



THE IMMUNO-ONCOLOGY TRANSFORMATION: *Implications for Managed Care*

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Held in conjunction with

AMCP MANAGED CARE & SPECIALTY PHARMACY **20**
ANNUAL MEETING **19**

MARCH 25-28  SAN DIEGO



Assessing the Clinical Benefits and Appropriate Use of Immuno-Oncology Agents

Joan H. Schiller, MD

Professor

University of Virginia

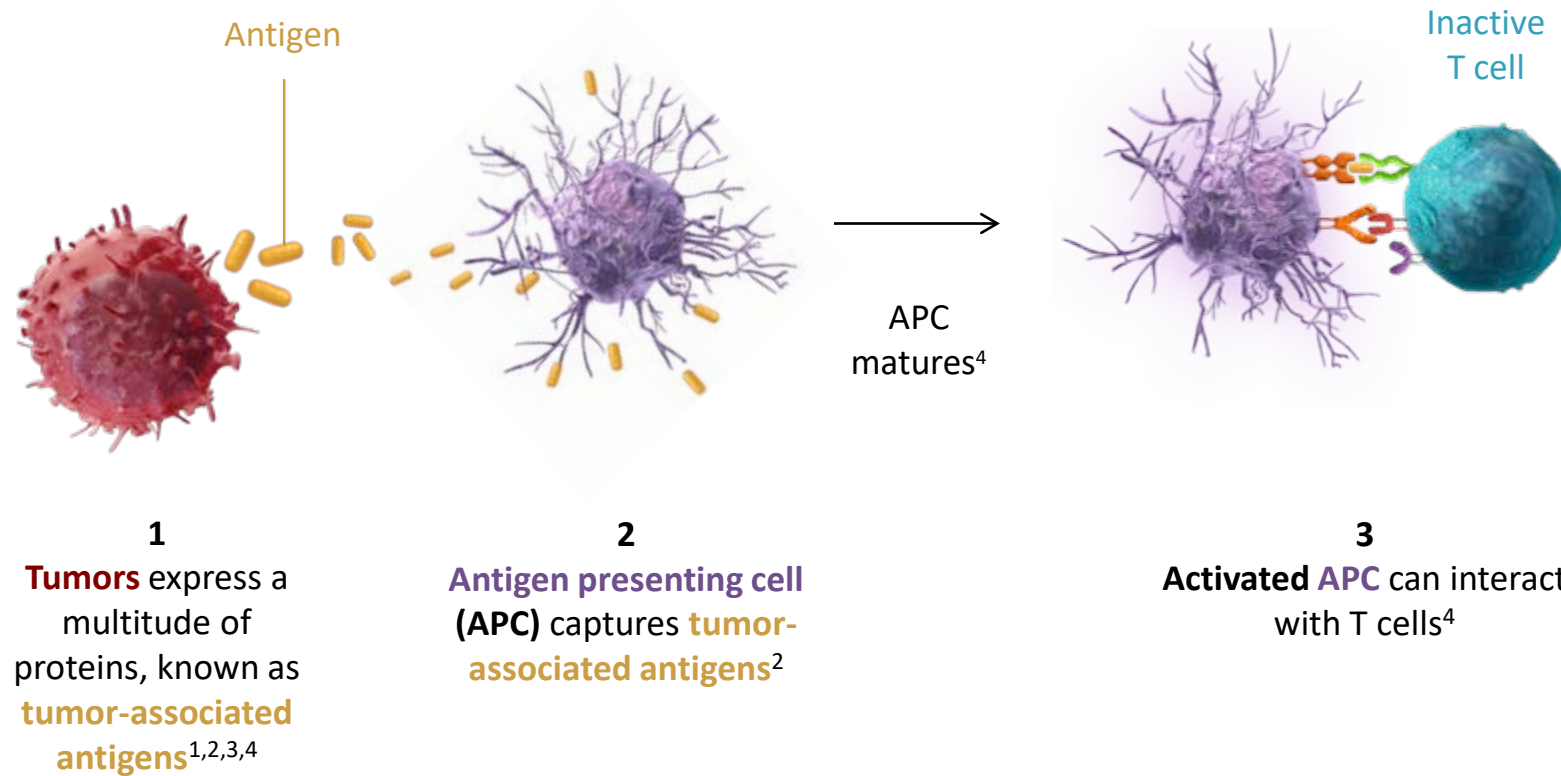


Evidence Pointing Toward Immune Reactivity to Tumors

- Tumors that have severe lympho-reticular infiltration have a better prognosis than those that do not.
- Certain tumors regress “spontaneously.”
- Increased incidence of primary and secondary malignancies (particularly lympho-reticular tumors) in immunodeficient patients.
- Antibodies and immune T lymphocytes have been detected in patients with tumors.
- The young and the very old have an increased occurrence of tumors.
- Animals can be specifically immunized against various types of tumors.

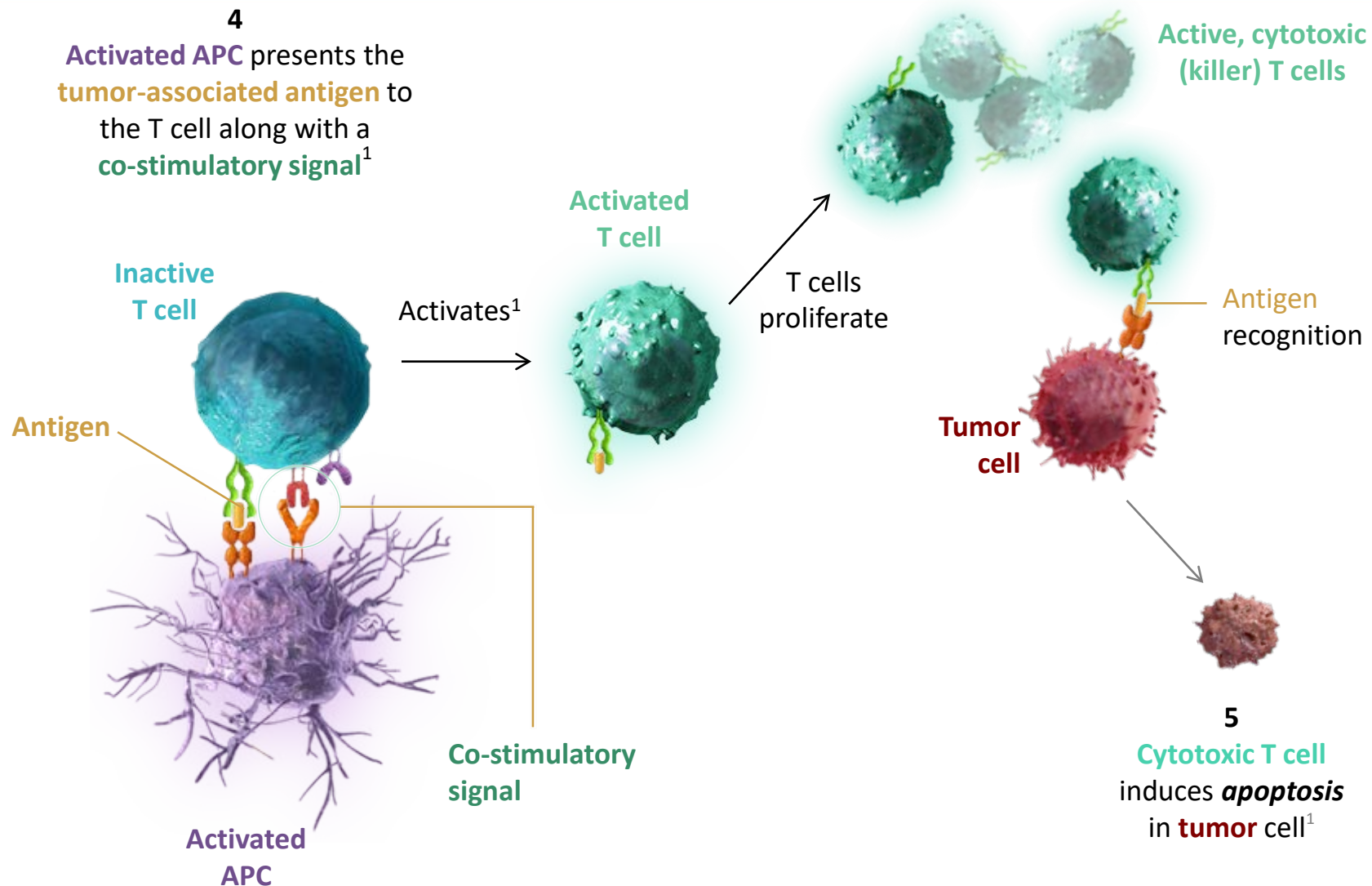
T-cell activation: tumor-associated antigens

Tumor-associated antigens can trigger a tumor-specific immune cell response:

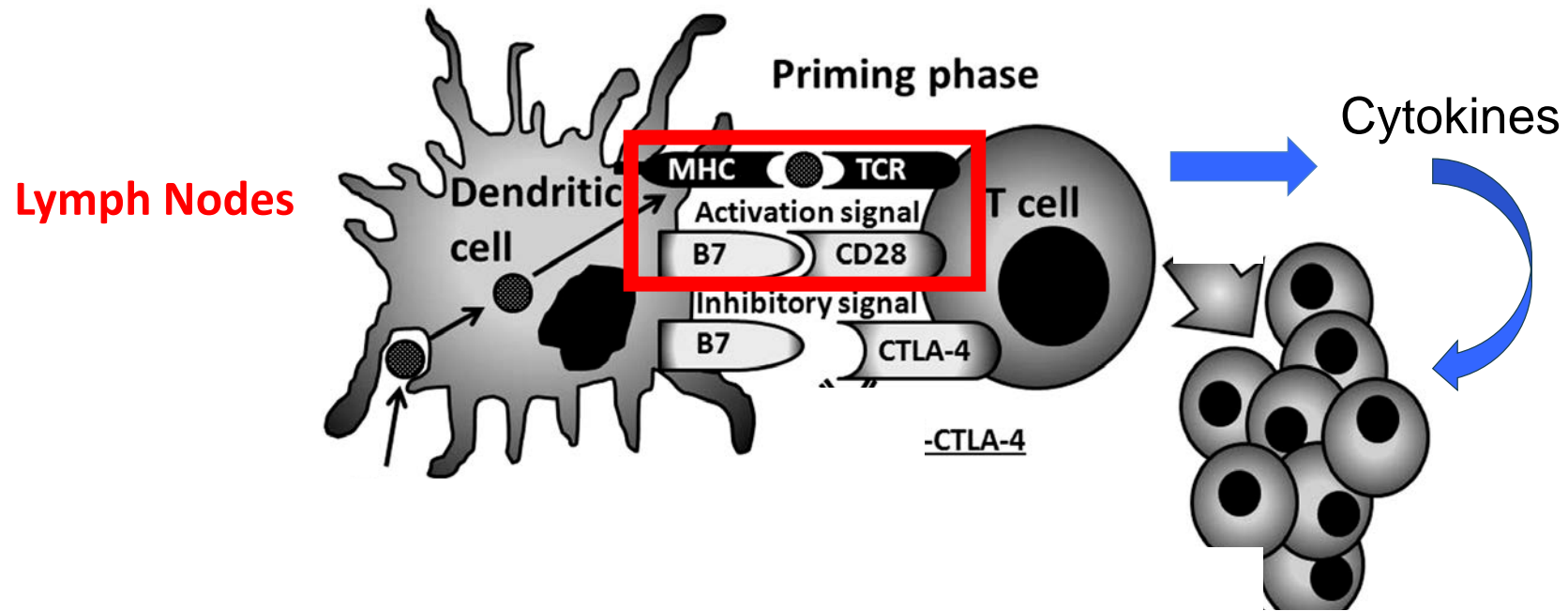


1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;11:252-264 2. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480:480-489 3. Heemskerk B, Kvistborg P, Schumacher TNM. The cancer antigenome. *EMBO J*. 2013;32(2):194-203 4. Boudreau JE, Bonehill A, Thielemans K, Wan Y. Engineering dendritic cells to enhance cancer immunotherapy. *Mol Ther*. 2011;19(5):841-853

T-cell activation: cytotoxic T cells



How Does T-Cell Activation Happen?



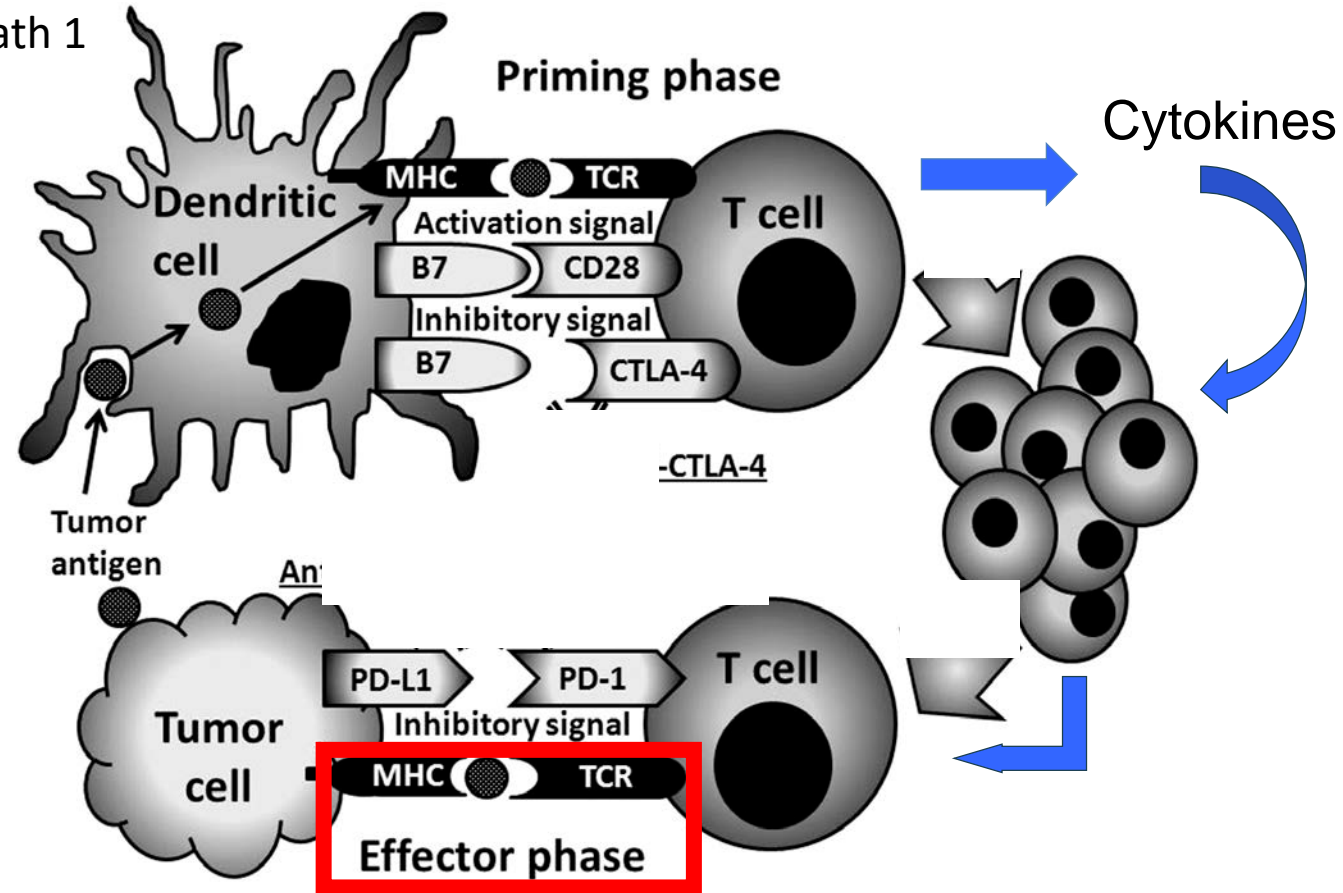
Activated T Cells → Recognize Tumor Associated Antigens on Tumor Cells

CTLA4: Cytotoxic T lymphocyte antigen 4

PD-1: Programmed death 1

PD-L1: PD ligand 1

Lymph Nodes



Tumor

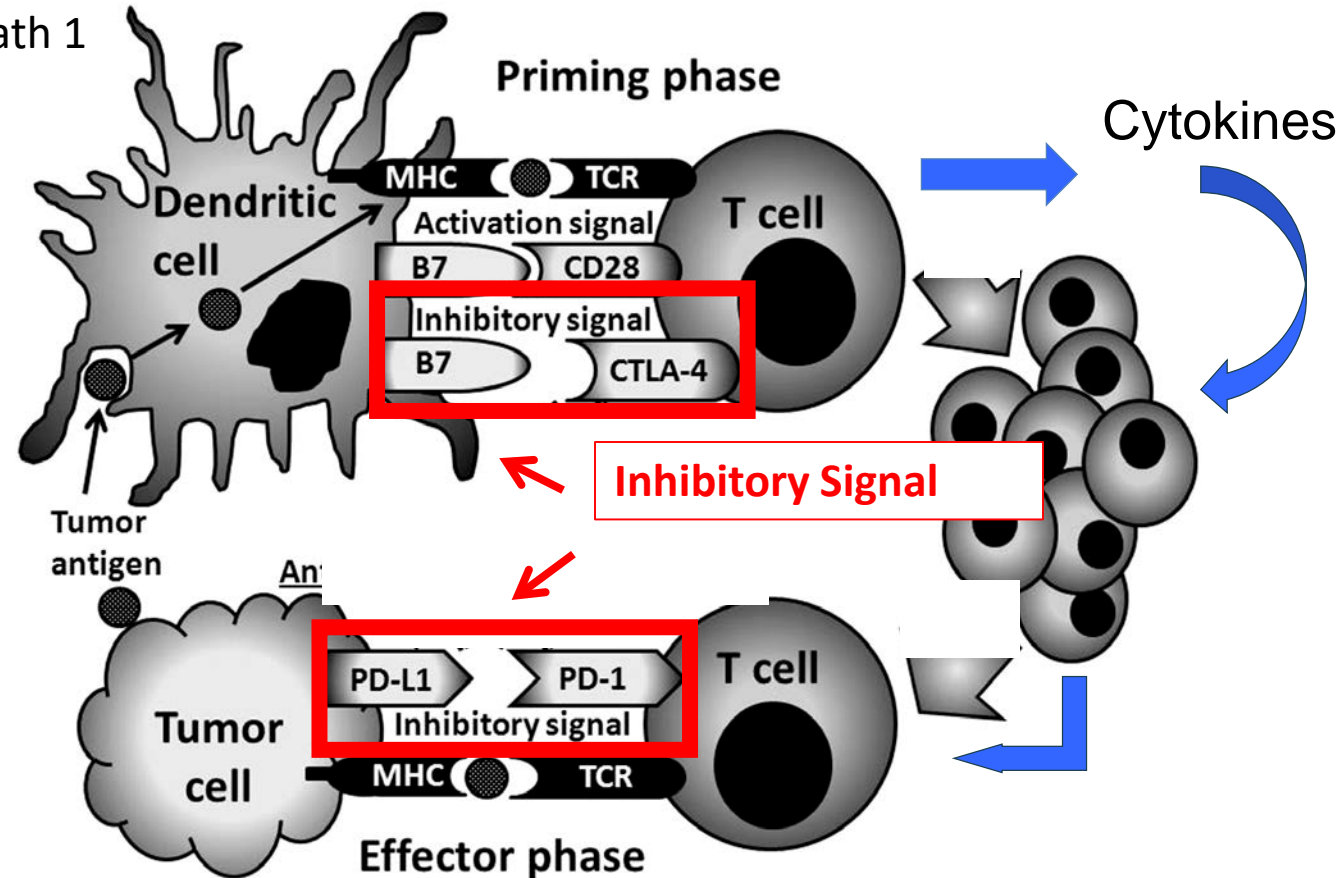
Turning It Off... Need to dampen down the immune system to keep it from running wild and to prevent autoimmune diseases

CTLA4: Cytotoxic T lymphocyte antigen 4

PD-1: Programmed death 1

PD-L1: PD ligand 1

Lymph Nodes



Tumor

So What Goes Wrong? CTLA-4 and PD-1/PD-L1 Inhibit Anti-tumor Immune Responses by

- Preventing Activation of the T Cells (CTLA-4) AND/OR
- Preventing Recognition of the Tumor cell

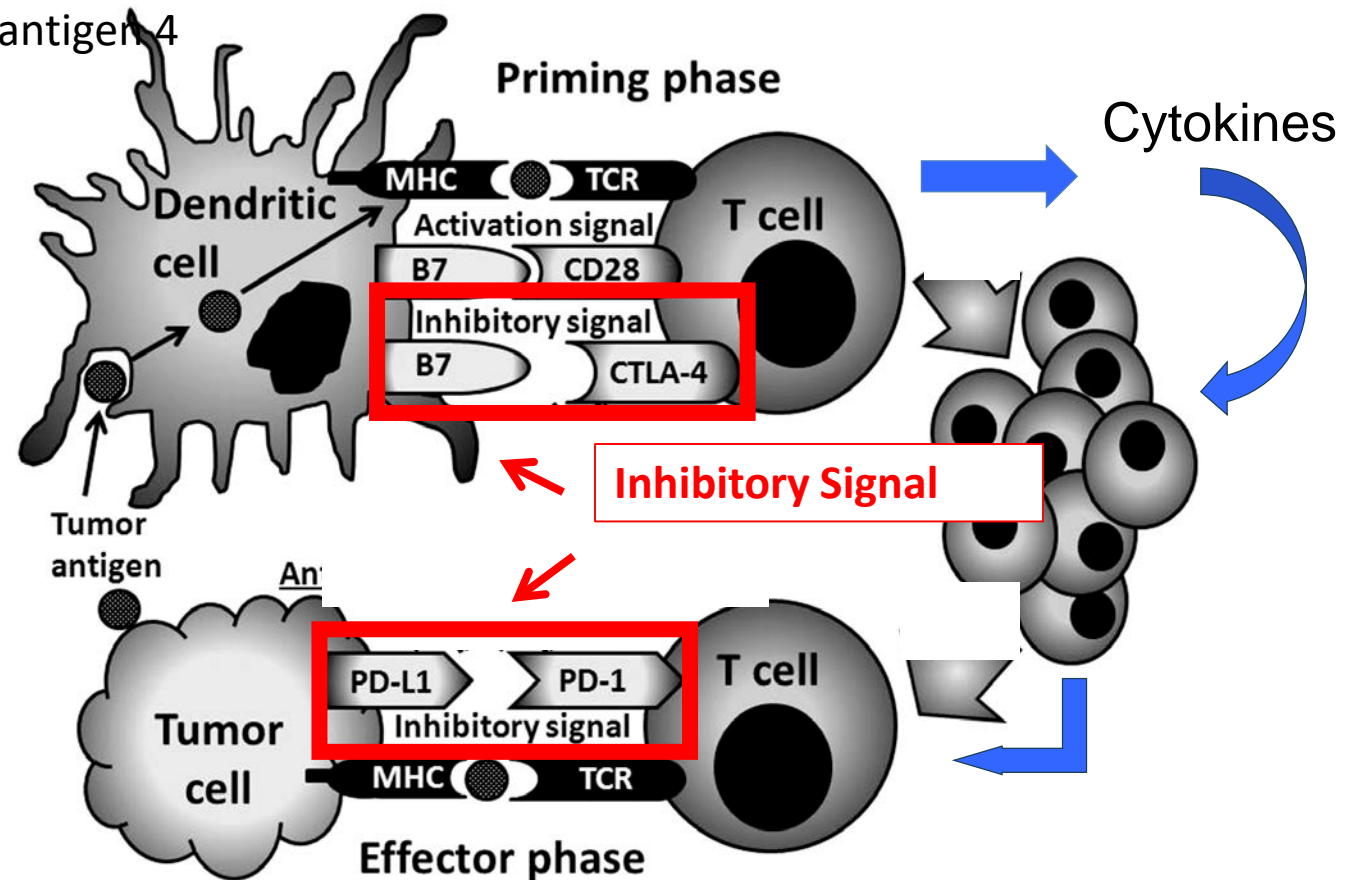
CTLA4: Cytotoxic T lymphocyte antigen 4

PD-1: Programmed death 1

PD-L1: PD ligand 1

Lymph Nodes

Tumor

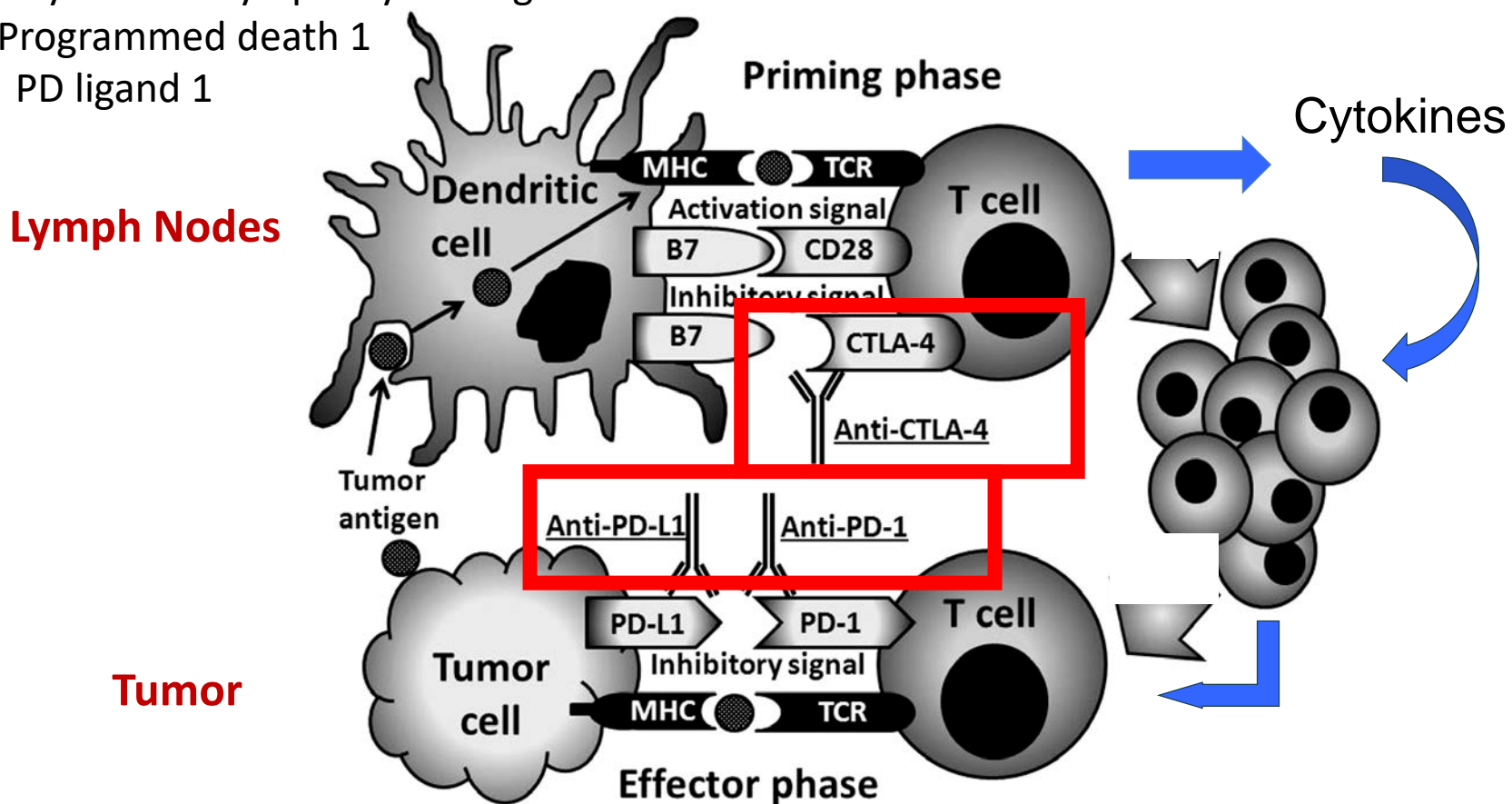


So What to Do? Inhibit CTLA4 (Ipilimumab) OR Inhibit PD1 or PDL1

CTLA4: Cytotoxic T lymphocyte antigen 4

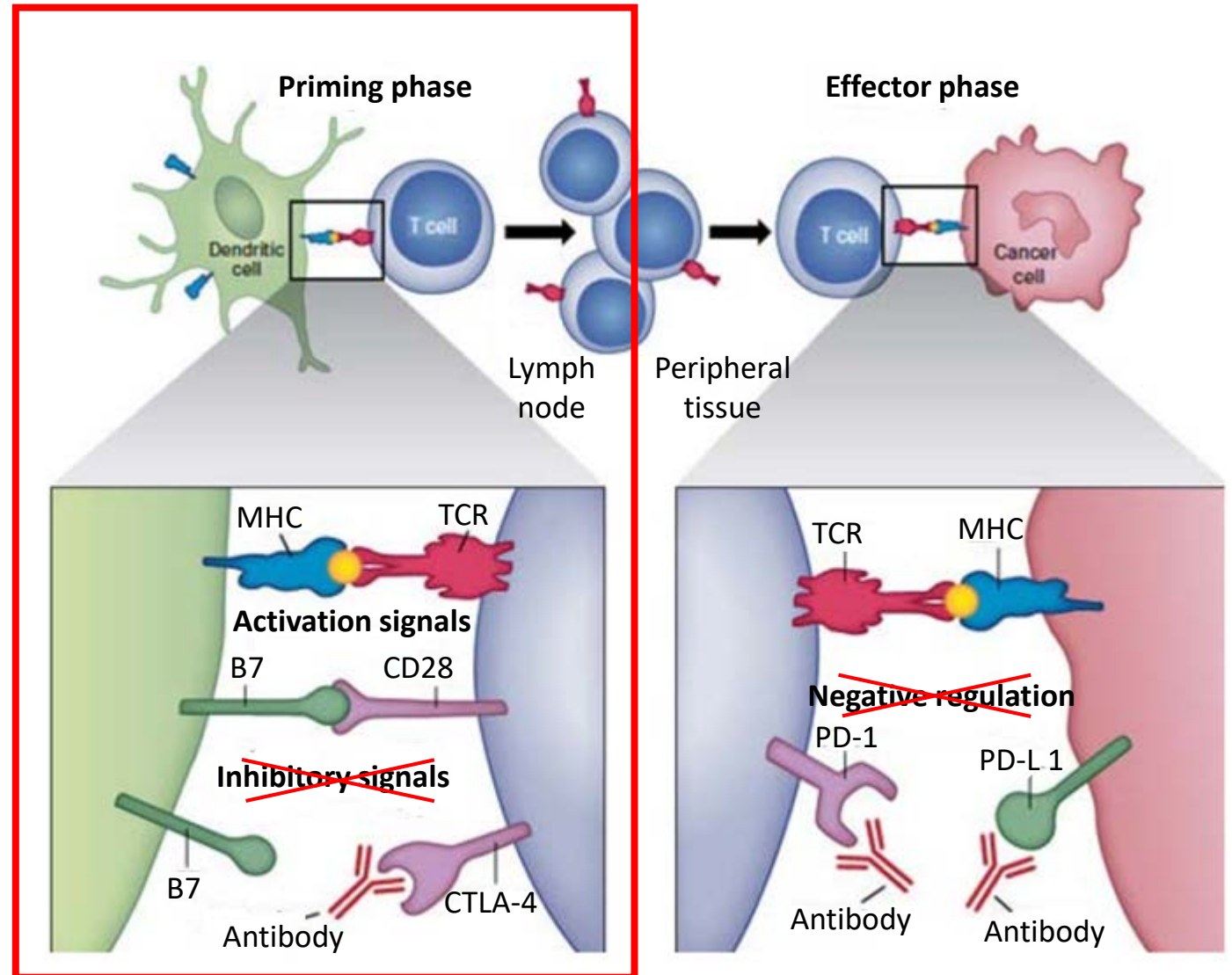
PD-1: Programmed death 1

PD-L1: PD ligand 1



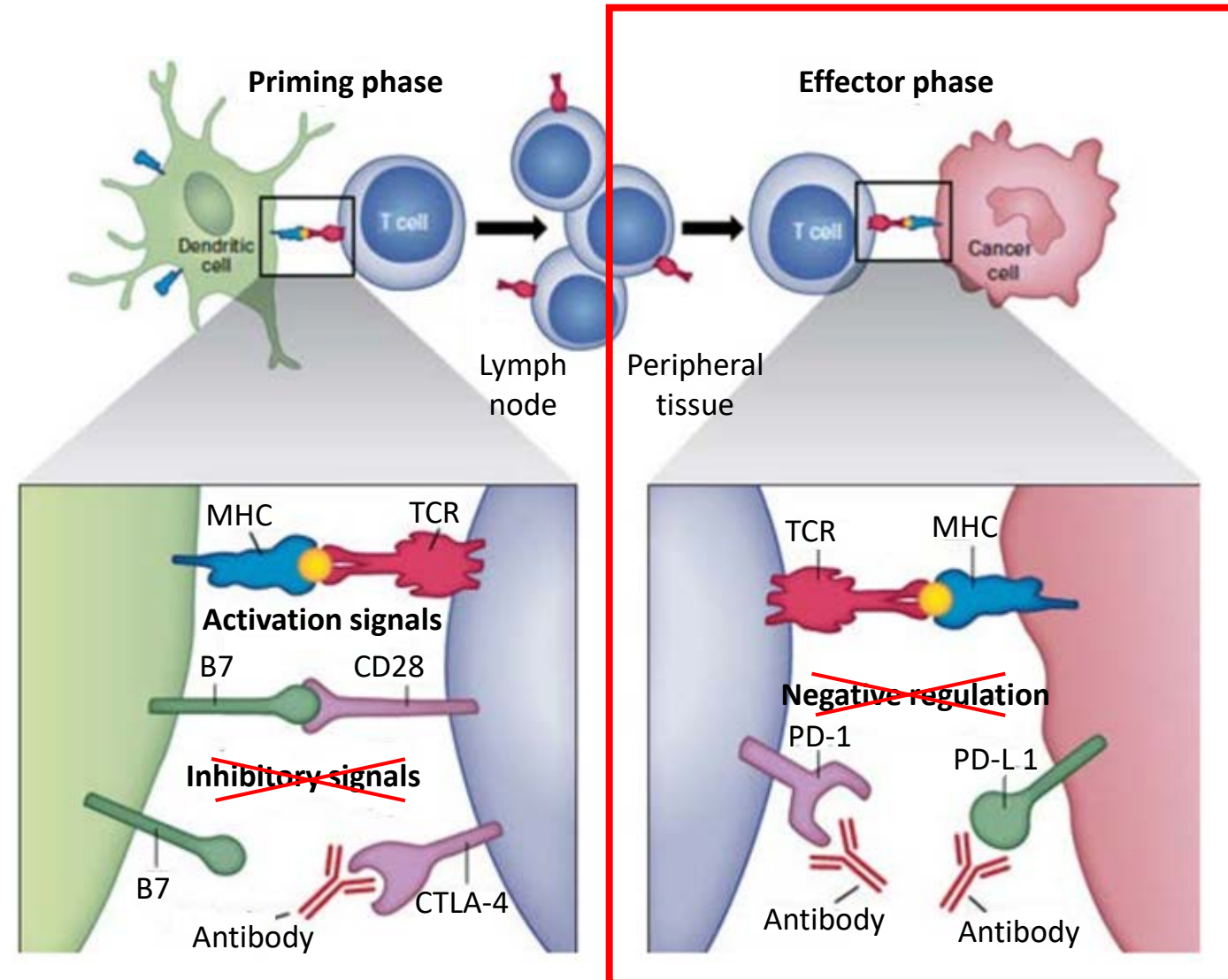
CTLA4 Antibodies: Inhibit the “Priming” Phase

- Antigen presentation and ligation of B7/CD28 co-activators results in T-cell activation: A GOOD thing for combating cancer, but a BAD thing which can result in autoimmune diseases if not stopped
- In the activated T cell, CTLA-4 competes with CD28 and acts as the brakes on T-cell activation by binding to B7
- By inhibiting CTLA-4, ipilimumab releases the natural braking system and restores T-cell activation, allowing T-cell proliferation to continue



PD-1 and PD-L1 Antibodies: Inhibit the Effector Phase

- PD-1 is an inhibitory receptor found on activated lymphocytes and monocytes
- Binds with PD-L1 on tumor cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T cell response: A BAD thing for combating cancer but a GOOD thing for preventing autoimmune diseases
- Inhibition of PD-1 associated with tumor immune escape

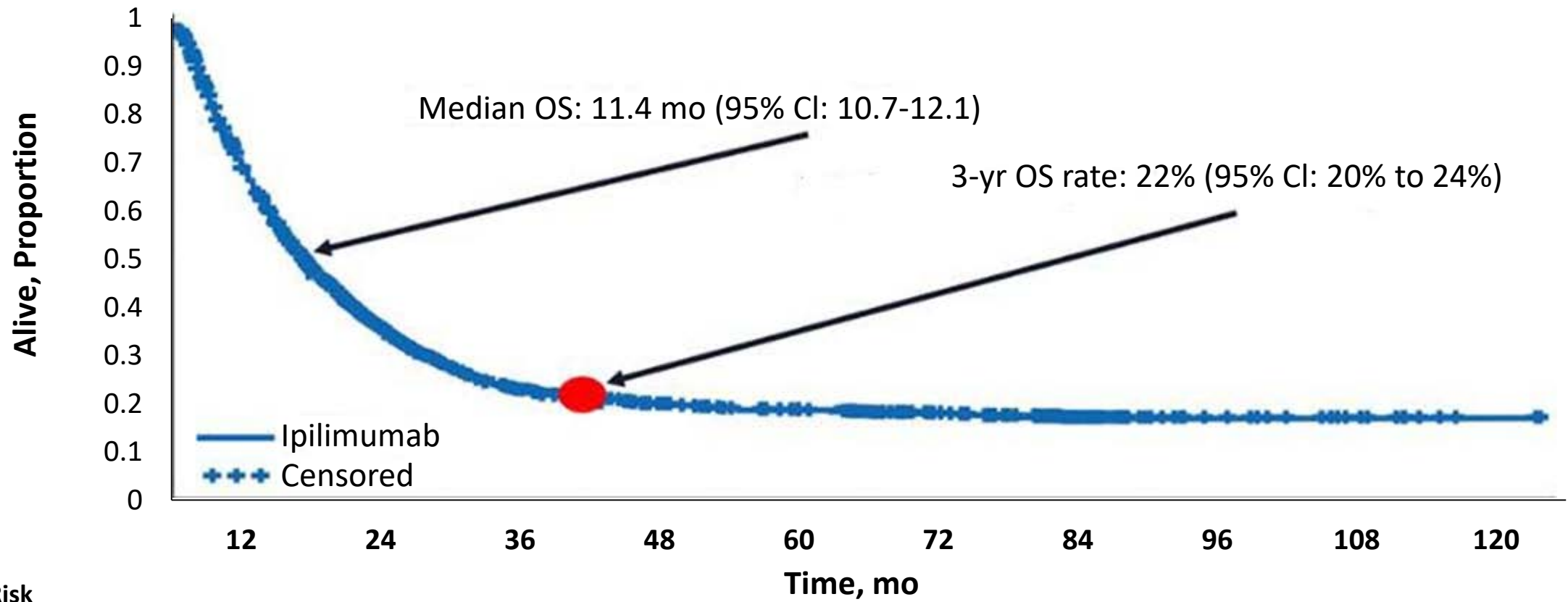




Available Immune Checkpoint Inhibitors

Drug	Mechanism
Ipilimumab	Anti-CTLA-4
Nivolumab	Anti-PD-1
Pembrolizumab	
Cemiplimab-rwlc	
Atezolizumab	Anti-PD-L1
Avelumab	
Durvalumab	

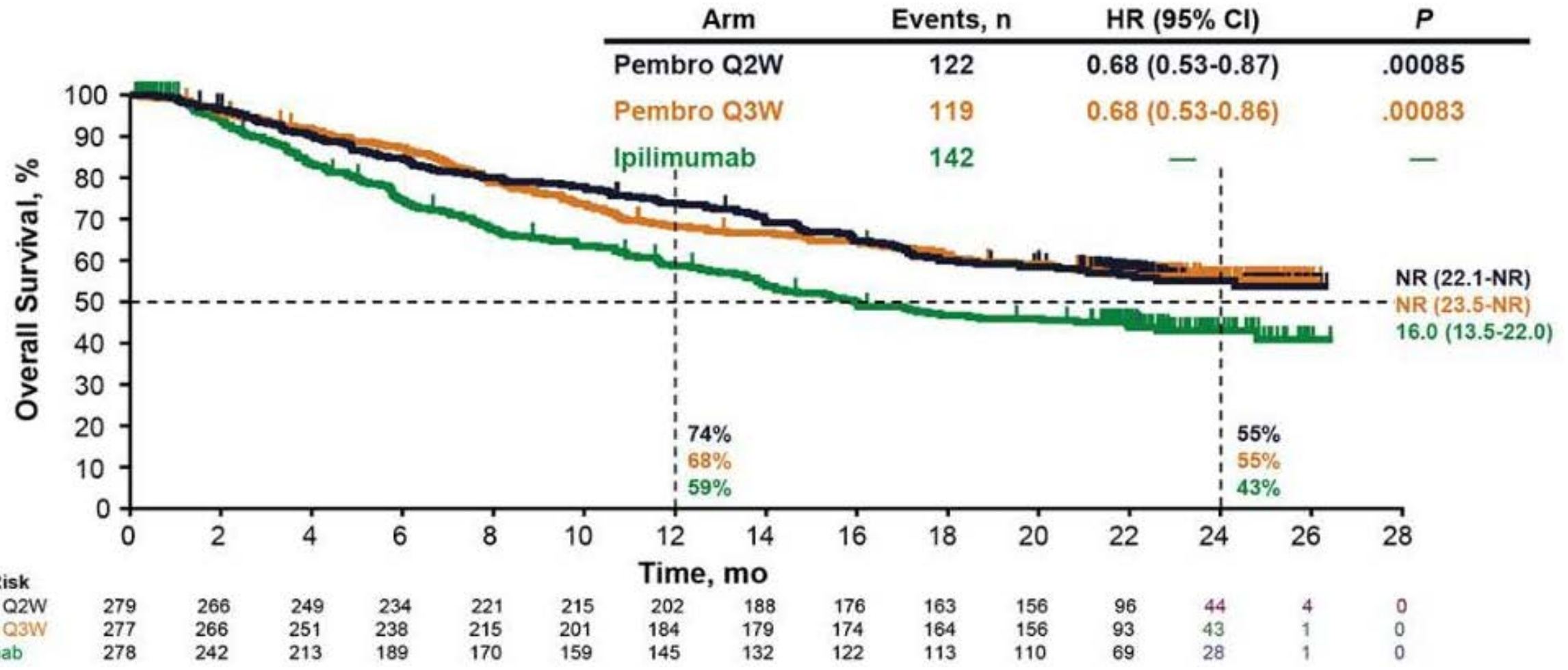
Ipilimumab OS at 3 years and Beyond in Phase 2 and 3 Trials of Melanoma



No. at Risk

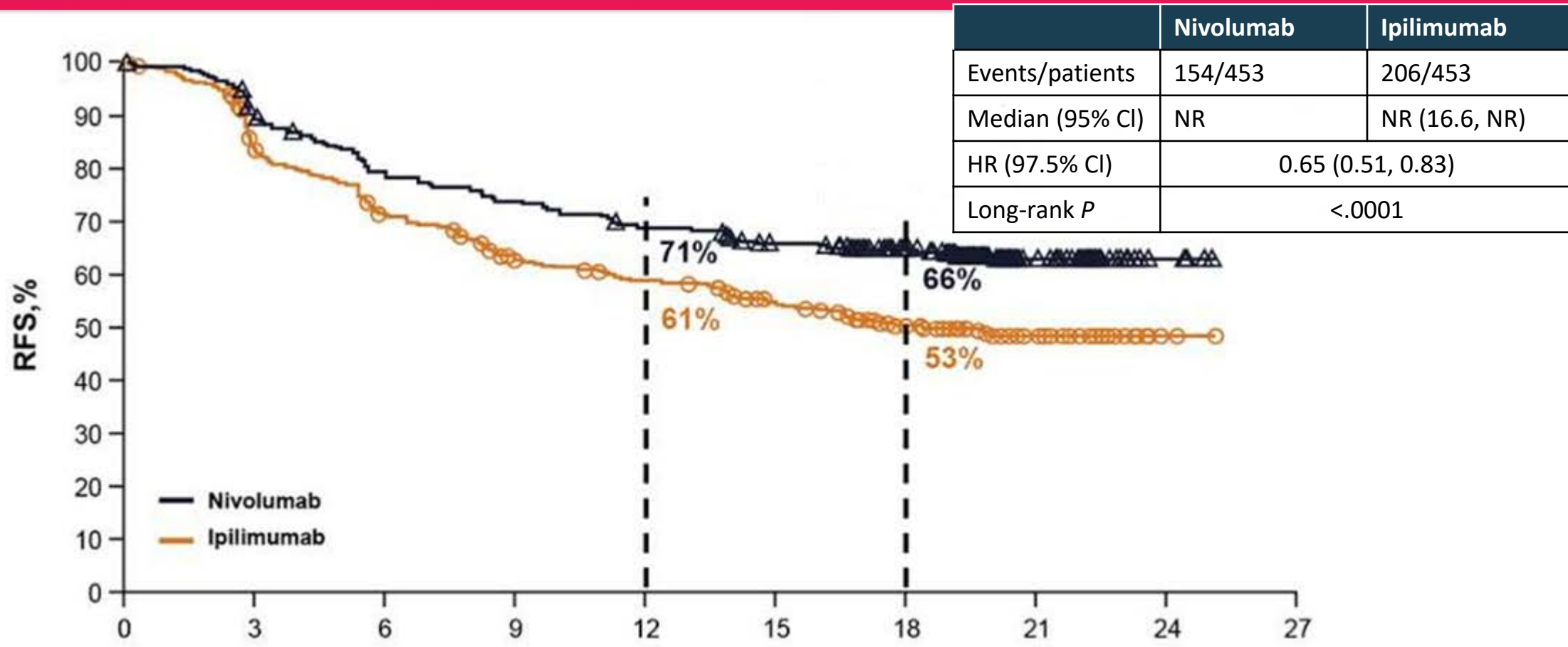
Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0
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Pembrolizumab vs. Ipilimumab in Advanced Melanoma: Keynote-006



Schachter J, Ribas A, Long GV, et al. *J. Clin. Oncol.* 2016;34 (15) Suppl Abstr 9504.

Nivolumab vs. Ipilimumab in Resected Stage III/IV Melanoma: CheckMate-238



No. at Risk	0	3	6	9	12	15	18	21	24	27
Nivolumab	453	399	353	332	311	291	249	71	5	0
Ipilimumab	453	364	314	209	252	225	184	56	2	0

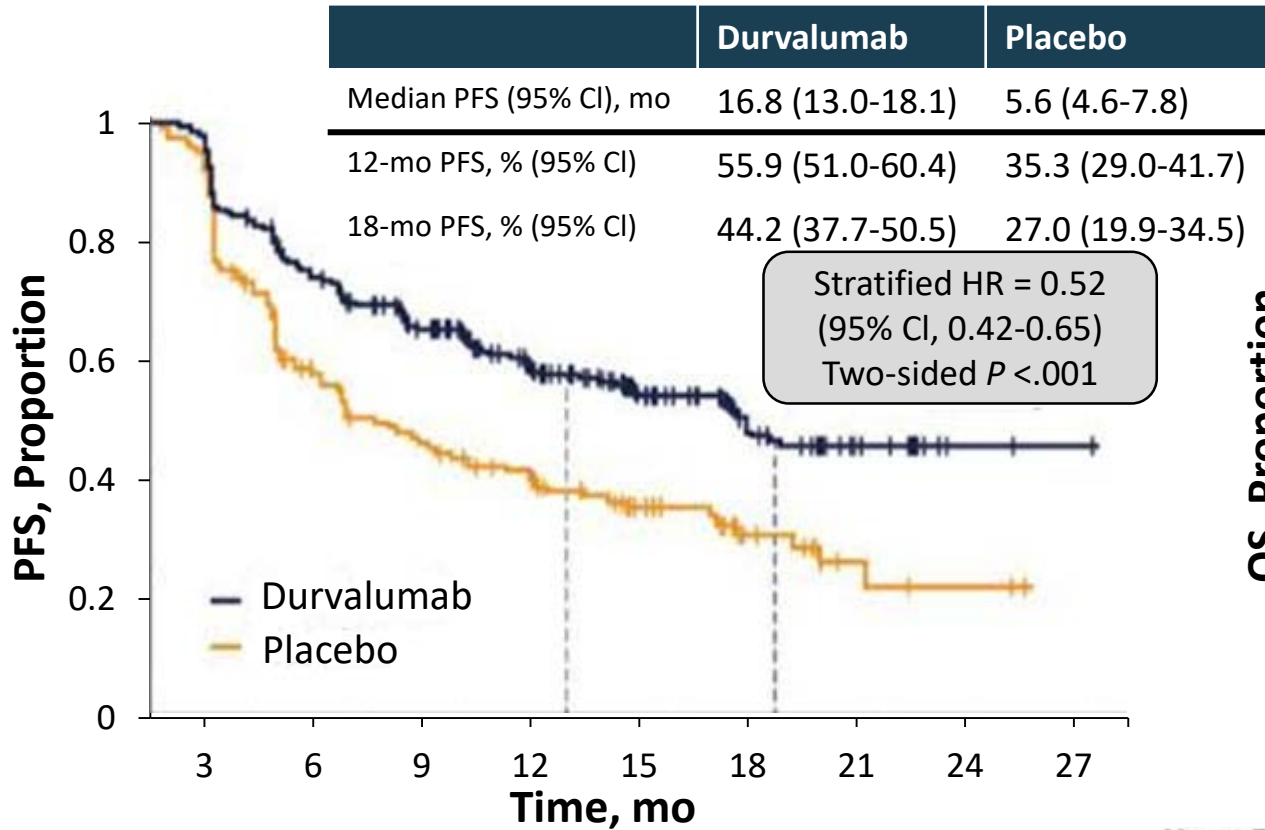
Weber J, Mandala M, Del Vecchio M, et al. *N Engl J Med.* 2017;377:1824-1835.

Durvalumab in Stage III NSCLC:

A: PFS and B: Survival: ITT population

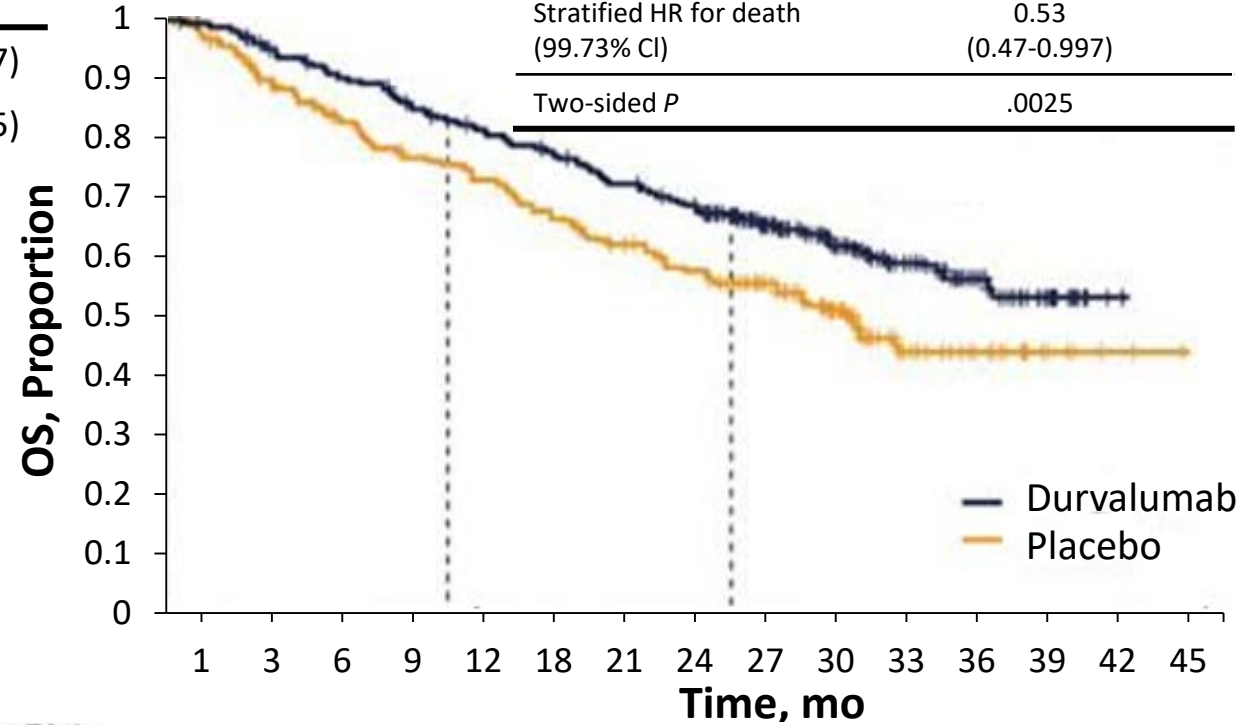
	Durvalumab	Placebo
Events, n/N	183-478	116-237
Median OS (96% CI), mo	NR (34.7 NR)	26.7 (22.9 NR)
12-mo OS Rate (95% CI), %	83.1 (79.4-86.2)	75.3 (69.2-80.4)
24-mo OS Rate (96% CI), %	66.2 (61.7-70.4)	55.6 (46.9-61.8)
Stratified HR for death (99.73% CI)	0.53 (0.47-0.997)	
Two-sided P	.0025	

A. PFS in the ITT Population¹



No. at Risk	3	6	9	12	15	18	21	24	27	
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

B. OS in the ITT Population²

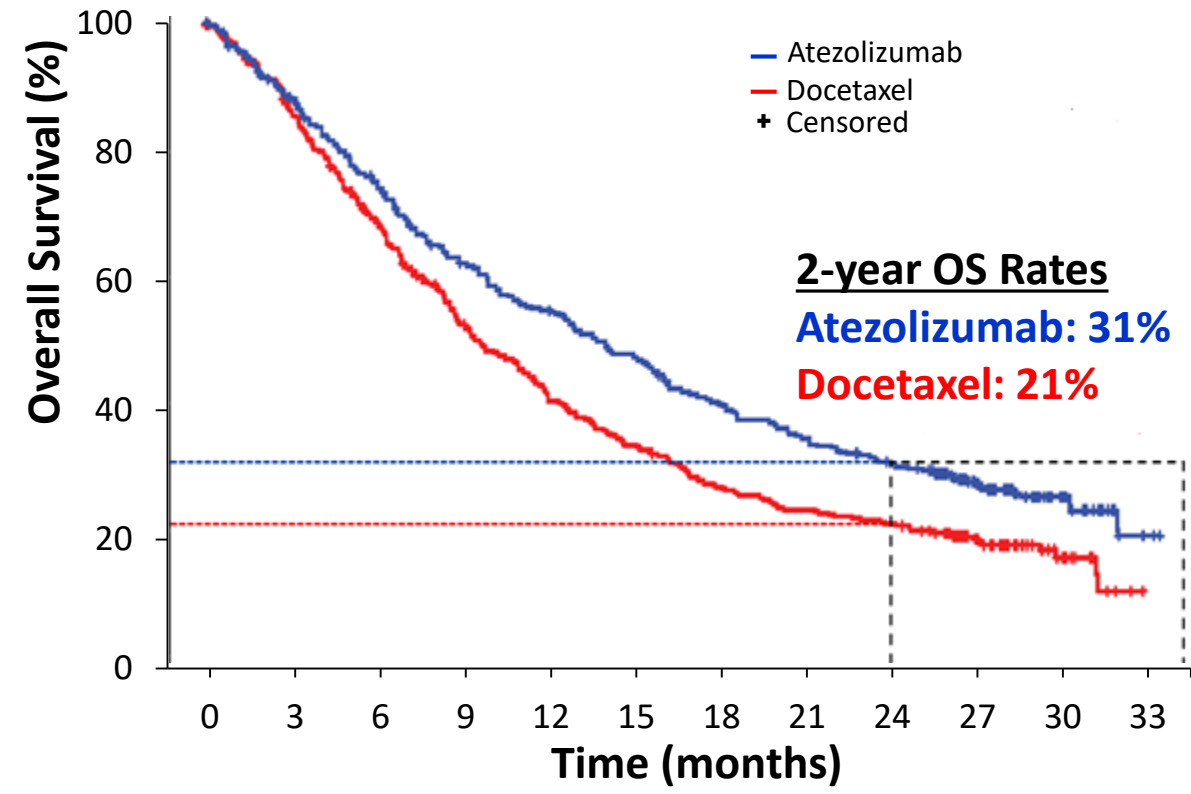
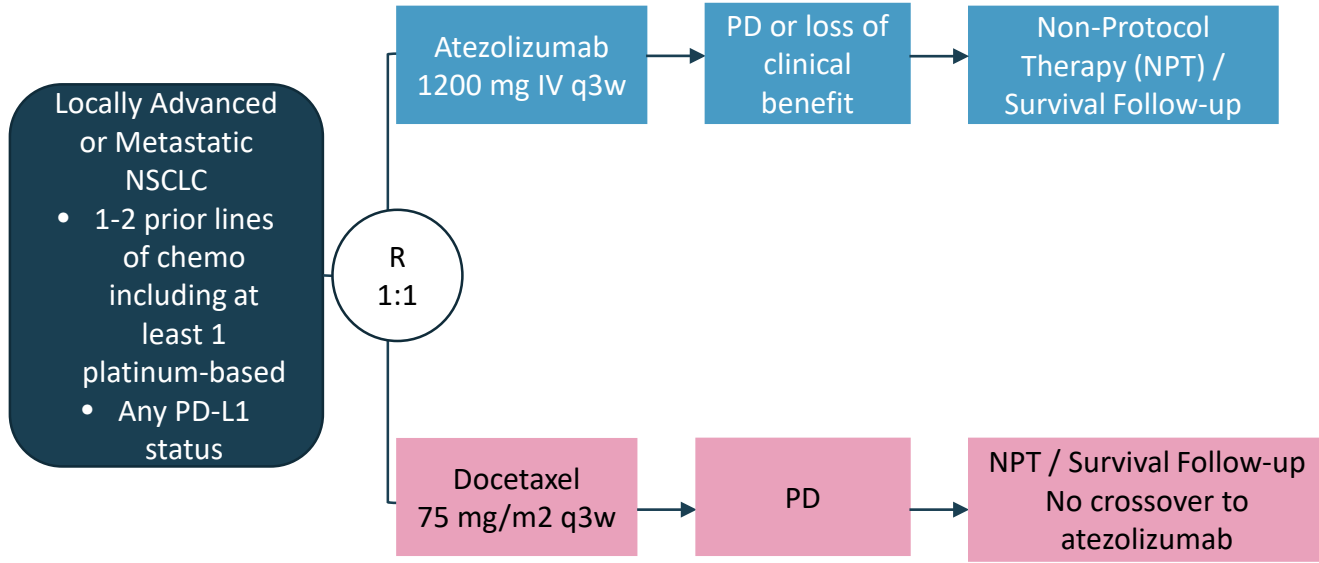


No at Risk	1	3	6	9	12	18	21	24	27	30	33	36	39	42	45	
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Antonia SJ, Villegas A, Daniel D, et al. *N Engl J Med.* 2017;377(20):1919-29.

Antonia SJ, Villegas A, Daniel D, et al. *N Engl J Med.* 2018;379(24):2342-50.

Long Term Survival at 2 years in OAK Trial: Atezolizumab vs Docetaxel in 2nd line+ NSCLC

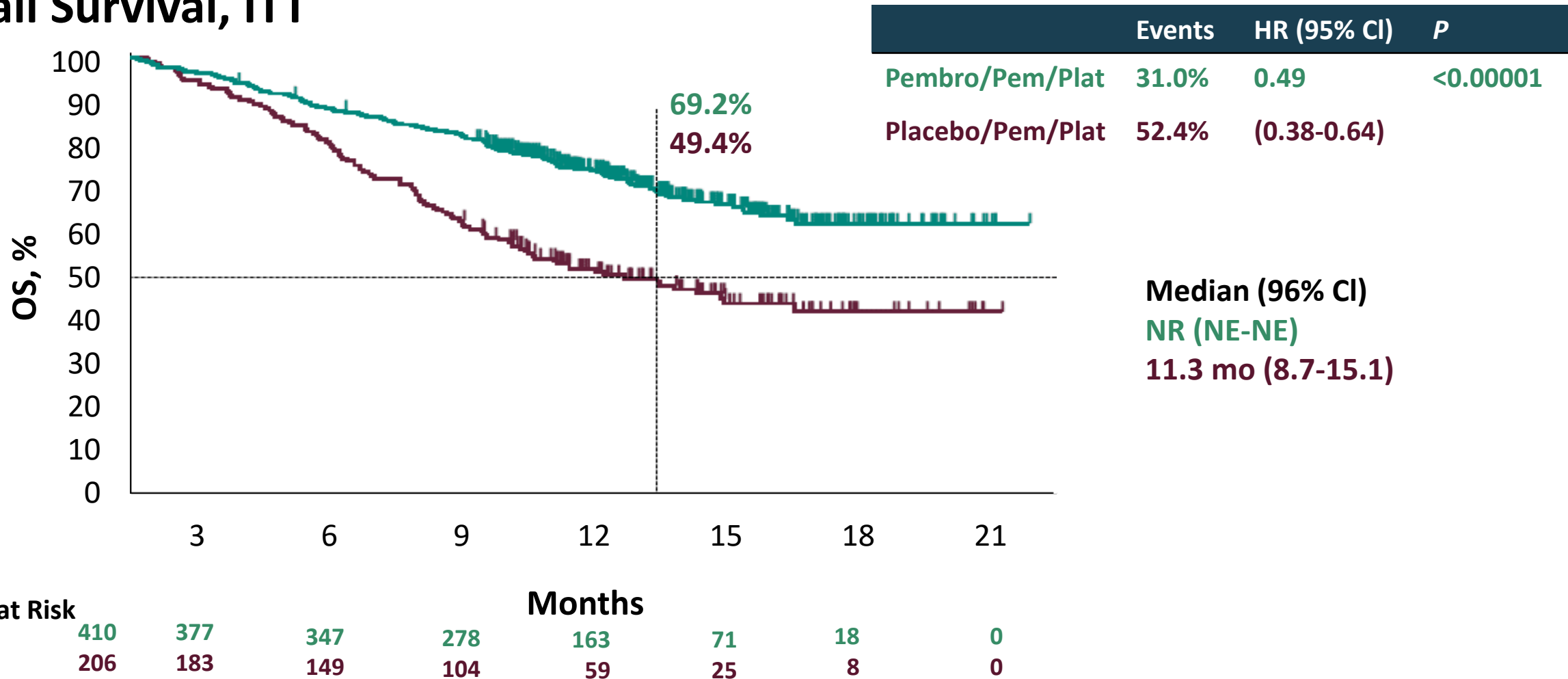


No. of Patients at Risk

Atezolizumab	425	363	305	248	218	188	157	136	119	71	27	2
Docetaxel	425	336	263	195	151	123	98	85	77	43	13	

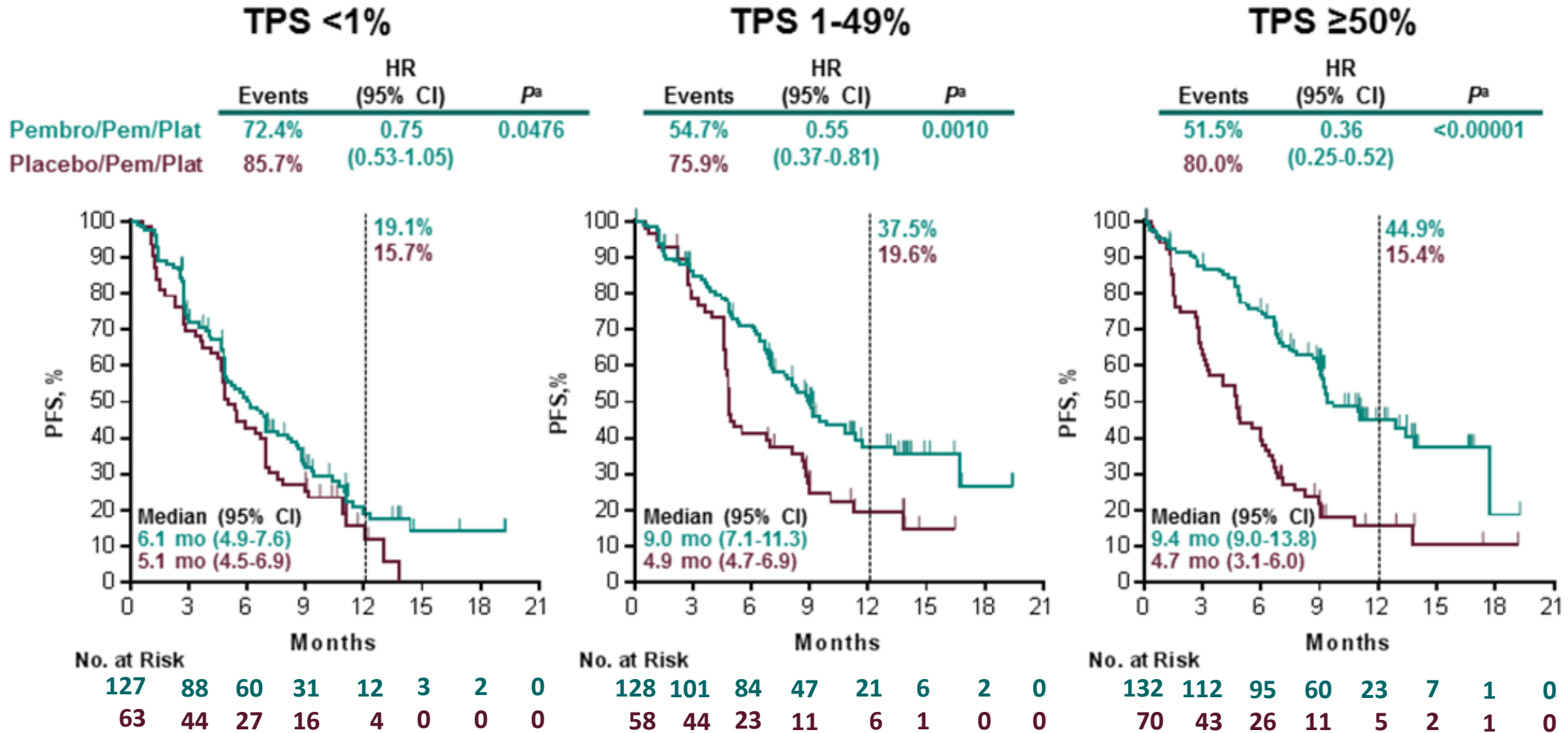
Phase 3 Trial of Chemo + Pembrolizumab or Chemo Alone for Previously Untreated NSCLC: Keynote-189

Overall Survival, ITT



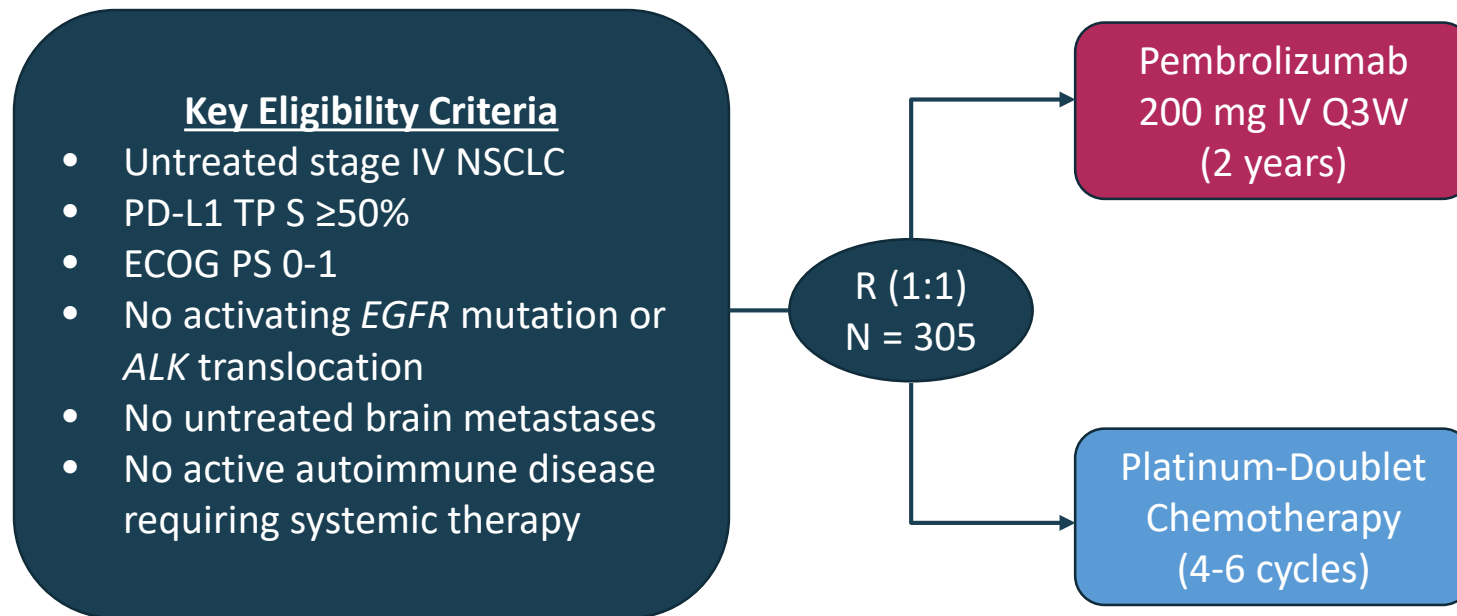
Data cutoff date: Nov 8, 2017

PD-L1 TPS Predicts PFS: Keynote-189



Pembrolizumab vs Chemo in 1st Line NSCLC

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

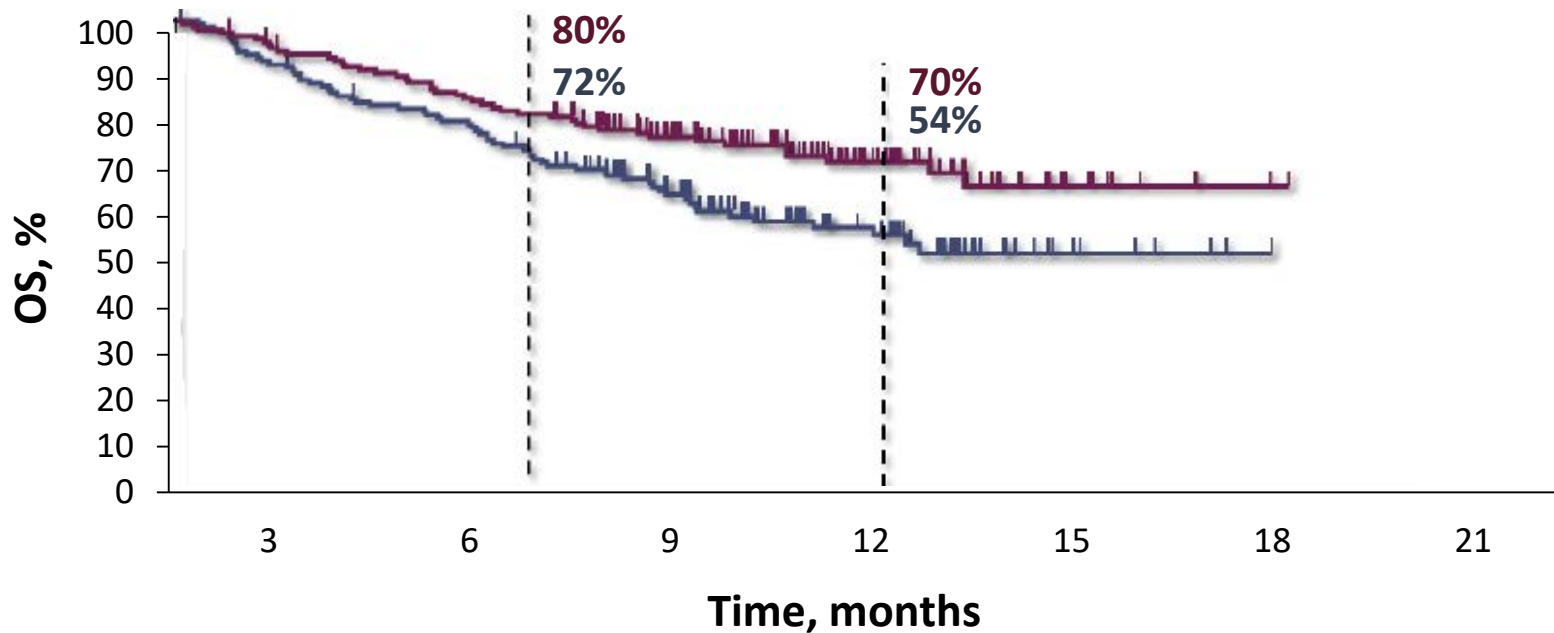
Exploratory: DOR

- Carbo + pemetrexed*
- Cis + pemetrexed*
- Carbo + gemcitabine
- Cis + gemcitabine
- Carbo + paclitaxel

Pembrolizumab vs Chemo in 1st Line NSCLC

Overall Survival

	Events, n	Median, mo	HR (95% CI)	P
Pembro	44	NR	0.60	0.005
Chemo	64	NR	(0.41-0.89)	

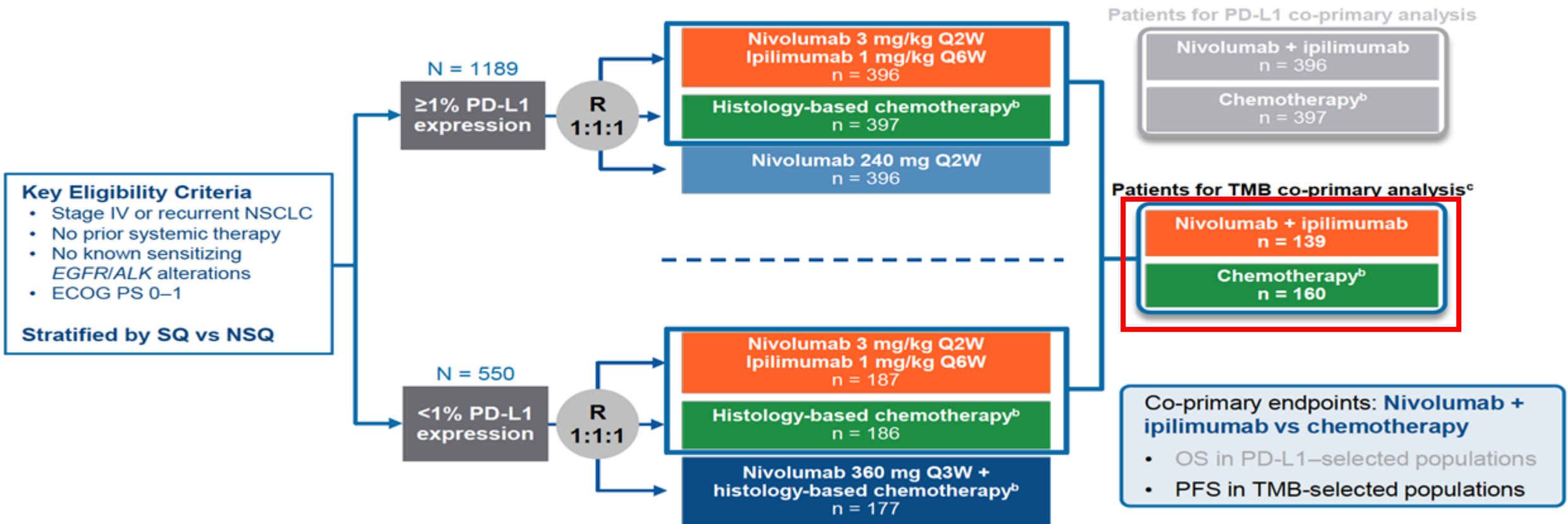


No. at risk

154	136	121	82	39	11	2	0
151	123	106	64	34	7	1	0

CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥ 10 mut/Mb)

CheckMate 227 Part 1 Study Design^a

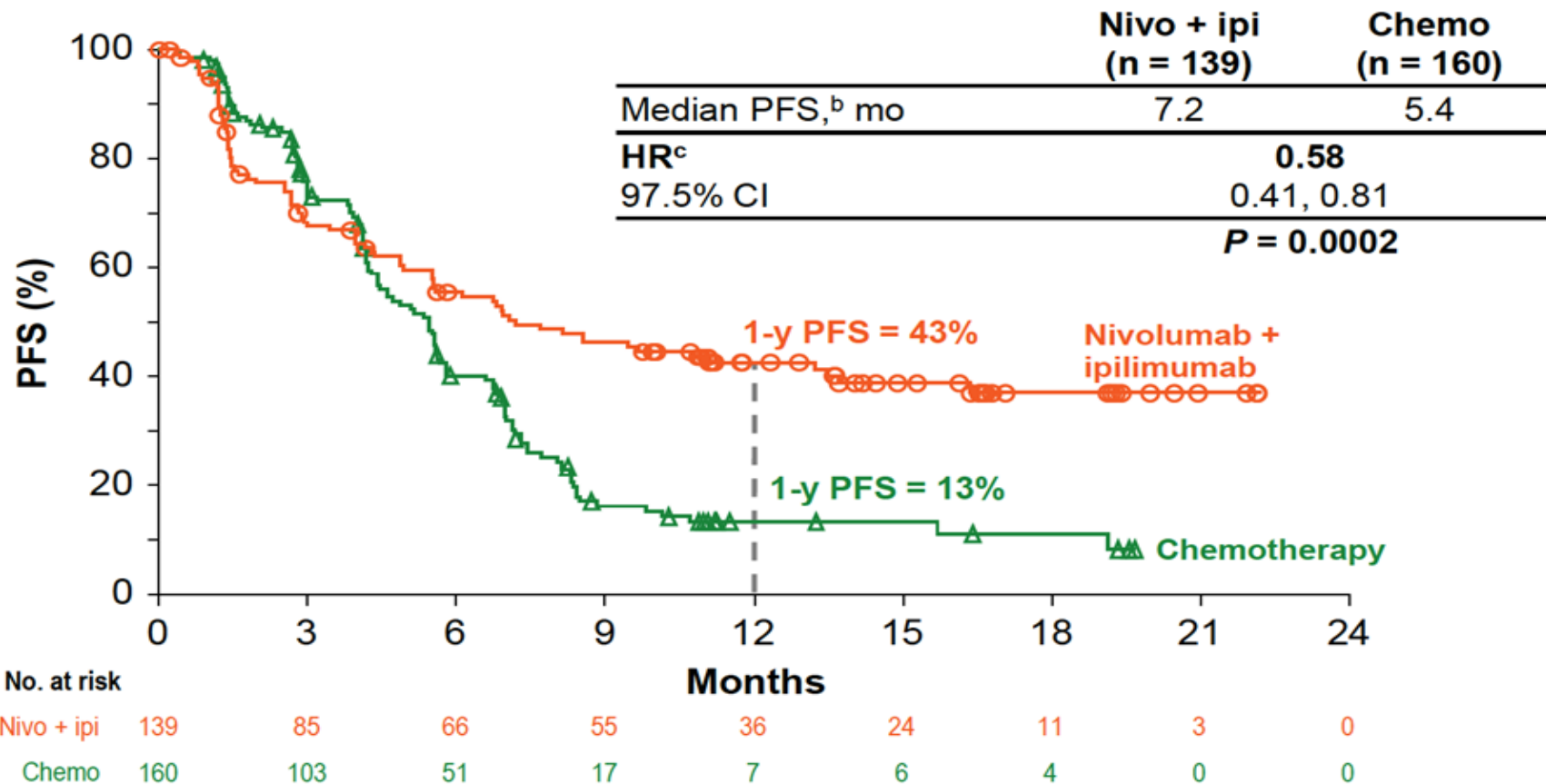


Database lock: January 24, 2018; minimum follow-up: 11.2 months

^aNCT02477826 ^bNSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; ^cSQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; ^cThe TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥ 10 mut/Mb

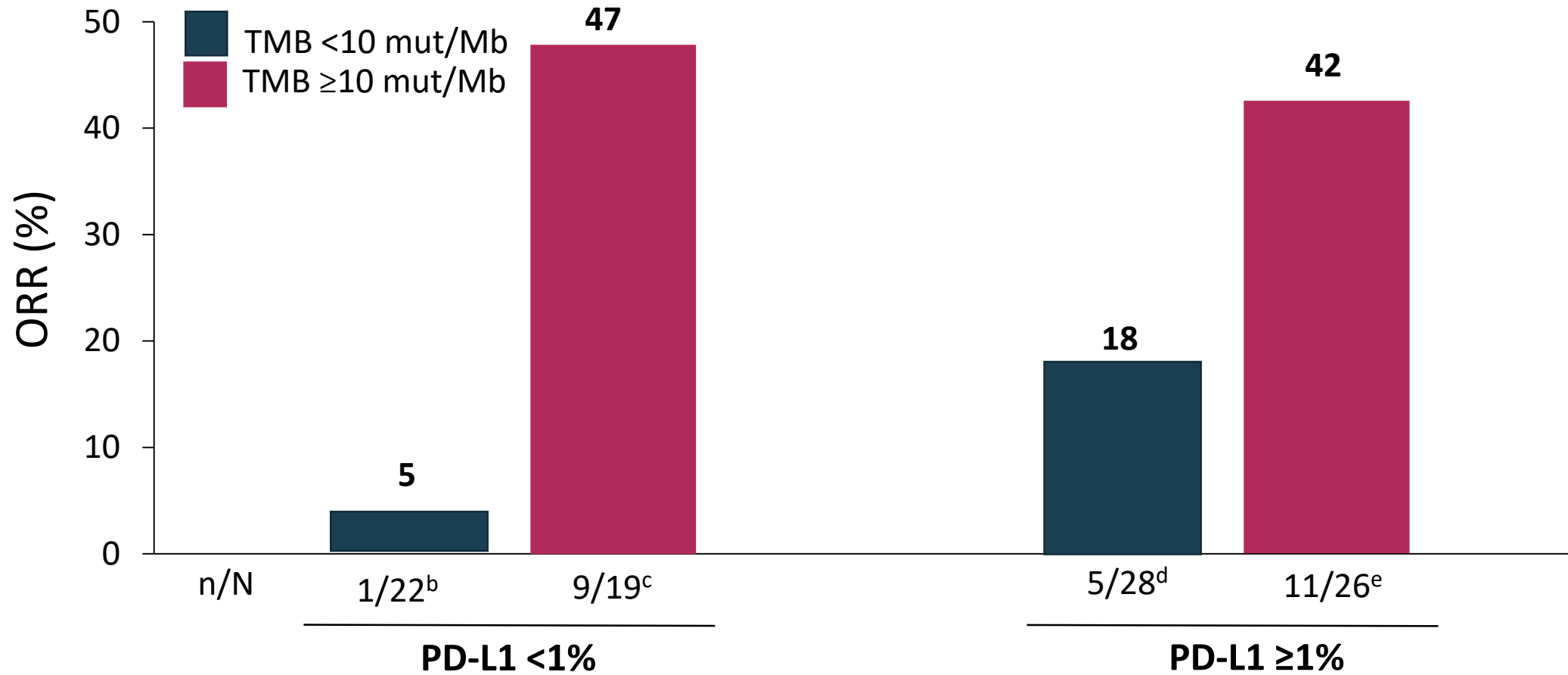
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥ 10 mut/Mb)

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥ 10 mut/Mb)^a



- In patients with TMB < 10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)^d

Responses Observed in TMB ≥ 10 mut/Mb Regardless of Tumor PD-L1 Expression



^aORR for all treated patients: 41% in PD-L1 $\geq 1\%$ subgroup (n=138) and 15% in PD-L1 < 1% subgroup 114; ^bCR=0; ^cCR=16%; ^dCR=4%; ^eCR=4%



Predicting Response: Neoantigens and Related Biomarkers

- Neoantigens
 - Tumors with a high burden of neoantigens have been shown to be more sensitive to immunotherapy
 - Being investigated in anti-CTLA-4 and anti-PD-1 therapy
- Tumor Mutational Burden (TMB)
 - May potentially be used as a surrogate to indirectly assess neoantigen load
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) status
 - May potentially be used as a surrogate to indirectly assess neoantigen load
- Tumor Microenvironment



Predicting response to Checkpoint inhibitors

Tumor microenvironment and the Inflamed Phenotype

“Hot” or “inflamed” tumors due to immune recognition

- High infiltration of CD8+ Tumor Infiltrating Lymphocytes (TILs)
- Presence of chemokines
- Type 1 interferon
- Melanoma and other tumor types

Predicting response to Checkpoint inhibitors Tumor microenvironment

Compliment
System

Lag-3

Single Cell
Characterization of
the Immunological
Microenvironment

- + MA11.06 - Prognostic Value of Complement System in NSCLC and its Association with PD-1 and PD-L1 Expression (Now Available)**
11:05 - 11:10 | Presenting Author(s): Luis M Montuenga | Author(s): Daniel Ajona, María José Pajares, Javier Freire, Javier Gomez-Roman, Elena Martinez-Terroba, Sergio Ortiz-Espinosa, Ana Lledo, Elisabeth Arenas-Lazaro, Jackeline Agorreta, Fernando Lecanda, Ruben Pio
- + MA11.07 - Expression of LAG-3 and NY-ESO-1 In Tumor Cells is Promising Biomarker Predicting Durable Clinical Benefit of PD-1 Blockade in Advanced NSCLC (Now Available)**
11:10 - 11:15 | Presenting Author(s): Hee Ryeong Jang | Author(s): Se Hyun Kim, Kyoung Jin Suh, Yu Jung Kim, Mi So Kim, Bhumsuk Keam, Tae Min Kim, Jin-Haeng Chung, Dong-Wan Kim, Dae Seog Heo, Jong-Seok Lee
- + MA11.08 - Discussant - MA 11.05, MA 11.06, MA 11.07 (Now Available)**
11:15 - 11:30 | Presenting Author(s): Erin Schenk
- + MA11.09 - Single-Cell Characterization of the Immunologic Microenvironment in Advanced-Stage, Oncogene-Driven NSCLC (Now Available)**
11:30 - 11:35 | Presenting Author(s): Julia Rotow | Author(s): Caroline McCoach, Ashley Maynard, David Naeger, Yaron Gesthalter, K Pallav Kolli, Spyros Darmanis, Trevor G Bivona, Collin Blakely, Jonathan Weissman
- + MA11.10 - Identification of Mismatch Repair Deficient Lung Adenocarcinomas Using Targeted Next-Generation Sequencing (Now Available)**
11:35 - 11:40 | Presenting Author(s): Navin Rajput Mahadevan | Author(s): Priyanka Shivadasani, Jonathan Nowak, Mark

Predicting response to Checkpoint inhibitors Tumor microenvironment (cont.)



MA11 - Biomarkers of IO Response (ID 912)

Type: **Mini Oral Abstract Session** | Track: **Immunooncology** | Presentations: 12

Now Available

Moderators: Govind Babu Kanakasetty, Shirish Gadgil

Coordinates: 9/25/2018, 10:30 - 12:00, Room 203 BD

T Cell Intrinsic vs Extrinsic PD-1 Blockade



MA11.01 - Comparative Efficacy of T-Cell Intrinsic Versus Extrinsic PD-1 Blockade to Overcome PD-L1+ Tumor-Mediated Exhaustion (Now Available)

10:30 - 10:35 | Presenting Author(s): Jordan Dozier | Author(s): Nan Chen, Jasmeen Saini, Navin Chintala, Prasad S. Adusumilli

CD3+ TIL Infiltration and FOXP3+/CD8+ Ratio



MA11.02 - Increased CD3+ TIL Infiltration and Low FOXP3+/CD8+ TIL Ratio Can Predict Anti-PD-1 Therapeutic Response in Non-Small Cell Lung Cancer Patients (Now Available)

10:35 - 10:40 | Presenting Author(s): Hyojin Kim | Author(s): Hyun Jung Kwon, Yeon Bi Han, Soo Young Park, Eun Sun Kim, Jin-Haeng Chung

TIL Infiltration and Cancer Nuclei



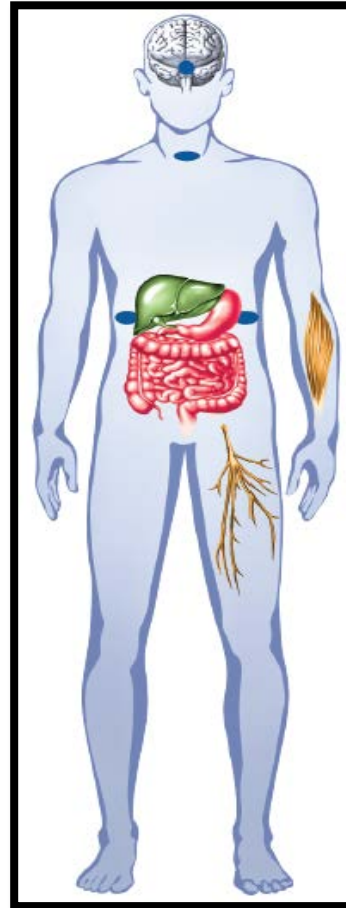
MA11.03 - Interaction of Tumor Infiltrating Lymphocytes and Cancer Nuclei Predicts Response to Nivolumab in Non-Small Cell Lung Cancer (NSCLC) (Now Available)

10:40 - 10:45 | Presenting Author(s): Xiangxue Wang | Author(s): Cristian Barrera, Cheng Lu, Vamsidhar Velcheti, Anant Madabhushi

Immune-Related Adverse Events (IRAEs)

Activation of the immune system against tumors can result in a novel spectrum of IRAEs

- May be due to cytokine release by activated T cells
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious
- Requires prompt recognition and treatment
- Requires patient and HCP education



Occasional (5%-20%) IRAEs Grade 3/4 Uncommon

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
 - Macropapular/pruritus
- Pneumonitis
- Hepatitis
- Pancreatitis
- Arthritis
- Neuropathies

Amos SM, Duong CP, Westwood JA, et al. *Blood*. 2011;118(3):499-509.

YERVOY immune-related adverse reactions management guide. October 2012.

Available at https://www.yervoy.co.uk/Images/6682_IrAR%20management%20guide%20731EMEA12PM014.pdf. Accessed September 2014;

Chin K, Ibrahim R, Berman D, et al. *Ann Oncol* 2008;19 Suppl 8: viii239–viii246. Abstr 787P.

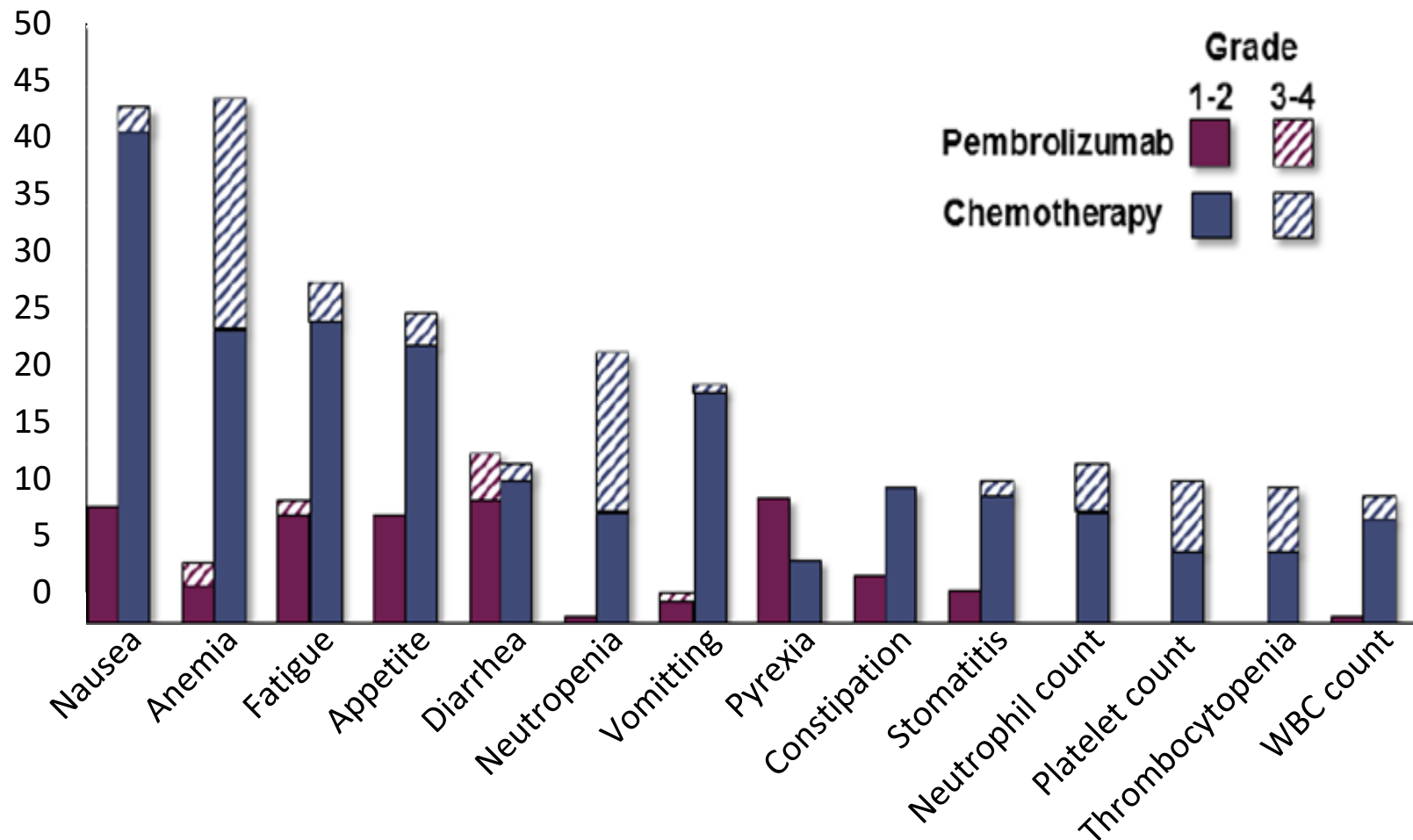


Safety and Tolerability of Therapy with Checkpoint Inhibitors

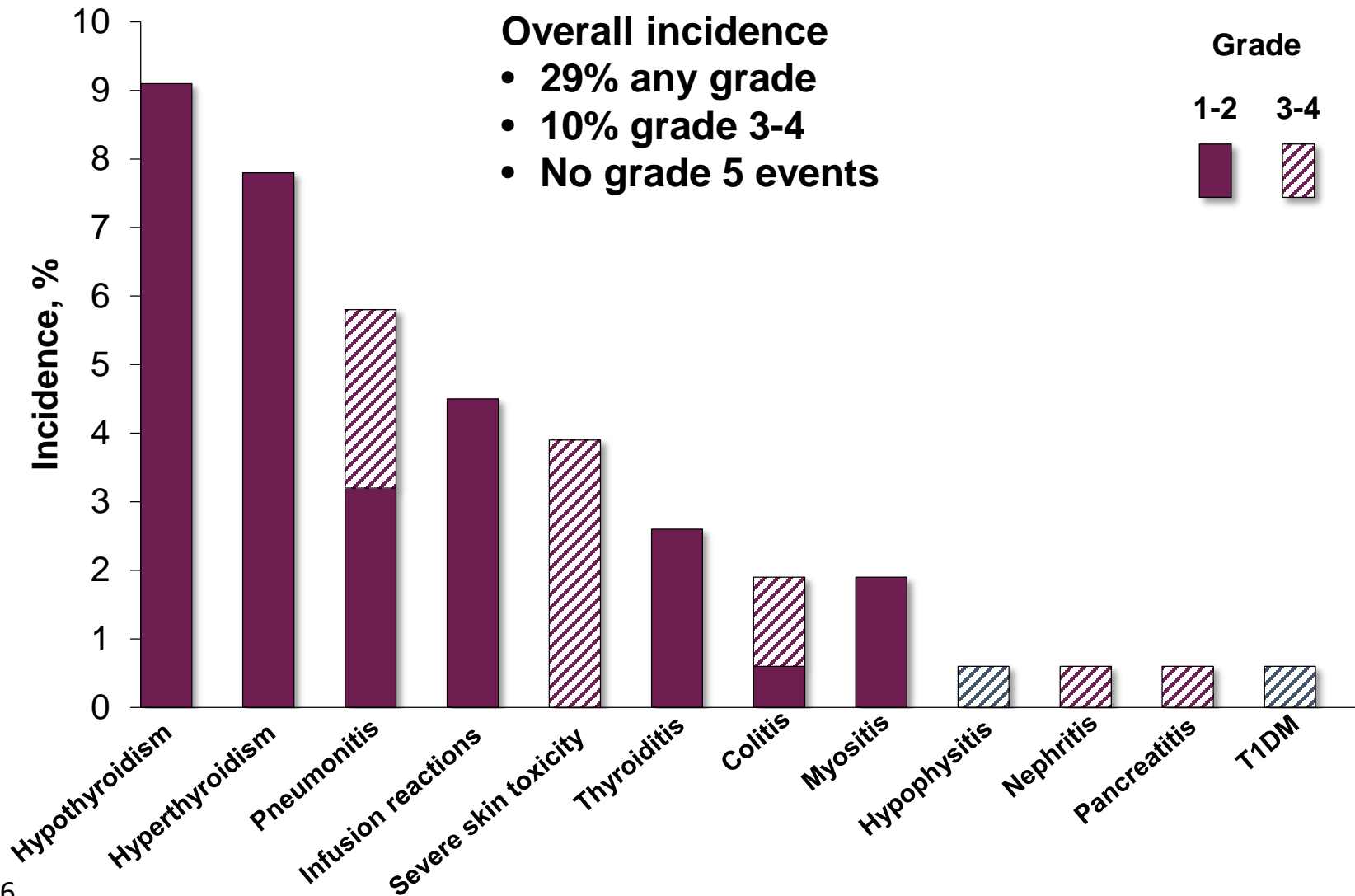
- Spectrum of observed toxicities:
 - GI: diarrhea and colitis
 - Pulmonary: pneumonitis (challenges in diagnosis)
 - Dermatologic: rash and pruritus
 - Hepatic toxicity (importance of plasma screening)
 - Endocrine: hypophysitis, hypothyroidism (importance of plasma screening)
- Timing for appearance of toxicities
- Fraction of patients with toxicities: Anti-PD-1 versus combined anti-PD-1 and anti-CTLA-4

Pembrolizumab vs Chemo in 1st Line NSCLC

Treatment-Related AEs With Incidence >10%



Immune-Mediated AEs With Pembrolizumab



Data cut-off: May 9, 2016.

All Providers Must Be Vigilant in Recognizing Diverse Toxicities

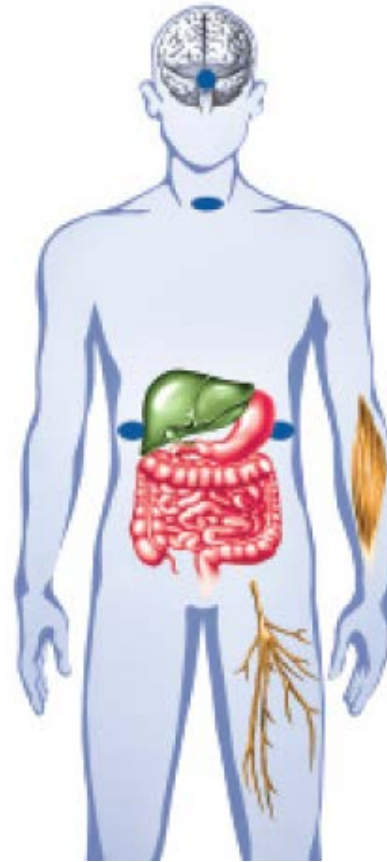
Hypophysitis

Thyroiditis

Adrenal
insufficiency

Colitis

Dermatitis



Pneumonitis

Hepatitis

Pancreatitis

Motor & sensory
neuropathies

Arthritis

- Less common: hematologic; cardiovascular; ocular, renal



IRAEs May Require Weeks of High Dose Steroids and Complex Management

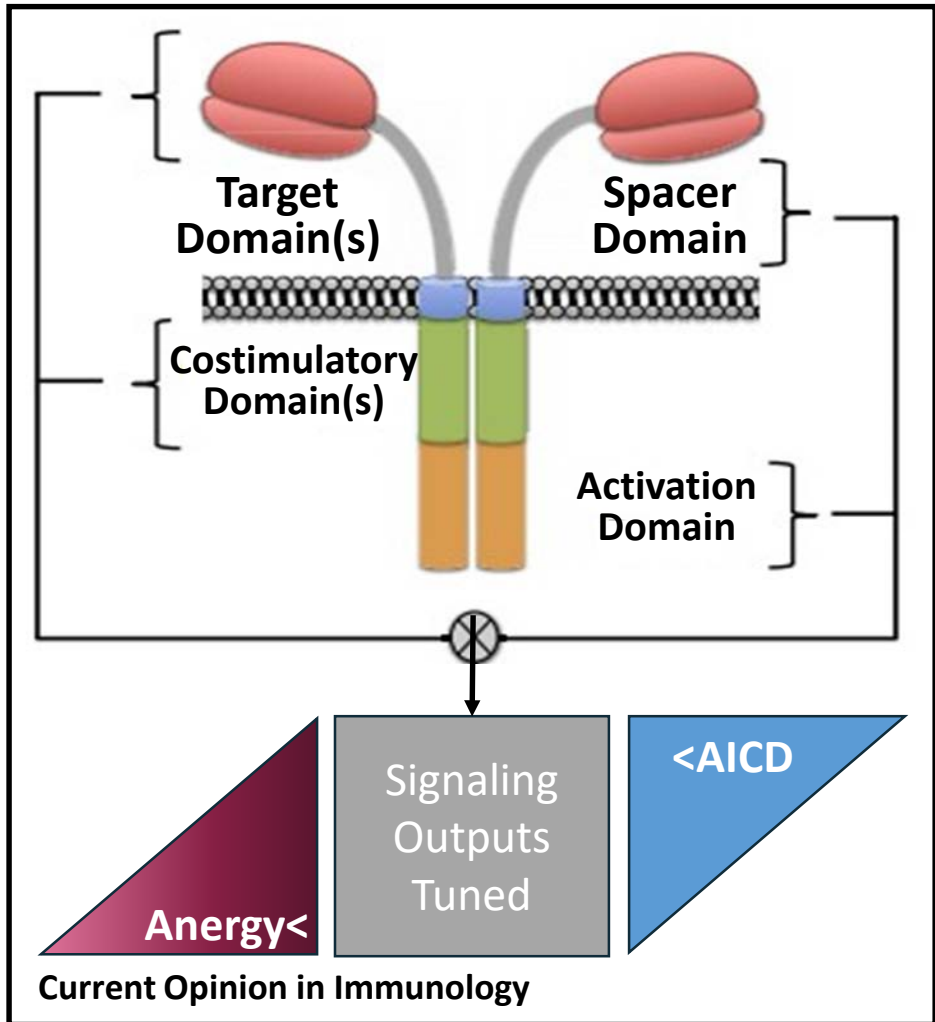
Grade	Management
Grade 1	<ul style="list-style-type: none">• Supportive care +/- hold drug
Grade 2	<ul style="list-style-type: none">• Hold drug• Re-dose at lower dose once toxicity resolved to \leq Grade 1• Low dose steroids if symptoms do not resolve in 1 week
Grade 3/4	<ul style="list-style-type: none">• D/C drug• R/o other etiologies• Consider empiric antibiotics, biopsy• High dose steroids• Taper over \geq 1 month until toxicity resolves to \leq Grade 1



Even Low Grade IRAEs Cannot Be Ignored

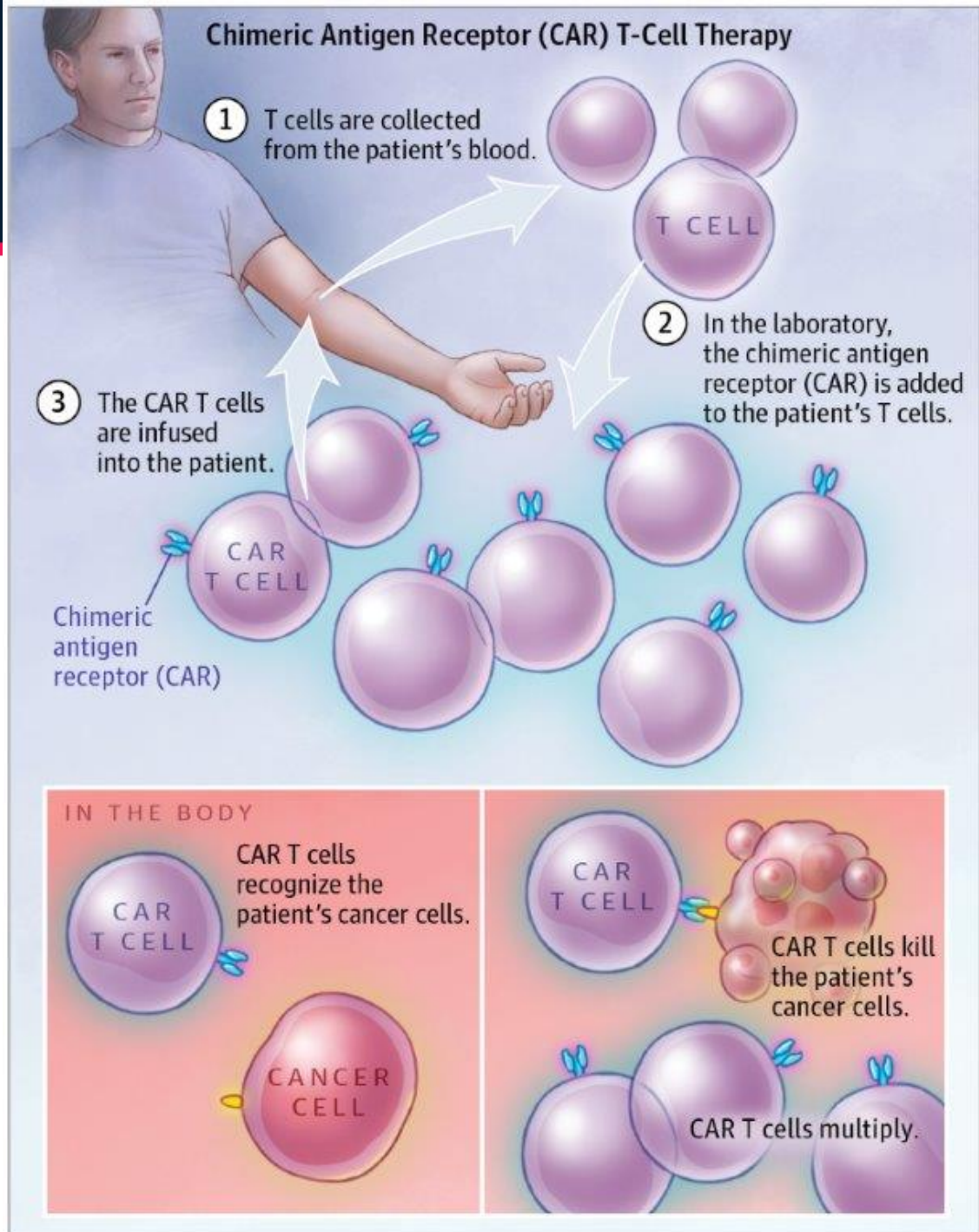
Grade	Management
Grade 1	<ul style="list-style-type: none">• Supportive care +/- hold drug
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Grade 3/4	<ul style="list-style-type: none">• D/C drug• R/o other etiologies• Consider empiric antibiotics, biopsy• High dose steroids• Taper over \geq 1 month until toxicity resolves to \leq Grade 1

Chimeric antigen receptor T-cell (CAR-T) Therapy



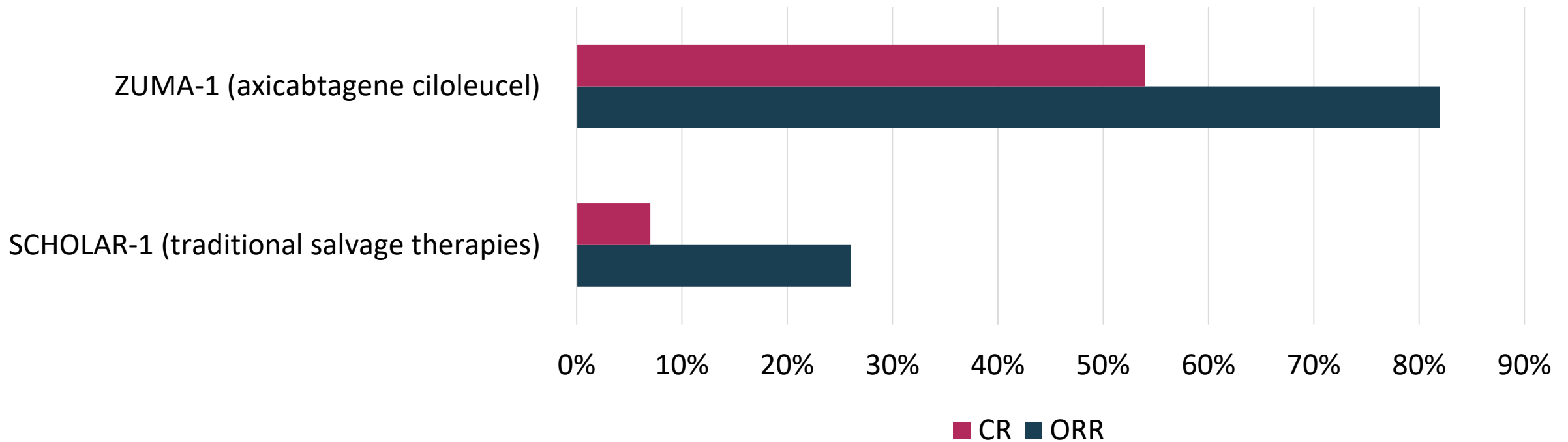
Chimeric antigen receptors (CARs) are fusion molecules typically composed of the following:

- An extracellular single chain variable fragment (scFv) of a monoclonal antibody (mAb) specific for a surface molecule on the tumor cell
- A spacer domain that provides flexibility and optimizes T cell and target cell engagement
- A transmembrane domain
- Signaling modules that trigger T cell effector functions



Axicabtagene Ciloleucel in Refractory Aggressive Non-Hodgkin Lymphoma (NHL)

*Complete Response (CR) and Objective Response Rate (ORR)
Compared with Traditional Salvage Therapies*

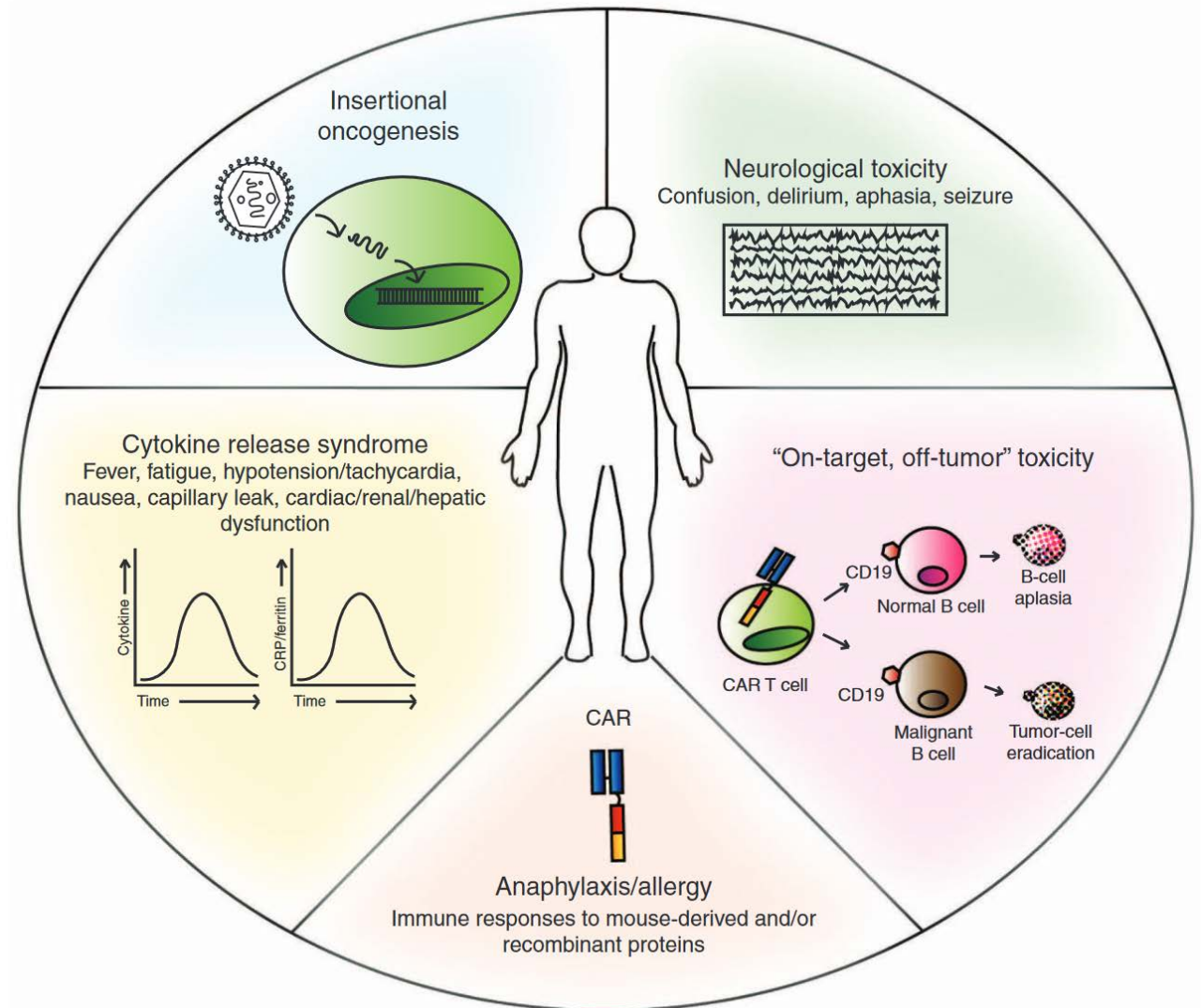


Crump M, Neelapu SS, Farooq U, et al. *Blood*. 2017;130(16):1800-1808.

Locke FL, Neelapu SS, Bartlett NL, et al. *Cancer Res*. 2017;77(13) Suppl Abstract CT019.

Toxicity of CAR-T Cells

- Neurologic toxicity: confusion, delirium, aphasia, seizures
- Anaphylaxis
- Cytokine release syndrome



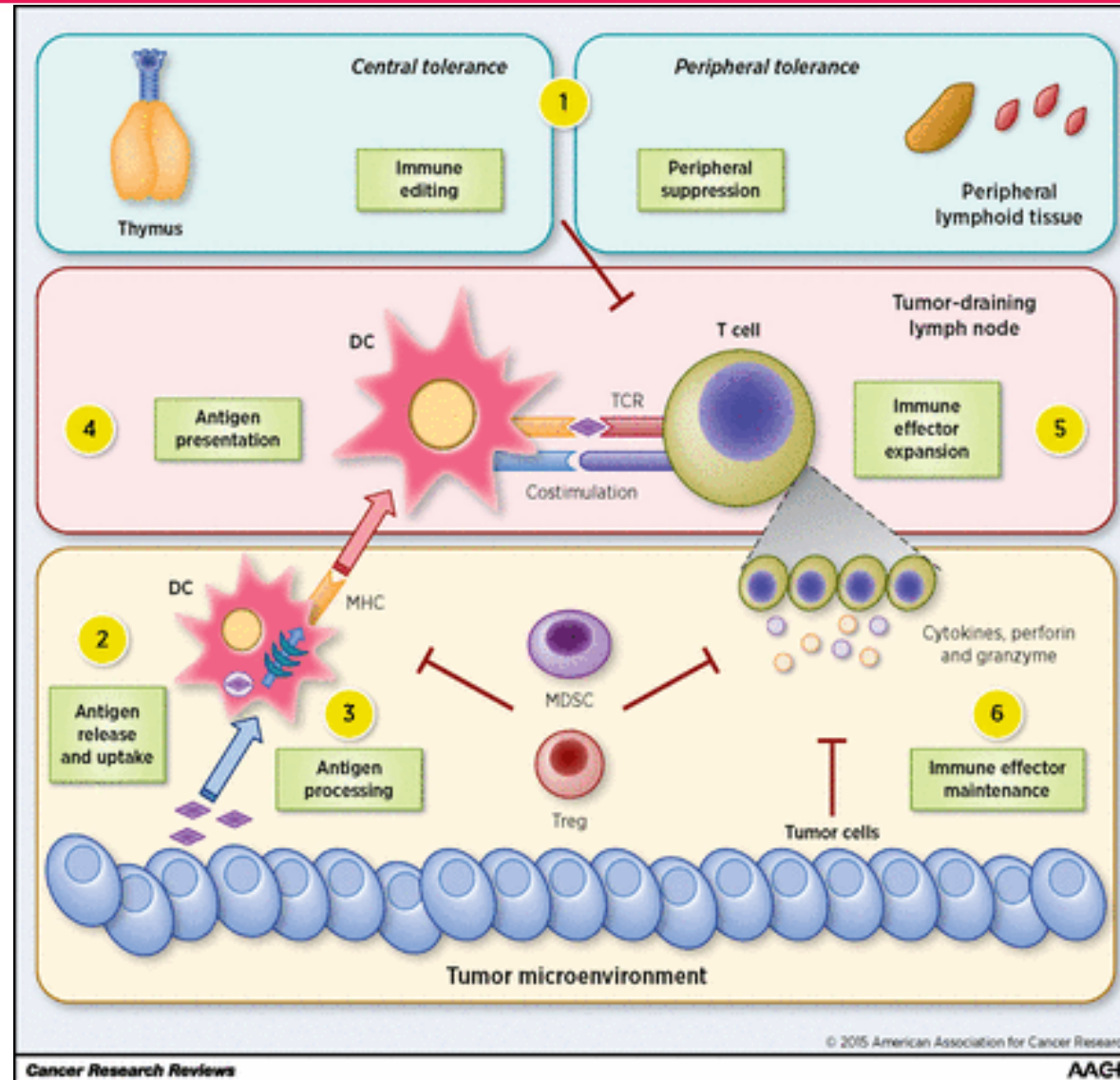


Characterizing the Manifestations of Cytokine Release Syndrome (CRS) Across Various Organ Systems

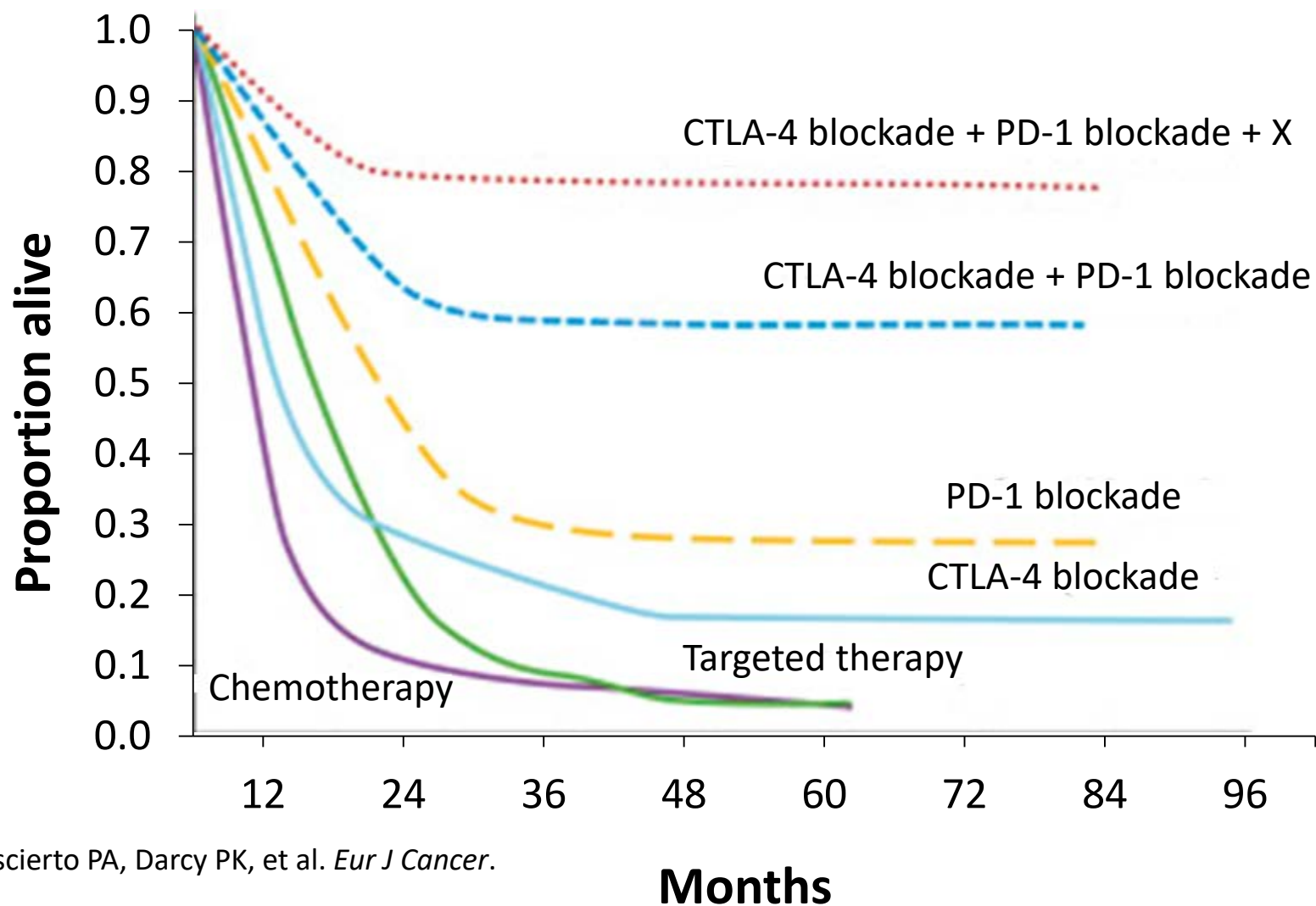
Organ system	Symptoms
Constitutional	Fever \pm rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia \pm bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

The Theory of Combination I-O Therapy

Multiple mechanisms that limit autoimmunity need to be overcome in cancer immunotherapy



Future Promise in Combination I-O Therapy





Summary

- The immune system is capable of recognizing and eliminating tumor cells in the tumor microenvironment
- Immune balance is maintained through the combination of activating and inhibitory signaling pathways that modulate the activity of effector cells, such as cytotoxic T cells and NK cells
- Among the latest innovations in cancer therapies are immuno-oncology agents: these include checkpoint inhibitor antibodies aimed at CTLA-4 and PD-1/L1 and CAR-T therapies
- These agents have demonstrated promise in the treatment of several tumor types, with findings often characterized by extended OS in the long-term
- Activation of the immune system against tumors can result in a novel spectrum of IRAEs with checkpoint inhibitors and CARs/NEs with CAR-T therapies
- Combination regimens offer further potential for future regimens, with a number of biomarkers being assessed to predict response to specific I-O therapies



PD-1/L1 Antagonist Activity Across Tumor Types

Active

- Melanoma
- Renal cancer (clear cell)
- NSCLC – adenocarcinoma
and squamous cell
- Head and neck cancer
- Urothelial (bladder) cancer
- Merkel Cell
- Mismatch repair deficient tumors
- Hodgkin Lymphoma
- Hepatocellular carcinoma
- Gastric and GE junction
- Cervical cancer
- PMBCL

Is the Cost Sustainable????

- Anal cancer
- Squamous Cell Ca of Skin
- **Small cell lung cancer**
- Triple negative breast cancer
- **Ovarian cancer**
- Thymic carcinoma
- Mesothelioma
- Diffuse large cell lymphoma
- Follicular lymphoma

Minimal to no activity

Prostate cancer
MMR+ Colon cancer
Myeloma
Pancreatic Cancer
ER+ breast cancer

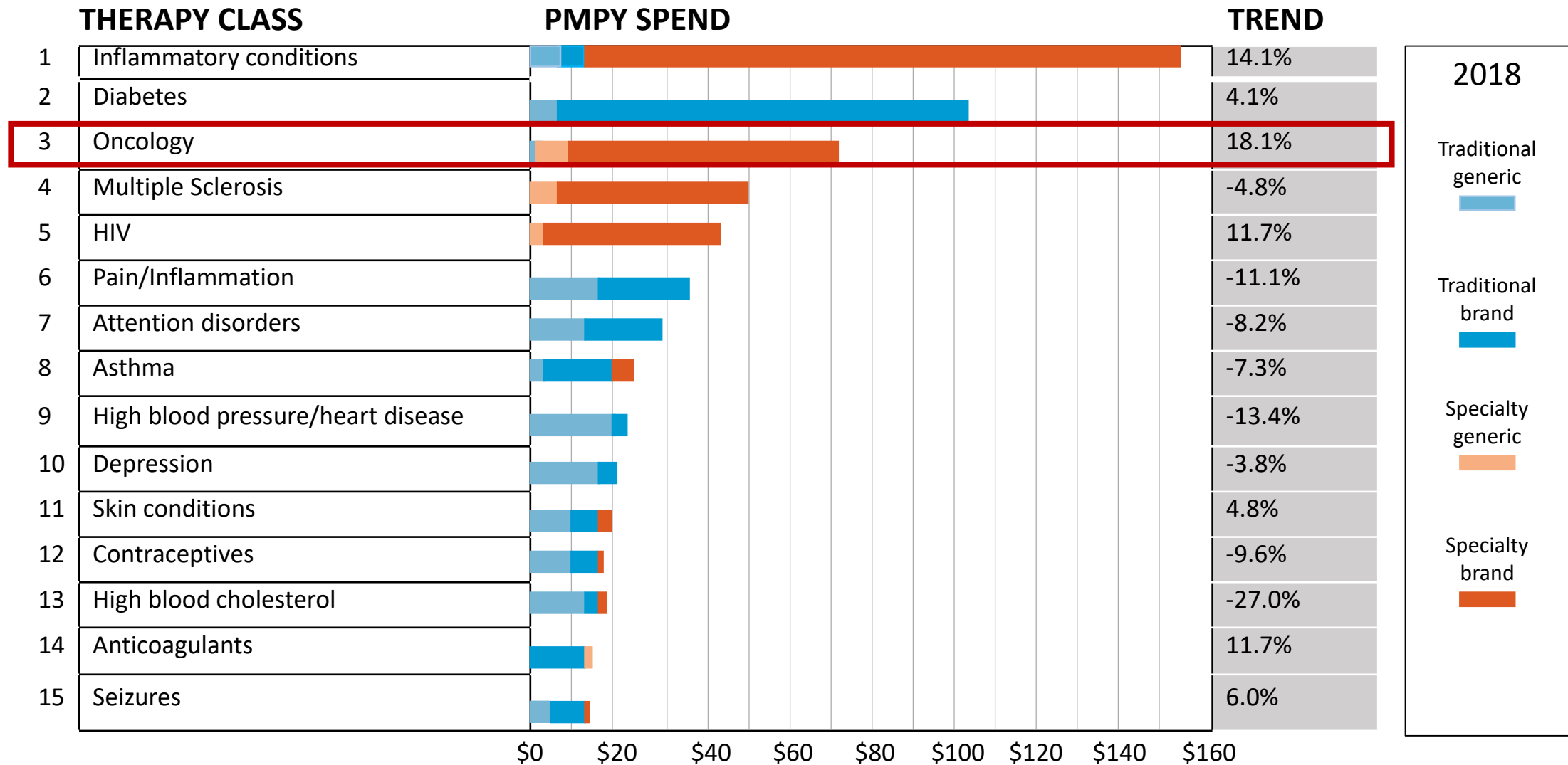


Medical and Pharmacy Benefit Design Strategies for Immuno-Oncology Agents

Jeffrey Dunn, PharmD, MBA

Vice President, Clinical Strategy and Programs and Industry Relations
Magellan Rx Management

Oncology Led All Classes of Drugs in Terms of Trend in 2018 with a Sizeable Specialty Component



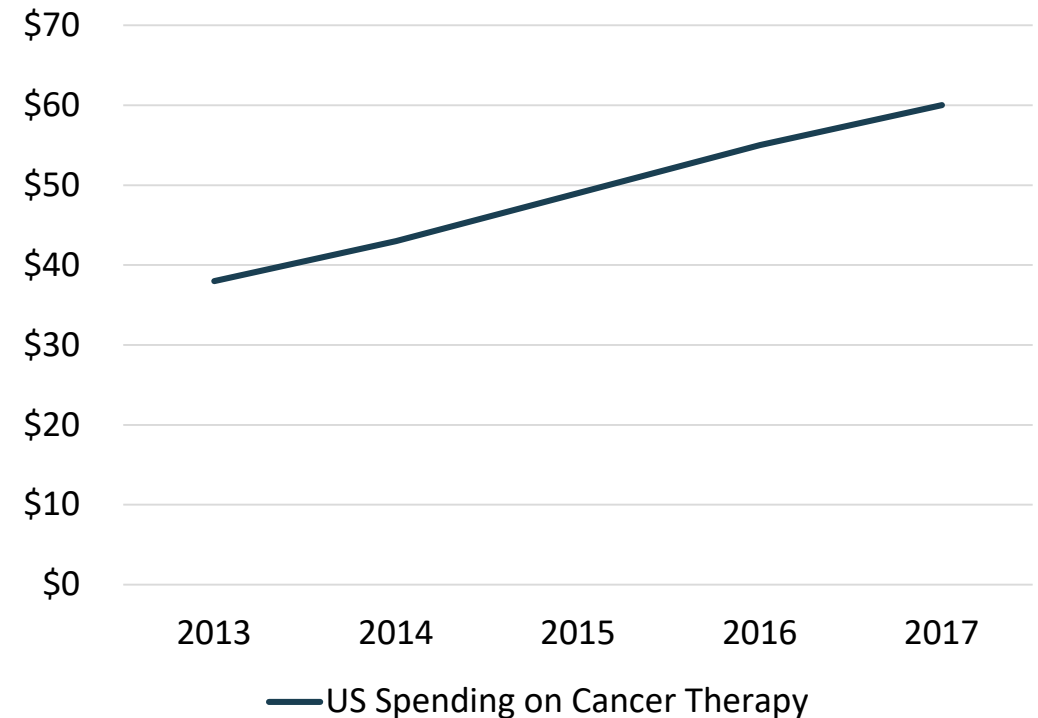
Spending on Oncology Therapies has Risen Consistently for Several Decades

- 73 new cancer therapies approved or indications expanded since 2012
- 16 new cancer drugs approved in 2017, all targeted therapies
- Global spending on cancer medications rose from \$96 billion in 2013 to \$133 billion in 2017
 - US led the trend with highest spend: 33% (2013) to 50% (2017) of global spend
- US cancer drugs expected to cost \$100 billion by 2022
- Median annual cost of new cancer drug doubled in last decade from \$75,000 to \$150,000
- 87% of cancer drugs are used by fewer than 10,000 patients each year
- 700 new molecules in late-stage development now

New Cancer Therapies Approved/Indications Expanded

2013	2014	2015	2016	2017	2018
12	10	21	11	16	3

Total US Spending Oncology Therapeutic Medicines, 2013-2017





Attitudes Toward the Management of Oncology Therapies Have Long Since Changed: Cancer is No Longer Untouchable

**Price and
value of therapies
rarely questioned**

**Vigorous debate about
the overall value* of
treatments**

**Pre-specialty
oncology drug era**

**Specialty
oncology drug era**

**Payers now actively apply
payment reforms and quality measurement
to cancer services**

*Clinical, pharmacoeconomic, humanistic, societal, etc.



Willingness to Manage Oncology

Oncology Management Strategies Willing to Implement

% of payers
(n = 45)

67%	Restricting specified regimens based on the patient's performance status when aligned with NCCN recommendations
67%	Incentivizing lower cost regimes when they carry the same level of compendia recommendation
47%	Limiting agents that are recently approved by the FDA under an accelerated approval pathway to patients who meet the study eligibility criteria used for FDA approval
31%	Not covering NCCN 2A recommendations if evidence is lacking
2%	Other (preferring a lower cost agent but only if NCCN 1 vs. 2A or lower)
7%	None of the above

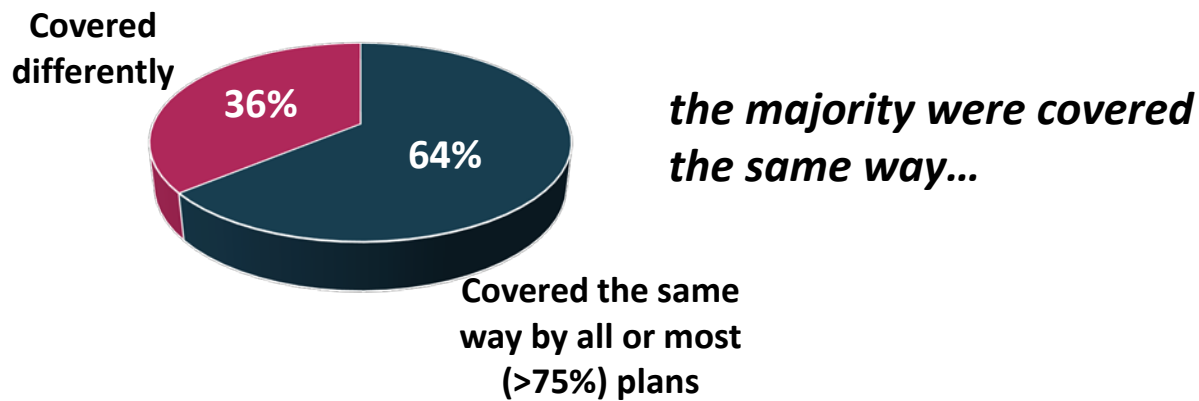


Formulary and Clinical Policy

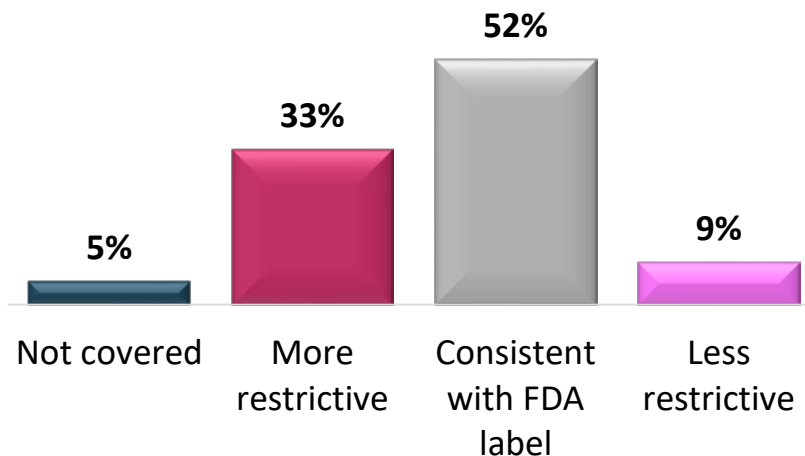
- Closed formularies are becoming more common
 - NDC block until review
 - Increasing number of excluded drugs
- Narrowing the number of preferred or covered products
- More restrictive policies/PA criteria: going beyond the label to consider clinical trial inclusion/exclusion
 - Restricted patient population
 - Stopping rules for nonresponse
 - More rigorous re-authorization criteria

Tufts Study on Restrictive Coverage

Across 3,417 decisions addressing coverage for 302 drug indication pairs...

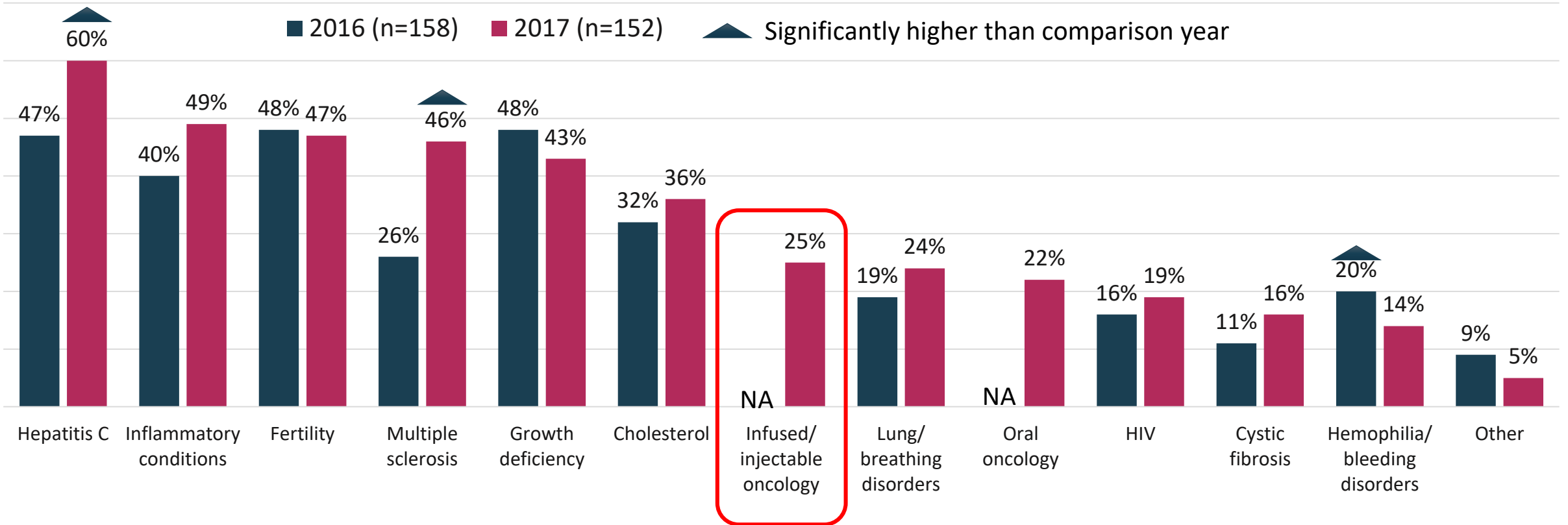


and specifically the decisions were...



- Health plans restricted coverage of drugs indicated for cancer less often than they did coverage of drugs indicated for other diseases
- Using multivariate regression, it was found that several drug-related factors were associated with less restrictive coverage, including indications for orphan diseases or pediatric populations, absence of safety warnings, time on the market, lack of alternatives, and expedited FDA review

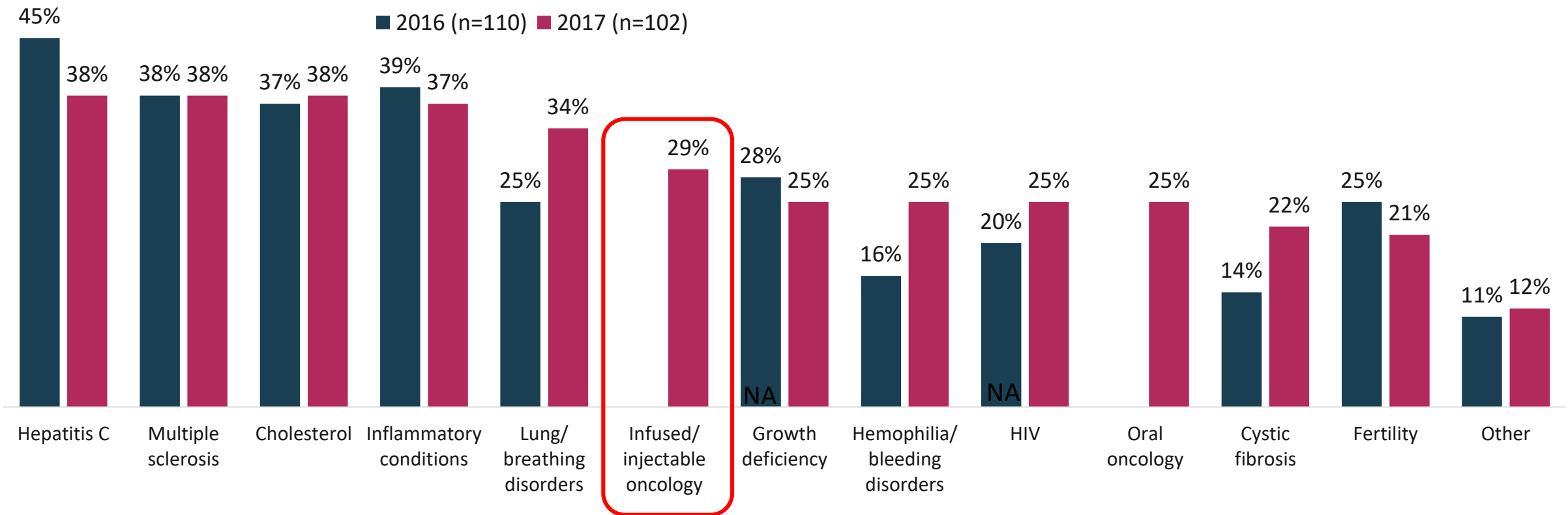
Formulary Exclusion Classes



Base: Respondents who have formulary exclusions in place. Multiple responses allowed. NA = not asked.

N=299 employer-based plans of all sizes

Classes Under Consideration for Formulary Exclusion



Base: Respondents who are considering formulary exclusions. Multiple responses allowed. NA = not asked.

N=299 employer-based plans of all sizes

Potential Factors in Oncology Formulary Decision Making



HEDIS = Healthcare Effectiveness Data and Information Set; JCAHO = Commission on Accreditation of Healthcare Organizations; NCQA = National Committee for Quality Assurance; PBM = pharmacy benefit manager.



Health Technology Assessment/Drug Review

- Payers are demonstrating more interest in Institute for Clinical Effectiveness Research (ICER) reviews and the potential for use of Cost Effectiveness Analysis (CER)
- Drug evaluation, contracting, etc. are contributing to large discrepancies between plan coverage and coverage policies



Use of ICER Reports by Payers

At what point were ICER reports used in the formulary decision process?

- 75% evidence source for preparing P&T recommendations
- 69% inform or validate the payer's own analysis
- 64% used during research process
- 56% used during the P&T review phase
- 33% use during coverage policy development

May 2015 Survey of AMCP eDossier Users (N=99)



Clinical Evidence & Cost-Effectiveness

- Organizations choose whether to include cost data as part of the P&T Committee Review process
- If cost data is not included, drugs are reviewed solely on clinical efficacy, safety, unmet need
- An administrative committee is then tasked with final formulary placement decisions based on:
 - P&T Committee's clinical evaluation
 - Cost-effectiveness data

Available Oncology Value Frameworks



American Society of Clinical
Oncology (ASCO) Value
Framework



National Comprehensive
Cancer Network (NCCN)
Evidence Blocks



Memorial Sloan Kettering
Cancer Center Drug Abacus



Institute for Clinical and
Economic Review (ICER)
Value Assessment
Framework



European Society for Medical
Oncology (ESMO) Magnitude
of Clinical Benefit Scale

Emphasis of Various Oncology Value Frameworks

Value Framework ⁶⁻¹⁰					
Emphasis	ASCO	NCCN	MSKCC	ICER	ESMO
Application					
Target stakeholder	Patient Physician	Patient Physician	Physician Policymaker	Payer Policymaker	Payer Policymaker
Conditions addressed	Oncology: solid, blood	Oncology: solid, blood, radiology, surgery	Oncology: solid, blood	All conditions, focus on new drugs of high impact	Oncology: solid, blood, radiology, surgery
Clinical trial data					
Breadth of evidence	1 trial, RCT	Published data, panel members' clinical experience, case reports	1 trial, registration trial of first indication (FDA label)	RCT meta-analysis and manufacturer- provided data	1 trial, RCT, comparative outcomes study, meta analysis
Trial sample size accounted	No	Yes	Yes	Yes	Indirectly, through lower bound of 95% CI
Allows for single-arm trials	Partially	Likely	Yes	Yes	No
Acknowledges trial contamination	No	Likely	No	Yes	Yes
Accounts for patient preference	No	Yes	Yes	No	No
Readout					
Outcomes	Net health benefit score	Evidence Blocks score	DrugAbacus price	Cost-effectiveness; budget impact	ESMO MCBS
Cost/price	Price (WAC or ASP+) per month or course of therapy	Affordability scale	Abacus price per month or course of therapy	Cost per year	Not specified, left to payers to evaluate

ASCO indicates American Society of Clinical Oncology; ASP, average sales price; CI, confidence interval; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; ICER, Institute for Clinical and Economic Review; MCBS, Magnitude of Clinical Benefit Scale; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; RCT, randomized controlled trial; WAC, wholesale acquisition cost.

Inputs of Various Oncology Value Frameworks

Value Framework⁶⁻¹⁰

Input	ASCO 2.0	NCCN	MSKCC	ICER	ESMO
Primary end points					
Efficacy	Advanced disease: HR (death), OS, PFS, response rate Adjuvant therapy: HR (death), OS, DFS	Vary, dependent on indication	Improvement in OS or surrogate end point	Vary, dependent on location	Advanced disease: OS, PFS, palliation of symptoms, response rate
Safety/toxicity	Based on side-effect frequency, grade	Effect on daily life	Grade 3/4; probability of discontinuing	Severe side effects	Grade 3/4; severe side effects
Secondary end points					
Treatment-free interval	Yes	No	No	No	No
Tail of the curve	Yes	No	No	No	No
Quality of life/palliation	Yes	No	No	Yes	Yes
Patient preferences	No	No	No	No	No
Epidemiologic factors					
Disease burden/incidence	No	No	Yes	Yes	No
Unmet need	No	No	Yes	No	No
R&D factors					
Novelty	No	No	Yes	No	No
Research cost	No	No	Yes	No	No
Cost					
Drug costs	Advanced disease: drug acquisition cost per month Adjuvant therapy: drug acquisition cost/entire treatment regimen	Total treatment cost	ASP/AWP	Total cost per person, total cost to payers	Not specified, left to payers to evaluate
Cost to healthcare system	No	Yes	Yes	Yes	No

ASCO indicates American Society of Clinical Oncology; ASP, average sales price; AWP, average wholesale price; DFS, disease-free survival; ESMO, European Society for Medical Oncology; HR, hazard ratio; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival;; R&D, research and development.



Scoring Algorithms of Various Oncology Value Frameworks

ASCO	NCCN	MSKCC	ICER	ESMO
Formulaic	Expert-based	Formulaic	Formulaic and expert-based	Formulaic

Outputs of Various Oncology Value Frameworks

Value Frameworks ⁶⁻¹⁰					
Output	ASCO	NCCN	MSKCC	ICER	ESMO
Health benefit	Net health benefit	Score (1-5) for each 5 key measures displayed as Evidence Blocks	No	Assessment of care value (high/intermediate/low)	A relative ranking of the magnitude of clinically meaningful benefit
Cost Readout	Directly reported as regimen cost (WAC or ASP) Advanced disease: drug acquisition cost per month Adjuvant therapy: drug acquisition cost for entire treatment	Reported as relative affordability, considers overall cost of intervention (eg, cost of drug, infusions, supportive care, management)	DrugAbacus value-based price per month or course of therapy; a user-generated value assessment directly compared with reported Medicare payment limit, 106% ASP	Cost per-year; cost-effectiveness of drug, with recommendations on what drug price should be to be cost-effective	Not specified; left to payers to evaluate
Drug, cost, relative, or absolute value	Yes	Yes	Yes	Yes	No
Cost to patient	Yes	No	No	No	No
Cost to healthcare system	No	Total drug and medical costs	Rarity per budget impact	Incremental cost-effectiveness ratio and budget impact	No

ASCO indicates American Society of Clinical Oncology; ASP, average sales price; ESMO, European Society for Medical Oncology; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; WAC, wholesale acquisition cost.

These Value Frameworks Lend Insight to Payer-led Management Interventions

THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

Step 1: Determine the regimen's CLINICAL BENEFIT						
1.A. Is Overall Survival (OS) reported?	YES. Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." Proceed to 1.D. OS Score Improvement in median OS (% change in median OS) > 0%-24% 25%-49% 50%-75% 76%-100% 5 At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving					OS Score
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	YES. Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." Proceed to 1.D. PFS Score Improvement in median PFS (% change in median PFS) > 0%-24% 25%-49% 50%-75% 76%-100% 5 At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death					PFS Score
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	YES. Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D. RR Score What was the reported response rate (CR + PR)? > 0%-20% 21%-40% 41%-60% 61%-80% 5 81%-100%					RR Score
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE. Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. Proceed to Step 2.					Clinical Benefit Score
Step 2: Determine the regimen's TOXICITY						
Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities (ie, calculate the sum of toxicities of grade 3-5 reported for each regimen) and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. Write this number in the box labeled, "Toxicity Score." The maximum allowable toxicity points are 20. Proceed to Step 3.					Toxicity Score
Toxicity Score	-20	-10	0	+10	+20	
Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)	Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	
Step 3: Determine Bonus Points						
3.A. PALLIATION BONUS. Are data related to the palliation of symptoms reported?	YES. If a statistically significant improvement in cancer-related symptoms is reported, award 10 points, and place this in the box labeled "Palliation Bonus Points." Proceed to Step 3.B. NO. No bonus points are awarded. Proceed to Step 3.B.					Palliation Bonus Points
3.B. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	YES. If a statistically significant improvement in treatment-free interval is reported, award points based on the table below, and place this in the box labeled "Clinical Benefit Bonus Points." This is the interval from completion of study treatment to initiation of next treatment. Proceed to 3.C. Bonus Points 0 5 10 15 20 % Change > 0%-19% 20%-35% 36%-49% 50%-74% ≥ 75% NO. No bonus points are awarded. Proceed to Step 3.C.					Treatment-Free Interval Bonus
3.C. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A) and the Treatment-Free Interval Bonus Points (Step 3.B). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 30. Proceed to Step 4.					Total Bonus Points
Step 4: Determine the regimen's NET HEALTH BENEFIT						
Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1), Toxicity Score (Step 2), and Bonus Points (Step 3). This yields a Net Health Benefit score. Write this number in the box labeled "Net Health Benefit." The maximum points available for Net Health Benefit are 130. Proceed to Step 5.					Net Health Benefit
Step 5: Determine the regimen's COST						
Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs per month. Drug Acquisition Cost (DAC): _____ / Month: Patient Co-Pay: _____						
Step 6: Summary Assessment - Advanced Disease Framework						
Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Patient Payment:		
/80	/20	/30	/130			

Score for individual agents or regimens based on efficacy, safety, and cost

Formulary Positioning

Step Edits

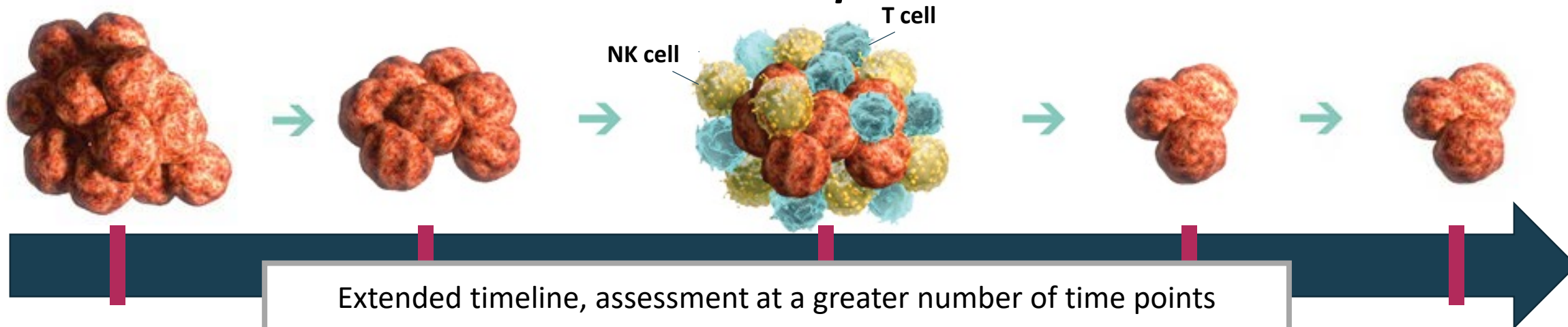
Clinical Pathways

Fundamental Differences Between I-O Therapies and Conventional Oncolytics Necessitate an Advanced Approach to Drug Evaluation

Conventional Oncolytics

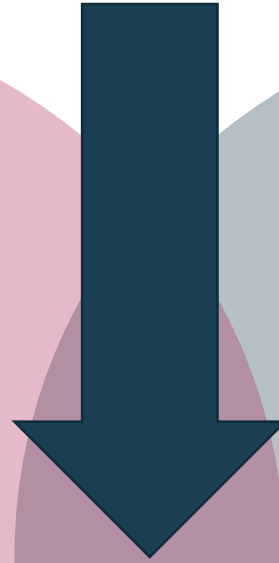


I-O Therapies



Magnitude and Duration Are Both Key Measures of Response for I-O Therapies

Magnitude

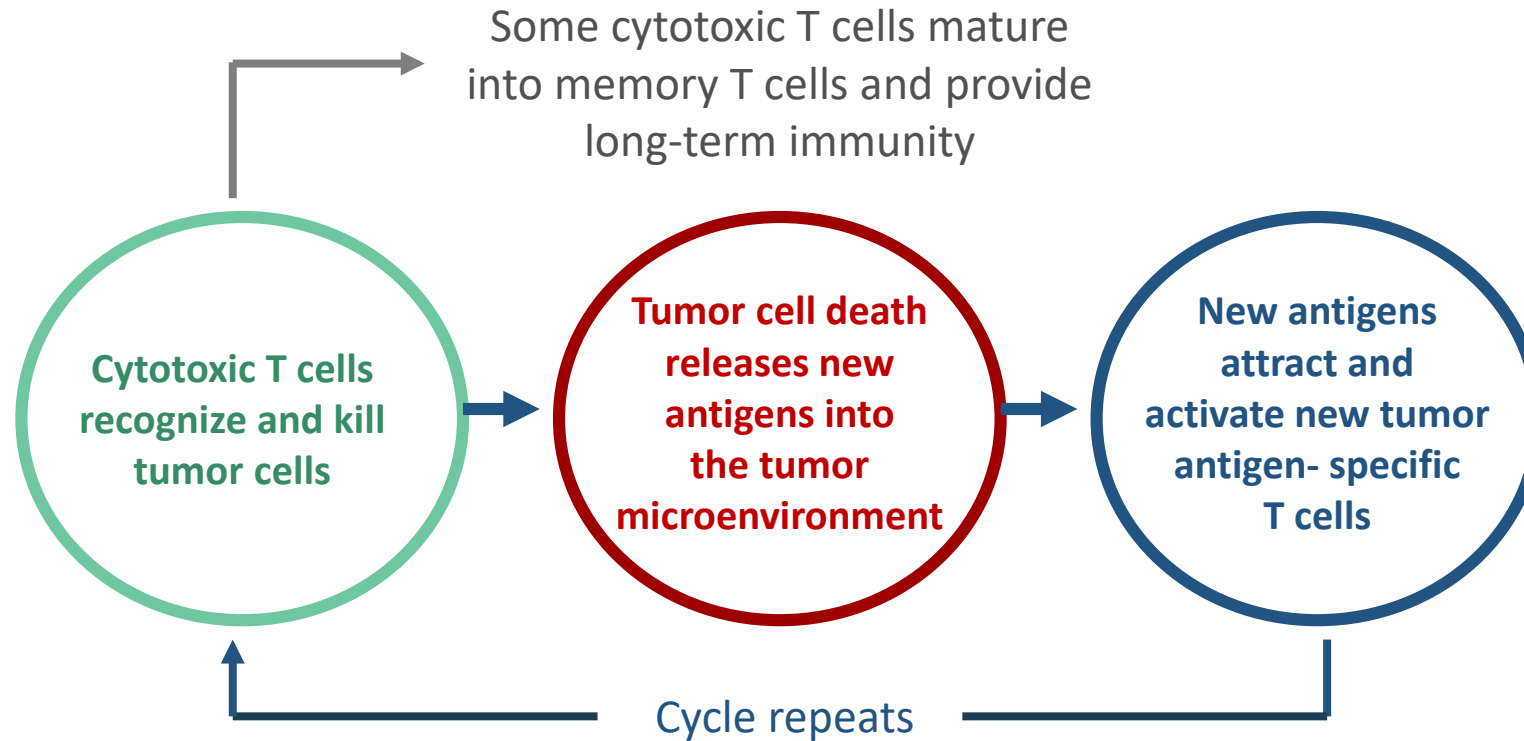


Duration



Immune Response with I-O Therapies Can Deepen and be Sustained Over Time

The immune response evolves and expands over time by constantly recognizing and remembering tumor antigens.



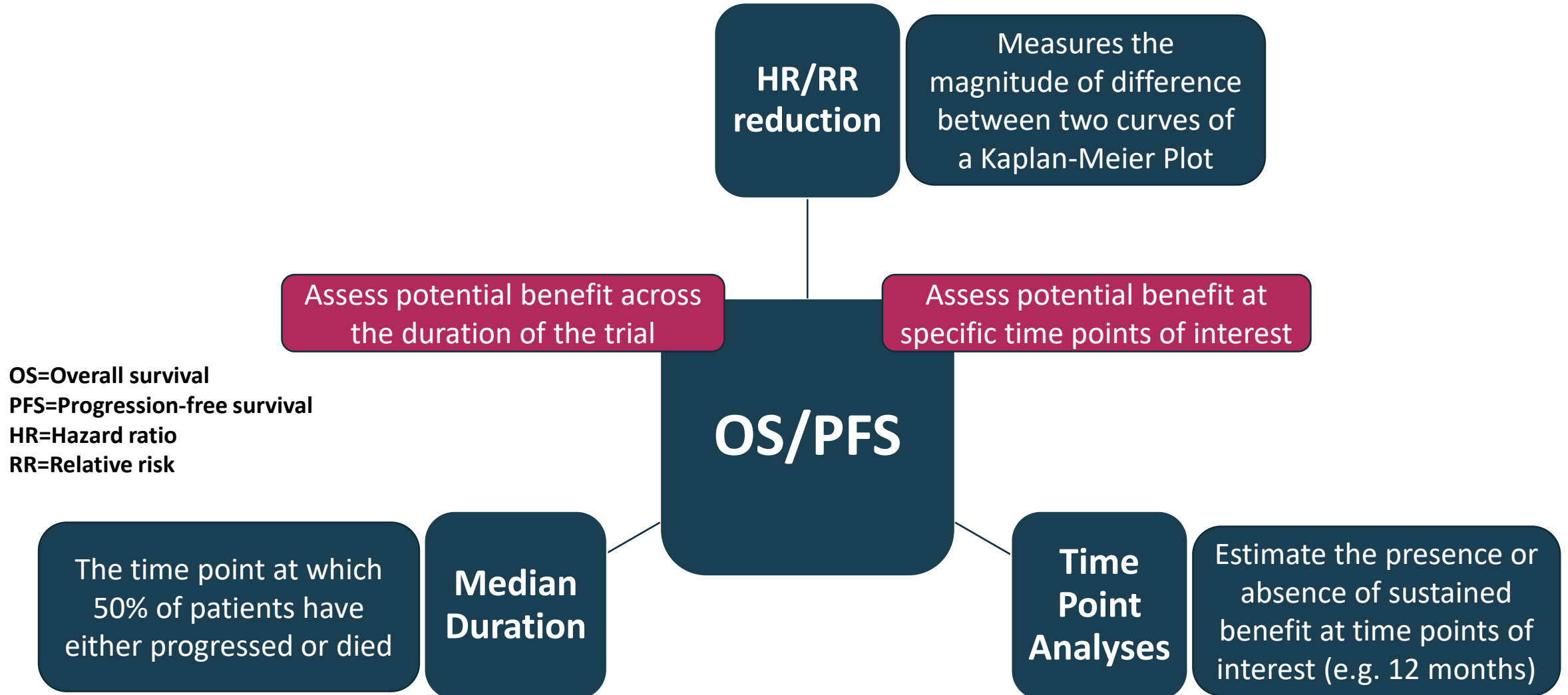
As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.



Key Oncology Outcomes Must Be Weighed and Evaluated Differently for I-O Therapies

- Overall Survival (OS)
 - The time from randomization until death from any cause
 - Gold standard in oncology outcomes where the aim is to prolong life
- Progression Free Survival (PFS)
 - The time from randomization until disease progression or death from any cause
 - Less influenced by subsequent therapy than OS and more relevant with targeted agents than response
- Objective Response Rate (ORR)
 - Direct or indirect measure of tumor burden
 - Measures a specific response to a therapeutic intervention rather than survival

A Comprehensive Approach to Assessing Outcomes for I-O Therapies





Value Frameworks May Not Be Adequately Calibrated for the Assessment of I-O Agents

- Twenty-three metastatic indications for 6 I-O agents were approved by the FDA from March 2011 to August 2017
 - Ten (43%) of the approvals were based on survival end points, while 13 (57%) were based on response rates
- Only 3 drug indications fulfilled the threshold defined for the survival rate of patients receiving standard care (minimum 20%) in the ASCO framework
- Nine indications achieved the required level of improvement in proportion to patients alive in the test regimen compared with the standard (above 50%)
- There was overlap between these 2 criteria for 3 drug indications, allowing them to gain the durable survival bonus points awarded by the ASCO framework
- Durable survival and response rates of modern I-O agents are rarely recognized as significant by current oncology value frameworks
 - This may be due to insufficient demonstration of efficacy of such agents or inappropriately calibrated value frameworks



Considerations on Pseudo-progression with I-O Therapies

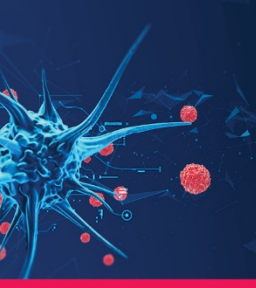
While uncommon, pseudo-progression is an important consideration when evaluating response to I-O therapies

	Disease progression	Pseudo-progression
Performance status	Deterioration of performance	Remains stable or improves
Systemic symptoms	Worsen	May or may not improve
Symptoms of tumor enlargement	Present	May or may not be present
Tumor burden		
Baseline	Increase	Initial increase followed by response
New lesions	Appear and increase in size	Appear then remain stable and/or subsequently respond
Biopsy may reveal	Evidence of tumor growth	Evidence of immune-cell infiltration

Wolchok JD, Hoos A, O'day S, et al. *Clin Cancer Res*. 2009;15(23):7412-20.

Hales RK, Banchereau J, Ribas A, et al. *Ann Oncol*. 2010;21(10):1944-51.

Eisenhauer EA, Therasse P, Bogaerts J, et al. *Eur J Cancer*. 2009;45(2):228-47.



Safety Considerations: Immune-mediated Adverse Reactions (imARs)

I-O Therapies that modulate immune pathways may enable the immune system to attack healthy cells along with tumor cells: these events are known as imARs

Throughout I-O treatment, HCPs should engage in the following:

- Educate and encourage patients and caregivers to monitor for and report symptoms of imARs
- Remain vigilant throughout and after treatment to minimize complications, some of which may be life threatening
- Use treatment algorithms to assist in managing immune-mediated Adverse Reactions

As research in immune system activation advances and more data are made available, understanding and appropriate management of imARs will evolve

Amos SM, Duong CP, Westwood JA, et al. *Blood*. 2011;118(3):499-509.

Gelao L, Criscitiello C, Esposito A, Goldhirsch A, Curigliano G. *Toxins (Basel)*. 2014;6(3):914-33.

Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeffer T. *BMC Med*. 2015;13:211.



Specialty Management Trends

- Utilization Management
 - Prior Authorization
 - Step Therapy
 - Quantity Limits
 - Site-of-Care Restrictions
 - ICER Evaluations
- Benefit Design
 - Specialty Formulary
 - Tier Status
 - Medical vs Pharmacy Benefit
 - Co-insurance/Deductibles
 - OOP Limitations
- Channel Management
 - Site of Care
 - Retail vs Specialty
- Coordination of Care
 - Disease Management
 - Specialty Care Management
- Contracting/Rebates
 - Preferred Products
 - Formulary Exclusions
 - Closed Formularies
 - Price Protection



Summary

- The specialty drug spend and trend for oncology has risen significantly and currently leads other classes in terms of growth
- Payer decision makers are increasingly tasked with managing these agents to provide quality health care that is economically sustainable
- Formulary decisions based on available evidence and value frameworks are crucial in managing the drug trend, but may require a revised approach for I-O agents
- A comprehensive evaluation of outcomes at various time points, incorporating both magnitude and duration of response is necessary for an accurate assessment of I-O agents
- A coordinated specialty management strategy is essential



Health Plan Strategies to Enhance Patient Outcomes with Immuno-Oncology Agents

John Fox, MD, MHA

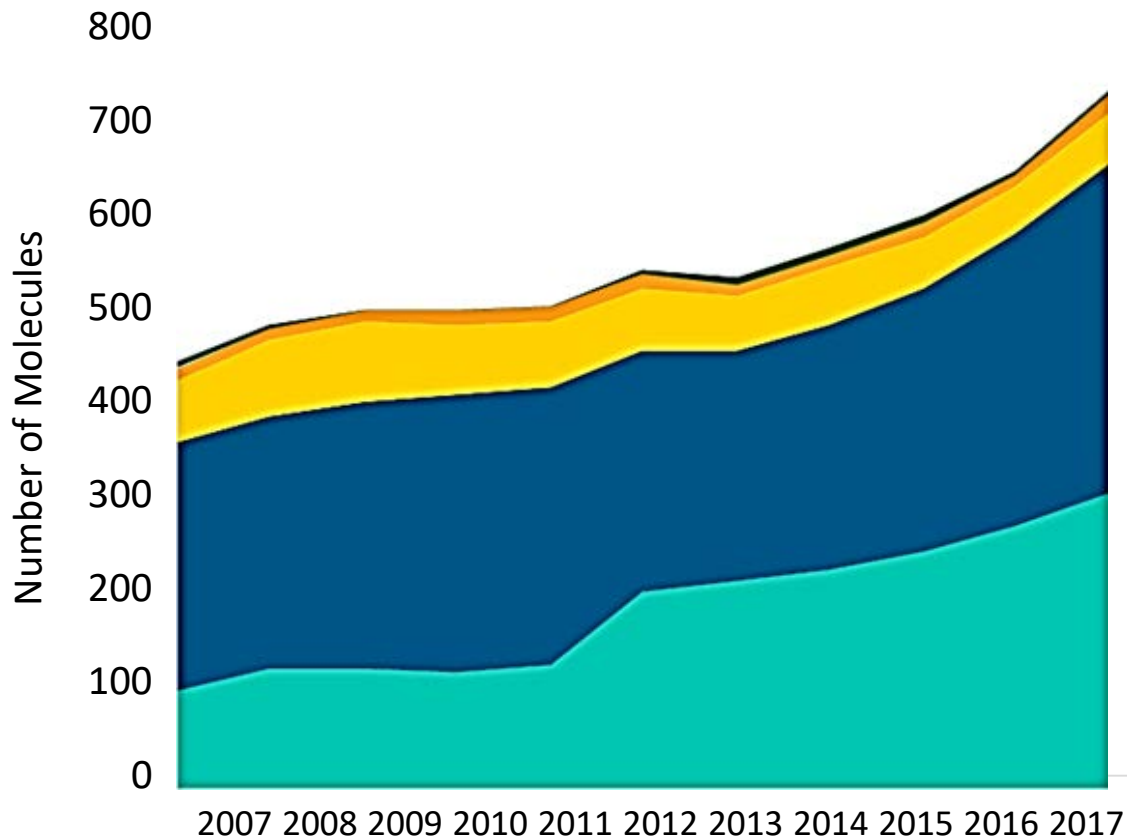
Vice President, Associate Chief Medical Officer

Medical Affairs

Priority Health

An Increasing Number of Targeted Oncology Agents are Being Developed

The Pipeline of Late Phase Oncology Molecules, 2007-2017



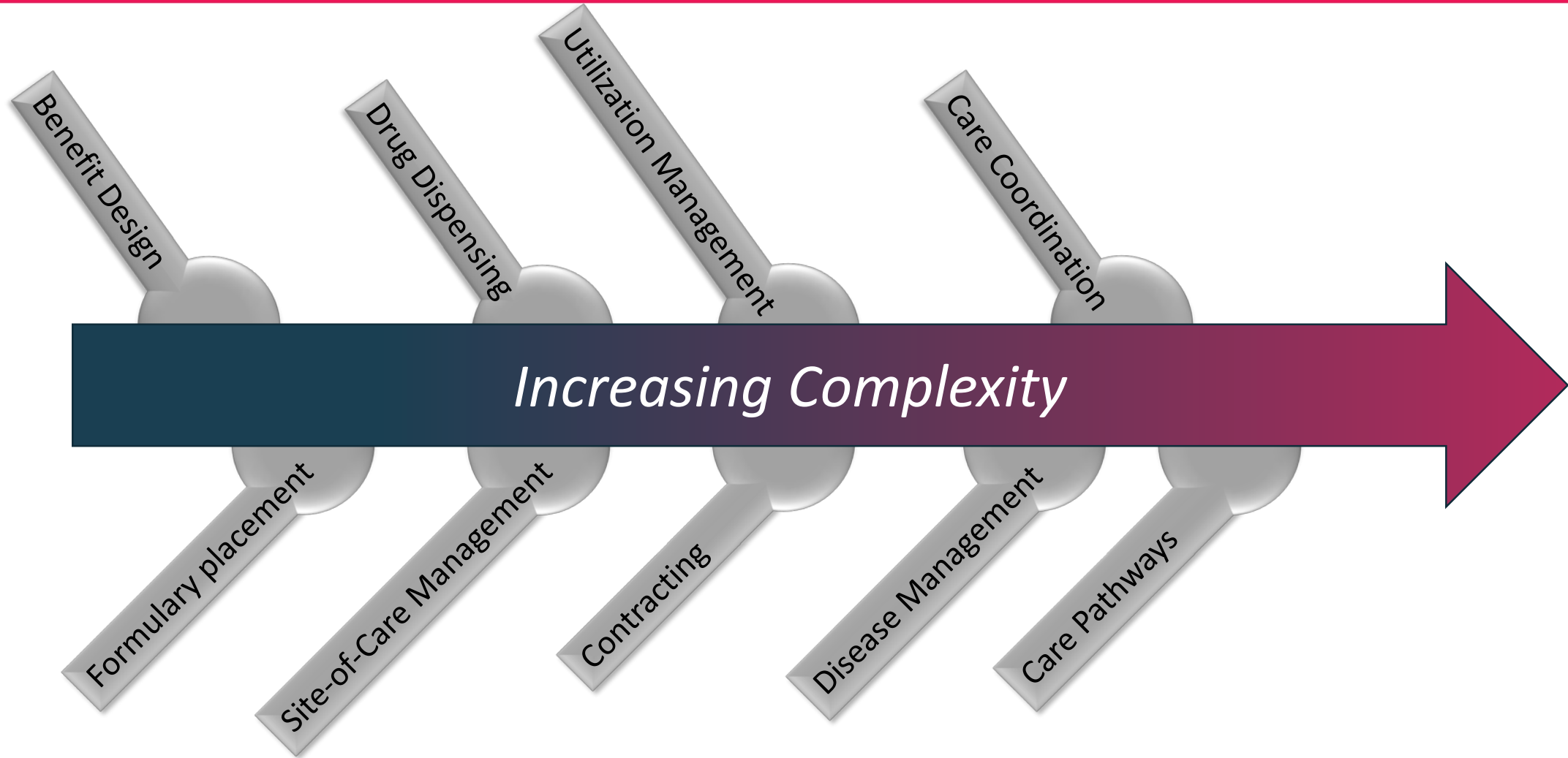
Year	2007 (434)	2017 (710)
Radiotherapies	0.9% (4)	0.4% (3)
Hormonals	3% (14)	2% (17)
Cytotoxics	15% (63)	8% (54)
Targeted Small Molecule	59% (254)	47% (335)
Targeted Biologics	23% (99)	42% (301)

Evolution of Treatment Development

Immuno-Oncology (I-O) Therapies



Payers Have a Number of Levers for Managing Oncology Drug Therapies





Utilization Management Strategies

- Prior authorization (PA)
 - Requires plan review for appropriate drug utilization and subsequent authorization
 - Frequently based on FDA-approved indication and labelling
 - Assessment of biomarker status
- Step therapy (ST)
 - The claims system “looks” for required drugs to use prior to coverage of requested agents, usually pharmacy benefit
- Quantity limits (QL)
 - Allows a limit to be placed on medications to ensure proper usage of dosage forms, allowing maximum daily dosages
 - Dose optimization
 - Vial size management
 - Partial fill for oral and self-administered therapies
- Edits
 - Age
 - Drug-Drug interactions
 - For the management of dosing/frequency
 - Retrospective DUR
- Care management
 - Pharmacy involvement/coordination, in-house vs. carve-out
 - Side effect and toxicity management

PA Remains the Most Prevalent Tool for Utilization Management Among Payers

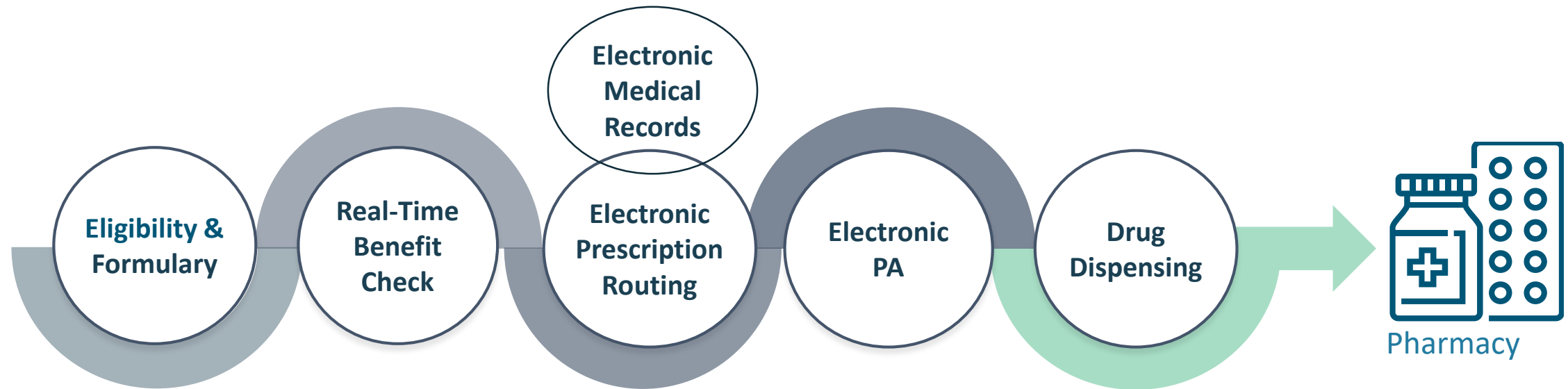
Use of Selected Utilization/Clinical Management Tools, Percentage of Plans	2017		
	Smaller Plans (\leq 400,000 Lives)	Medium/Large Plans (>400,000 Lives)	All Plans
Site-of-care program	44%	95%	61%
Partial fill program	56%	60%	58%
Prior authorization*	92%	95%	93%
Electronic prior authorization	21%	45%	29%

N by size in 2017=39 small, 20 medium/large plans. N in 2016=58.

*Used a PA program for specialty drugs in the medical benefit.

ePA=electronic prior authorization; PA=prior authorization.

Data Management and Support Can Streamline Patient Access and Drug Dispensation



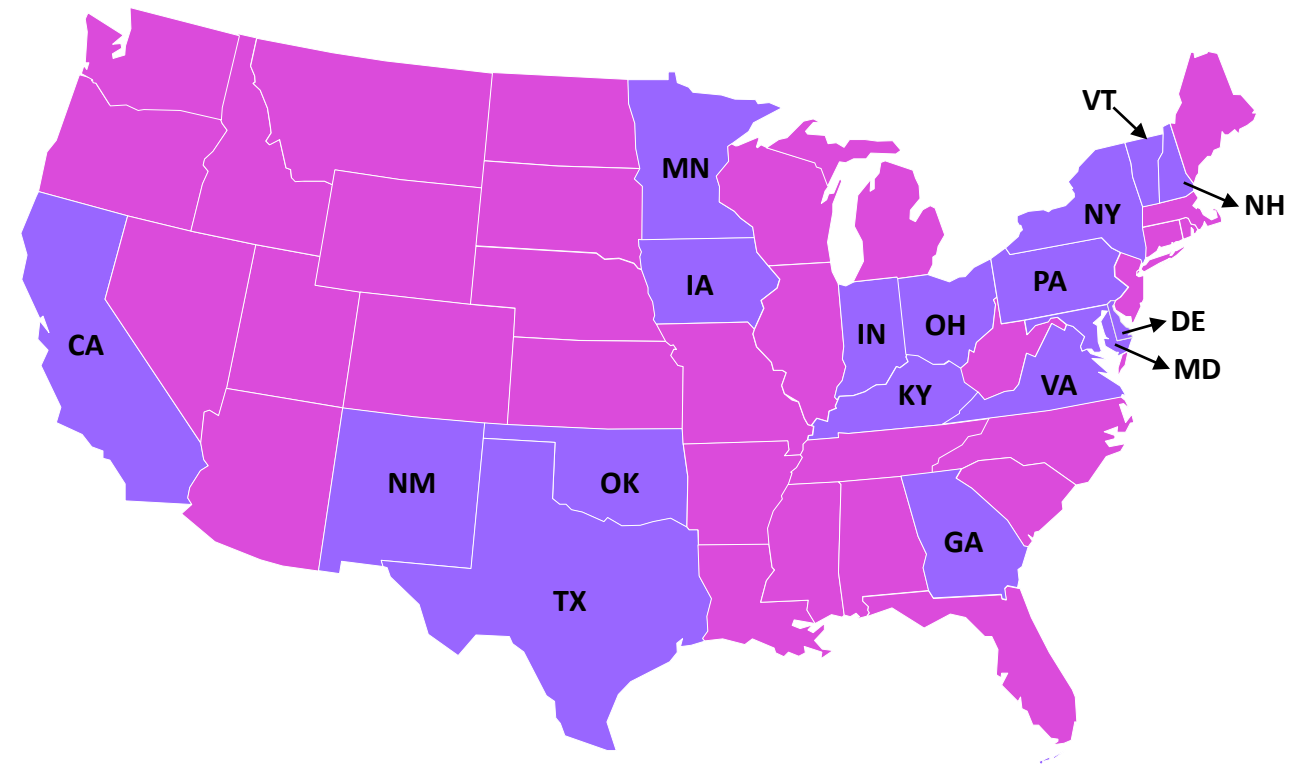
The services should:

- Exchange information so that the prescriber (staff) only needs to enter it once
- Have a common “ID” so that the different transactions can be linked by multiple entities at different times
- Complete all actions required to get the patient on the right medication as soon as possible
- Integration of electronic medical records (EMRs) potentiates efficiency


Evolving Restrictions on Established Utilization Management Processes

- 17 states require all commercial health care plans to use an electronic prior authorization form in compliance with a national standard.
- Several states set time limits for prior authorization approvals.
- At least 18 states require exceptions to step therapy, specify time limits to respond to override requests or limit time step therapy can be mandated.
- Some states prohibit use of step therapy for patients who have gone through it previously with another health plan.

States Requiring Electronic Prior Authorization in Compliance with the NCPDP SCRIPT Standard



NCPDP=National Council for Prescription Drug Programs



Statewide Formularies Are Being Proposed to Drive Coverage Consistency and Uniform Access

- Specifically for providers who receive state funds
- Coordinate with a wide array of stakeholders:
 - The state Medicaid authority
 - Health and Human Services organizations
 - State hospitals
 - Department of Corrections/County Sheriff's Office (jails/prisons)
- Current bills related to statewide formularies do not:
 - Mandate what a prescriber can and can't prescribe
 - Directly affect the informed consent/medication decision process, which is highly individualized
 - Preclude a facility from having a non-formulary request or med pre-authorization system in place

Statewide Pharmaceutical Program. State of California. <https://www.documents.dgs.ca.gov/pd/contracts/PHARMA/CDFMasterRev31-07-01-17.pdf>.

Updated July 1, 2017. Accessed February 2019.

Munshi KD, Mager D, Ward KM, Mischel B, Henderson RR. *J Manag Care Spec Pharm*. 2018;24(2):124-131.

Oncology PA: The Role of Companion and Complimentary Diagnostics



Companion Diagnostics

- Specified on the drug label (21 therapies to date, >50% in NSCLC)
 - e.g., ALK+ for crizotinib in NSCLC
- Typically among inclusion criteria for pivotal trials
- Required for PA



Complimentary Diagnostics

- Predictive of response but not required
 - KRAS/NRAS/BRAF for cetuximab in colorectal cancer
- Assay may be integrated into pivotal trials but not part of inclusion criteria
- May be incorporated into more rigorous PA requirements



Oncology PA: Current and Potential Future Criteria for I-O Agents

- A number of PD-1/L1 checkpoint inhibitors feature companion and complimentary diagnostics that may be incorporated into PA criteria
- These assays are based on PD-L1 titers predictive of response
- Companion Diagnostics:
 - PD-L1 immunohistochemical (IHC) 22C3 pharmDx assay for pembrolizumab
 - Ventana PD-L1 for atezolizumab
- Complimentary Diagnostics:
 - PD-L1 IHC 28-8 pharmDx for nivolumab
 - Ventana PD-L1 for durvalumab
- Role of lab developed tests vs. FDA approve tests



Sample PA Criteria for Immuno-therapy in Metastatic NSCLC

Pembrolizumab

PA Requirements Related to NSCLC:

1. Following disease progression on or after platinum-containing chemotherapy, and EGFR- or ALK-targeted therapies for EGFR- or ALK-mutated disease, in a patient whose tumor expresses PD-L1 [Tumor Proportion Score (TPS) $\geq 1\%$] as determined by an FDA-approved test
2. *First-line treatment* (no prior chemotherapy treatment for metastatic NSCLC) in a patient whose tumor has high PD-L1 expression (TPS $\geq 50\%$) as determined by an FDA-approved test, with no EGFR- or ALK-mutated disease
3. *First-line treatment* in a patient with non-squamous NSCLC in combination with pemetrexed and carboplatin, with no EGFR- or ALK-mutated disease
4. *First-line treatment* in patient with squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel

Nivolumab

PA Requirements Related to NSCLC:

Following disease progression with previous

- a) platinum-based chemotherapy or
- b) EGFR or ALK targeted Tx for EGFR/ALK mutated Dz

Atezolizumab

PA Requirements Related to NSCLC:

- Experienced disease progression during or following 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 atezolizumab
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2



Balancing Benefit Design and Member Cost-Sharing Levers

- **Member cost-sharing**

- High financial toxicity
- High cost share reduces access to care for many patients
- Adherence declines as cost rises, which may overall healthcare costs

- **Benefit design factors**

- Medical vs pharmacy
- Copay vs coinsurance/deductibles
 - Copay accumulator programs
- Medicare Part B step therapy
- Specialty tiers
- In-network vs out-of-network

Medical Claim Site-of-Care Optimization

Theoretical Site of Care Example: Monoclonal Antibody

Place of Service	Cost per Unit	Units	Cost Per Claim	Claims per Year	Annual Cost
MD office	\$30	215	\$6,450	7	\$45,150
HOPD (average)	\$48	215	\$10,320	7	\$72,240
HOPD (highest cost hospital)	\$150	215	\$32,250	7	\$225,750

HOPD=hospital outpatient department.

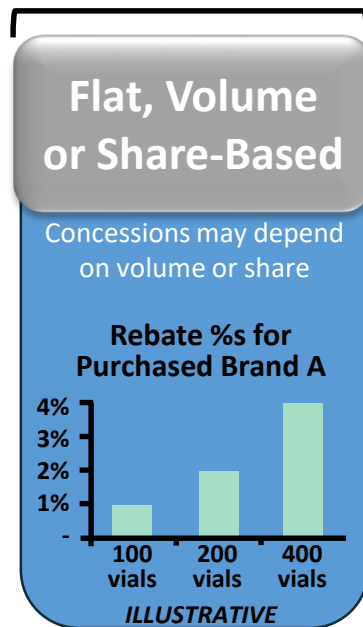
Internal Utilization and Pricing Data.

Dispensation or administration outside of the hospital/facility setting is favorable when possible in terms of cost management and is central to site of care optimization efforts

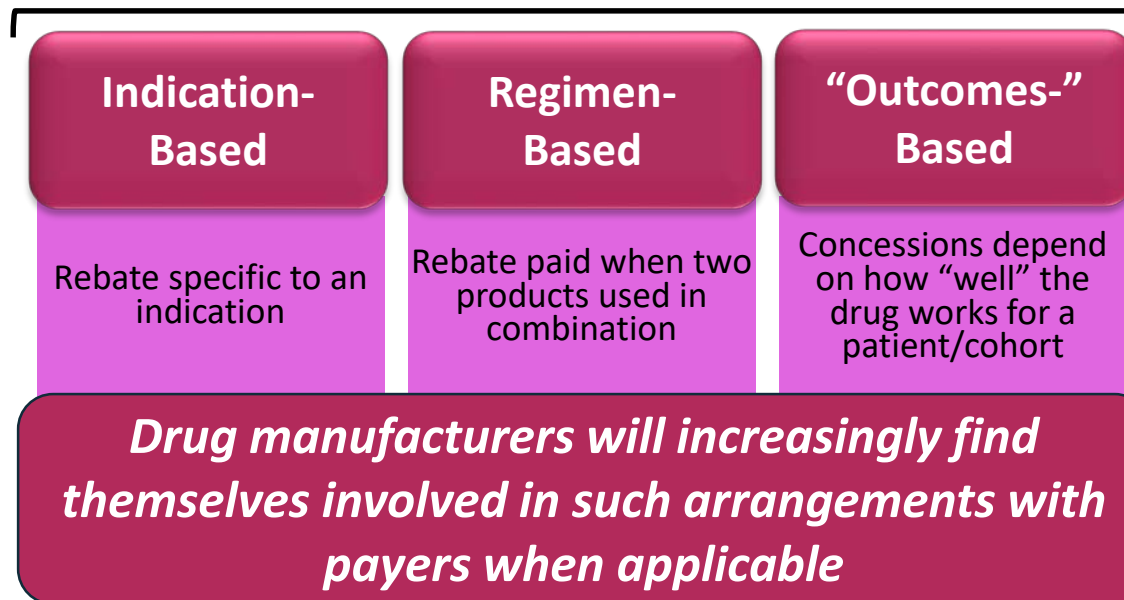
Specialty Drug Contracting Approaches

45% of private payers were involved in pay-for-performance and risk-sharing programs in 2010; the number rose to 62% in 2013, and usage of these programs was estimated to be as high as 75% in 2016

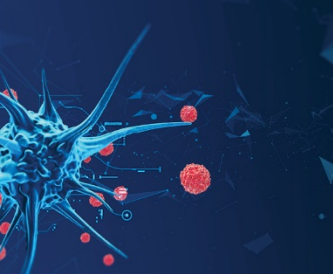
Traditional Contracting



Value-Based Contracting



Increasing Data & Complexity



Contracting with High-Quality, Cost-Efficient Providers: Oncology Practices

- Among oncology practices positively deviant in terms of charges to payers, the more cost-effective practices shared several key attributes ostensibly linked to an integrated care approach:
 - multicomponent health care system
 - conservative use of imaging
 - ongoing discussion of treatment options, risks, and benefits
 - early and standardized palliative care referrals
 - expanded access to ambulatory rapid response and same day management
 - optimized use of RNs for appropriate clinical interventions (proactive outreach, telephonic advice/triage for ED avoidance, hospital use avoidance)



CMS OCM Program

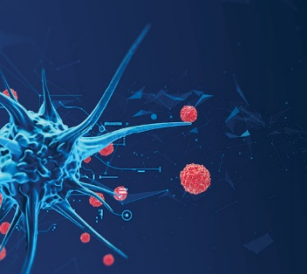
- 5-year episode-of-care (EOC) program applicable to high-volume cancers (expected to cover 90% of cancer types)
- Medicare FFS program as part of a multi-payer model—applies to physician practices and PSA arrangements for provider-based services; but not to PPS exempt cancer hospitals
- Medicare pays \$160 per beneficiary per month (PBPM) for a 6-month EOC (\$960 per EOC), plus a retrospective performance-based payment
 - Payments in addition to Medicare FFS payment
- Performance-based payments (semi-annual)
 - Based on meeting applicable quality measures (preliminary set specified) – “performance multiplier” determines % of performance-based payment
 - Based on reducing cost at least 8% below a target threshold, with a 20% cap
 - Two-side risk allowed by no takers (yet)



Care Coordination Improves Outcomes

NCI Study

- Meta-analysis of 52 studies found care coordination improved 81% of outcomes, including screening, patient experience, quality end-of-life care
- Most common care programs were:
 - Patient navigation
 - Home telehealth
 - Nurse case management



Care Coordination Reduces Confusion and Costs

Meridian Health Systems:

- Care coordinator communicates with patient, family, multiple specialists
- Reduces unnecessary imaging and testing
- Reduces hospitalizations from manageable complications such as dehydration.
- Earns patient satisfaction scores higher than 90%



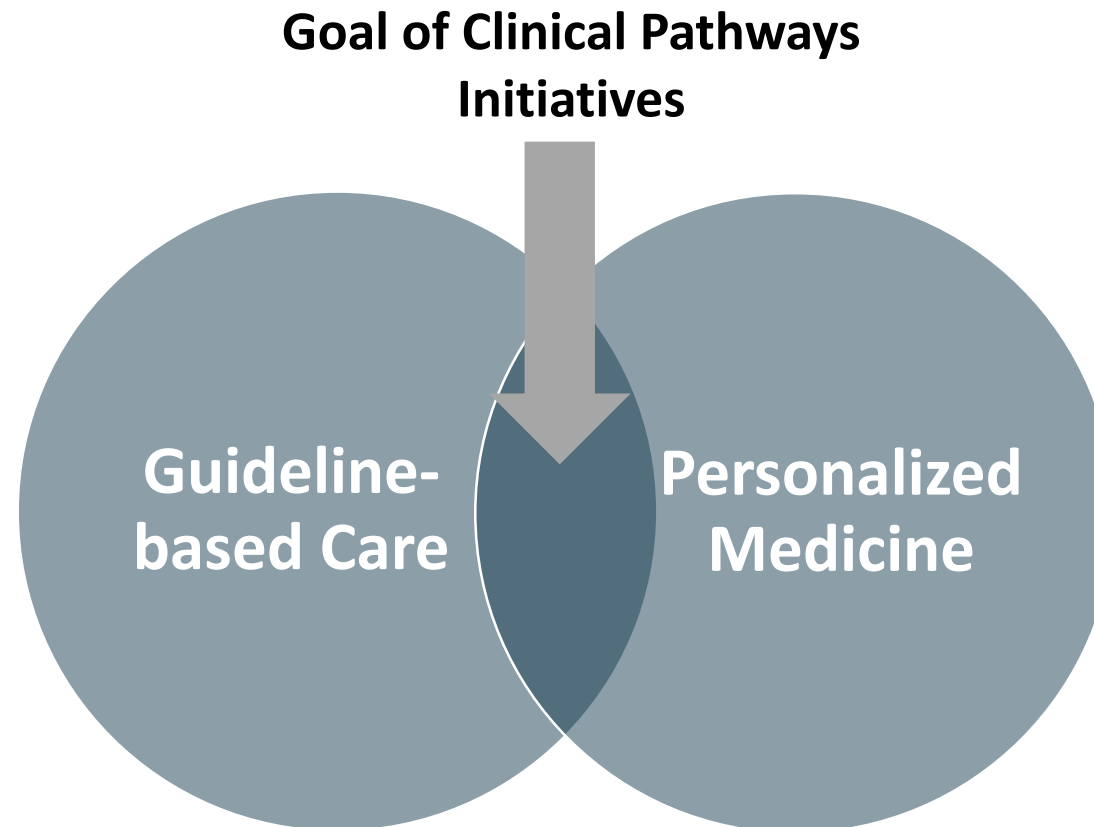
Health Coaching Component of Care Coordination Reduces Costs, Increase Satisfaction

- **Stanford**

- Health coaches discuss goals for life with advanced cancer patients facing treatment failure or with less than three-year anticipated survival at diagnosis
 - Estimated reduction in costs, mostly from end-of-life care, of 14.5%
- Health coach/nurse team assessed symptoms at intervention call center using decision-support systems.
 - Pre-stocked, individualized medication bundles were made available
 - Decreased ED visits, hospitalizations
 - Estimated cost reduction of 14%

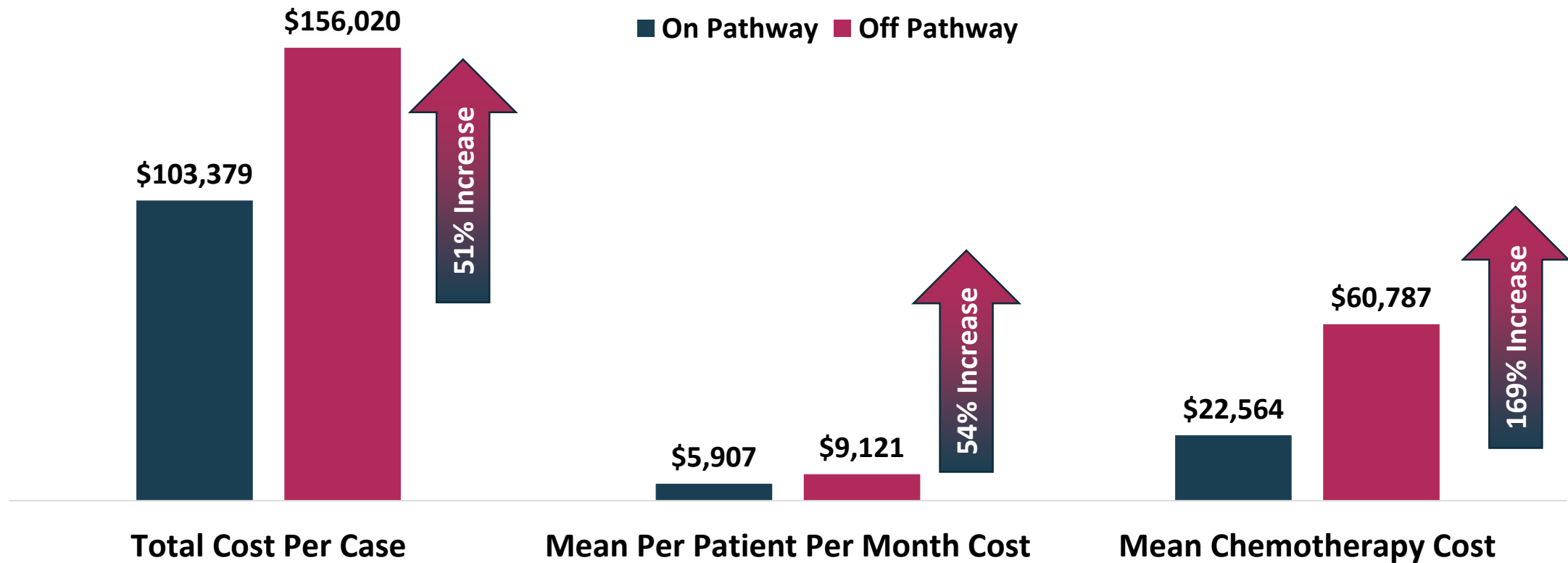
Clinical Pathways Initiatives Aim to Reduce Treatment Variability While Allowing Individualized Care in Oncology

Balancing treatment *standardization* with *personalization* is cited among the top three challenges in cancer care for more than a third of MCOs



Pathways Have Been Associated with Cost Savings in Oncology

The McKesson/US Oncology Experience in Colorectal Cancer Pathways





Providers Support Guidelines and Pathways

- Oncologists are rapidly adopting guidelines and pathways, too:
 - Practices report compliance with pathways increased 42% from 2014-2016 and twice as fast 2016-2017
 - 78% of oncologists used guidelines in 2017, up from 53% in 2016
- Increasingly, practicing oncologists play a central role in pathway development
- When efficacy and safety are comparable

The State of Cancer Care in America, 2017: A Report by the American Society of Clinical Oncology. *J Oncol Pract.* 2017;13(4):e353-e394.

The 2018 Genentech Oncology Trend Report 10th ed. <https://www.genentech-forum.com/oncology-trends.html>. South San Francisco, CA: Genentech; 2018

Greenapple R. *J Oncol Pract.* 2013;9(2):81-3.



Summary

- Oncology treatment costs continue to rise sharply, driven by multi-therapy regimens and targeted therapies
- Utilization management more important than ever, but some traditional methods are now legislatively restricted and new ones may have unintended negative consequences
 - For I-O therapy specifically, companion and complimentary diagnostics may play a role in PA criteria according to predicted response
- In addition to streamlined PA methodology and site-of-care initiatives, disease management, care coordination, and clinical pathways offer innovative solutions in oncology management



THE IMMUNO-ONCOLOGY TRANSFORMATION: *Implications for Managed Care*

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