lead Rx asset	Pembrolizumab KEYTRUDA (anti-PD-1)	Nivolumab OPDIVO (anti-PD-1)	Durvalumab (anti-PD-L1)	Atezolizumab (anti-PD-L1)	Avelumab (anti-PD-L1)
Diagnostic partner	Dako	Dako	Ventana	Ventana	Dako
Clones	22C3	28-8	SP263	SP142	?
Machines Utilized	Link 48	Link 48	BenchMark ULTRA	BenchMark ULTRA	?
Compartment	TM	TM	TM	TC/IC	?
Variables	% of cells	% of cells	% of cells	% of cells	?
Definition of positive	PD-L1(+): >1% Strong(+): >50%	PD-L1(+): >1% Strong(+): >5%	PD-L1(+): ≥25%	TC / IC 3(+) TC / IC 2(+) TC / IC 1(+) TC / IC 0(−)	?
	Approved				

IC, immune cells; TC, tumor cells; TM, tumor membrane.

Summary of PD-L1+ Cutoffs



Rizvi N, et al.
ASCO 2015
Abstract 8032
Phase 1/2 data, N=200

Garon EB, et al.
N Engl J Med
2015;372:2018-2028.
Phase 1, N=824
(KEYNOTE 001)

Aguiar P, et al.
ESMO 2015
Abstract P332
Pooled analysis,
N=199

Spira AI, et al.
ASCO 2015
Abstract 8010
Phase 2 data, N=287
(POPLAR)

How to Treat the Low PD-L1 Patient

- Despite differences in histological subtype, antibody reagents used and cutoffs, trend is towards lower ORR for lower PD-L1 epression
- New agents may be needed to boost the ORR in the low expressing population
- New agents alone or in combination may boost the overall ORR irrespective of PD-L1 expression
- Treatment options for patients failing anti-PD-1 checkpoint inhibitors

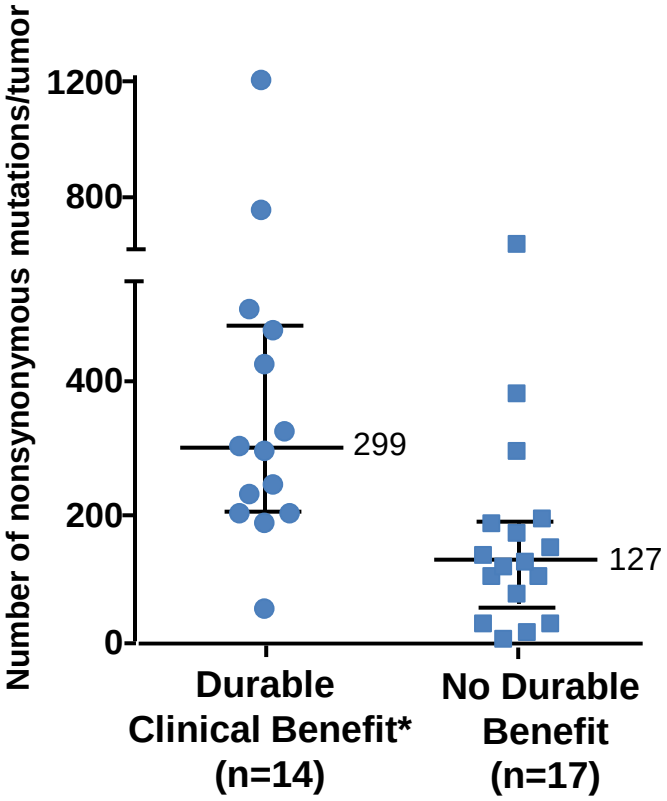
CheckMate 012: Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy

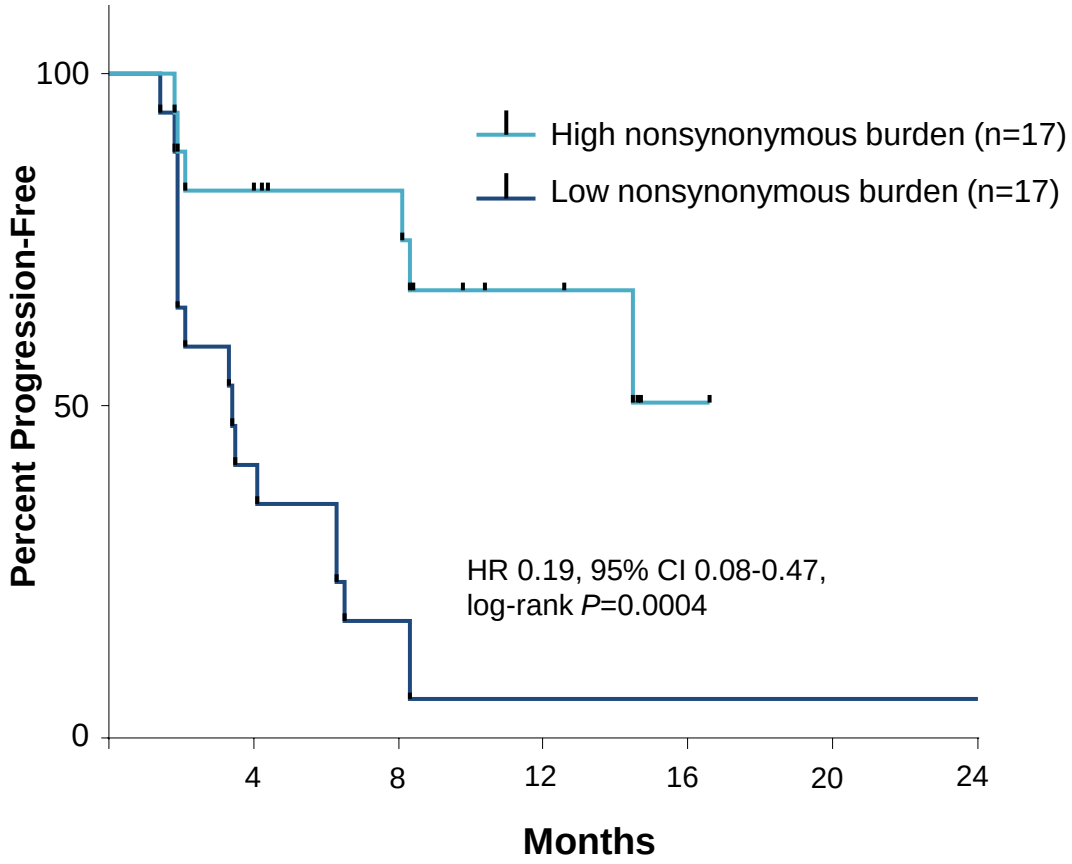
	Nivo 1 + Ipi 1 Q3W	Nivo 1 Q2W + Ipi 1 Q6W	Nivo 3 Q2W + Ipi 1 Q12W	Nivo 3 Q2W + Ipi 1 Q6W
Confirmed ORR, %	13	25	39	31
Unconfirmed PR, %	3	3	5	8
Confirmed DCR, %	55	58	74	51
ORR in PD-L1 ≥1% (+)	8	24	48	48
ORR in PD-L1 negative	15	14	22	0

Rizvi, et al WCLC 2015

Mutation Burden and Sensitivity to PD-1 Blockade in NSCLC

- Mutation burden was associated with improved objective response, durable clinical benefit, and longer PFS in patients treated with pembrolizumab
  - The median nonsynonymous mutation burden was 299 in the group of patients with durable clinical benefit versus 127 in the group of patients with no durable benefit (Mann-Whitney *P*=0.0008).

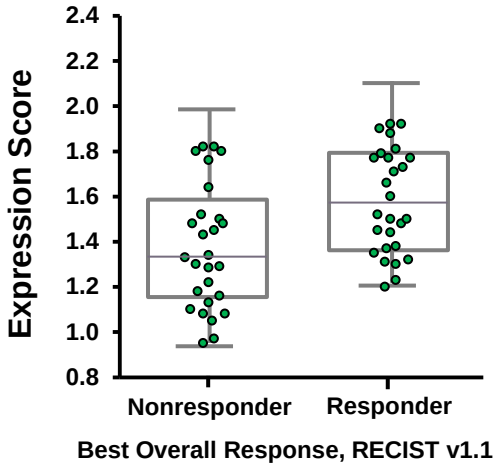




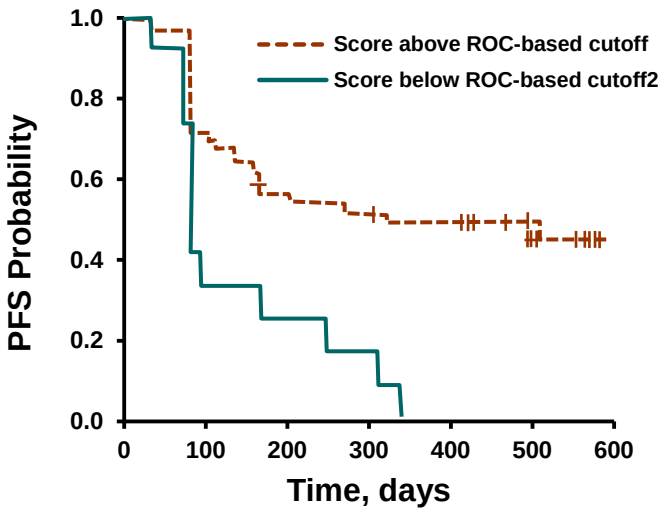
*Partial or stable response lasting >6 months. Rizvi N, et al. *Science.* 2015;348(6230):124-128.

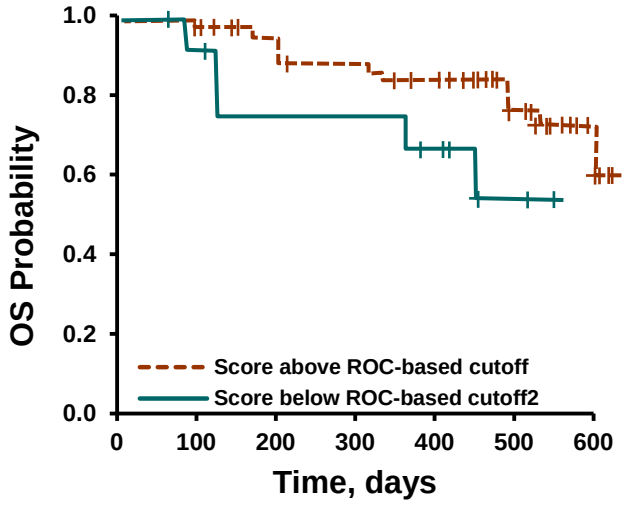
Association of Response to Pembrolizumab With an Interferon-Inflammatory Immune Gene Signature in Melanoma

- The 28-gene immune signature showed statistically significant associations with ORR (*P*=0.027) and PFS (*P*=0.015)



PFS and OS in patients with INF-γ signature score above and below the cutoff

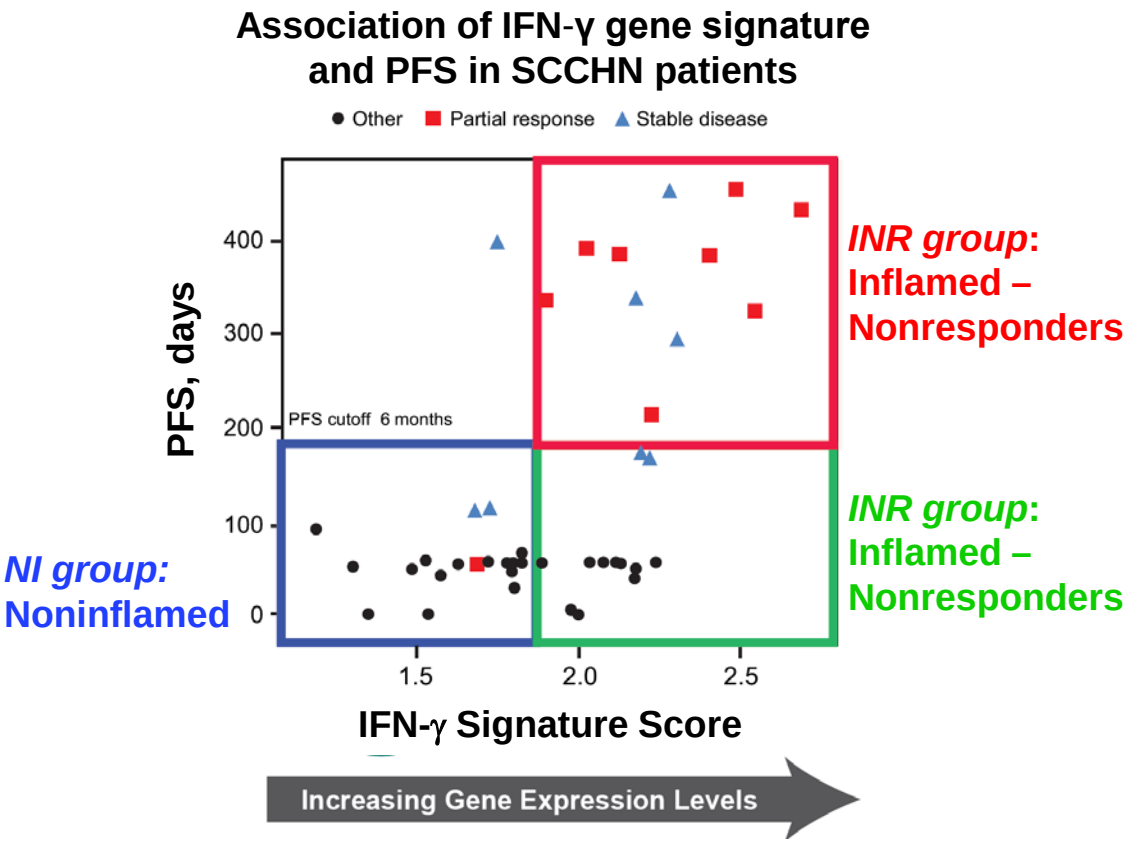




ROC=receiver operating characteristic. Ribas A, et al. ASCO 2015. Abstract 3001.

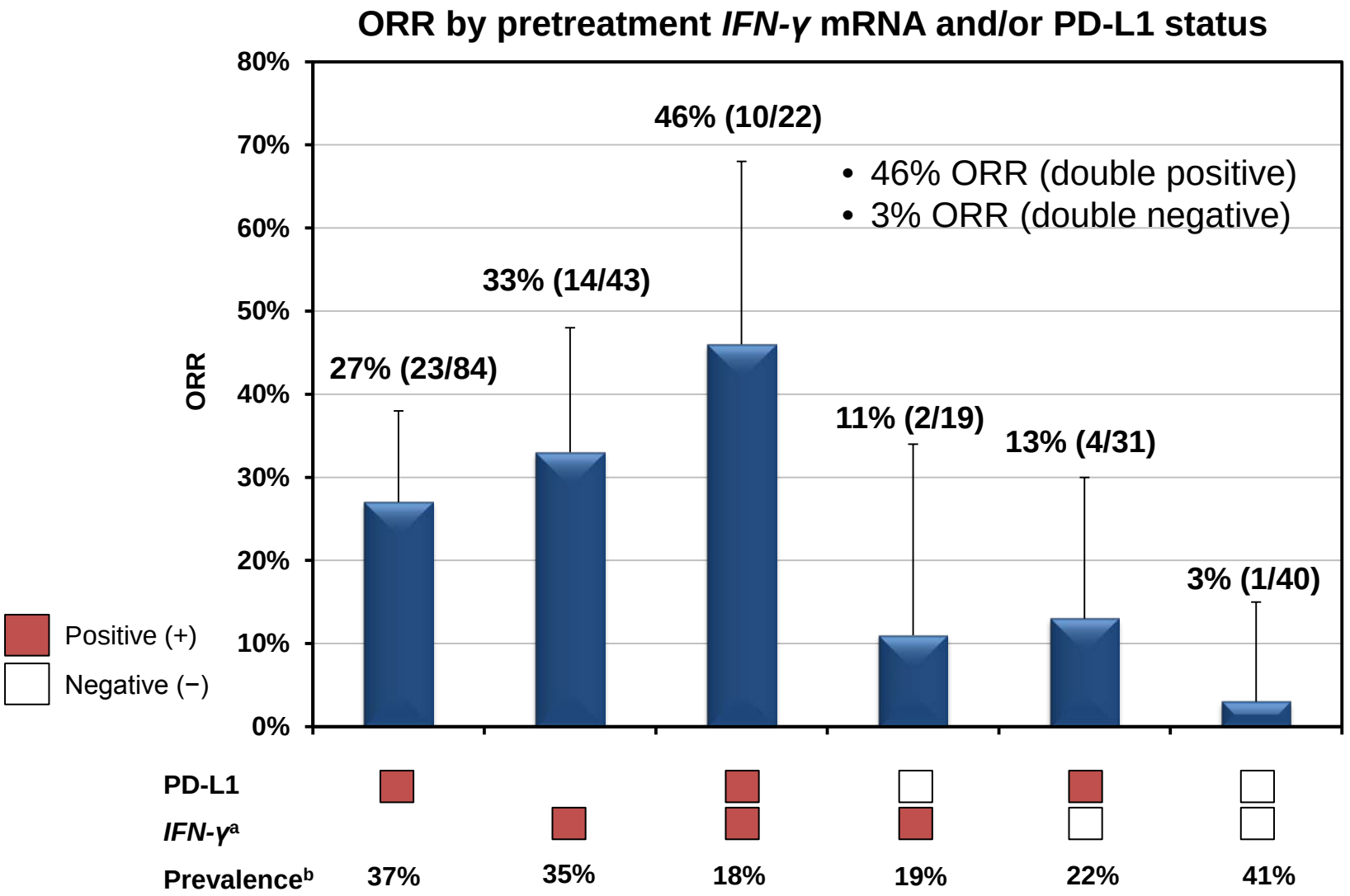
Correlation of Gene Expression Signatures and Clinical Outcomes in PD-L1(+) SCCHN Patients Treated With Pembrolizumab

- The immune-related gene expression signatures identified in melanoma patients were independently tested in 43 patients with R/M PD-L1(+) SCCHN treated with pembrolizumab in the KEYNOTE-012 study
- Significant association was observed between the identified gene signatures and best overall response and PFS



Siewert TY, et al. ASCO 2015. Abstract 6017.

Pretreatment PD-L1(+) and IFN-γ(+) NSCLC Patients May Respond Best to Durvalumab Monotherapy



[a]IFN-γ positivity was defined by a cycle threshold of less than 25. [b]Calculated prior to PD-L1 status enrichment; Error bars indicate 95% CIs; *IFNγ(–)* ORR=8% (6/79); PD-L1(–) ORR=5% (5/92). Higgs BW, et al. ECC 2015. Abstract 15LBA.

Phase 3 First-Line Combination NSCLC Trials (all PD-L1 unselected)

Treatment	N	Arms		
Checkmate 227		Ipi, Nivo	Chemo	OS
Mystic		Durva, Treme	Chemo	PFS
Neptune	800	Durva, Treme	Chemo	OS
IMpower 111	400	Atezo	Chemo	PFS
IMpower 130	400	Atezo	Chemo	PFS
IMpower 150	1200	Atezo, Chemo, Bev	Chemo, Bev	PFS
IMpower 131	1200	Atezo, Chemo	Chemo	PFS

Current IO Combinations in Development Exploit Similar Mechanisms

Target	Agent	Combination	Mechanisms Provided by the Combination
4-1BB	PF-05082566	Pembrolizumab	Co-stimulation agonist and checkpoint inhibitor
LAG-3	BMS-986016	Nivolumab	Two checkpoint inhibitors
LAG-3	LAG-525	PDR001	Two checkpoint inhibitors
OX40	MOXR0916	Atezolizumab	Co-stimulation agonist and checkpoint inhibitor
CD27	Varlilumab	Nivolumab	Co-stimulation agonist and checkpoint inhibitor
B7-H3	MGA-271	Pembrolizumab	Co-stimulation agonist and checkpoint inhibitor

Opportunity for a T-cell expanding agent to be developed in the future

Summary and Conclusions

- Immunotherapy has played a surprisingly important role in NSCLC; chemo and targeted therapies have led historically
- Single agent anti-PD1 tends to benefit patients who express PD-L1
  - The large majority do not respond however
- Combination immunotherapies must employ multiple complementary immune activation mechanisms
  - Ultimately T cells require an agonist signal through the IL-2 pathway
- Agonizing the IL-2 pathway may increase the number and duration of responders for patients with lung cancer

Clinical and Biomarker Strategy for NKTR-214 Development

Translating into the Clinic

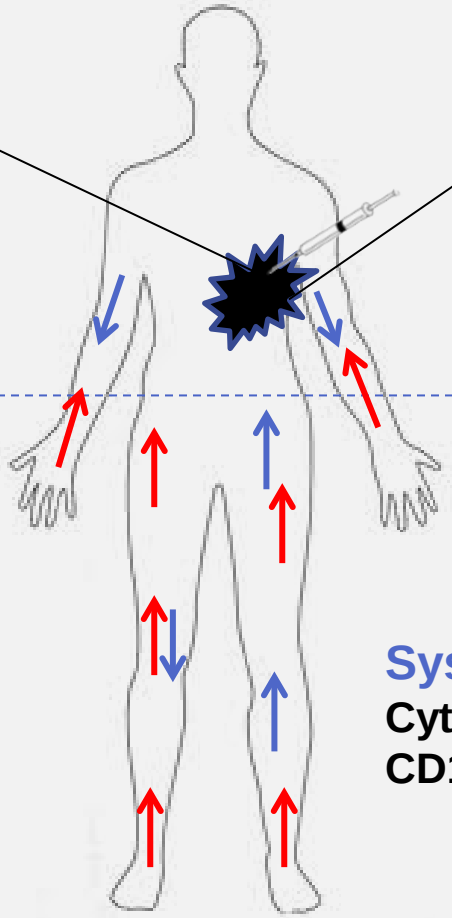
Dr. Adi Diab
MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

4 Pillars of Immunotherapy

TLR Activation
(Innate arm)

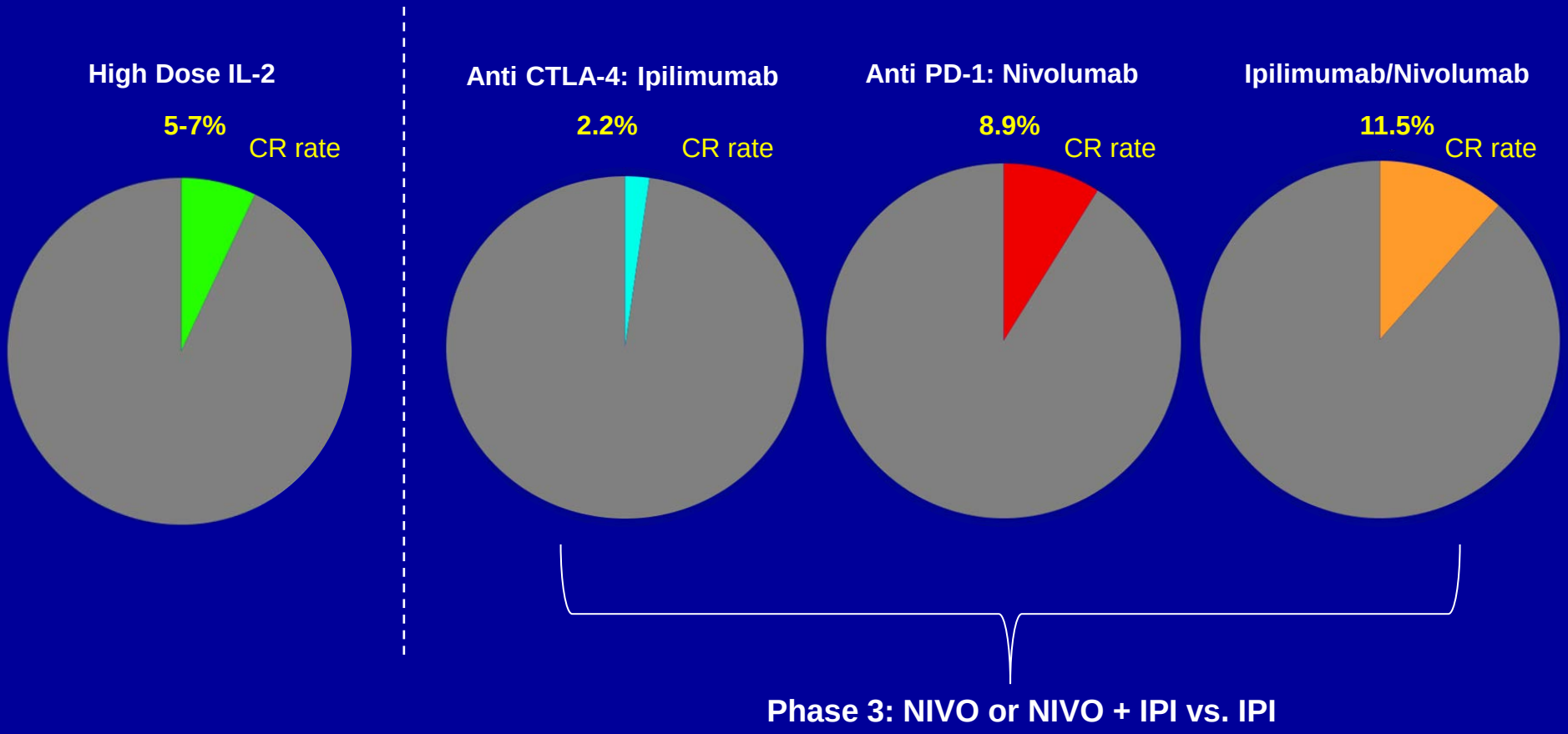
CD40 Activation
(Innate arm)



Systemic 1(Adaptive arm)
Checkpoints blockade:
CTLA-4/PD-1blockade

Systemic 2 (Adaptive & Innate arms)
Cytokine therapy:
CD122: Biased IL-2/ IL-15 complex

Complete Response Rate in Immunotherapy Metastatic Melanoma

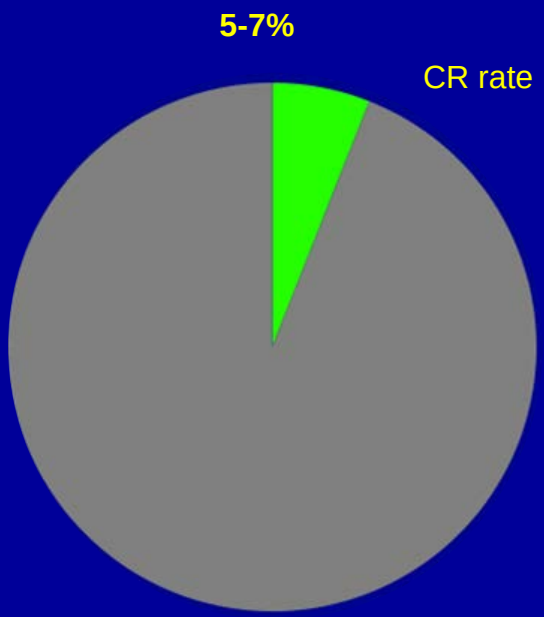


Larkin J et al. *N Engl J Med* 2015. DOI: 10.1056/NEJMoa1504030

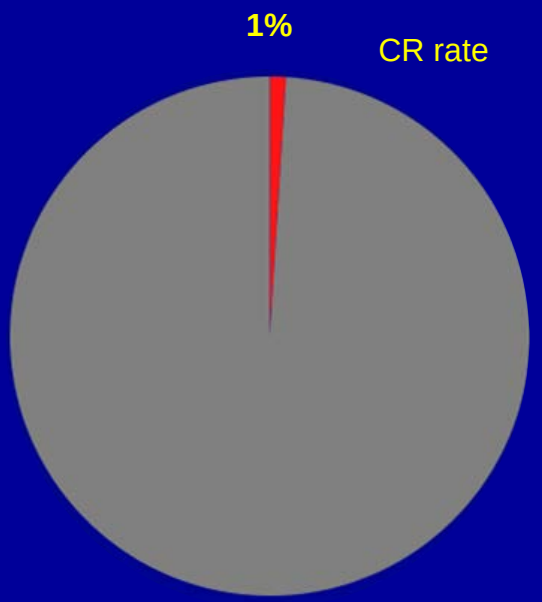
Atkins MB, et al. *J Clin Oncol.* 1999;17:2105-2116.

Complete Response Rate in Immunotherapy Renal Cell Carcinoma

High Dose IL-2



Anti PD-1: Nivolumab



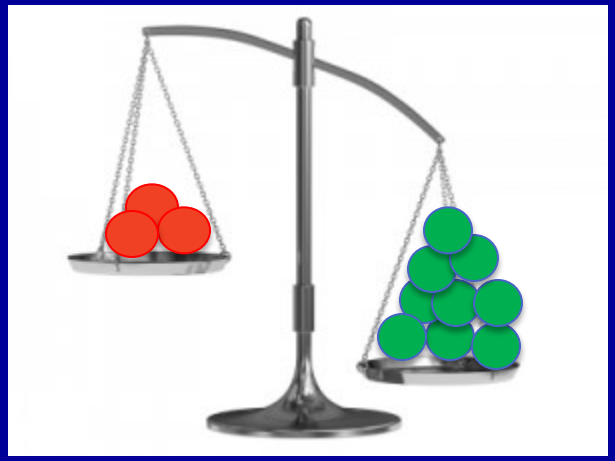
Fisher RI et al .*Cancer J Sci Am.* 2000 Feb;6 Suppl 1:S55-7.

Fyfe G, et al. *J Clin Oncol.* 1995 Mar;13(3):688–696.

Motzer et al, *New Engl. J. Med,* 2015, Nivolumab vs Everolimus.

How to Improve Clinical Benefit of IL-2

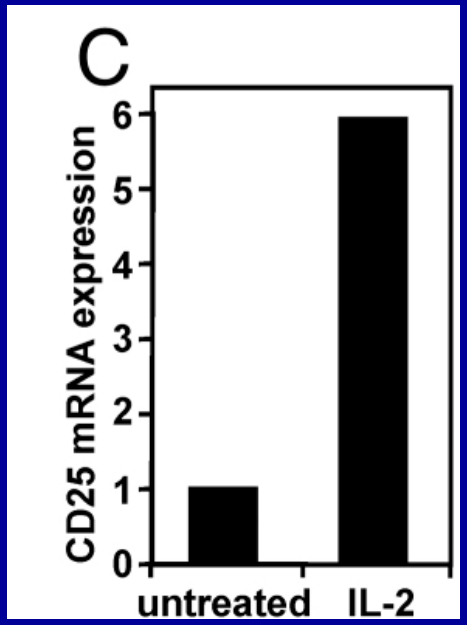
Decrease Toxicity

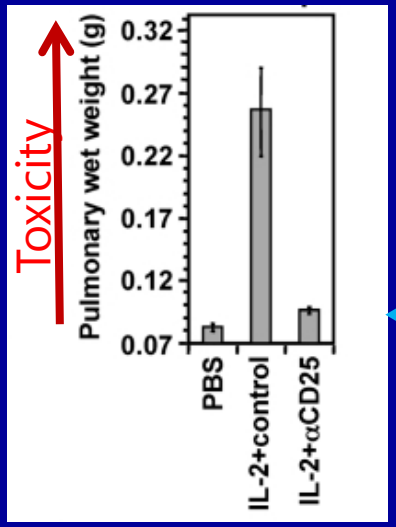


Increase Efficacy

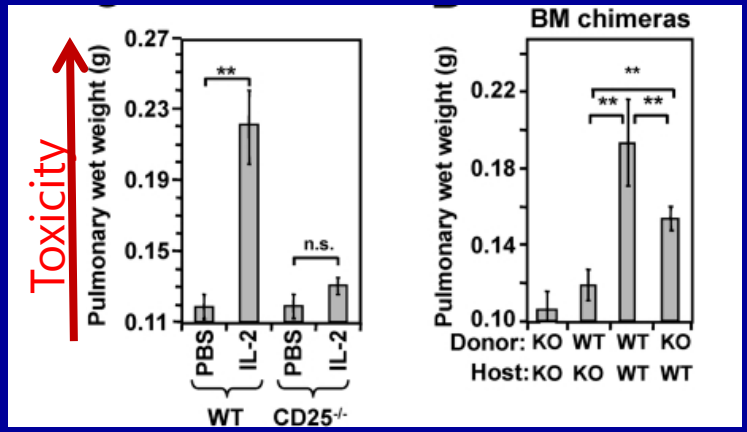
Vascular Leak Syndrome/Capillary Leak Syndrome: The Critical Role of CD25/IL-2Rα

CD25 expressed on lung endothelial cells
(blood vessels)



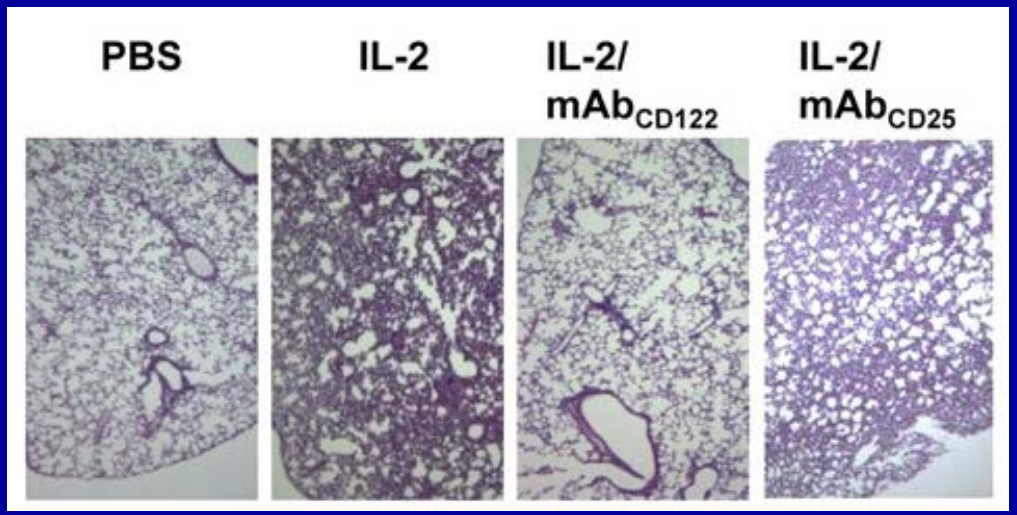


Blocking CD25



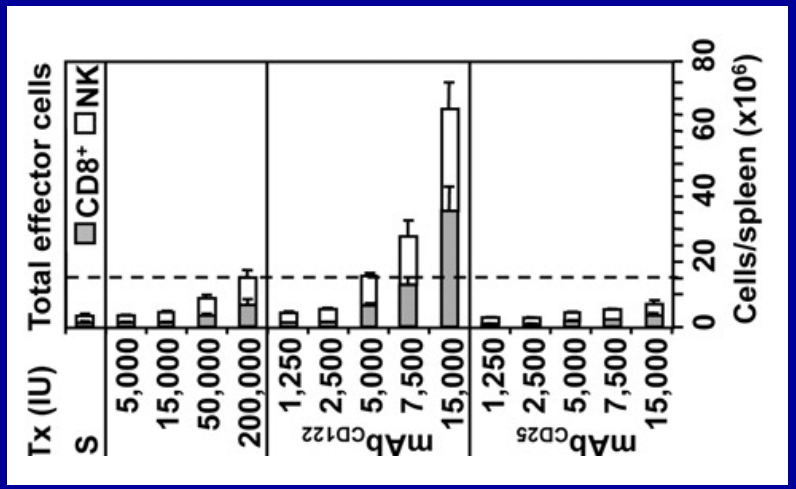
Improved IL-2 Immunotherapy by Selective Stimulation of IL-2 Receptors on Lymphocytes and Endothelial Cells

NKTR-214 mitigates both the immune suppression and the stimulation of CD25 expressed on endothelial cells



T/NK cell proliferation

Immune suppression



IL-2

Activate CD122

Activate CD25

IL-2 as Immune Inhibitor/Stimulator

The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases

David Klatzmann[1–3] and Abul K. Abbas[4]

THE JOURNAL OF IMMUNOLOGY

CUTTING EDGE

Cutting Edge: A Regulatory T Cell-Dependent Novel Function of CD25 (IL-2Rα) Controlling Memory CD8$^+$ T Cell Homeostasis[1]

Rahul Sharma, Lingjie Zheng, Umesh S. Deshmukh, Wael N. Jarjour, Sun-sang J. Sung, Shu Man Fu,[2] and Shyr-Te Ju[2,3]

Interleukin 2 Signaling Is Required for CD4$^+$ Regulatory T Cell Function

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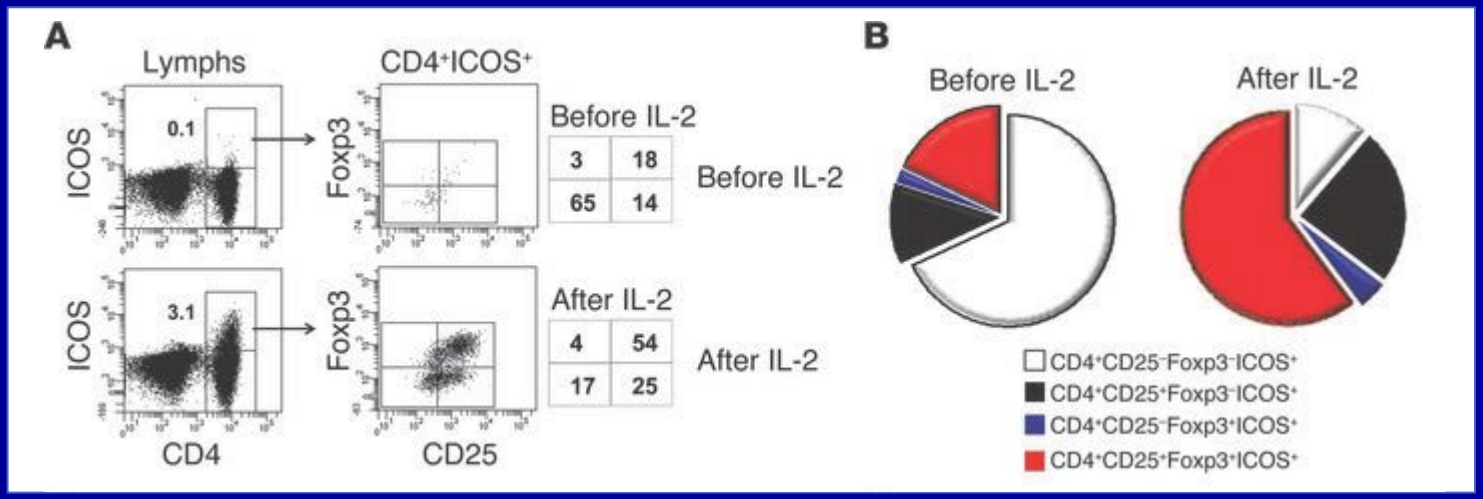
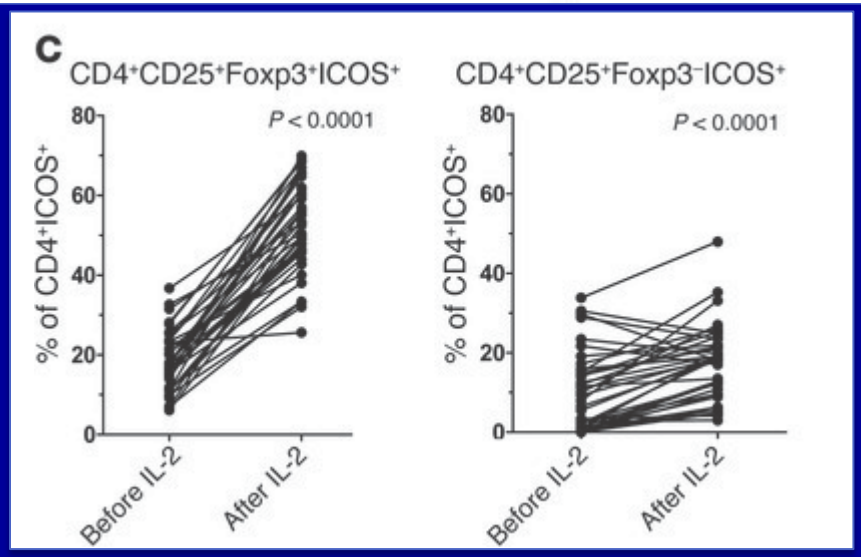
IL-2 Therapy Promotes Suppressive ICOS$^+$ Treg Expansion in Melanoma Patients

HD IL2 increases CD4+CD25+Foxp3+ICOS+



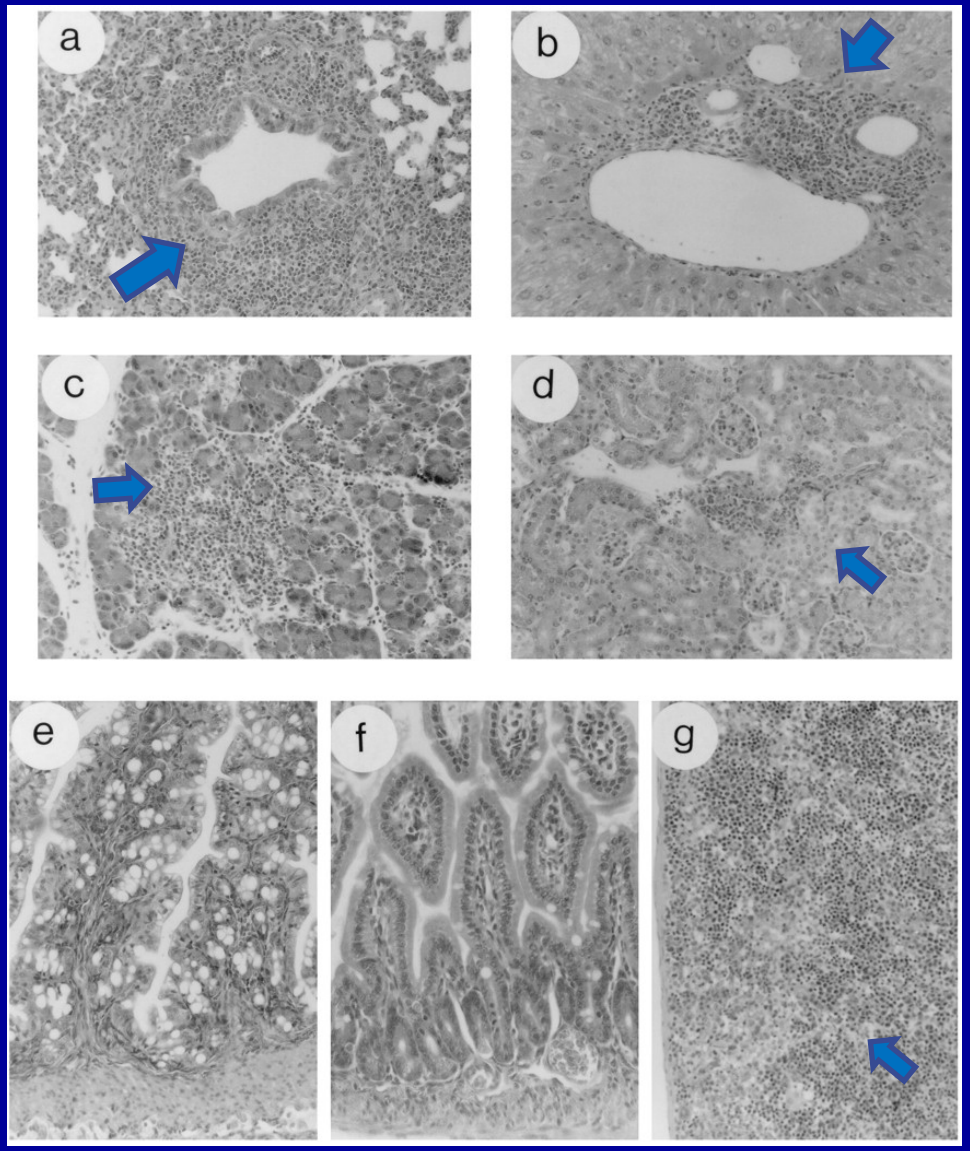
Suppressive T regulatory cells



NKTR-214 does not promote Treg expansion

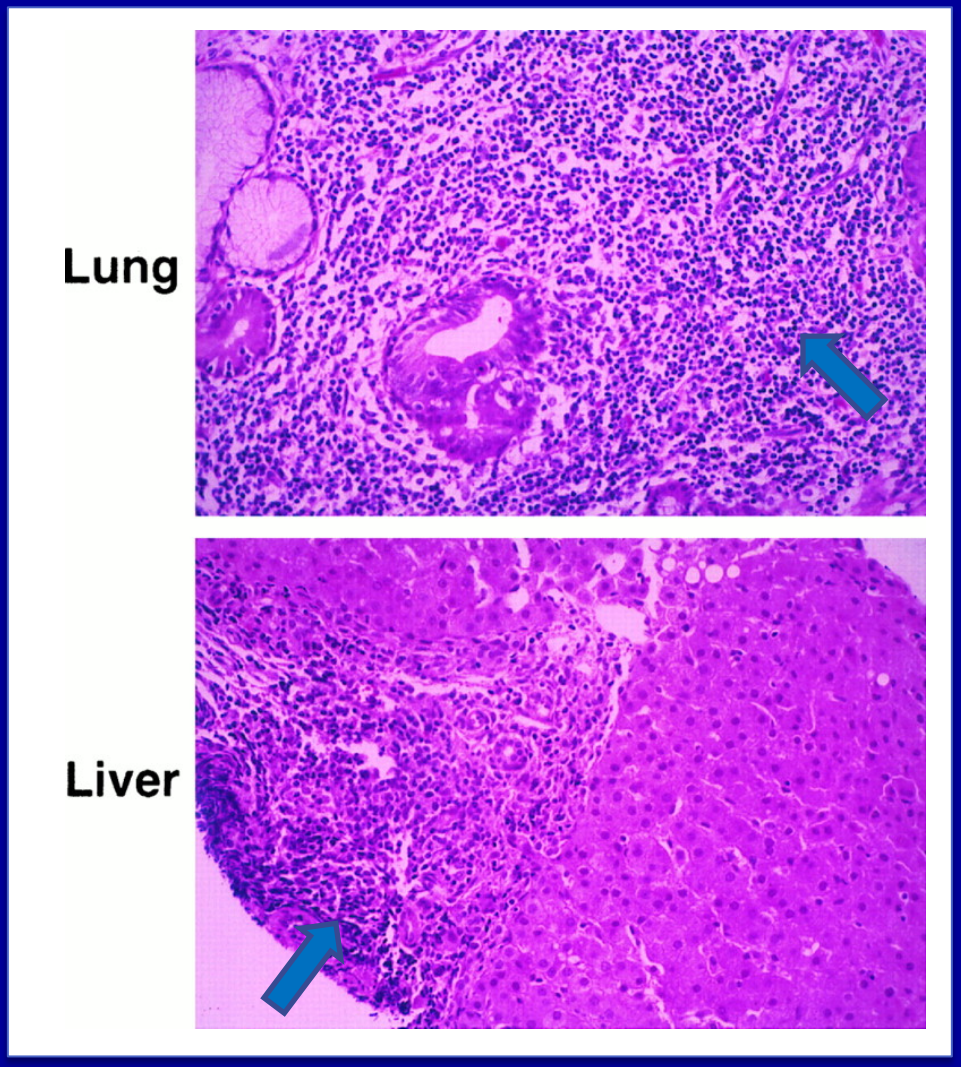
Sim G et al J Clin Invest. 2014;124(1):99–110. doi:10.1172/JCI46266.

Phenotype of IL-2R α/CD25 KO



Extensive lymphocyte hyperplasia in all tissues

Human Immune Disorder Arising From Mutation of the α Chain of the Interleukin-2 Receptor



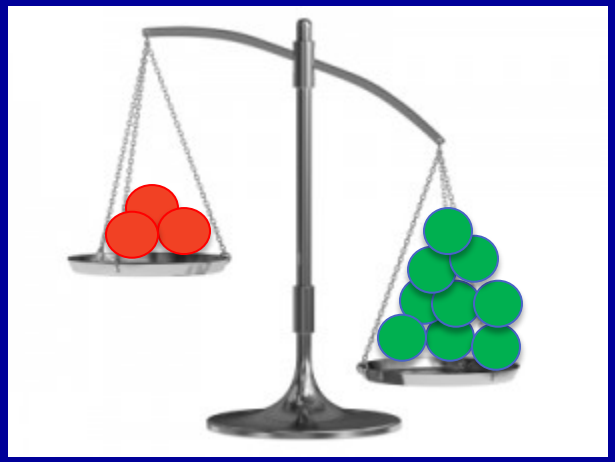
Extensive lymphocytic infiltration of tissues, including lung, liver, gut, and bone, is observed, accompanied by tissue atrophy and inflammation.

Nigel Sharfe et al. *PNAS* 1997;94:3168-3171

How to Improve Clinical Benefit of IL-2

Biased activation of IL-2Rβγ (CD122/132)
with reduced IL-2Rα (CD25) binding

Decrease Toxicity



Increase Efficacy

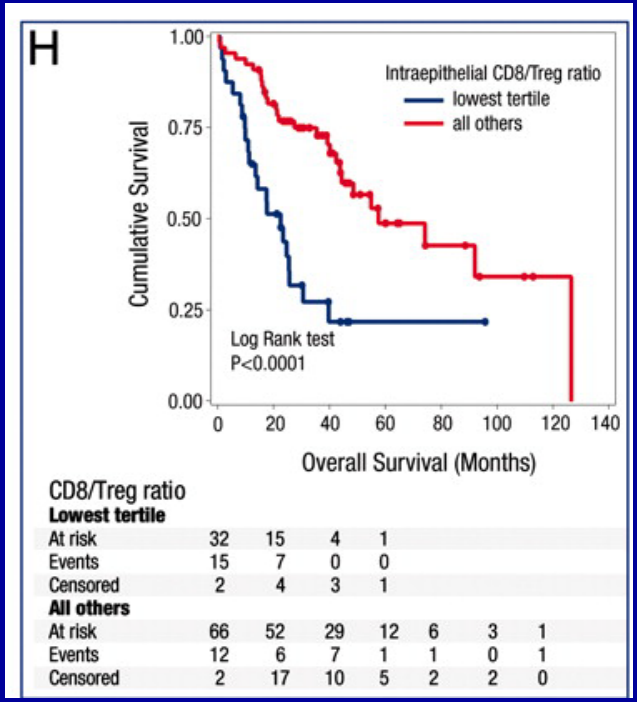
NKTR-214

Nonclinical Toxicology Summary

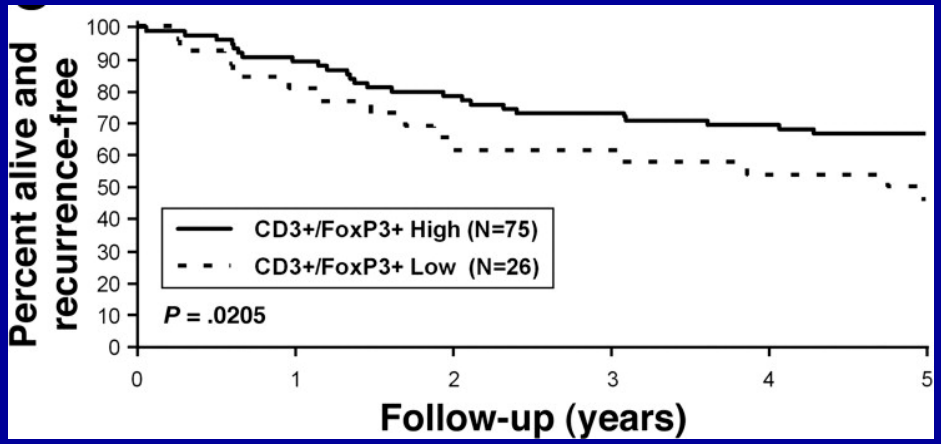
- Findings from toxicology studies were consistent with the immunostimulatory mechanism of action of NKTR-214
- NKTR-214 results compared to IL-2 (literature):
  - No hypotension, vascular leak or anemia in animals
  - NKTR-214 was better tolerated despite higher cytokine exposure
- Similar degree of immune stimulation at MTD compared to that seen at efficacious dose levels
- NKTR-214 has a wider therapeutic margin compared to IL-2

Intraepithelial CD8+ Tumor-Infiltrating Lymphocytes and a High CD8+ / Regulatory T Cell Ratio are Associated With Favorable Prognosis in Ovarian Cancer

Ovarian Cancer



Colon Cancer

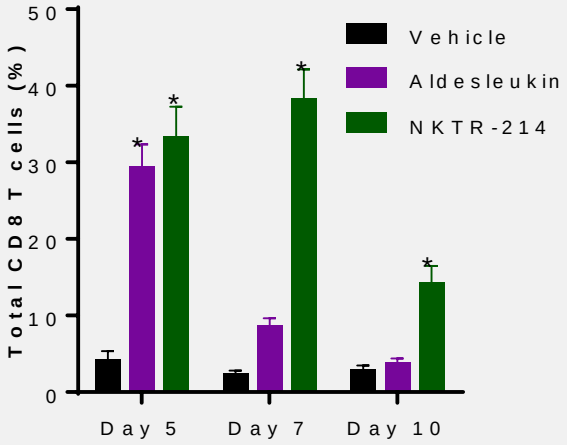


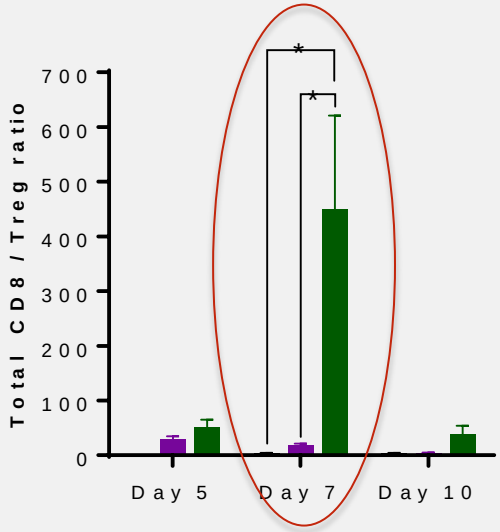
Multiple clinical and pre clinical studies have demonstrated that an elevated CD8/Treg ratio at the tumor site is associated with a better prognosis.

Eiichi Sato et al. *PNAS* 2005;102:18538-18543

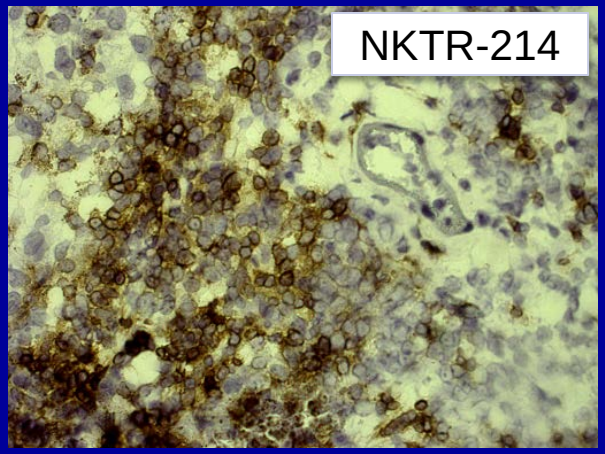
Frank A. Sinicrope et al. *Gastroenterology*, 2009; 137: 1270–1279

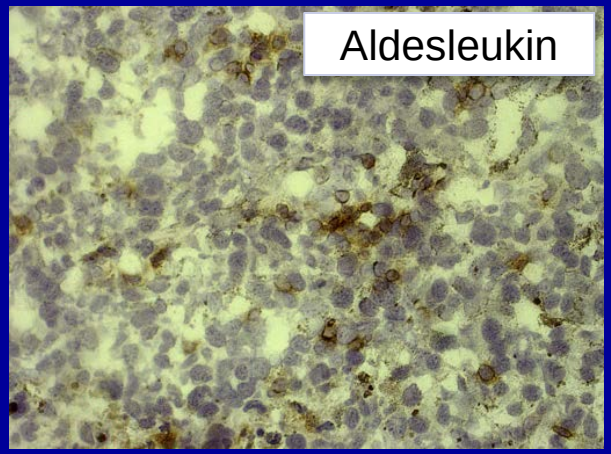
NKTR-214 vs. Aldesleukin Single Agent in B16
(Tumor Infiltrating Lymphocytes)





Greater than 400 fold increase in CD8/Treg ratio

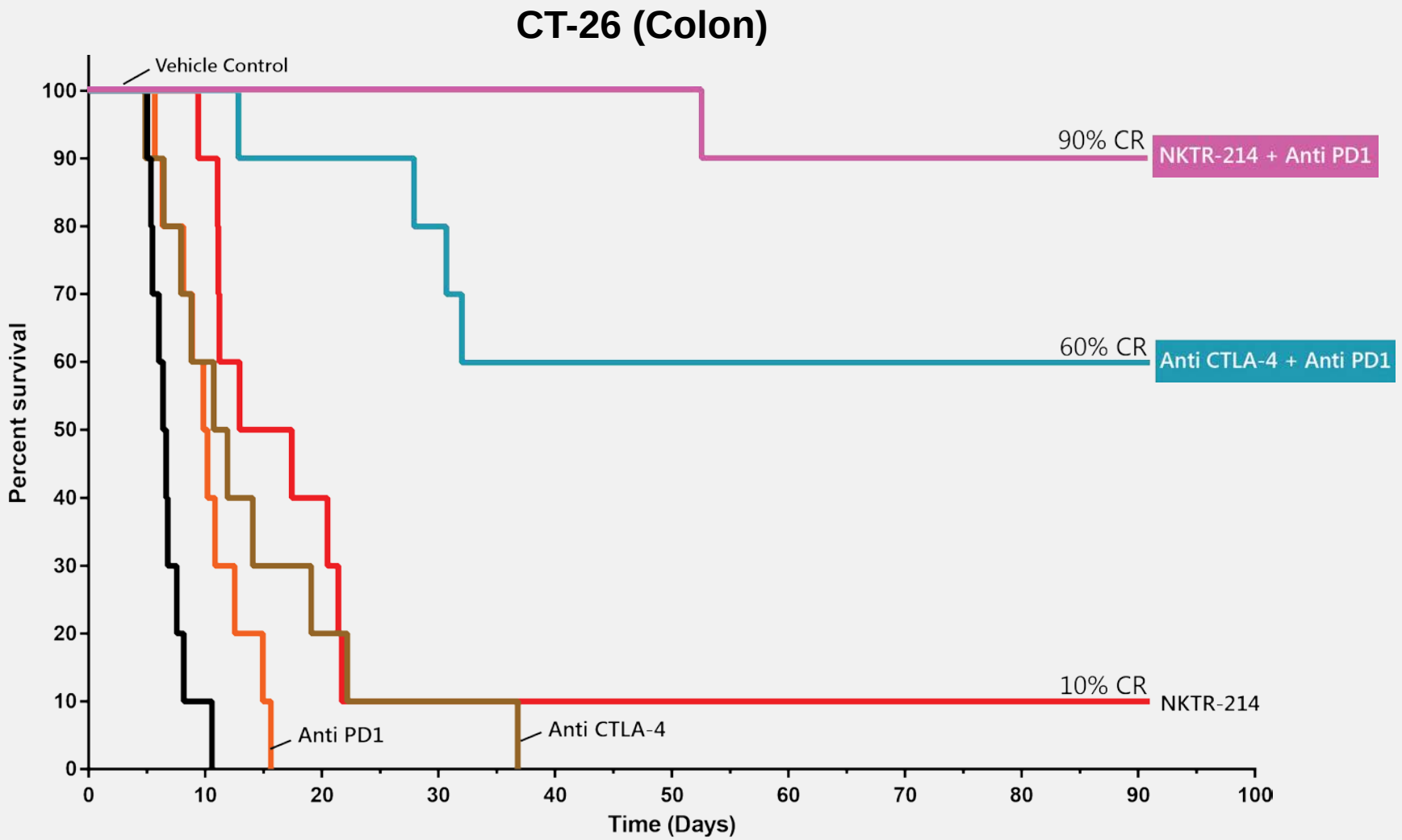




B16F10 melanoma, C57Bl/6 mice
NKTR-214, 2mg/kg i.v. single-dose
Aldesleukin, 3mg/kg i.p. qdx5
N=6-13/group
*, $p<0.05$, ANOVA with Tukey's post-test

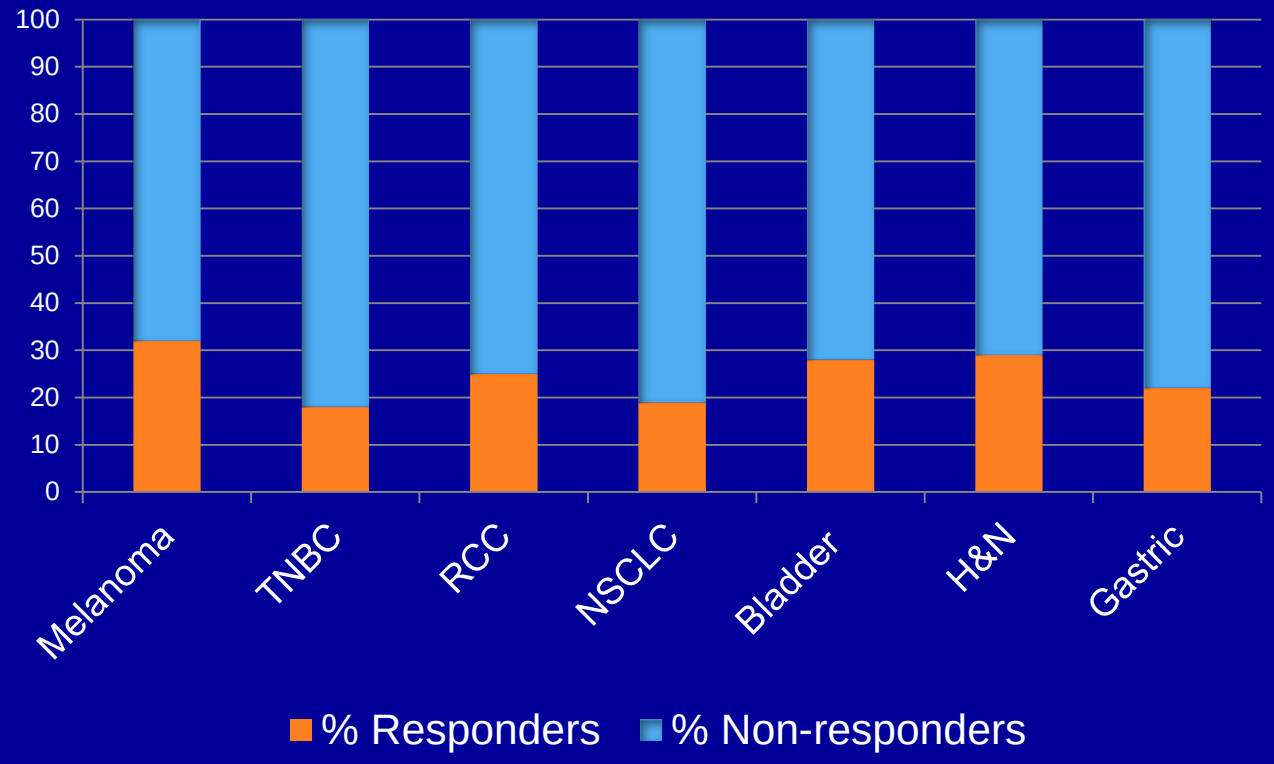
Tumor cells, purple
CD8 T cells, brown

Synergistic Response With NKTR-214 & Anti-PD-1 Combination in Mouse Colon Cancer Model



Source: Nektar Therapeutics. CT-26 Colon Model, End Points: Tumor Volume Growth to 400% Deep Tumor Lesion, N=12; Dosing: NKTR-214: 0.8 mg/kg Q9Dx3; Anti CTLA-4: 100 µg; Anti PD1: 200 µg; NKTR-214, 0.8 mg/kg (Day 4) + Anti PD1 200 µg (Day 0); Anti CTLA-4, 100 µg (Day 0) + Anti PD1, 200 µg (Day 0)

The Majority of Patients Do Not Respond to Anti-PD1/PD-L1 Across Multiple Tumor Types



Melanoma: Opdivo (nivolumab) package insert
TNBC: Nanda et al, San Antonio Breast Cancer Conference 2014
RCC: Motzer et al, *New Engl. J. Med* 2015, Nivolumab vs Everolimus
NSCLC: Borghaiei et al, *New Engl. J. Med* 2015, Nivolumab vs. docetaxel non-squamous non-small cell lung cancer
Bladder: Plimack et al, ASCO 2015, pembrolizumab for urothelial bladder cancer, Keynote 012
H&N: Seiwert et al, ASCO 2015, pembrolizumab in head and neck cancer (HNSCC) Keynote 012
Gastric: Bang et al, ASCO 2015, pembrolizumab in gastric cancer Keynote 012

Advantages of NKTR-214 Over Checkpoint Inhibitors

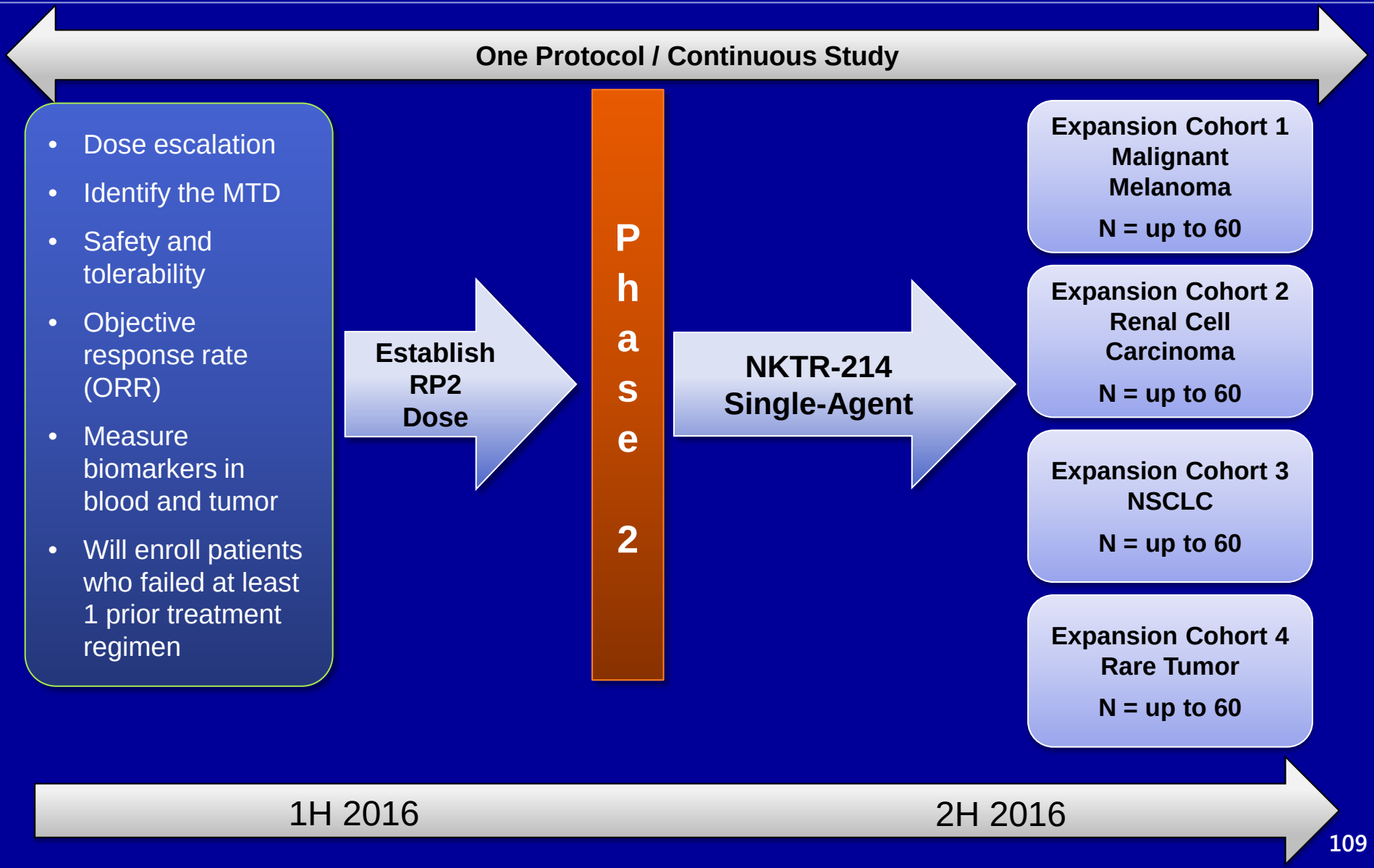
- Pre-clinical animal models in multiple cell lines demonstrated superior single agent activity of NKTR-214 vs. anti-PD1 and anti-CTLA-4
- NKTR-214 leads to greater expansion of CD8+ memory effector T cells vs. checkpoint inhibitors
- NKTR-214 increases NK cells
- Combination strategies with IO therapies that have non-overlapping mechanisms of action can lead to improved efficacy

Phase 1/2 Clinical Plan

Initial Planned Study Sites & Investigators

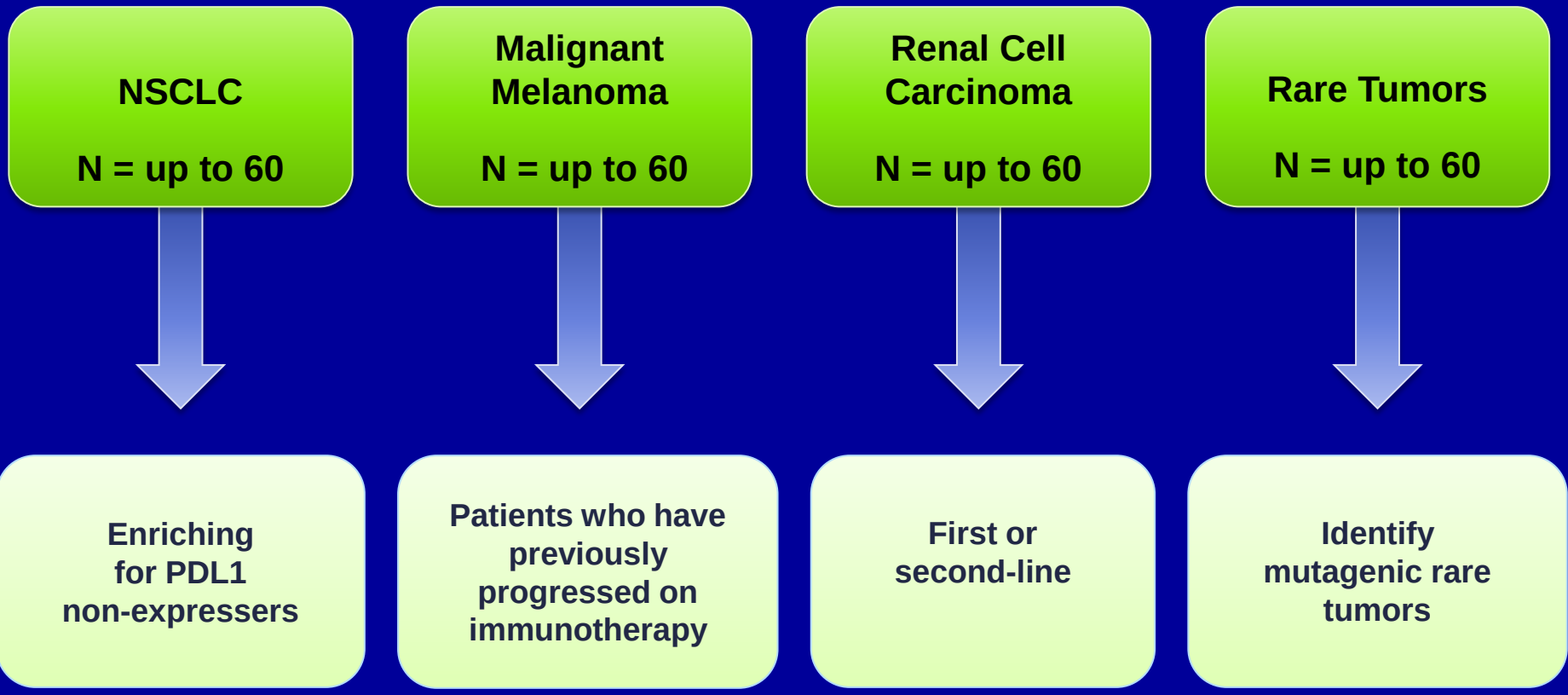
- MD Anderson Cancer Center
  - Patrick Hwu, MD & Adi Diab, MD
- Yale Cancer Center
  - Mario Sznol, MD
- California Pacific Medical Center
  - Kevin Kim, MD

NKTR-214 Phase 1/2 Clinical Trial: Single-Agent Strategy



Clinical Development Opportunities for Expansion Cohorts for Potential Accelerated Pathways

Single-Agent Cohorts



Phase 1/2 Primary and Secondary Endpoints

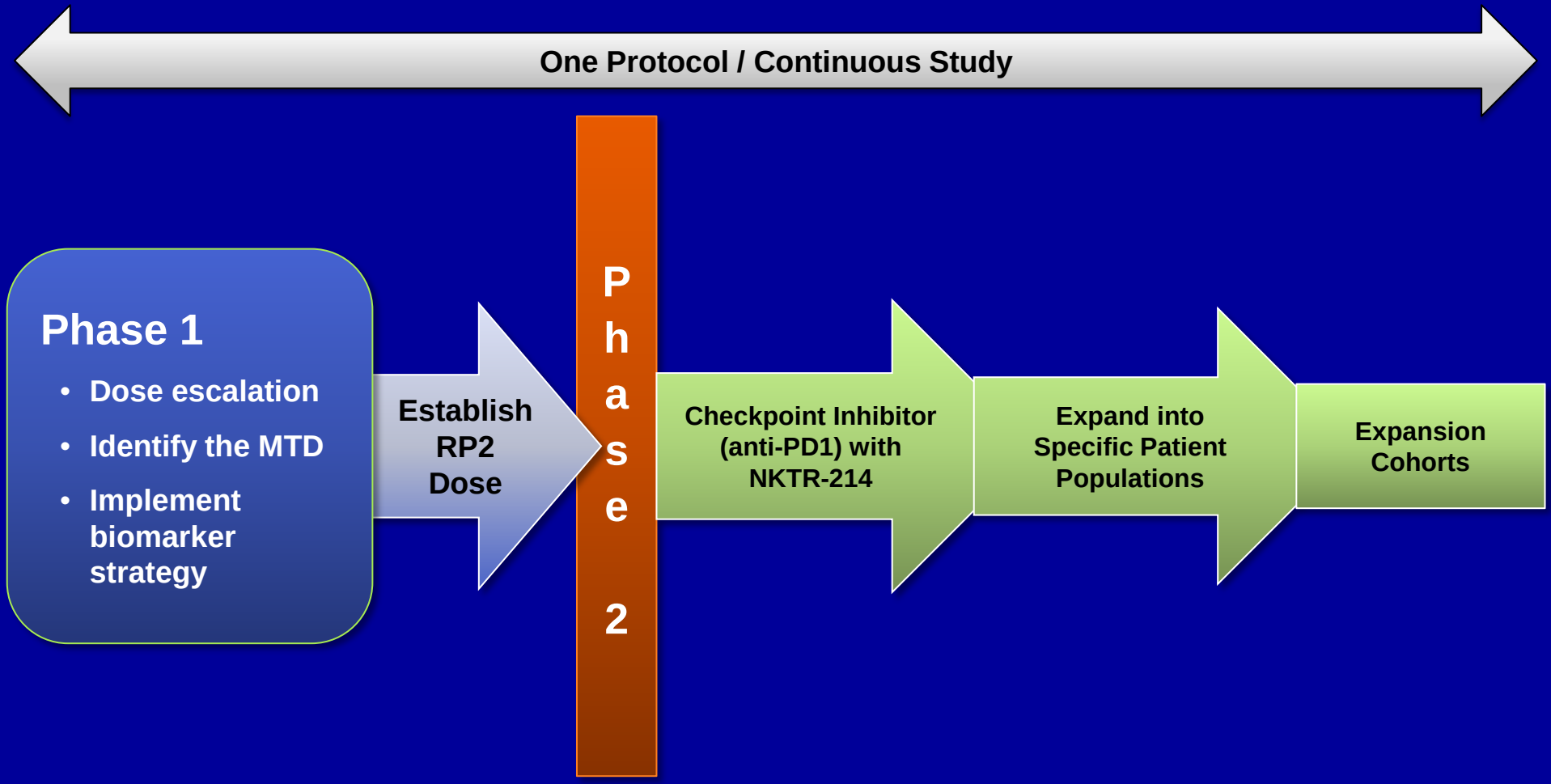
Primary Endpoints

- Identify the maximum tolerated dose (MTD)
- Safety and tolerability
- Objective response rate (ORR)

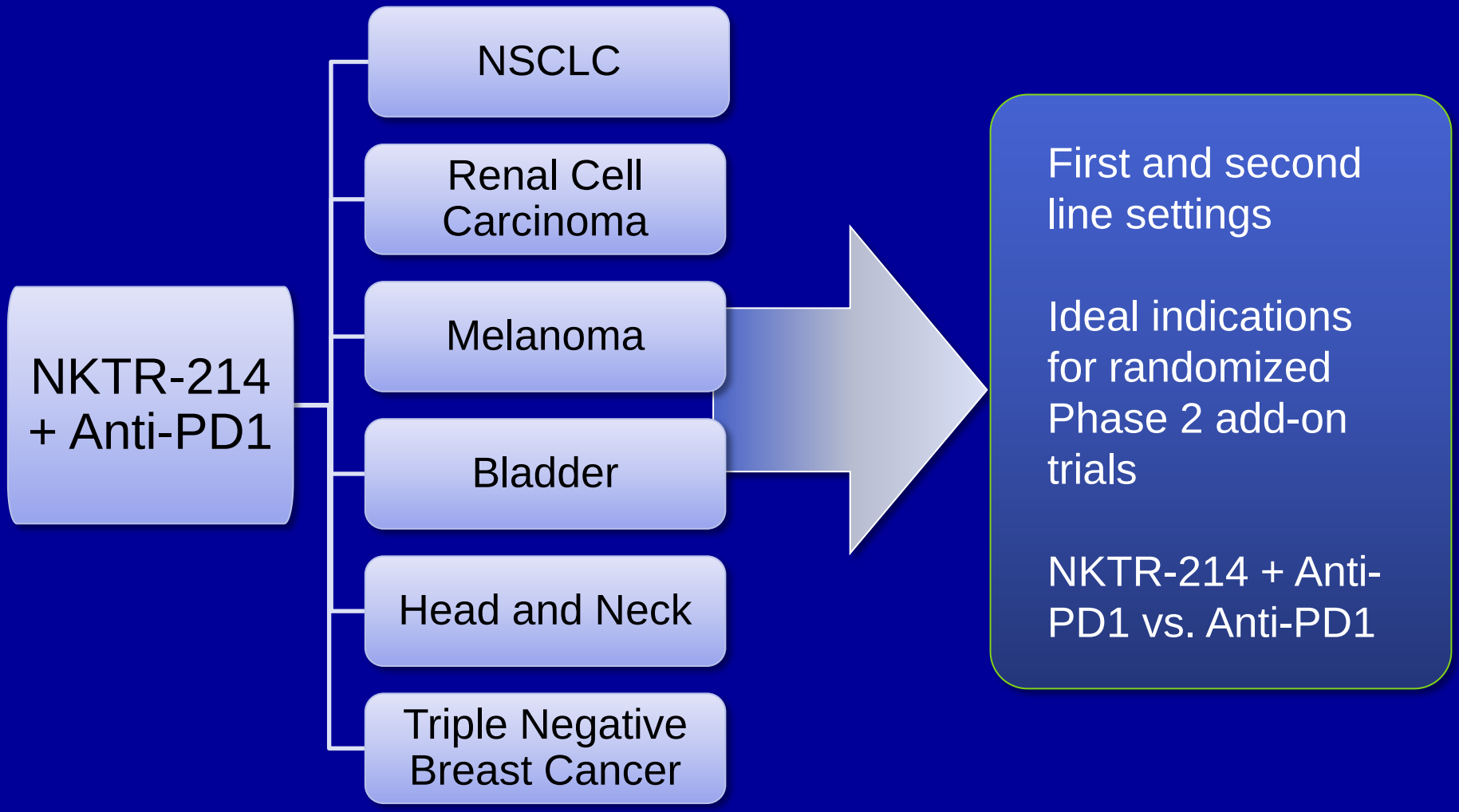
Secondary Efficacy Endpoints

- Clinical benefit rate
- Median time to response
- Duration of response
- Total lymphocyte count
- Progression free survival
- Overall survival
- Biomarkers in blood and tumor tissue

NKTR-214 Phase 1/2 Clinical Trial: Combination or Sequential Strategy



Clinical Development Opportunities for Combination or Sequential Therapy

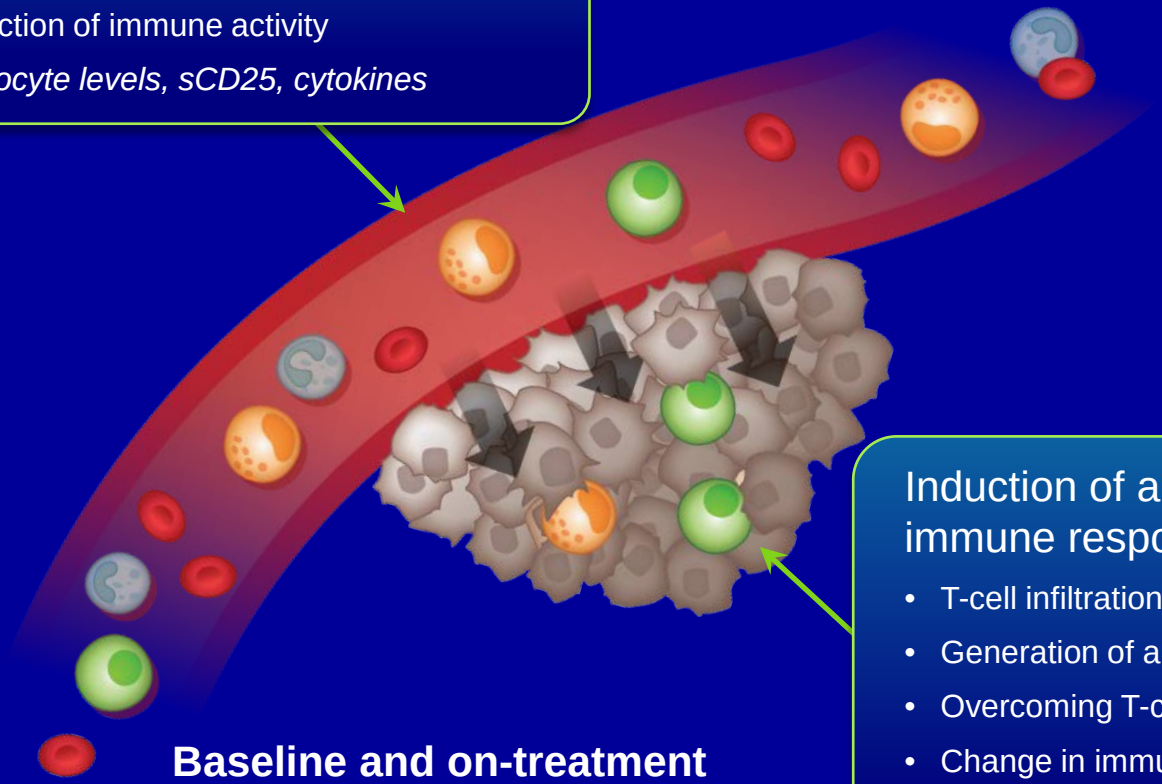


Strategy to Identify Predictive and Diagnostic Biomarkers for NKTR-214

Primary pharmacodynamics of NKTR-214

- IL-2 pathway activation
- Induction of immune activity

Lymphocyte levels, sCD25, cytokines



Baseline and on-treatment measurements in blood and tumor

Induction of an anti-tumor immune response

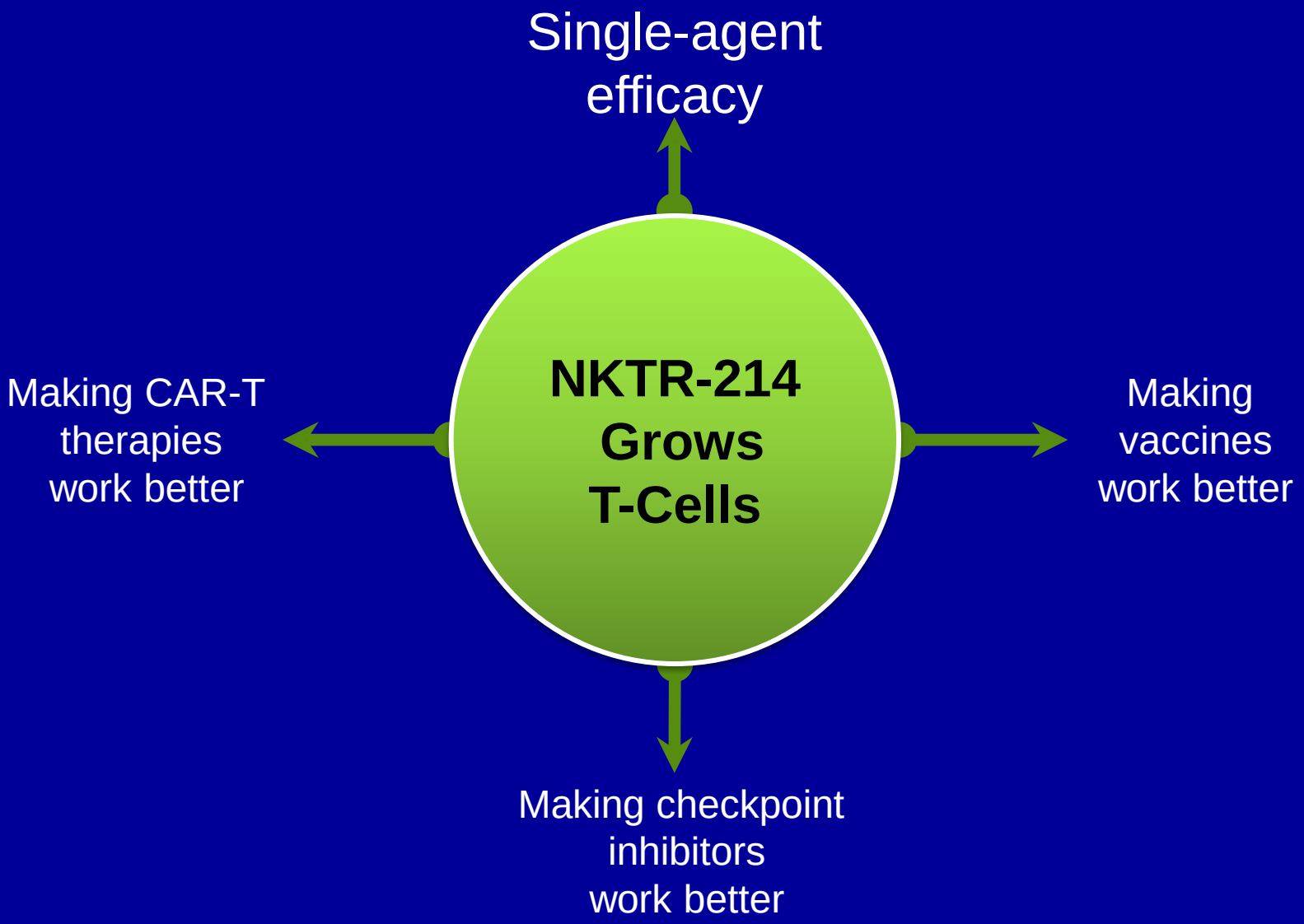
- T-cell infiltration
- Generation of an immuno-activated environment
- Overcoming T-cell exhaustion
- Change in immune tolerance to tumor

IHC, TIL analysis and enumeration, gene expression changes, T-cell receptor repertoire, mutational load

Key Takeaways

- NKTR-214 grows T cells
- NKTR-214 increases Natural Killer (NK) cells
- NKTR-214 could potentiate all IO therapies
- NKTR-214 could become the ideal immune-stimulating agent

NKTR-214 Opportunity

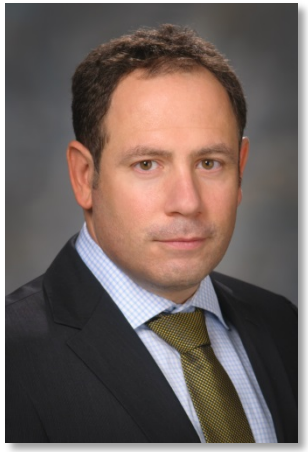


Oncology:
Expert Panel

Michael Atkins, M.D.

Deputy Director of the Georgetown-Lombardi Comprehensive Cancer Center in Washington, DC and Professor of Oncology and Medicine

(Hematology/Oncology) at Georgetown University School of Medicine



Adi Diab, M.D.

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Naiyer Rizvi, M.D.

Director of Thoracic Oncology and Director of Immunotherapeutics, Columbia University Medical Center

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