Updates on Immune Checkpoint Inhibitors and Implications for Managed Care and Specialty Pharmacists

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Disclosure

Dr. Adams has disclosed that he has served as a consultant for Amgen.

The clinical reviewer, Megan May, PharmD, BCOP, has no actual or potential conflict of interest in relation to this program.

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Learning Objectives

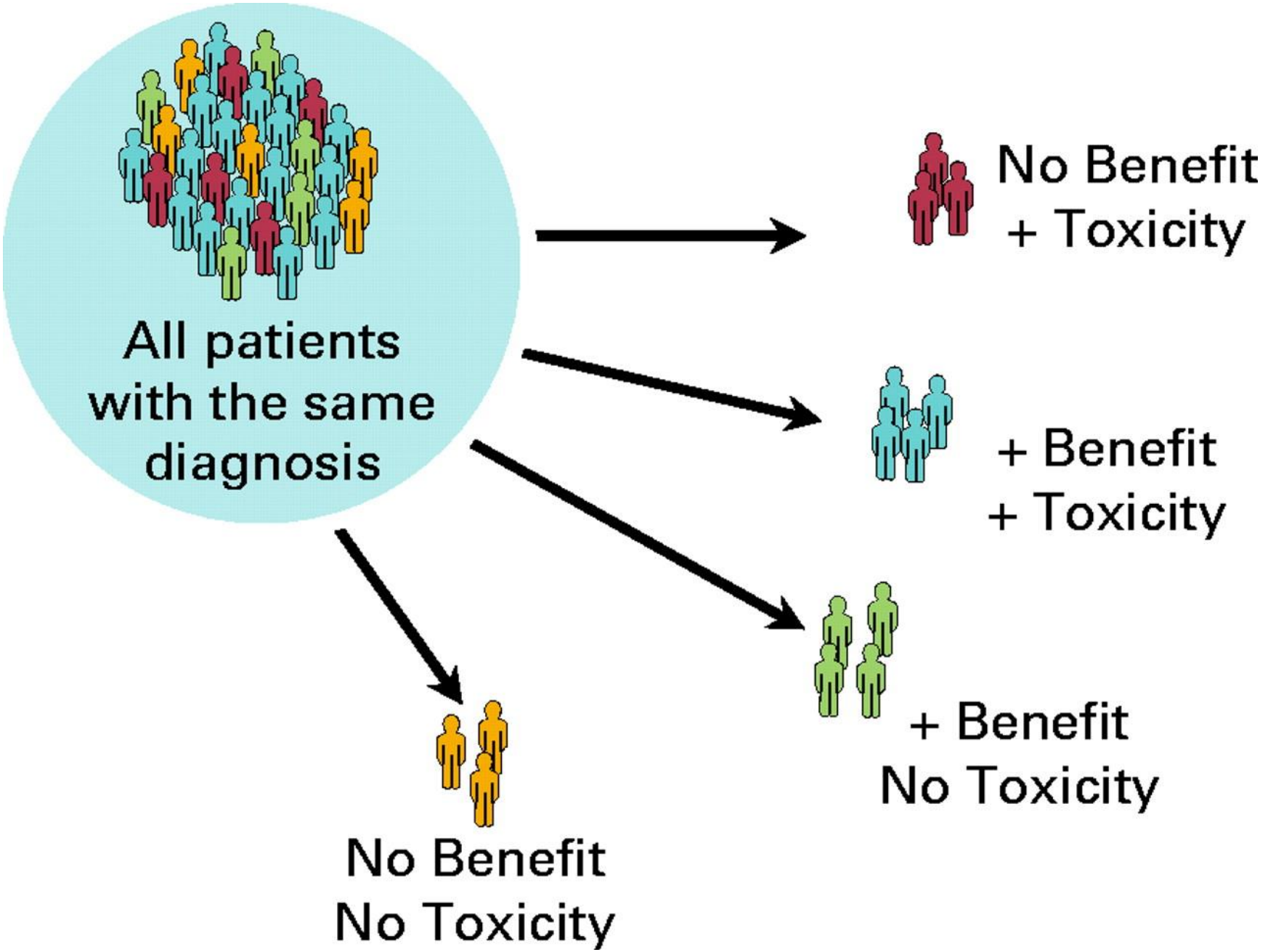
- **Discuss** the use of checkpoint inhibitor and checkpoint inhibitor combination regimens in patients with cancer, including indications and efficacy
- **Examine** the emerging checkpoint inhibitor and checkpoint inhibitor combination regimens being evaluated in clinical trials for the treatment of cancer and how to be poised for incorporation for formulary and clinical pathway development
- **Identify** appropriate prognostic and predictive biomarkers in the treatment of cancer with checkpoint inhibitors alone or in combination regimens
- **Demonstrate** pharmacist-driven strategies to recognize and effectively prevent or manage toxicities of checkpoint inhibitor and checkpoint inhibitor combination therapies

Checkpoint Inhibitors

Drug	Dose	Indications (see prescribing information for details)
Atezolizumab (PD-L1i)	1200 mg IV over 60 min q3weeks	NSCLC, bladder CA, **SCLC**, **breast CA (TNBC)**
Avelumab (PD-L1i)	800 mg IV over 60 min q2weeks	Merkel cell carcinoma, bladder CA, **renal cell CA**
Durvalumab (PD-L1i)	10 mg/kg IV over 60 min q2weeks	NSCLC, bladder CA
Nivolumab (PD-1i)	240 mg IV over 30 min q2weeks or 480 mg IV over 30 min q4weeks	Melanoma, NSCLC, **SCLC**, **renal cell CA**, Hodgkin lymphoma, head and neck CA, bladder CA, **MSI-H/dMMR colorectal CA**, **hepatocellular CA**
Pembrolizumab (PD-1i)	200 mg IV over 30 min q3weeks	Melanoma, NSCLC, **SCLC**, Hodgkin lymphoma, head and neck CA, bladder CA, **MSI-H/dMMR CA**, gastric CA, **NHL**, **esophageal CA, cervical CA, hepatocellular CA**, Merkel cell carcinoma**, renal cell CA, endometrial CA**
Cemiplimab-rwlc (PD-1i)	350 mg IV over 30 min q3weeks	**Cutaneous squamous cell carcinoma**
Ipilimumab (CTLA-4i)	3 or 10 mg/kg IV over 90 min q3weeks	Melanoma, **renal cell CA, MSI-H/dMMR colorectal CA**

CA, cancer; CTLA-4i, cytotoxic T-lymphocyte-associated protein 4 inhibitor; dMMR, mismatch repair deficient; IV, intravenously; MSI-H, microsatellite instability-high; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PD-1i, programmed cell death protein 1 inhibitor; PD-L1i, programmed death-ligand 1 inhibitor; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

Bavencio [prescribing information]; 2019.; Imflinzi [prescribing information]; 2019.; Keytruda [prescribing information]; 2019.; Libtayo [prescribing information]; 2019.; Opdivo [prescribing information]; 2019.; Tecentriq [prescribing information]; 2019.; Yervoy [prescribing information]; 2019.

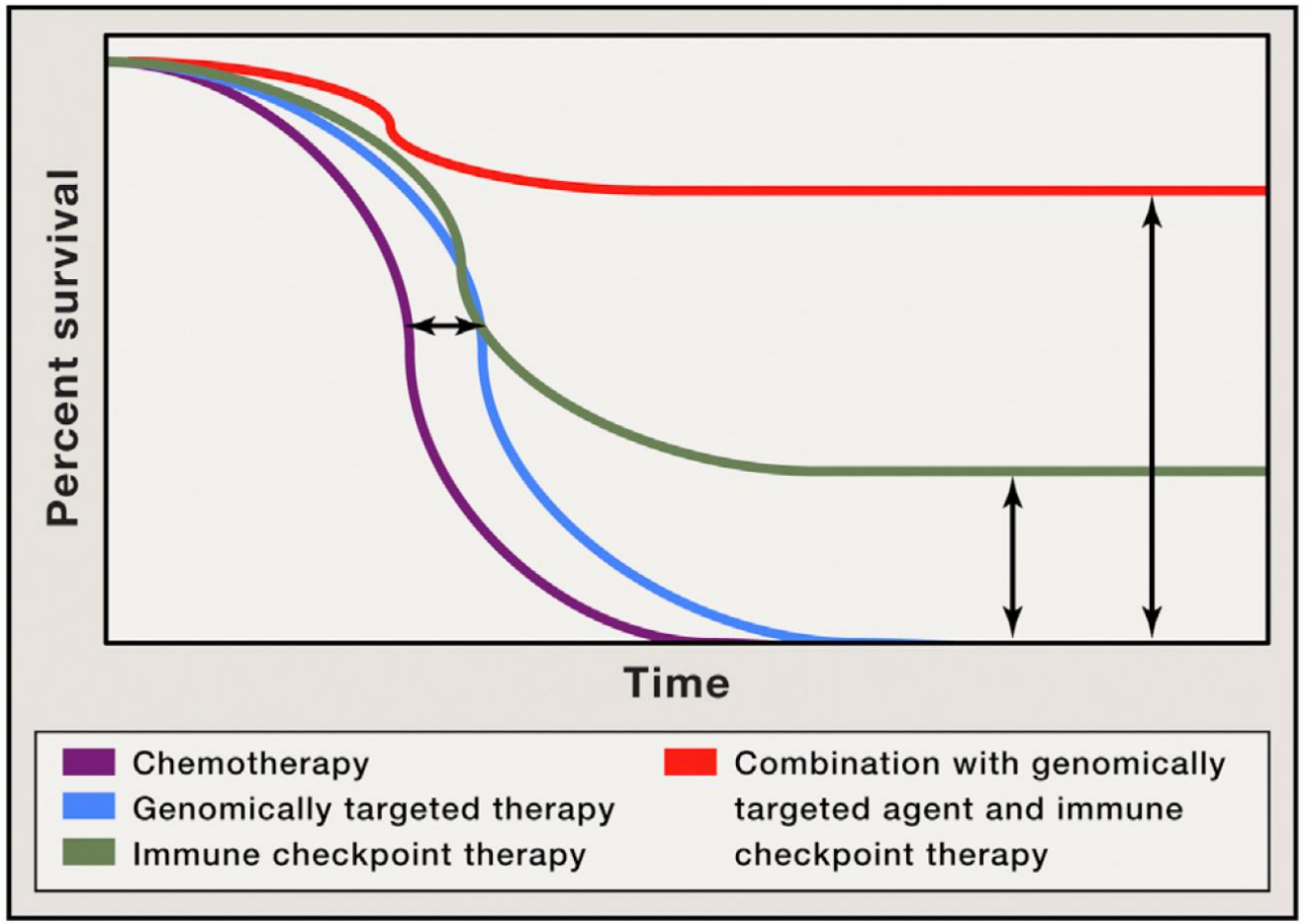


Walgren RA, et al. *J Clin Oncol.* 2005;23(29):7342-9.

Optimizing Immunotherapy Outcomes

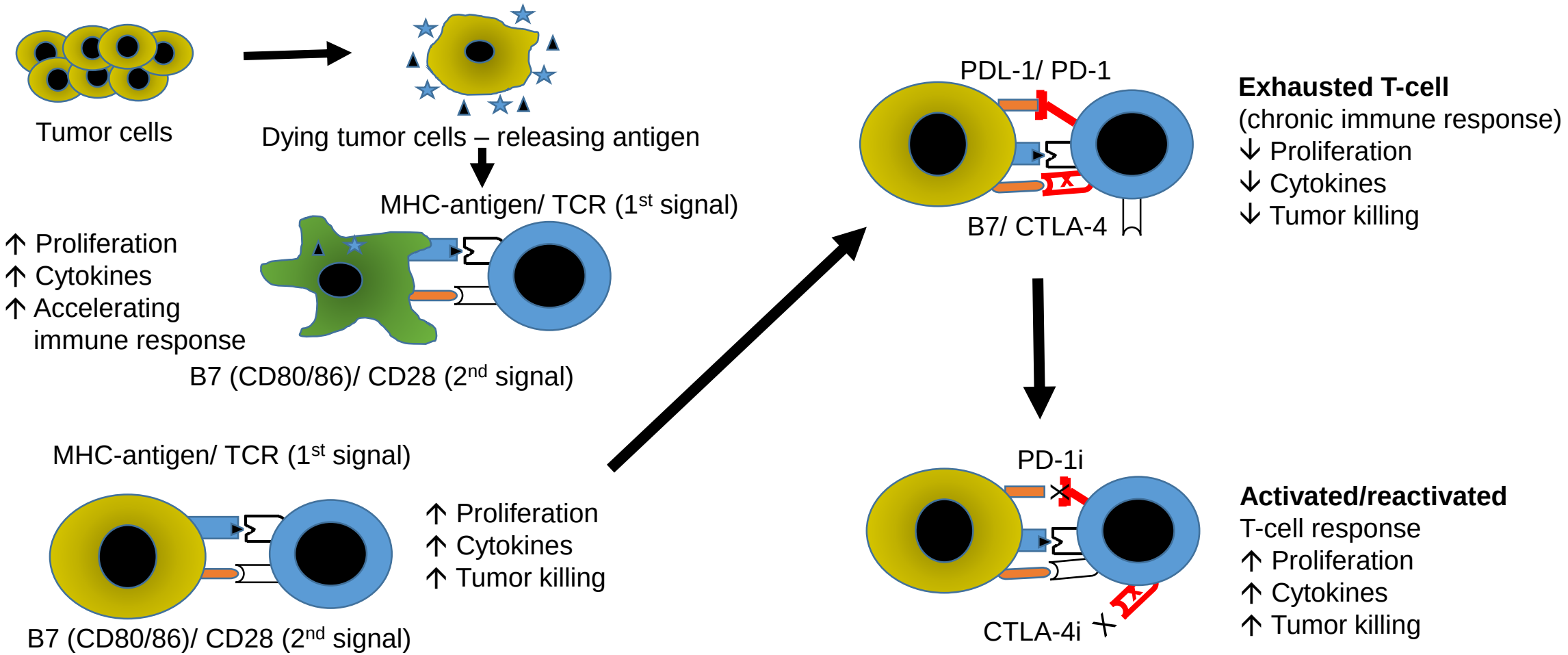
- Better selection of patients
- Combine treatments to increase immune recognition
- Combine treatments to decrease immune ESCAPE

Moving the Plateau Up



Sharma P, Allison JP. *Cell*. 2015;161(2):205-14.

Immuno-Oncology 2-Step



*Antigen-presenting cell taking up cancer antigen and **activating T-cell response***

MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, t-cell receptor.

Wagner LM, Adams VR. *Onco Targets Ther*. 2017;10:2097-106.

Diseases Utilizing New ICI Treatments

SCLC
ICI + Chemo
ICI + ICI

Hepatocellular CA
ICI

Breast CA (TNBC)
ICI + Chemo

Colorectal CA
(MSI-H or dMMR)
ICI +/- ICI

Cutaneous squamous cell CA
ICI

Renal CA
ICI + ICI
ICI + VEGFi

Gyn/onc (endometrial and cervical CA)
ICI + VEGFi

Chemo, chemotherapy; ICI, immune checkpoint inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Atezolizumab for First-Line Treatment in SCLC

Patients with extensive-stage SCLC
Statified by
ECOG PS 0-1
Gender
CNS mets
(only treated, stable mets allowed)

→ Atezolizumab 1200 mg IV d1
Carboplatin AUC5 IV d1
Etoposide 100 mg/m^2 IV on d1, 2, and 3
Repeat q21days x 4; then
Atezolizumab 1200 mg IV q3weeks
N=201

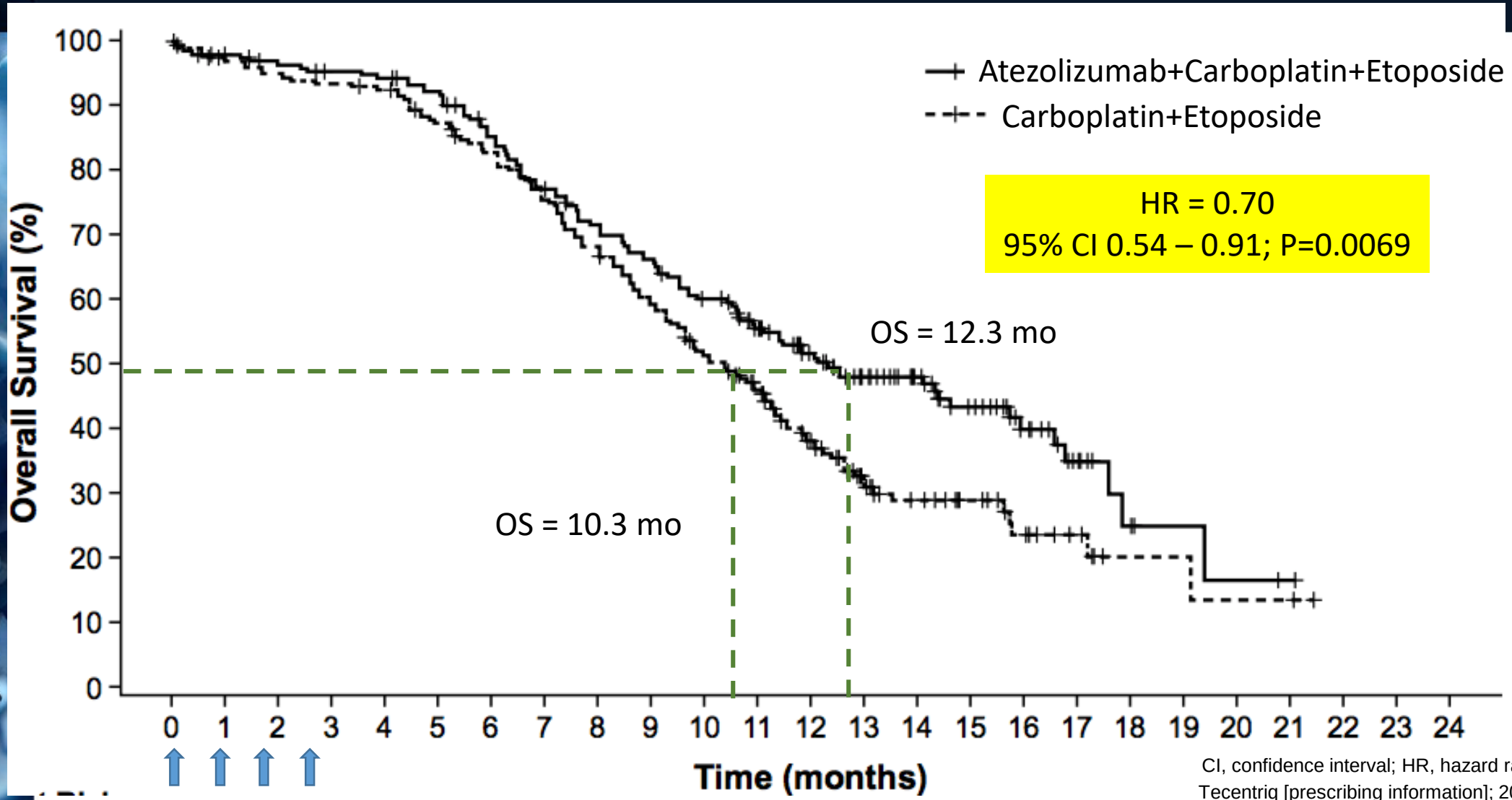
→ Placebo IV d1 and d15
Carboplatin AUC5 IV d1
Etoposide 100 mg/m2 IV on d1, 2, and 3
Repeat q21days x 4
N=202

Primary endpoints: PFS and OS in ITT population
Secondary endpoints: ORR and DOR

AUC, area under the curve; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; mets, metastases; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Tecentriq [prescribing information]; 2019.

Small Cell Lung Cancer: Overall Survival



CI, confidence interval; HR, hazard ratio.
Tecentriq [prescribing information]; 2019.

Potential Practice-Changing Impact

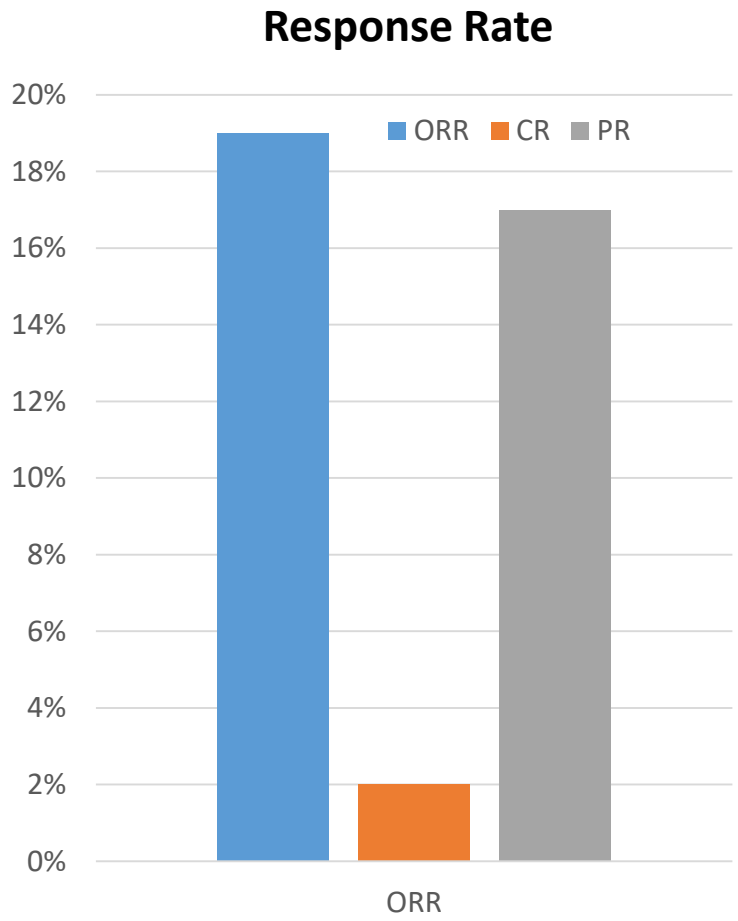
- Cycle 1 for SCLC is commonly given inpatient
- The cost/reimbursement of atezolizumab given as an inpatient could be an issue
- When reviewing the OS curve and time to separation, is atezolizumab essential with the first couple of cycles?

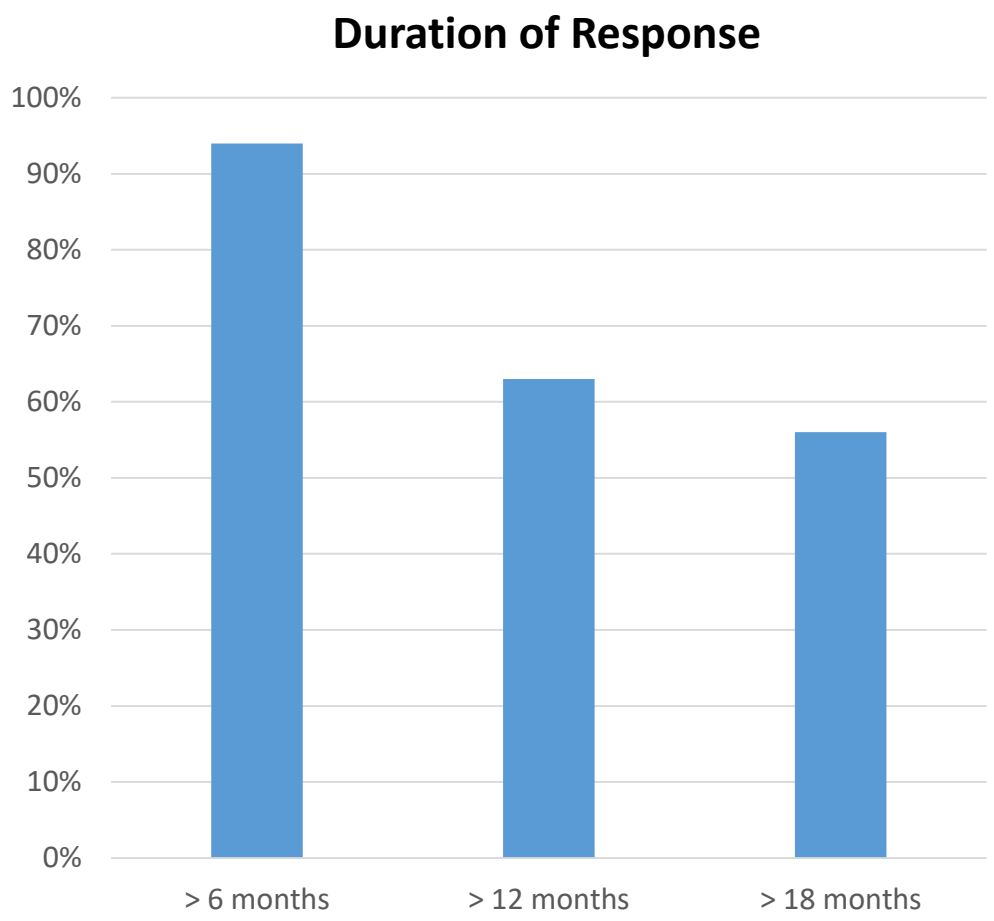
Pembrolizumab for Third-Line and Later Treatment in SCLC

- Accelerated approval based on combined data from 2 non-comparative trials (n=83)
- Used after a platinum-containing regimen plus an additional regimen
- Monotherapy with pembrolizumab 10 mg/kg q2weeks (n=19) or 200 mg IV q21days (n=64)
- Primary endpoints: ORR and DOR

Keytruda [prescribing information]; 2019.

Pembrolizumab for Third-Line and Later Treatment in SCLC





CR, complete response; PR, partial response.

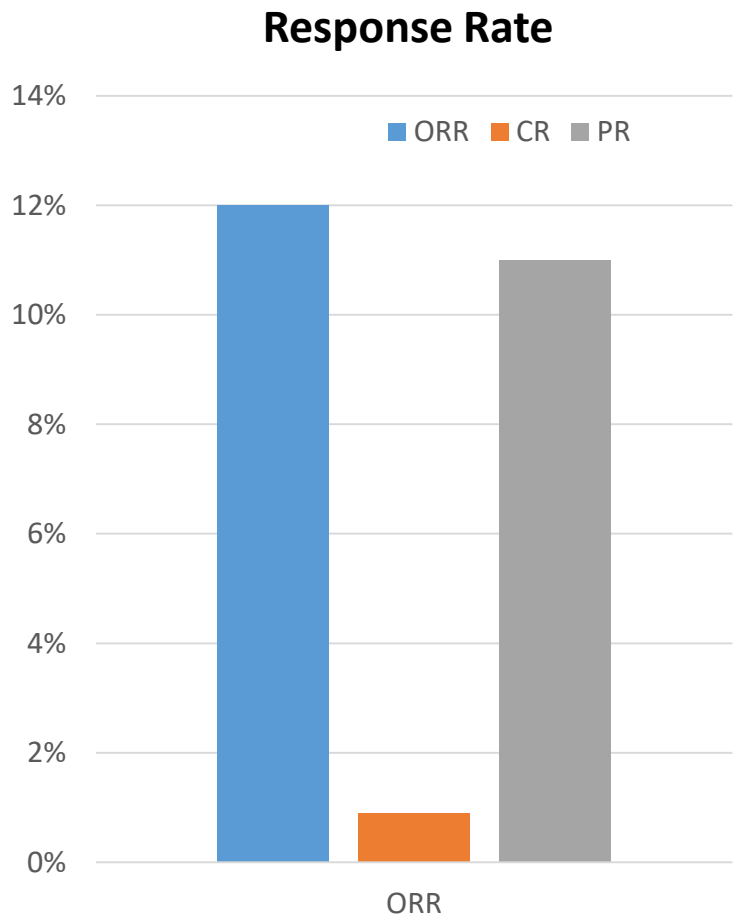
Keytruda [prescribing information]; 2019.

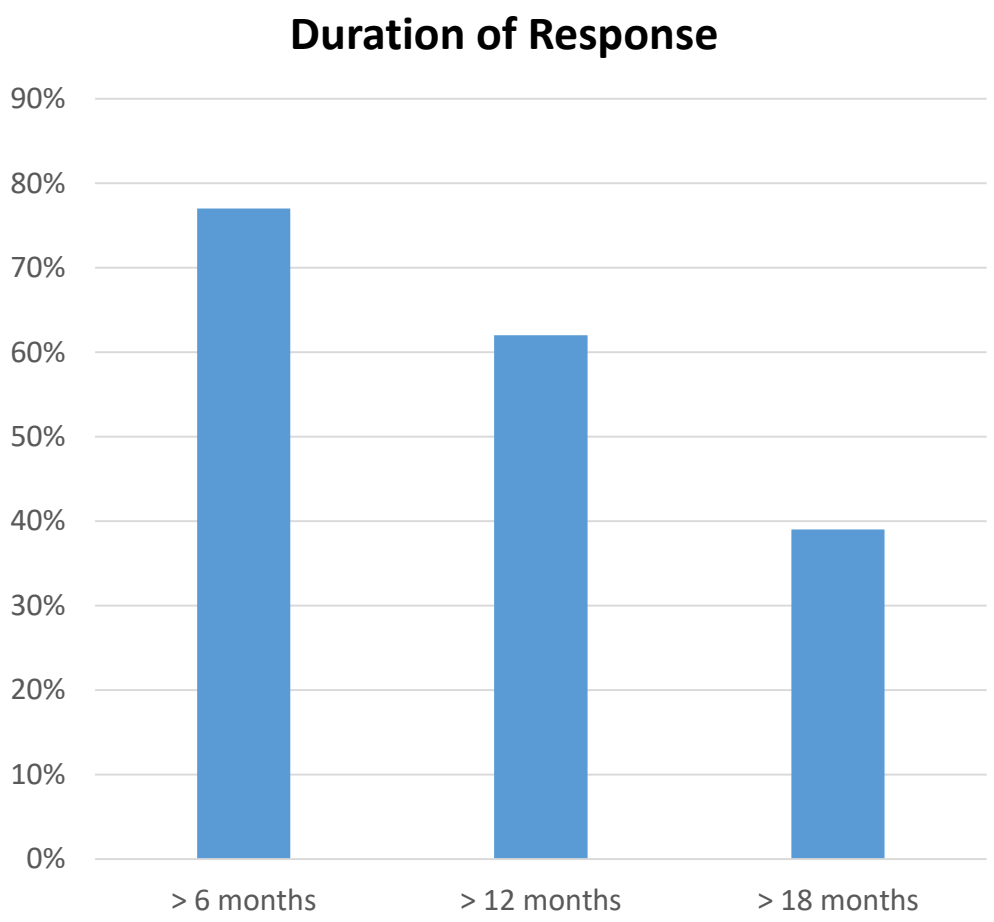
Nivolumab for Third-Line and Later Treatment in SCLC

- Accelerated approval based on ORR and DOR in a non-comparative trial (n=109)
- Used after a platinum-containing regimen plus an additional regimen
- Monotherapy with nivolumab 3 mg/kg IV q2weeks
- Primary endpoints: ORR and DOR

Opdivo [prescribing information]; 2019.

Nivolumab for Third-Line and Later Treatment in SCLC





Opdivo [prescribing information]; 2019.

Potential Practice-Changing Impact

- Essentially all patients will receive an ICI with SCLC
  - *ICIs won't replace other therapies*
- Cycle 1 for SCLC is commonly given inpatient, which may impact the use of atezolizumab due to the cost/reimbursement when given as an inpatient
- Patients who do not receive atezolizumab as first-line therapy will get pembrolizumab or nivolumab in the third-line setting
  - Response rates are low, but DOR is remarkable

Atezolizumab for Metastatic TNBC

Patients with unresectable advanced or metastatic TNBC
N=902
Stratified by prior taxane use and PD-L1 status (<1%)
Liver metastasis

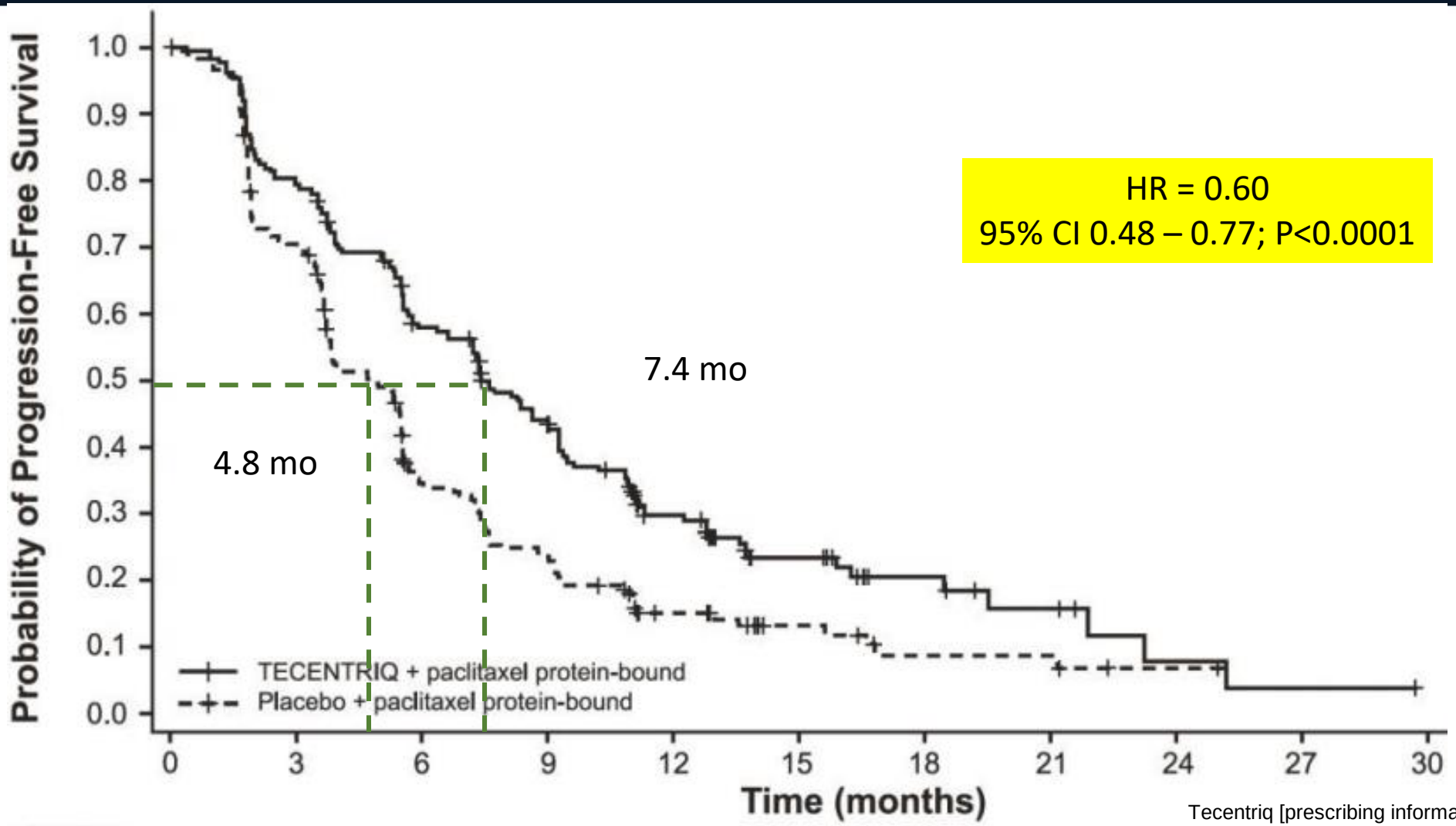
→ Atezolizumab 840 mg IV d1 and d15
Nab-paclitaxel 100 mg/m^2 IV d1, 8, and 15
Repeat q28days
N=451

→ Placebo IV d1 and d15
Nab-paclitaxel 100 mg/m^2 IV d1, 8, and 15
Repeat q28days
N=451

Primary endpoints: PFS and OS in ITT population
Secondary endpoints: ORR and DOR

Tecentriq [prescribing information]; 2019.

Metastatic TNBC: Progression-Free Survival



HR = 0.60
95% CI 0.48 – 0.77; P<0.0001

Tecentriq [prescribing information]; 2019.

Potential Practice-Changing Impact

- Nearly all patients with metastatic TNBC will receive atezolizumab
  - New agent added to armamentarium of 16 agents:

    Paclitaxel, nab-paclitaxel, vinorelbine, capecitabine, ixabepilone, doxorubicin, liposomal doxorubicin, gemcitabine, eribulin, docetaxel, cyclophosphamide, epirubicin, carboplatin, cisplatin, olaparib, and talazoparib

268,600 new breast CA cases estimated in 2019

↓ 10%-20% are triple negative

26,860 to 53,720 cases are TNBC

↓ 6% are metastatic

1,611 to 3,222 cases are metastatic TNBC

Joe BN, et al. https://www.uptodate.com/contents/clinical-features-diagnosis-and-staging-of-newly-diagnosed-breast-cancer. Accessed November 14, 2019.;
National Cancer Institute. Breast Cancer Treatment (Adult) PDQ. https://www.ncbi.nlm.nih.gov/books/NBK65744/#CDR0000062787__2008.

Avelumab Plus Axitinib as First-Line Treatment for mRCC

Phase III, randomized, open-label study in advanced renal cell carcinoma (clear cell component)

Previously untreated advanced renal cell carcinoma with clear cell component

ECOG PS 0-1
Geographic region
N=886

Randomize 1:1

Avelumab 10 mg/kg IV q2weeks (x 3 doses = 6-week cycles) + axitinib 5 mg PO BID (continuous dosing) (*n=442*; *n=270* PD-L1+)

Sunitinib 50 mg PO daily (continuous for 4 weeks then 2 weeks off = 6-week cycle) (*n=444*; *n=290* PD-L1+)

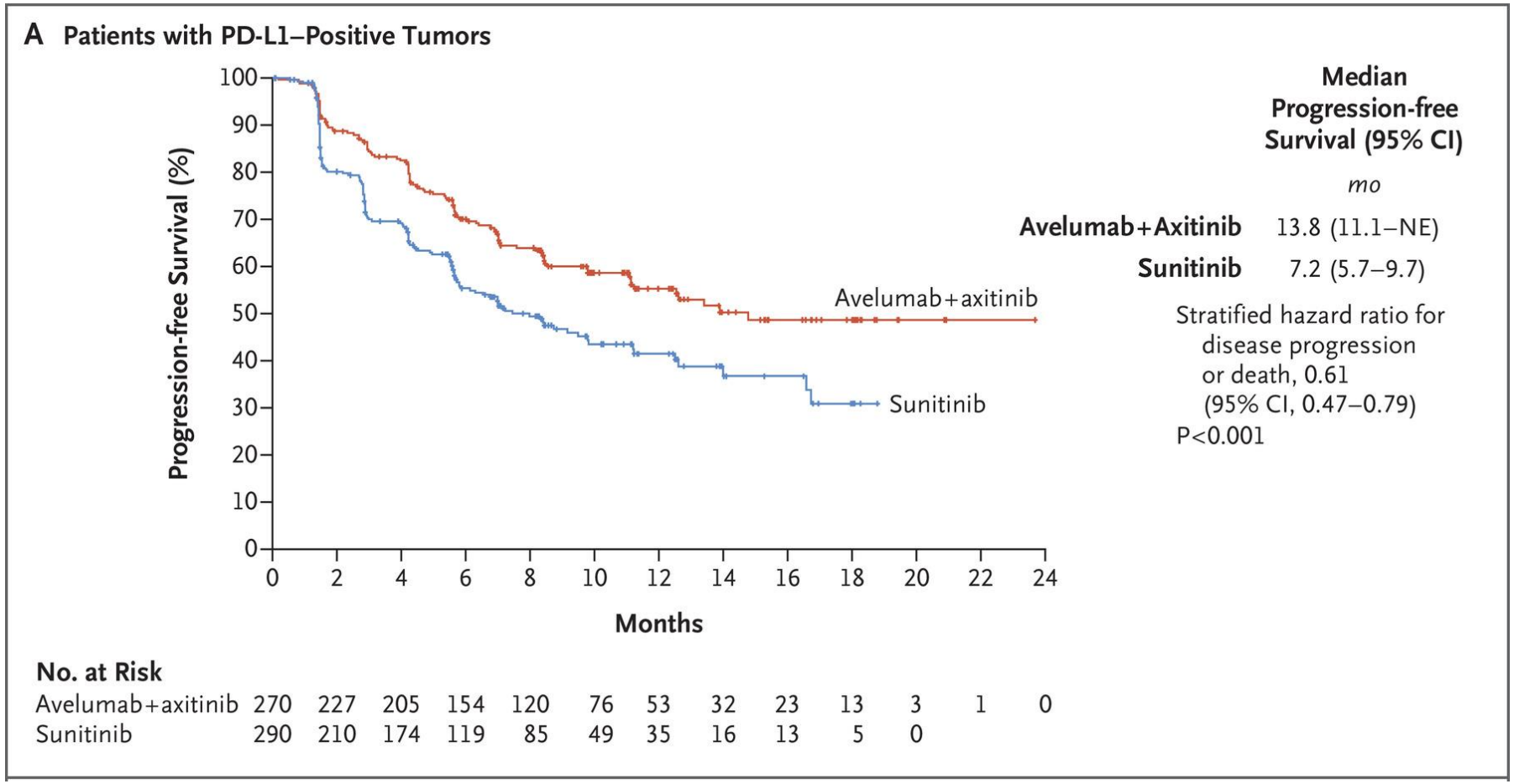
PD-L1+ tumors:
560/886 = 63.2%

<u>Primary endpoints:</u> PFS and OS (in PD-L1+ status)
<u>Secondary endpoint:</u> PFS and OS (not based on PD-L1 status)

BID, twice daily; mRCC, metastatic renal cell carcinoma; PO, by mouth.

Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-15.

Avelumab Plus Axitinib as First-Line Treatment for mRCC



Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-15.

Pembrolizumab Plus Axitinib as First-Line Treatment for mRCC

Phase III, randomized, open-label study in advanced renal cell carcinoma

Previously untreated advanced renal cell carcinoma with clear cell component

Stratified by risk category
N=861

Randomize 1:1

Pembrolizumab 200 mg IV q3weeks (up to 24 months) + axitinib 5 mg PO BID (titration up if tolerated)
N=432

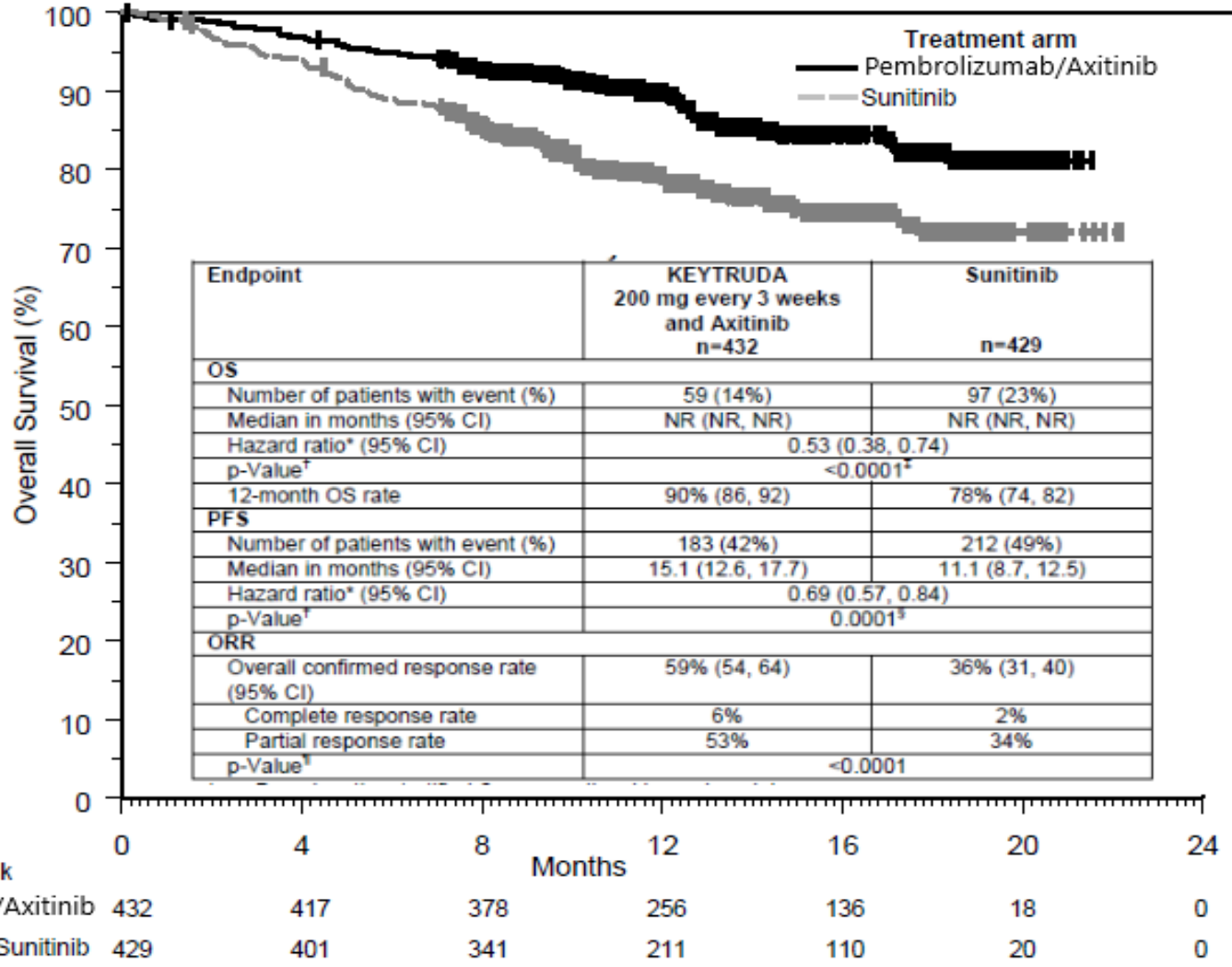
Sunitinib 50 mg PO daily (continuous for 4 weeks then 2 weeks off = 6-week cycle)
N=429

<u>Endpoints:</u> PFS, ORR, and OS

Keytruda [prescribing information]; 2019.

Pembrolizumab Plus Axitinib as First-Line Treatment for mRCC

Figure 13: Kaplan-Meier Curve for Overall Survival in KEYNOTE-426

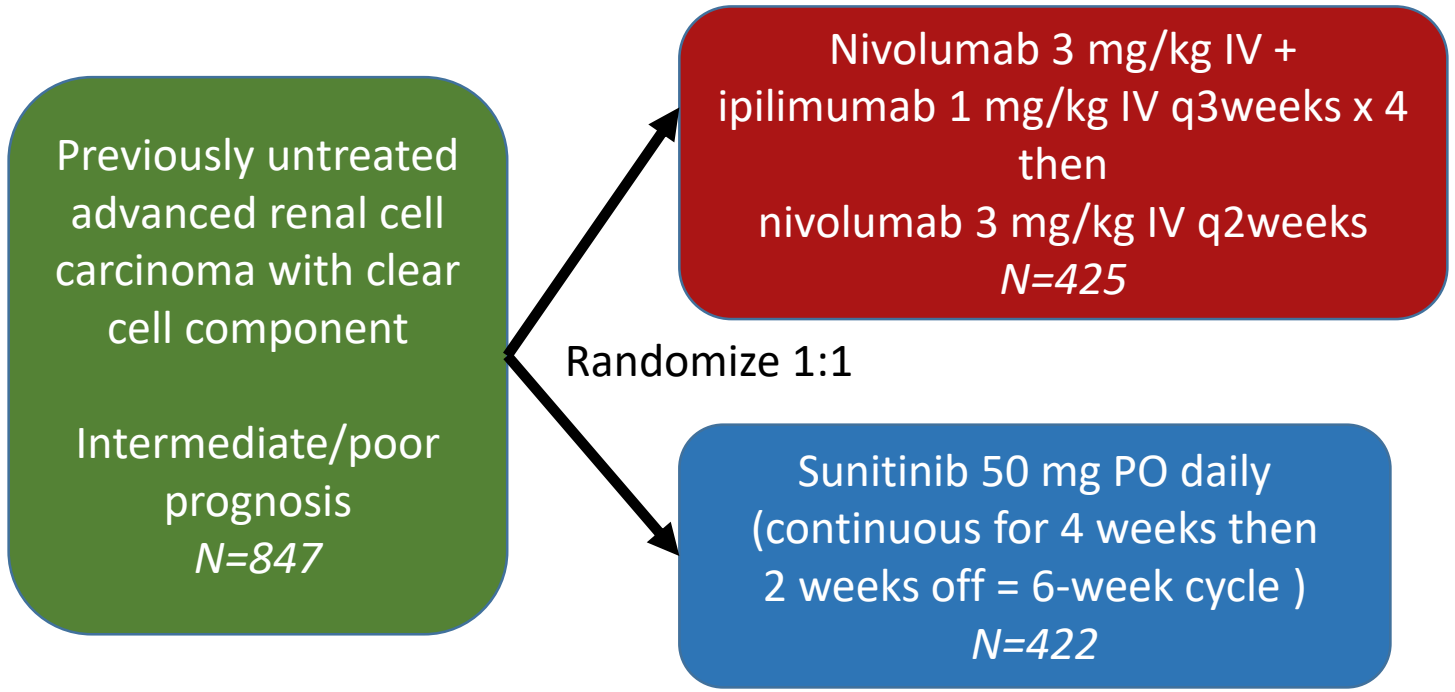


Endpoint	KEYTRUDA 200 mg every 3 weeks and Axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	<0.0001‡	
12-month OS rate	90% (86, 92)	78% (74, 82)
PFS		
Number of patients with event (%)	183 (42%)	212 (49%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.57, 0.84)	
p-Value†	0.0001§	
ORR		
Overall confirmed response rate (95% CI)	59% (54, 64)	36% (31, 40)
Complete response rate	6%	2%
Partial response rate	53%	34%
p-Value¶	<0.0001	

Keytruda [prescribing information]; 2019.

Nivolumab Plus Ipilimumab as First-Line Treatment for mRCC

Phase III, randomized, open-label study in advanced renal cell carcinoma (clear cell component)

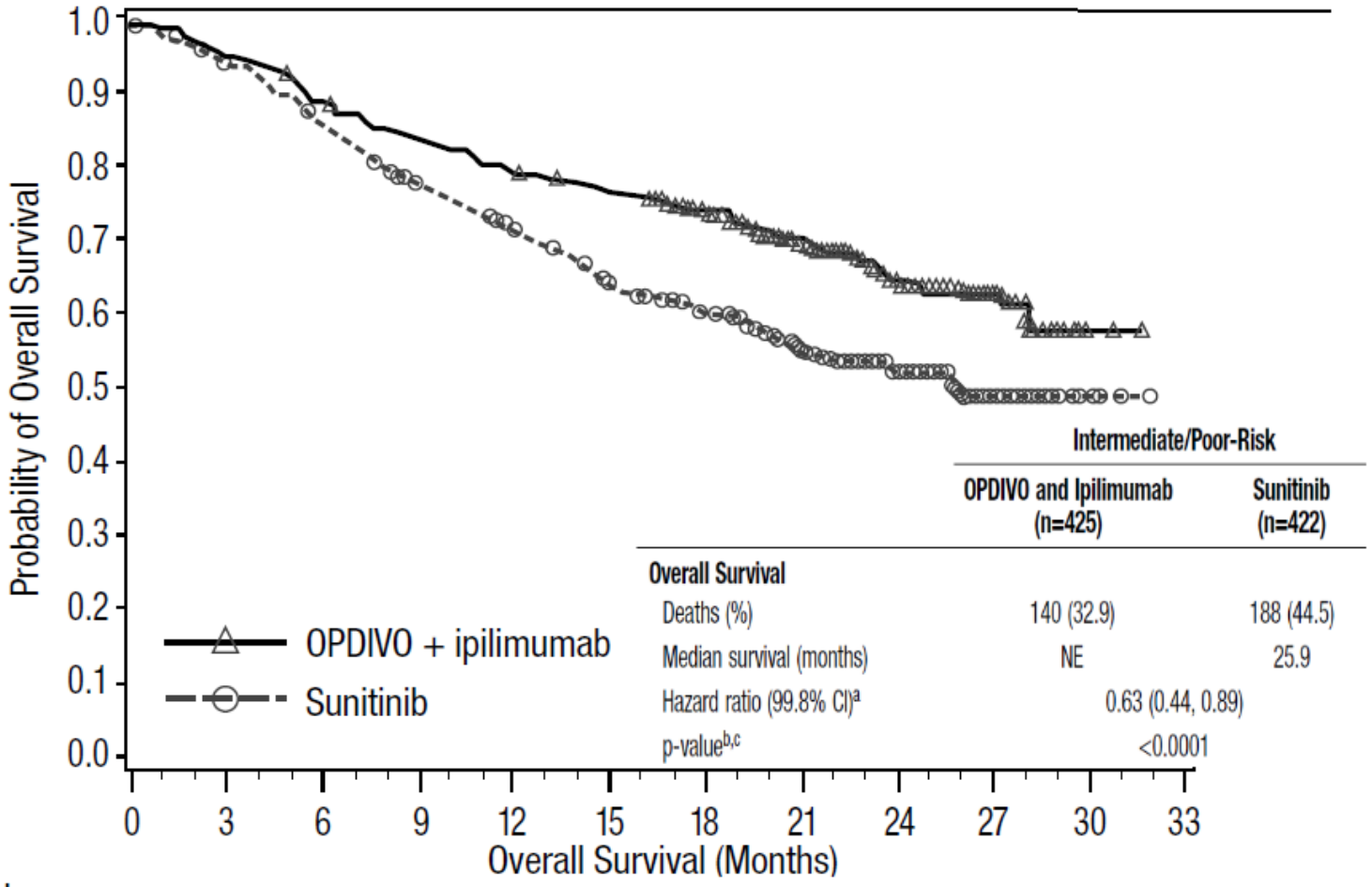


Endpoints: PFS, ORR, and OS

Opdivo [prescribing information]; 2019.

Nivolumab Plus Ipilimumab as First-Line Treatment for mRCC

Figure 10: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214



Intermediate/Poor-Risk	OPDIVO and Ipilimumab (n=425)	Sunitinib (n=422)
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	

OPDIVO + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

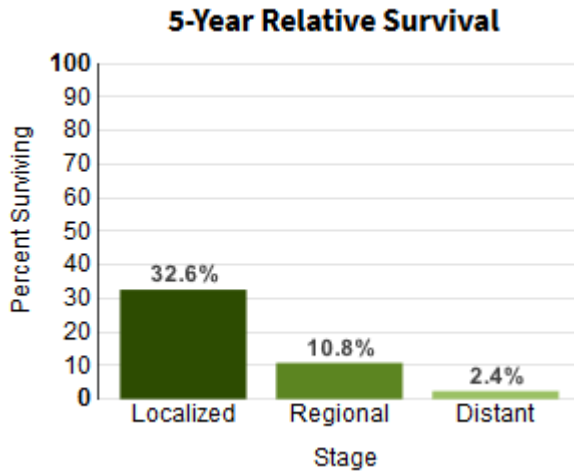
Opdivo [prescribing information]; 2019.

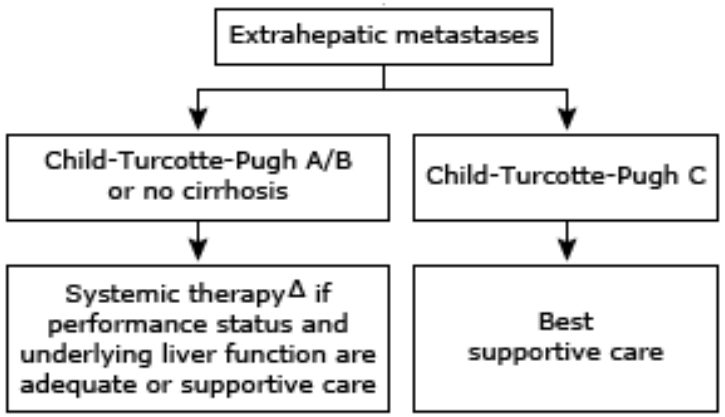
Potential Practice-Changing Impact

- Essentially all patients will receive an ICI with advanced/metastatic renal cell cancer in combination
- There are only 2 active moieties: immunotherapy and targeted therapy (TKI w/VEGFi)
  - Current debate: ICI plus TKI (VEGFi) or dual ICI
- Based on risk categories, some patients with favorable risk could still start on a TKI in first-line setting, then use an ICI in second-line therapy

TKI, tyrosine kinase inhibitor.

Hepatocellular Cancer: Background





BSC, best supportive care.

Treatment	Outcome: OS (months)	Comment
Sorafenib vs. placebo (1st line)	10.7 vs. 7.9	1st treatment to show efficacy
Lenvatinib vs. sorafenib	13.6 vs. 12.3	OS not significant; PFS and response rate improved
Regorafenib vs. placebo (2nd line)	10.6 vs. 7.8	Efficacy after sorafenib
Cabozantinib vs. placebo (2nd line)	10.2 vs. 8.0	Efficacy after sorafenib
Ramucirumab vs. BSC	8.5 vs. 7.3	Efficacy after sorafenib

National Cancer Institute. https://seer.cancer.gov/statfacts/html/livibd.html.; National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Published August 1, 2019.

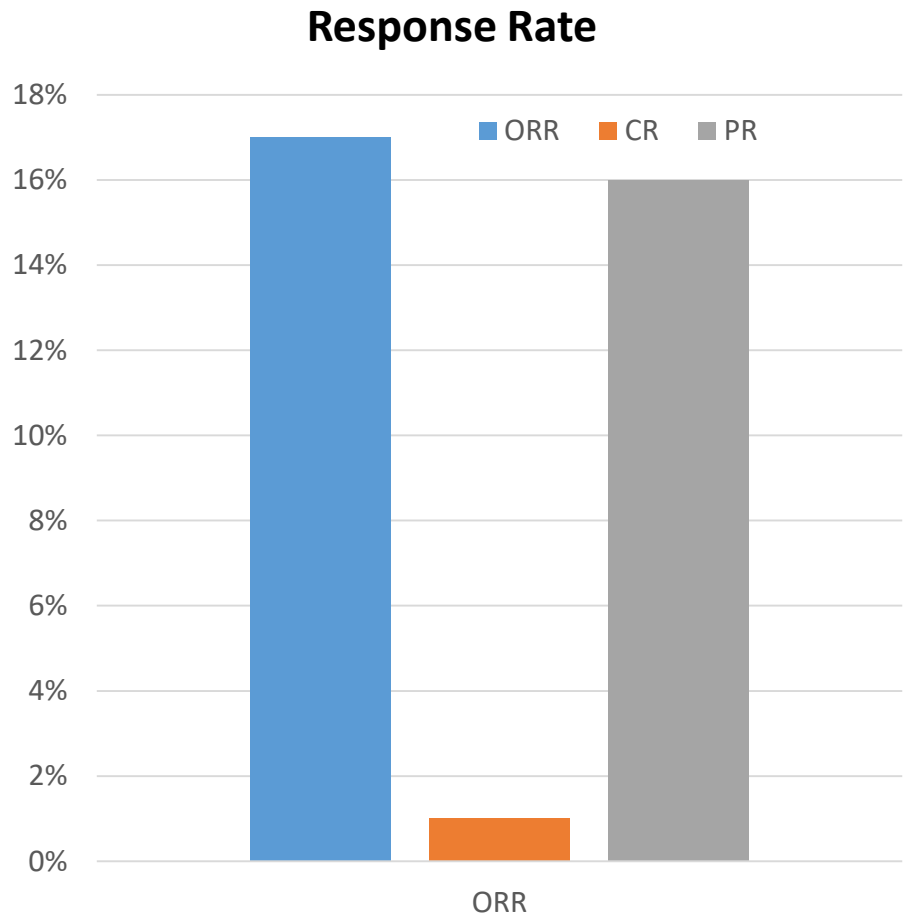
Pembrolizumab for Second-Line Treatment of HCC

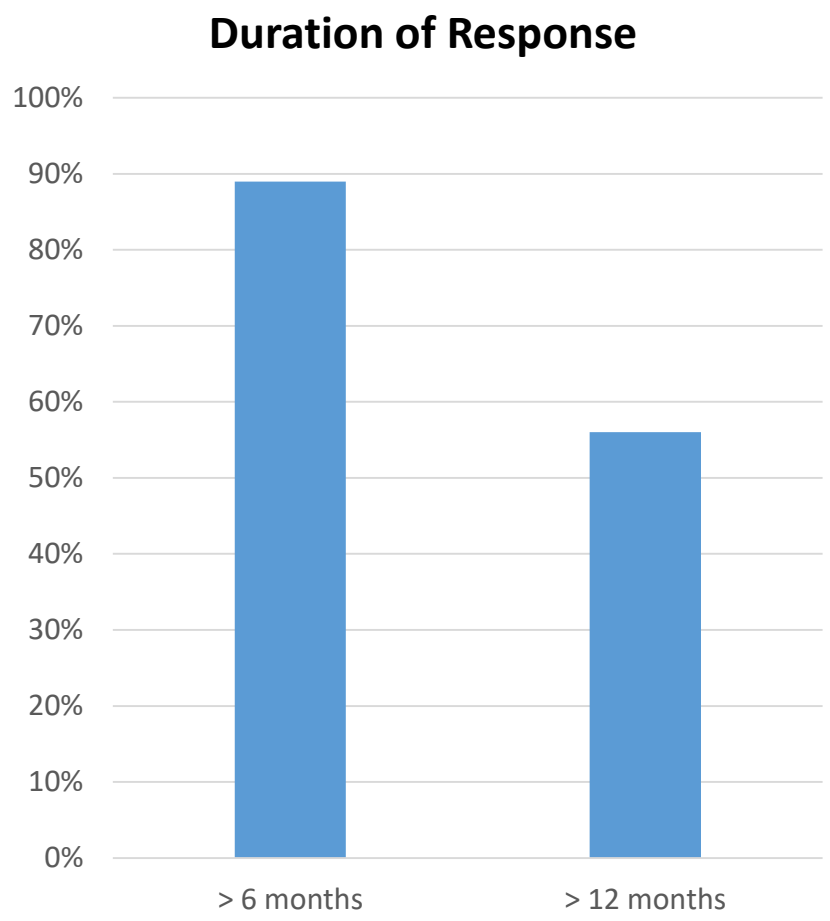
- Accelerated approval based on combined data from a single-arm, multicenter trial (n=104)
- Used after first-line sorafenib
  - Patients had Child-Pugh class A disease
- Monotherapy with pembrolizumab 200 mg IV q21days
- Primary endpoints: ORR and DOR

HCC, hepatocellular carcinoma.

Keytruda [prescribing information]; 2019.

Pembrolizumab for Second-Line Treatment of HCC





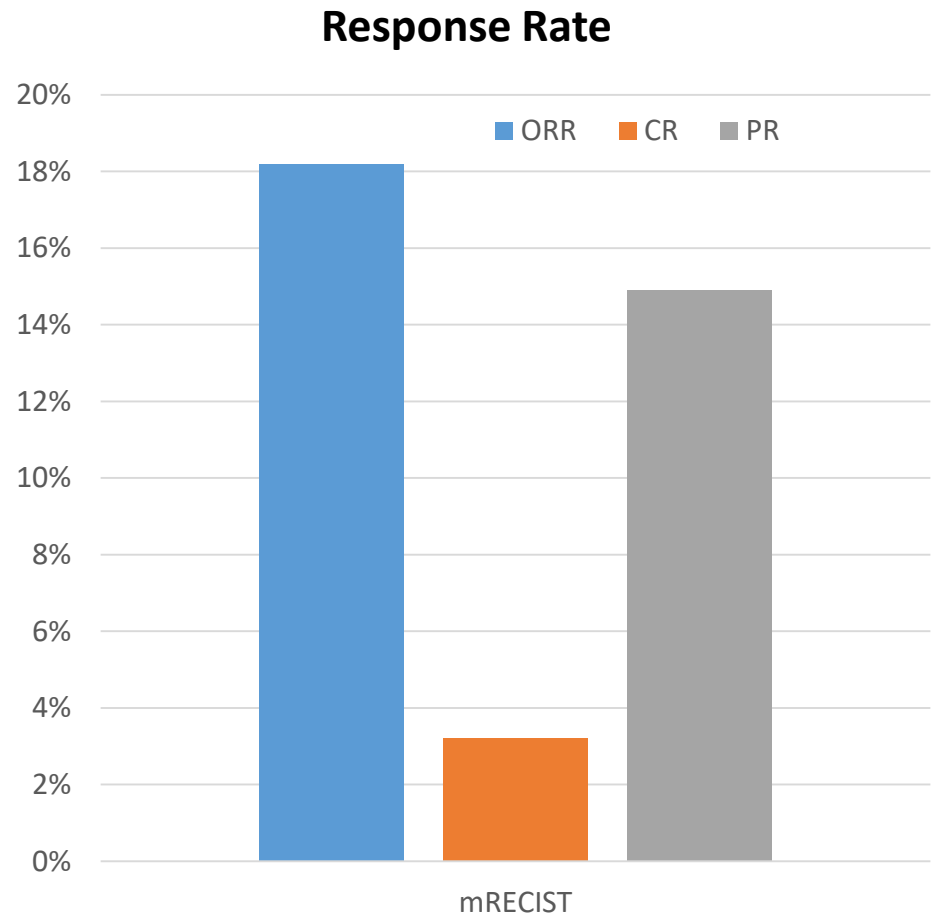
Keytruda [prescribing information]; 2019.

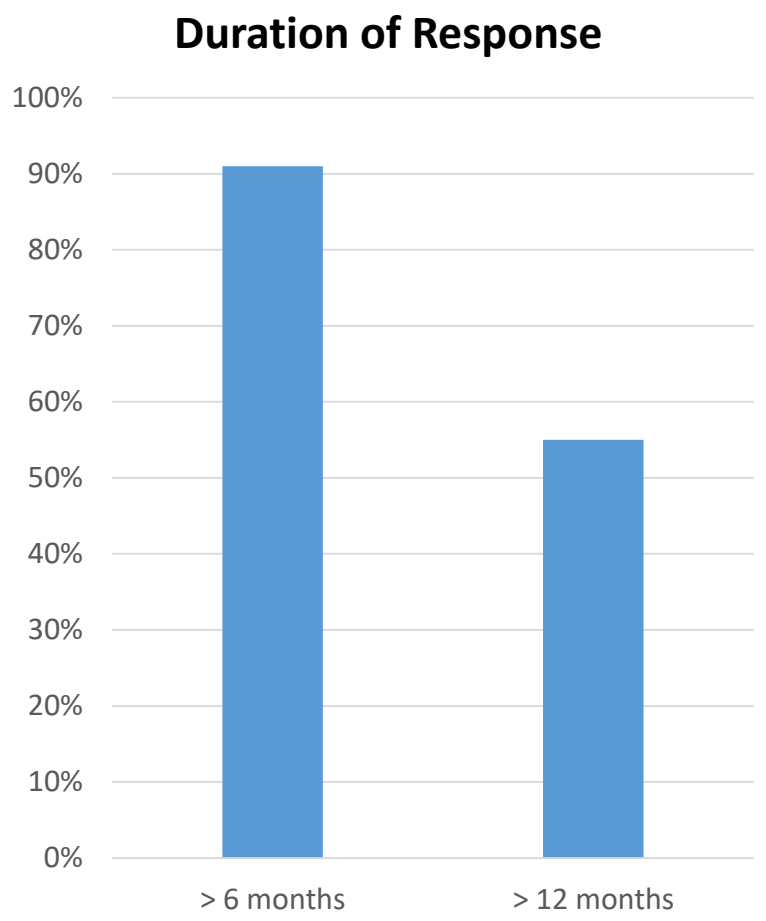
Nivolumab for Second-Line Treatment of HCC

- Accelerated approval based on combined data from a single-arm, multicenter trial (n=154)
- Used after first-line sorafenib
  - Patients had Child-Pugh class A disease
- Monotherapy with nivolumab 3 mg/kg IV q2weeks
- Primary endpoints: ORR and DOR

Opdivo [prescribing information]; 2019.

Nivolumab for Second-Line Treatment of HCC





Opdivo [prescribing information]; 2019.

Potential Practice-Changing Impact

- Metastatic HCC carries a grim prognosis
  - Survival expectation approximately 12 months
- There are only 2 active moieties: ICI and targeted therapy (TKI w/VEGF)
  - Current debate: ICI monotherapy or targeted therapy for second-line treatment
- For the relatively small proportion of patients responding to an ICI, more than half have a response lasting more than 1 year

MSI-H or dMMR Colorectal Cancer

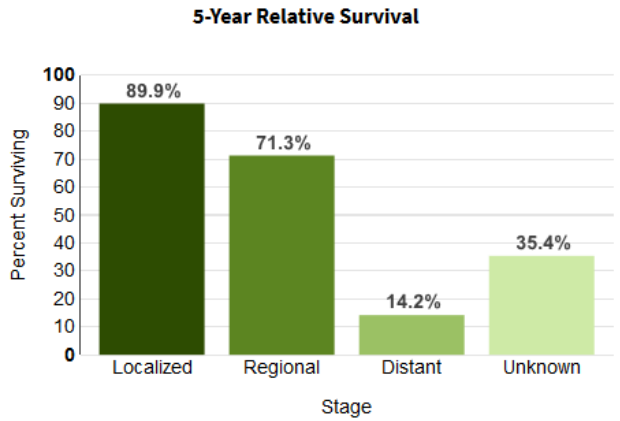
145,600 new CRC cases estimated in 2019

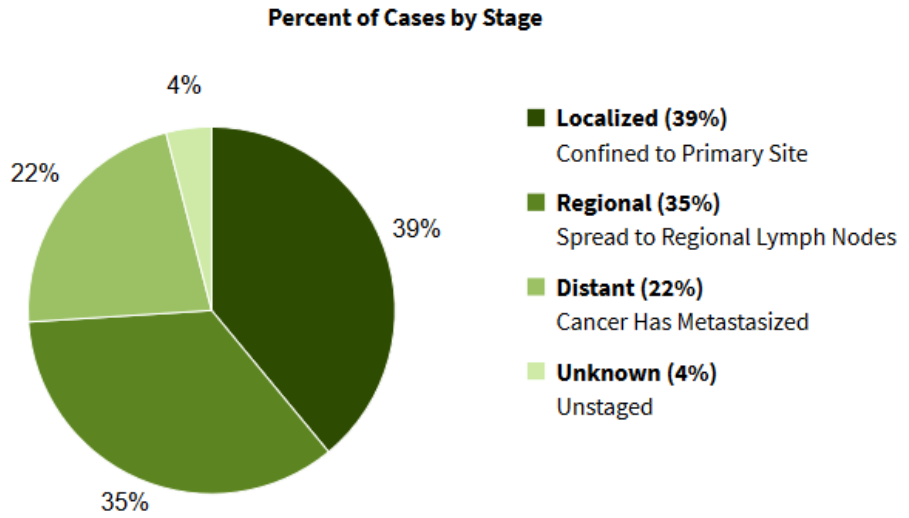
↓ 5% are MSI-H/dMMR

7,280 MSI-H/dMMR cases

↓ 22% are metastatic

1,602 are eligible for ICI treatment





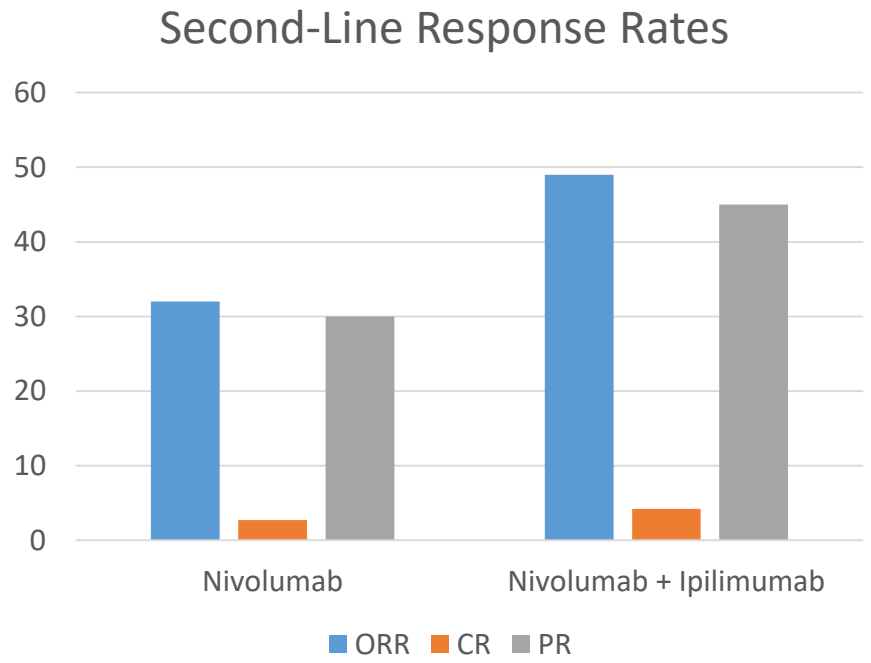
CRC, colorectal cancer.

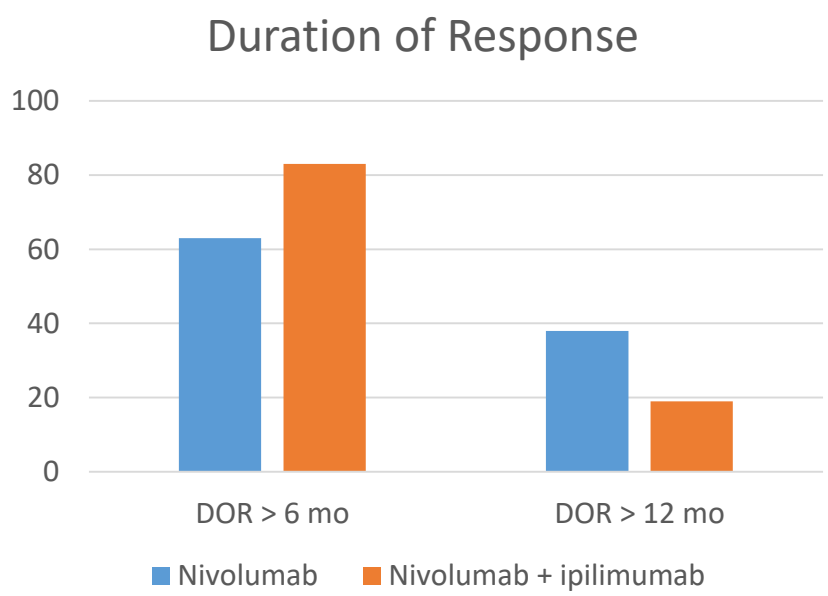
Clark JW, Grothey A. https://www.uptodate.com/contents/systemic-chemotherapy-for-nonoperable-metastatic-colorectal-cancer-treatment-recommendations/print. Updated October 30, 2019.; National Cancer Institute. https://seer.cancer.gov/statfacts/html/colorect.html.

Nivolumab +/- Ipilimumab for MSI-H/dMMR mCRC

Checkmate 142 (second-line for mCRC with MSI-H or dMMR)

Open-label, phase II trial: patients failed 1+ therapies with 5FU and oxaliplatin or irinotecan (54% of patients had 3+ prior therapies)





5FU, 5-fluorouracil.

Opdivo [prescribing information]; 2019.

Pembrolizumab Activity Against Multiple MSI-H/dMMR CRC

Summary from 5 uncontrolled, open-label, multi-cohort, single-arm trials

Pembrolizumab 10 mg/kg IV q2weeks or 200 mg IV q3weeks
(All patients had 1+ prior regimens)

	N	ORR		DOR range (months)
		n (%)	95% CI	
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)

In all patients with various diseases (n=149),
ORR = 40% (7.4% CR, 32.2% PR) and 78% had a DOR ≥ 6 months

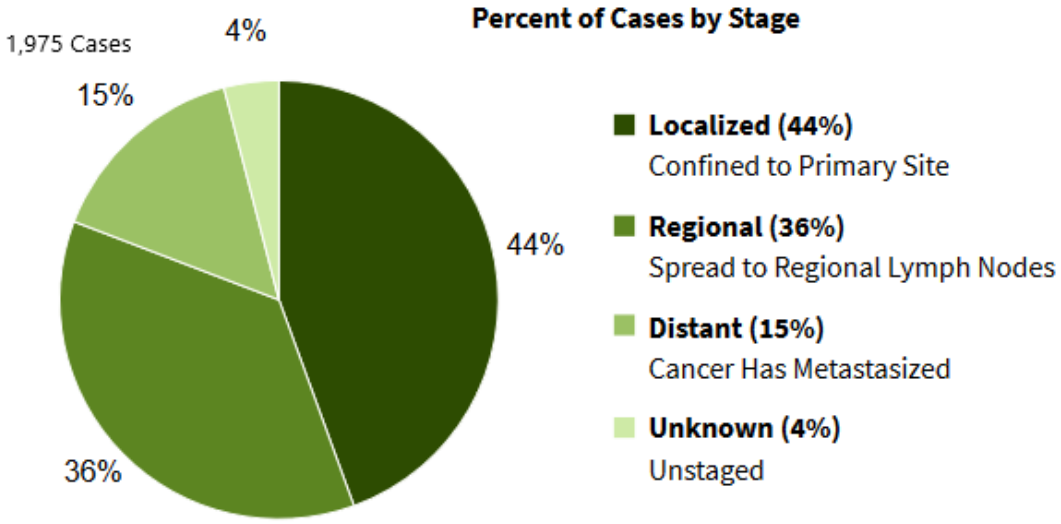
Pembrolizumab [prescribing information]; 2019.

Potential Practice-Changing Impact

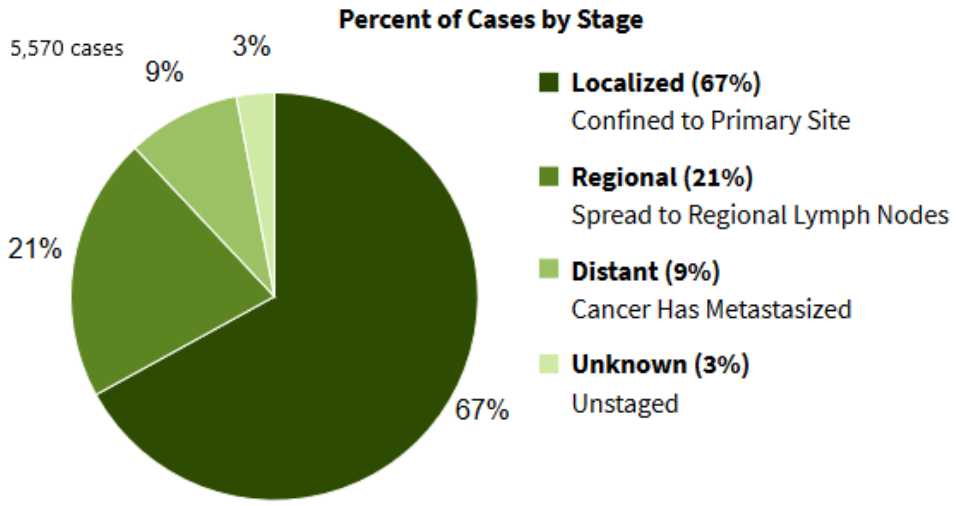
- Metastatic CRC that is MSI-H or dMMR is relatively uncommon
- Monotherapy with pembrolizumab or nivolumab as second-line treatment generates a response in approximately one-third of patients
- Combination therapy with nivolumab and ipilimumab as second-line therapy generates a response in approximately half of patients
- The DOR is impressive at 6 months but starts trailing off at 12 months
  - However, this is relatively high as a second-line treatment
- Patients with an MSI-H or dMMR phenotype will likely receive an ICI and maybe dual-ICI therapy

Endometrial and Cervical Cancer: Background

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Cervical Cancer



Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Uterine Cancer



National Cancer Institute. https://seer.cancer.gov/statfacts/html/cervix.html.; National Cancer Institute. https://seer.cancer.gov/statfacts/html/corp.html.

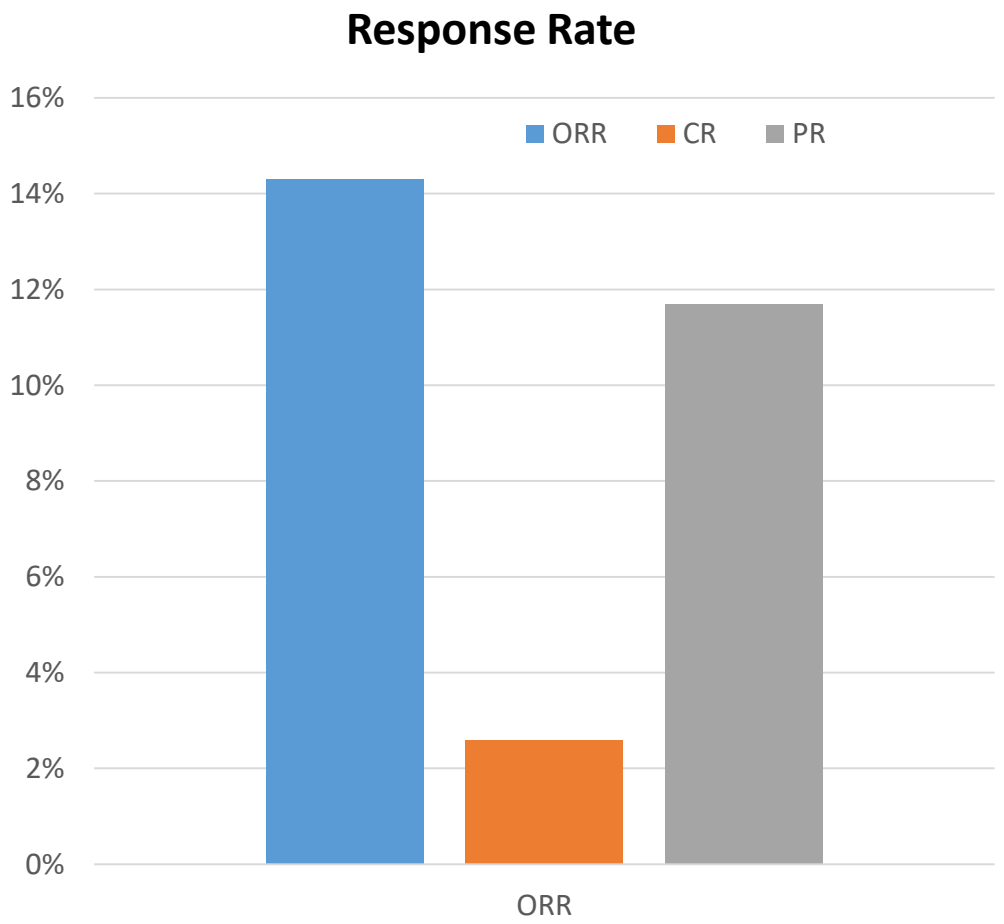
Pembrolizumab for Second-Line Treatment of Cervical CA

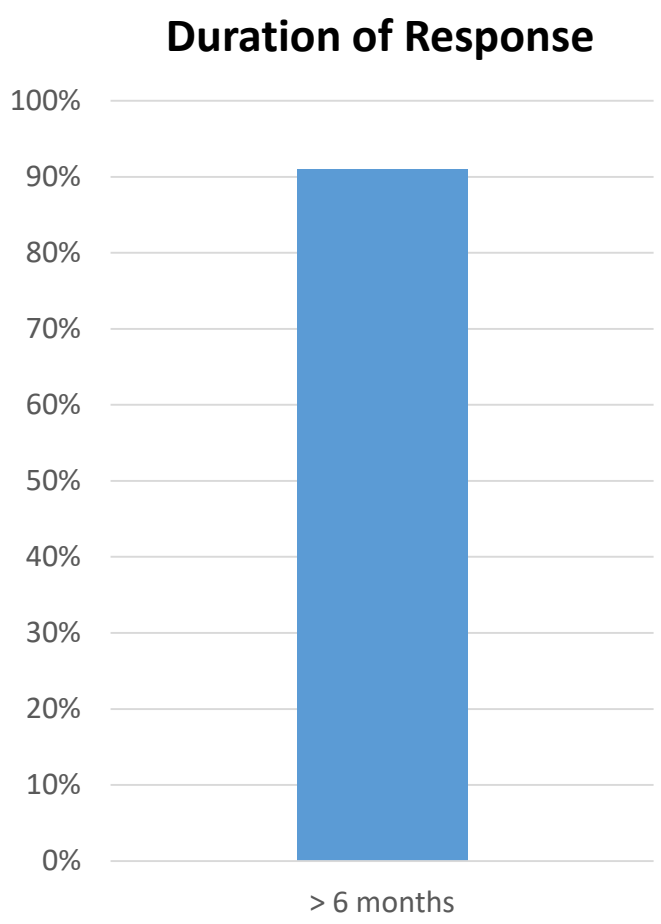
- Accelerated approval based on combined data from a single-arm, multicenter trial (cohort-E) (n=98)
- Recurrent or metastatic cervical cancer and CPS > 1 after at least 1 chemotherapy regimen for metastatic disease
- Monotherapy with pembrolizumab 200 mg IV q21days
- Primary endpoints: ORR and DOR

CPS, combined positive score.

Keytruda [prescribing information]; 2019.

Pembrolizumab for Second-Line Treatment of Cervical CA





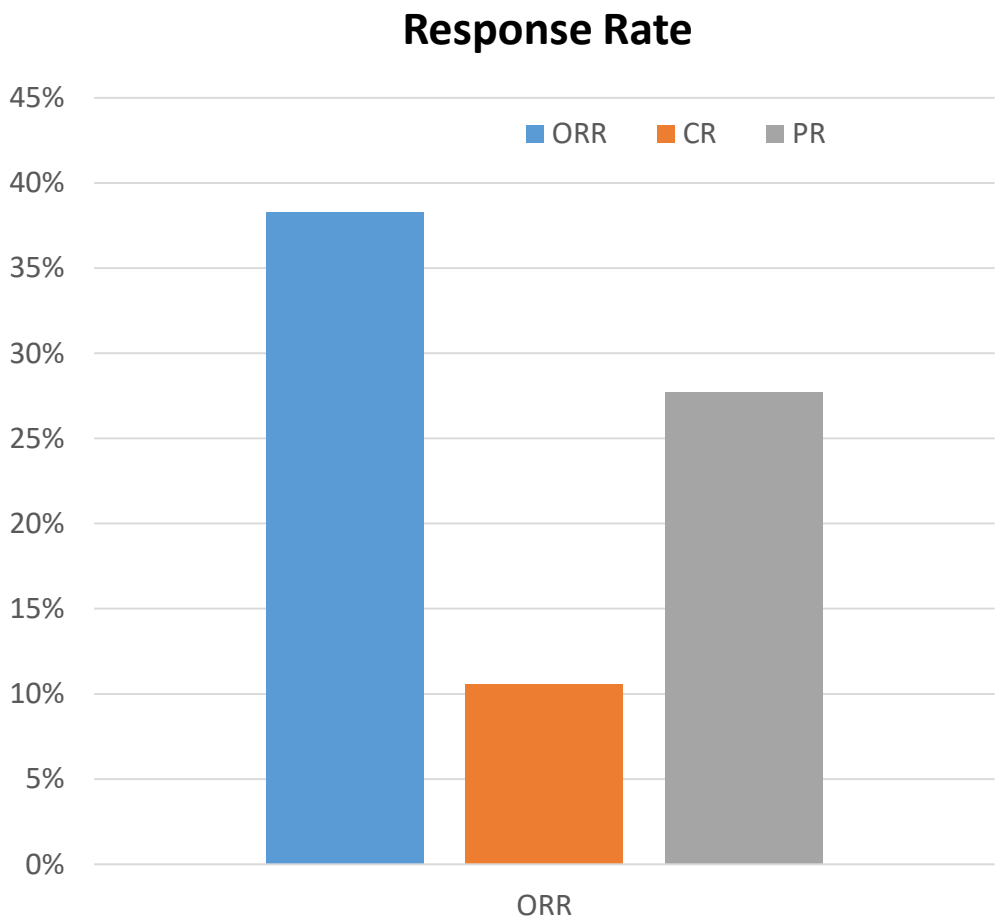
Keytruda [prescribing information]; 2019.

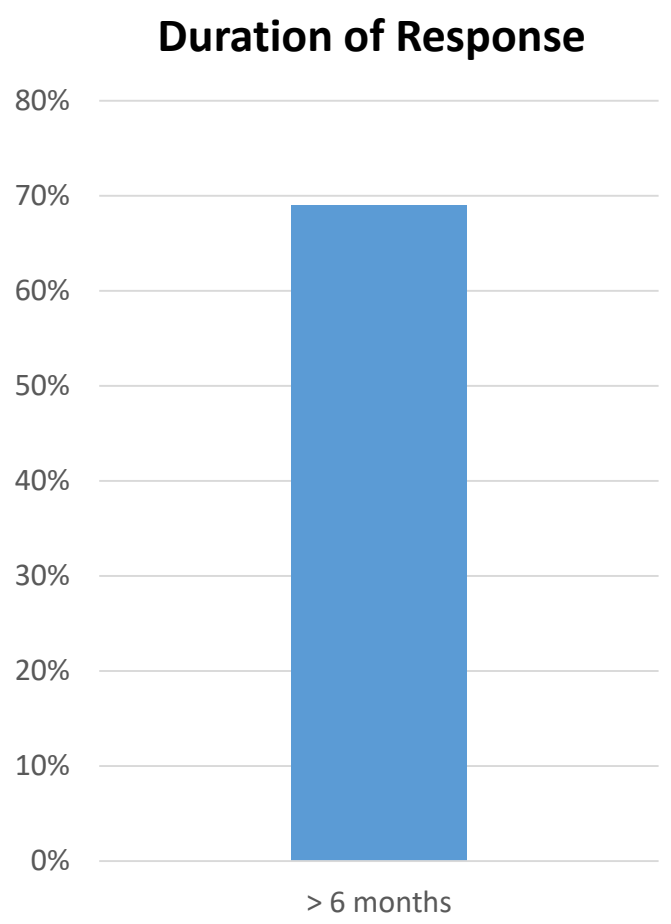
Pembrolizumab for Second-Line Treatment of Cervical CA

- Accelerated approval based on combined data from a single-arm, multicenter trial (n=108)
- Recurrent or metastatic endometrial cancer after at least 1 chemotherapy regimen (10% had dMMR or MSI-H)
- Combination therapy with pembrolizumab 200 mg IV q21days and lenvatinib 20 mg PO daily
- Primary endpoints: ORR and DOR

Keytruda [prescribing information]; 2019.

Pembrolizumab for Second-Line Treatment of Cervical CA





Keytruda [prescribing information]; 2019.

Potential Practice-Changing Impact

- The gyn/onc clinicians will use pembrolizumab for second-line cervical cancer in CPS-positive patients (> 1%)
- They will also use pembrolizumab and lenvatinib in endometrial cancer patients in the second-line setting
- Neither of these situations is common
  - There are no large, randomized trial data to evaluate outcomes
  - However, DOR looks good at 6 months

New Agent: Cemiplimab-rwlc

- PD1 inhibitor – similar to pembrolizumab or nivolumab
- Approved to treat metastatic cutaneous squamous cell carcinoma in non-surgical candidates
- Administered as a 350-mg dose IV over 30 minutes q3weeks

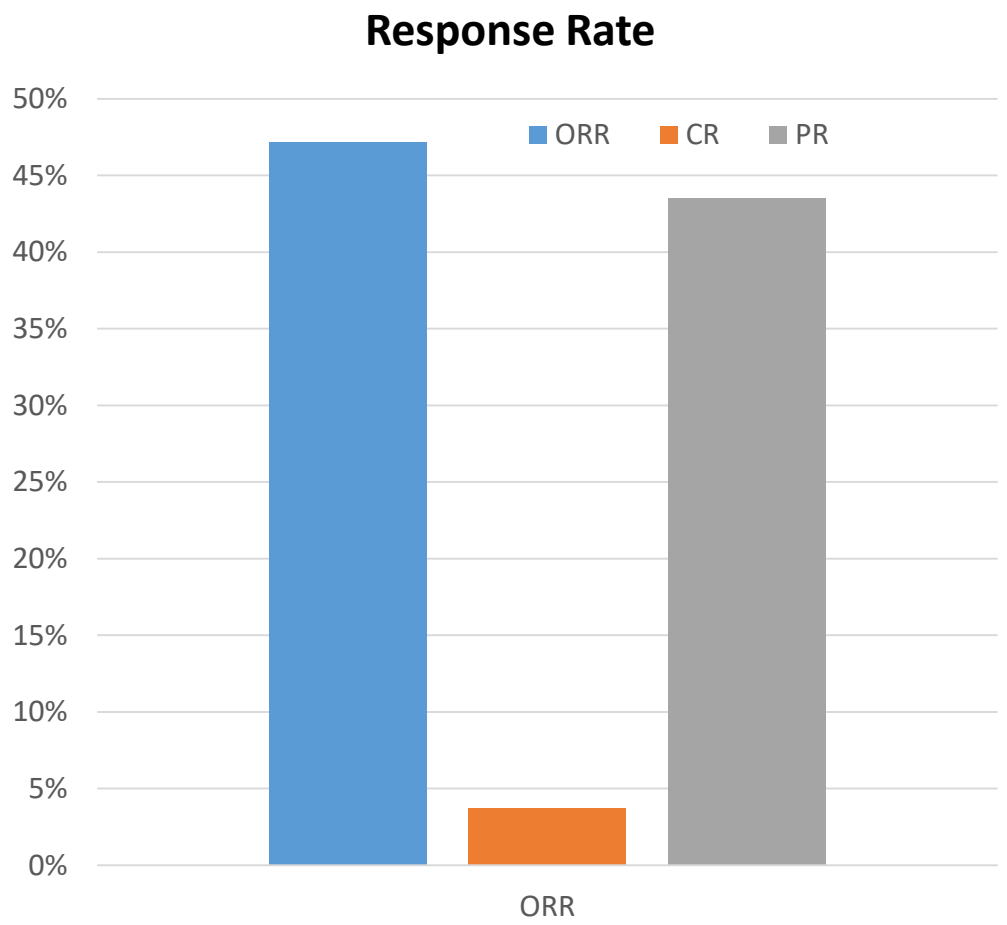
Libtayo [prescribing information]; 2019.

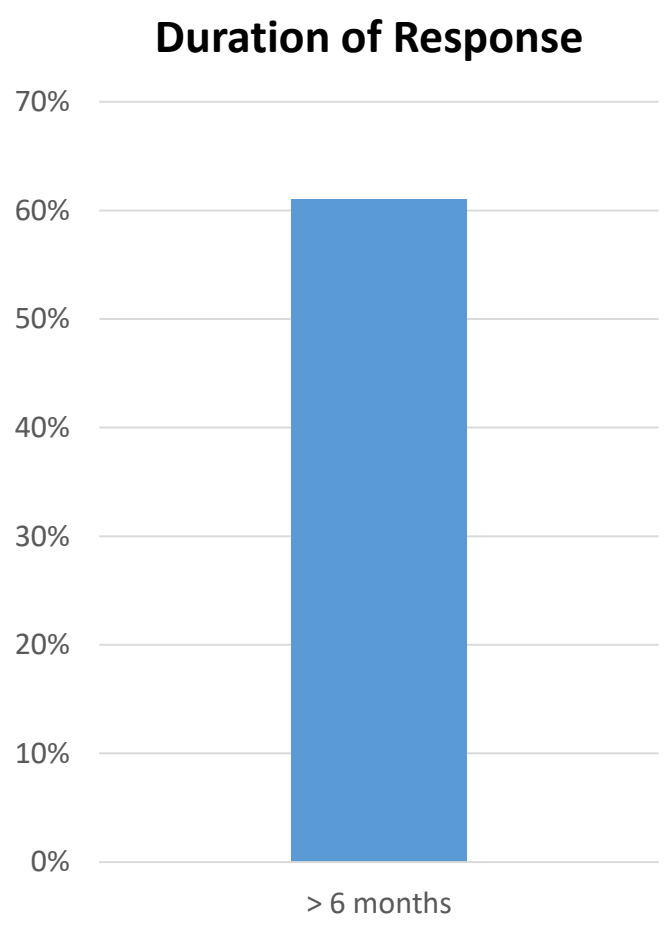
Cemiplimab for Metastatic Cutaneous Squamous Cell CA

- Approval based on combined data from 2 single-arm, open-label multicenter trials (n=108)
- Patients were not candidates for surgery or curative radiotherapy
- Monotherapy with cemiplimab 350 mg IV q21days
- Primary endpoints: ORR and DOR
  - Divided by metastatic or locally advanced disease

Libtayo [prescribing information]; 2019.

Cemiplimab for Treatment of Unresectable Cutaneous Squamous Cell CA





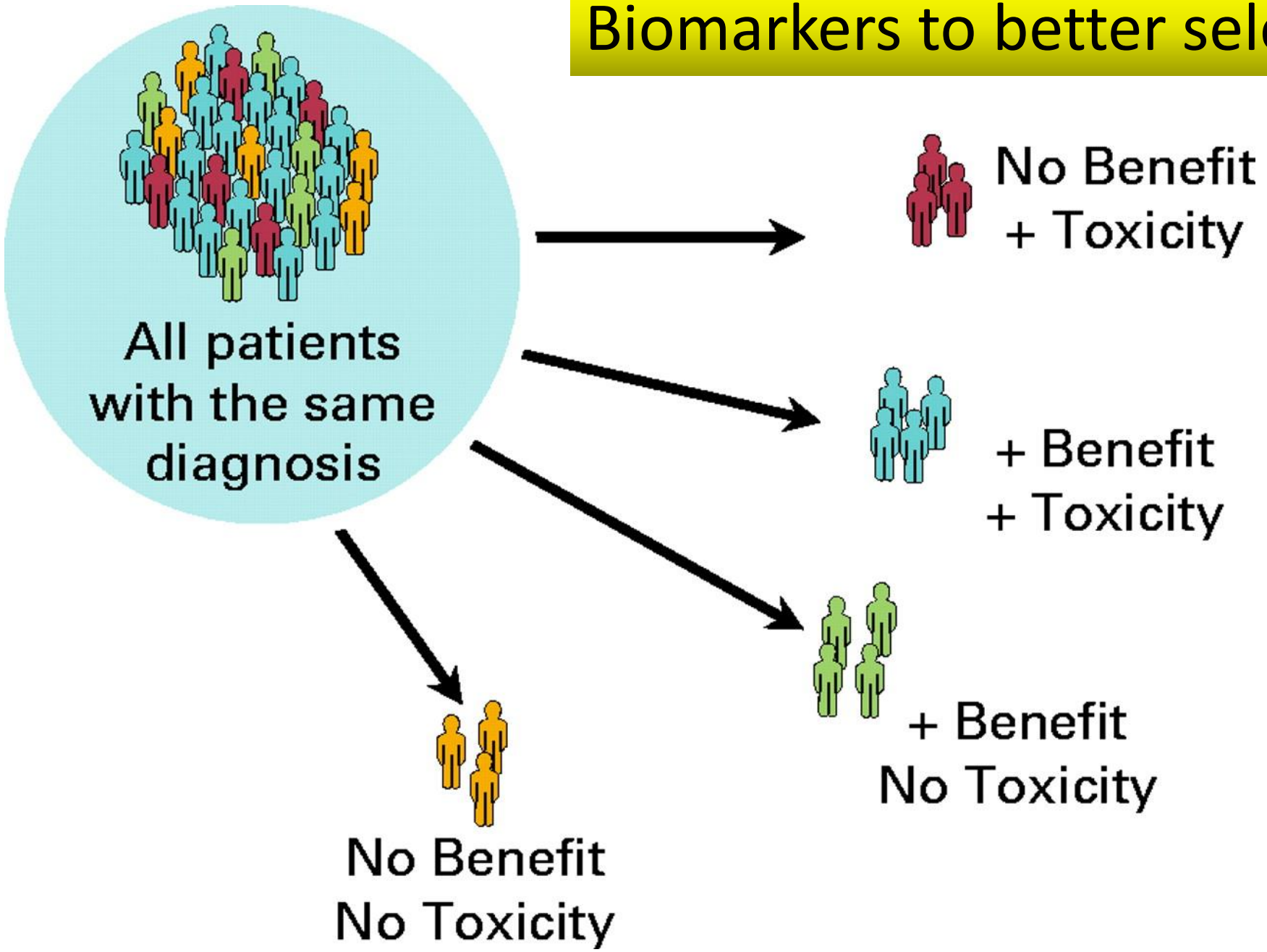
Libtayo [prescribing information]; 2019.

Potential Practice-Changing Impact

- The approved indication is not common
  - However, some early data were recently presented showing the value of cemiplimab as neoadjuvant therapy, making lesions surgically resectable
- Dermatologist will likely be referring patients to oncologist for treatment and, if the neoadjuvant approach works well, the number of potential patients could increase substantially

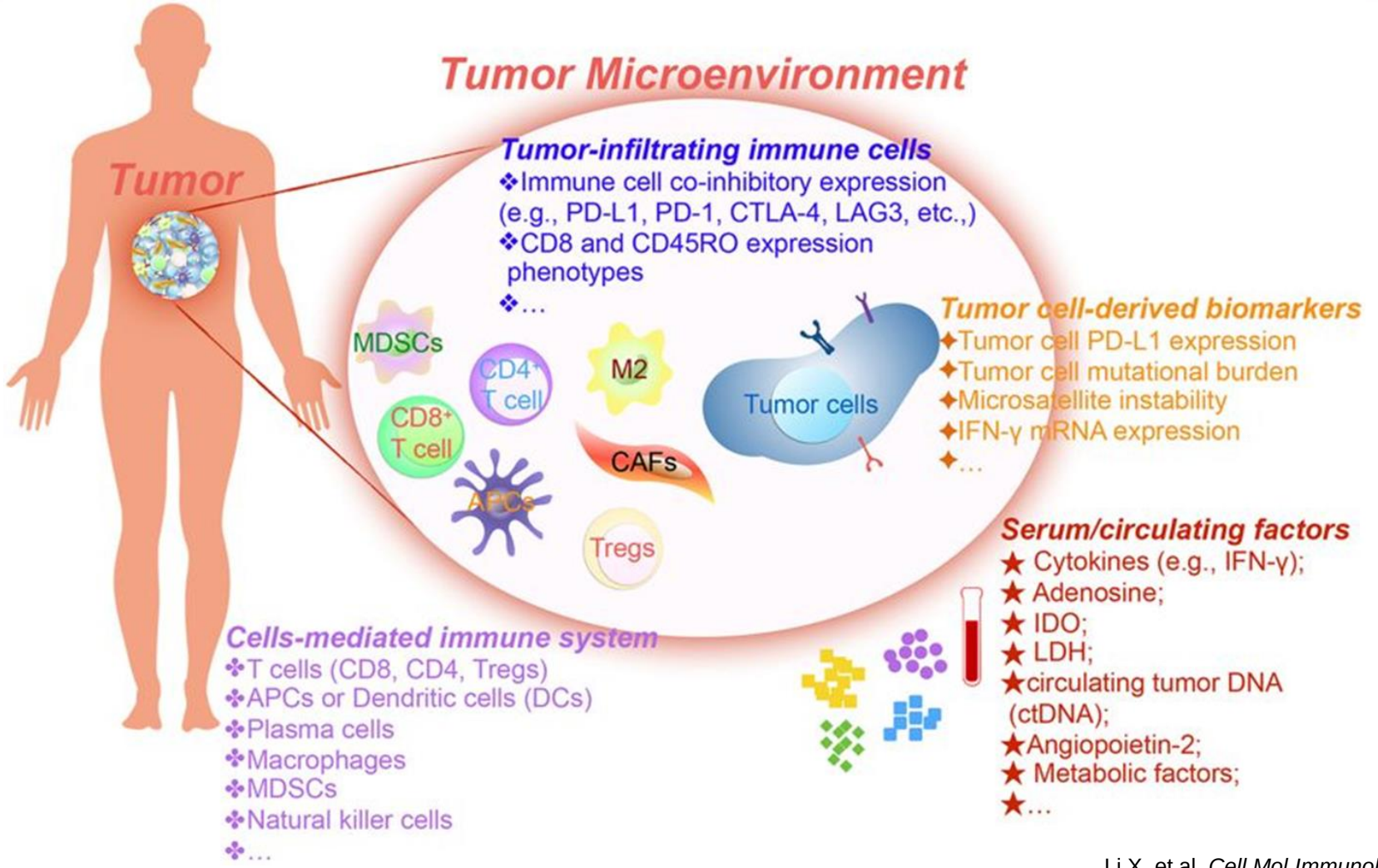
Gross N, et al. *Ann Oncol.* 2019;30(suppl_5).;
Libtayo [prescribing information]; 2019.

Biomarkers to better select patients



Walgren RA, et al. *J Clin Oncol.* 2005;23(29):7342-9.

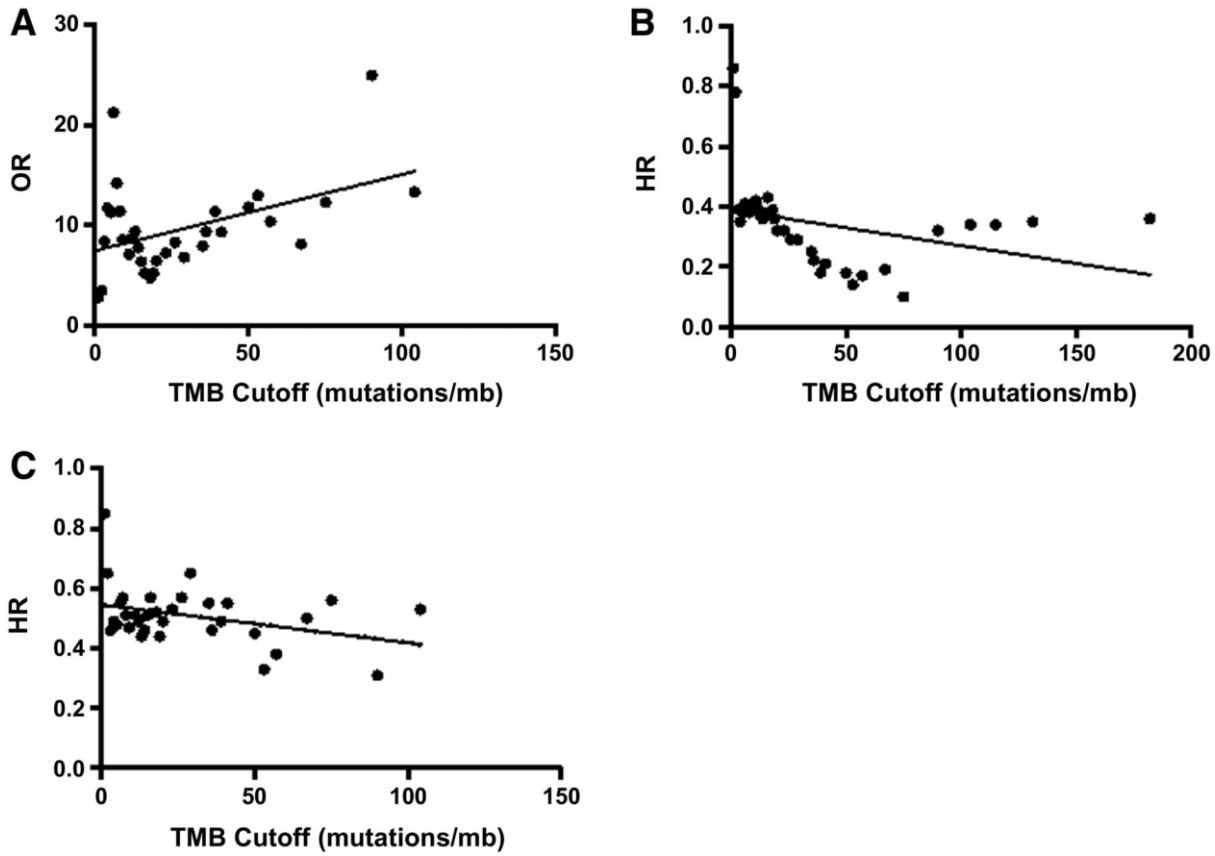
The Tumor Microenvironment is Complex



Li X, et al. *Cell Mol Immunol.* 2019;16(1):28-39.

Higher TMB Predicts Favorable Outcome With PD-1/PD-L1 Inhibitor

- TMB is the number of somatic mutations per Mb of DNA
- Tumors with high TMB often have features of DNA damage, such as MSI-H or dMMR, but not always



Mb, megabase; TMB, tumor mutational burden.

Goodman AM, et al. *Mol Cancer Ther*. 2017;16(11):2598-608.

Tumor Immune Infiltrate is Critical for ICI Activity

- Tumor neoantigens associated with increased T-cell activation and immune cell infiltration in an “inflamed” tumor microenvironment
  - Compartmentalization of immune cells in tumor center and at the invasive margins
  - Dense T-lymphocyte infiltrate – CD3+, CD8+, CD45RO+, Th1
  - Interferon-γ
- Involvement of other cell subsets (e.g., Treg cells, macrophages) may confer better or worse prognosis, depending on the context

Th1, T helper cells; Treg, regulatory T-cells.

Havel JJ, et al. *Nat Rev Cancer*. 2019;19(3):133-50.

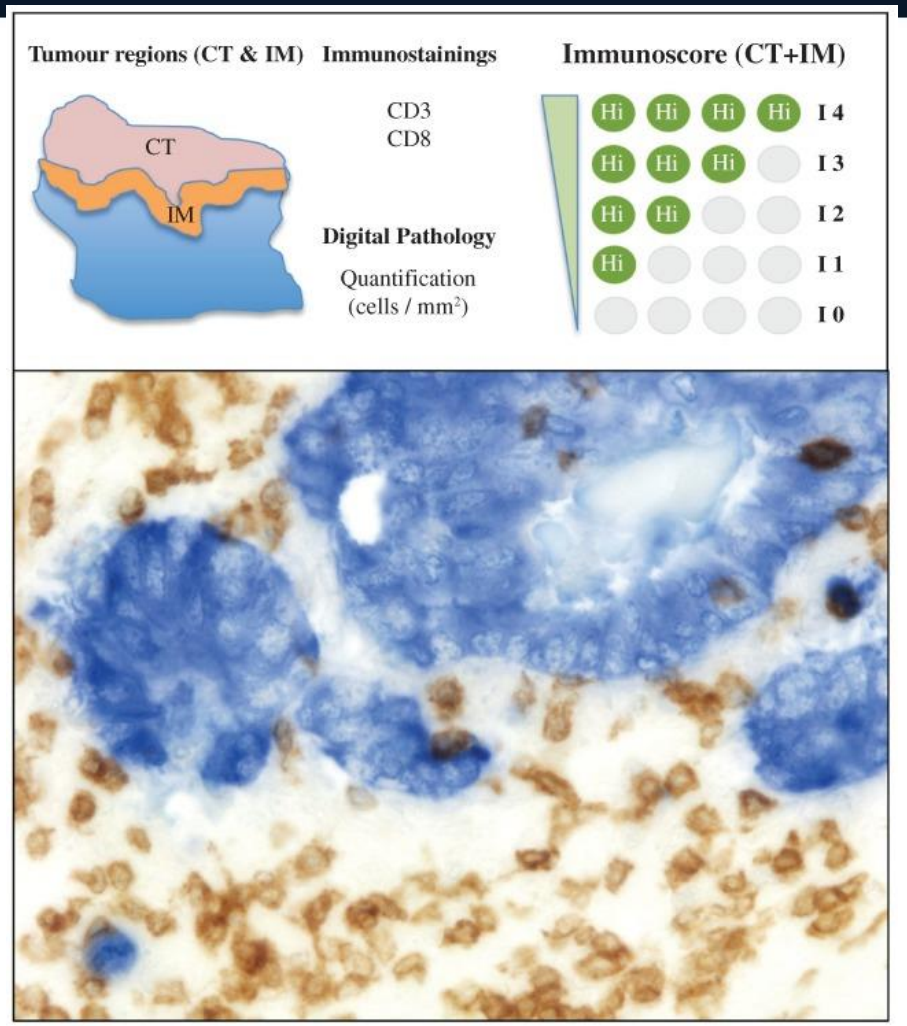
High Levels of PD-L1 Expression Are Associated with Better Outcomes With PD-1/PD-L1 Inhibition

- Reflects adaptive resistance to T-cell infiltration into tumors
- Identifies tumors most likely to respond to immune checkpoint inhibition
- Up to 20% of patients with tumors that stain negative or low for PD-L1 expression respond to ICIs
- Multiple factors influence PD-L1 expression:
  - Antibody
  - Test platform
  - Positivity threshold
  - Cells of interest
  - Tumor material

Havel JJ, et al. *Nat Rev Cancer*. 2019;19(3):133-50.

Immunoscore Defines Immune Infiltrate in Tumors

- Classification based on standardized quantification of CD3+ and CD8+ T-cell densities at tumor-specimen center and invasive margins
- Prognostic biomarker to estimate risk of recurrence in patients with stage I-III colon cancer
- Potential predictive biomarker



Galon J, et al. *J Pathol.* 2014;232(2):199-209.

Emerging Biomarkers

Gene Expression Profiles

- Signatures profiling inflammation-specific genes
  - Gamma interferon-inducible genes – define “hot”, inflamed tumors
- Immune gene signatures
  - T-cell, B-cell, natural killer (NK) cell involvement; T-cell surface markers
- Cytokines and chemokines

Peripheral Blood

- Myeloid-derived suppressor cells (MDSCs)
  - Recruited to tumor microenvironment
  - Suppress effector cell responses
  - Present in tumor tissue and blood
- Circulating tumor DNA (ctDNA)

Havel JJ, et al. *Nat Rev Cancer*. 2019;19(3):133-50.

Next Generation Sequencing

- PD-L1 protein expression is dynamic and is an imperfect predictor of tumor response to PD-L1 blockade
- Next generation whole exome and targeted gene panel sequencing can identify TMB and specific genetic mutations

Toxicity Evaluation of Combination Therapy with Overlapping Toxicities

PJ is a 60-year-old man with stage IV adenocarcinoma of the lung. His PS is 1 and he is in relatively good shape. Labs are normal or near normal. Pathology reports no actionable mutation and low PD-L1 (tumor proportion score [TPS] -8%).

He is prescribed chemotherapy plus an ICI:

Carboplatin, pemetrexed, and pembrolizumab

How would you manage a rash that develops after 6 weeks of therapy and has persisted for 1 week without treatment (grade 2)?

Evaluating Overlapping Toxicity

Table 2. Adverse Events of Any Cause in the As-Treated Population.*

Event	Pembrolizumab Combination (N=405)		Placebo Combination (N=202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Diarrhea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)
Pyrexia	79 (19.5)	1 (0.2)	30 (14.9)	0
Peripheral edema	78 (19.3)	1 (0.2)	26 (12.9)	0

Roughly 10% of rash is due to pembrolizumab and 10% is from pemetrexed

Gandhi, L. *N Engl J Med*. 2018;378(22):2078-92.

Handling Toxicity Per Protocol

- Reduction of 1 chemotherapy agent and not the other agent is appropriate if, **in the opinion** of the Investigator, the toxicity is clearly related to one of the treatments. If, **in the opinion of the Investigator**, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications.
- If the toxicity is related to the combination of 3 agents, **all 3 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications**. Subjects may have chemotherapy discontinued and continue on pembrolizumab/saline placebo alone. Similarly, subjects may discontinue pembrolizumab/saline placebo and continue on chemotherapy alone, if appropriate.

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	AUC 5 Maximum dose 750mg	AUC 3.75 Maximum dose 562.5mg	AUC 2.5 Maximum dose 375mg	Discontinue
Pemetrexed	500mg/m2	375 mg/m2	250 mg/m2	Discontinue
Pembrolizumab/placebo	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

ICI held: not dose-reduced

Gandhi, L. *N Engl J Med*. 2018;378(22):2078-92.

The Case of Rash

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

General Management of Adverse Events

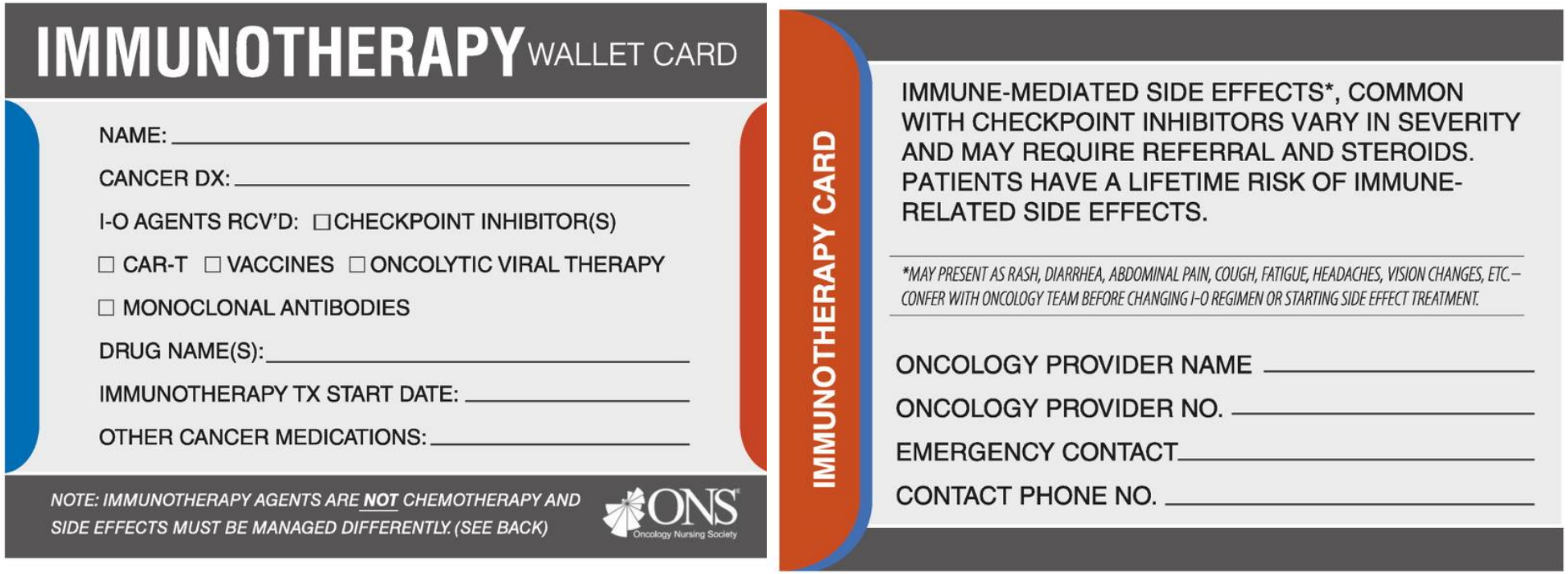
Grade 1	Grade 2	Grade 3	Grade 4
Contine ICI Monitor for symptoms every 2-3 days	Suspend ICI Consider restarting when grade I Corticosteroids may be started (Pred or MethylPred 0.5 mg/kg)	Suspend ICI Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks) Additional immune suppression for refractory patients	Discontinue therapy Hospitalize Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks) Additional immune suppression for refractory patients

See organ-specific recommendations

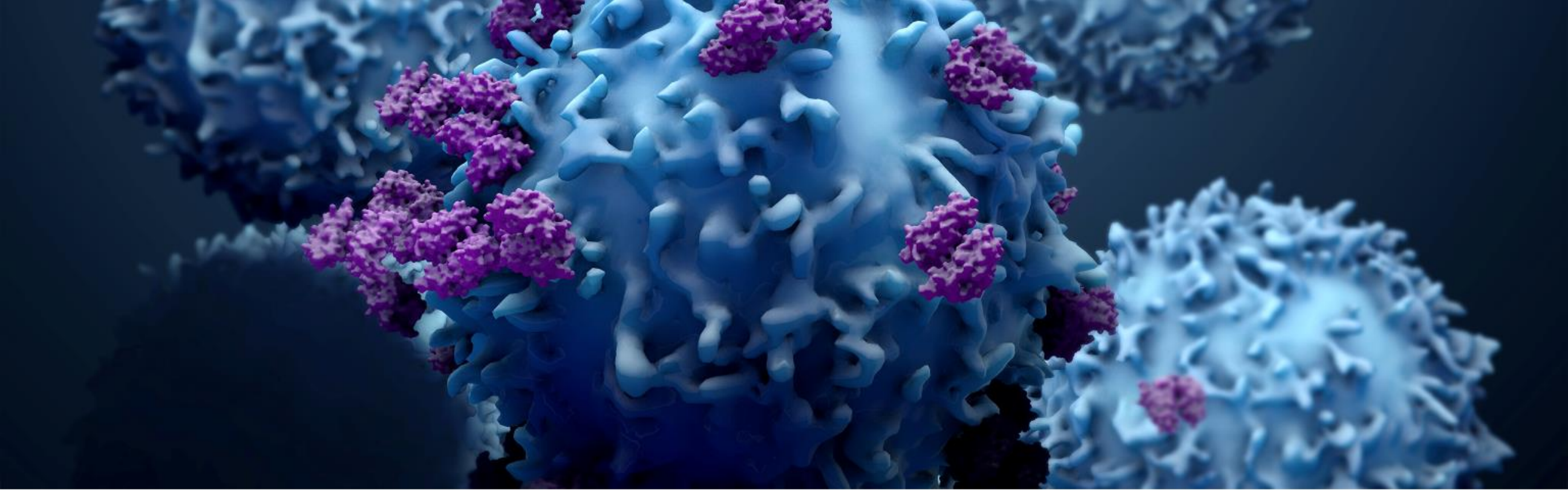
MethylPred, methylprednisolone; Pred, prednisolone.

Brahmer JR, et al. *J Clin Oncol*. 2018;36(17):1714-68.

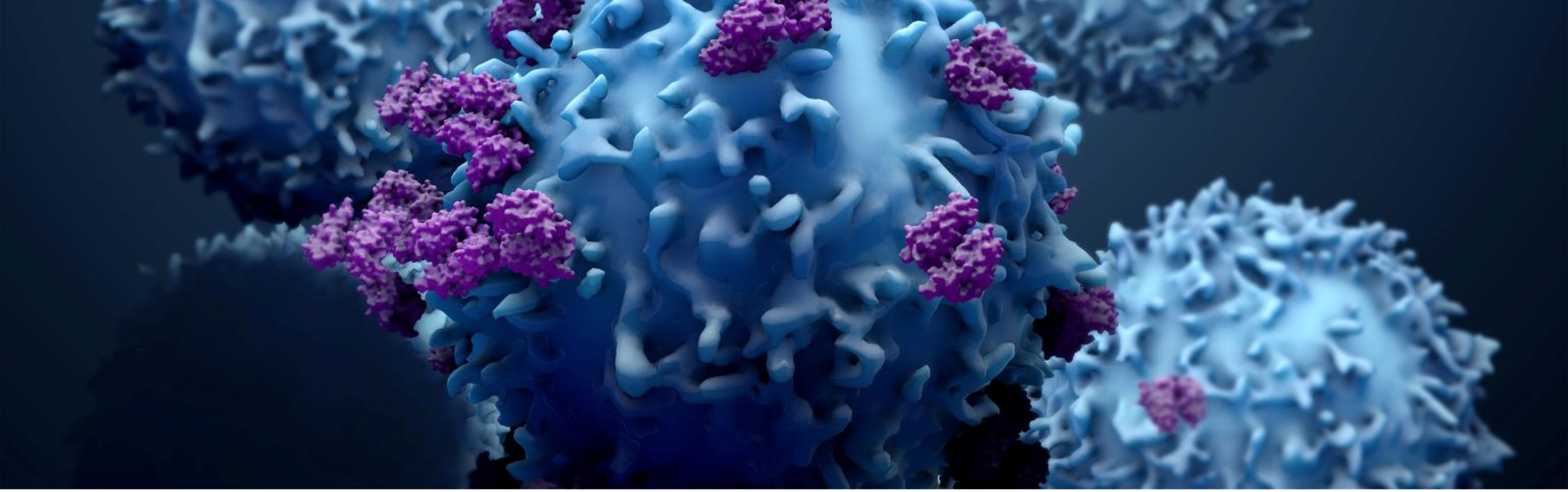
Communication Tool



American Society of Clinical Oncology. www.asco.org/supportive-care-guidelines. Accessed February 16, 2018.



Questions & Answers



Thank You!