Treating and Managing BRAF-Mutated Melanoma: Clinical Pearls for Oncology Pharmacists

An *Ask-the Experts* Forum

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Faculty

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Dr. Finnes is the Senior Manager, Pharmacy Cancer Center Research at the Mayo Clinic Cancer Center in Rochester, MN. She obtained her PharmD degree from Drake University in Des Moines, Iowa and is Board Certified in Oncology Pharmacy. Dr. Finnes is the Director of the Mayo Clinic Cancer Center Pharmacy Shared Resource, provides input on oncology clinical trials during protocol development, authors drug templates, and offers recommendations for therapy and supportive care via a Medication Therapy Management Clinic. She also manages patients with immunotherapy toxicities as part of an immune checkpoint inhibitor clinic. Dr. Finnes is the chair of the Alliance for Clinical Trials in Oncology Pharmacy Committee and President-Elect of the Hematology Oncology Pharmacy Association. Her research interests include melanoma, immune checkpoint inhibitors and effects of concurrent medications on cancer treatment.

Disclosures

Dr. Roman has no relevant affiliations or financial relationships with a commercial interest to disclose.

Dr. Finnes has no relevant affiliations or financial relationships with a commercial interest to disclose.

The clinical reviewer, Megan May, PharmD, BCOP has no relevant affiliations or financial relationships with a commercial interest to disclose.

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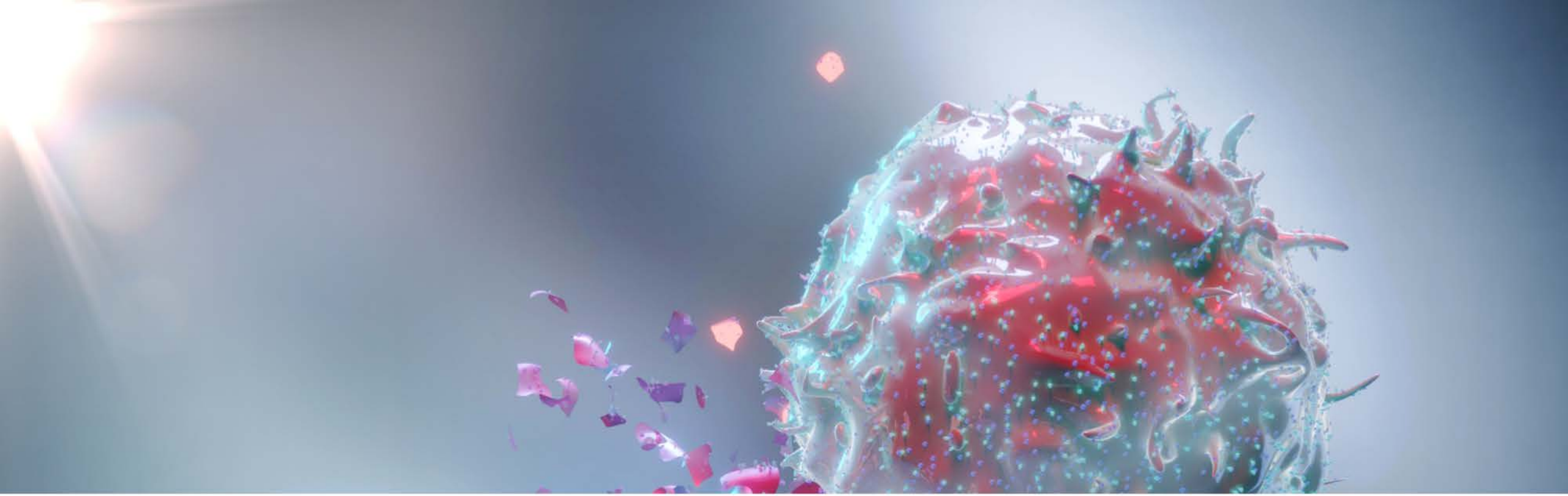
Credits: 1.25 hour (0.125 CEU)
Type of Activity: Application

Learning Objectives

- **Differentiate** available BRAF and MEK inhibitor agents for the treatment of BRAF-mutated melanoma
- **Discuss** aspects of BRAF, MEK inhibitor, and immune checkpoint inhibitor sequencing
- **Describe** appropriate treatment strategies for BRAF-mutated melanoma based on patient-specific factors and clinical efficacy data
- **Formulate** approaches to effectively manage unique adverse events when utilizing BRAF and MEK inhibitor agents in the treatment of BRAF-mutated melanoma

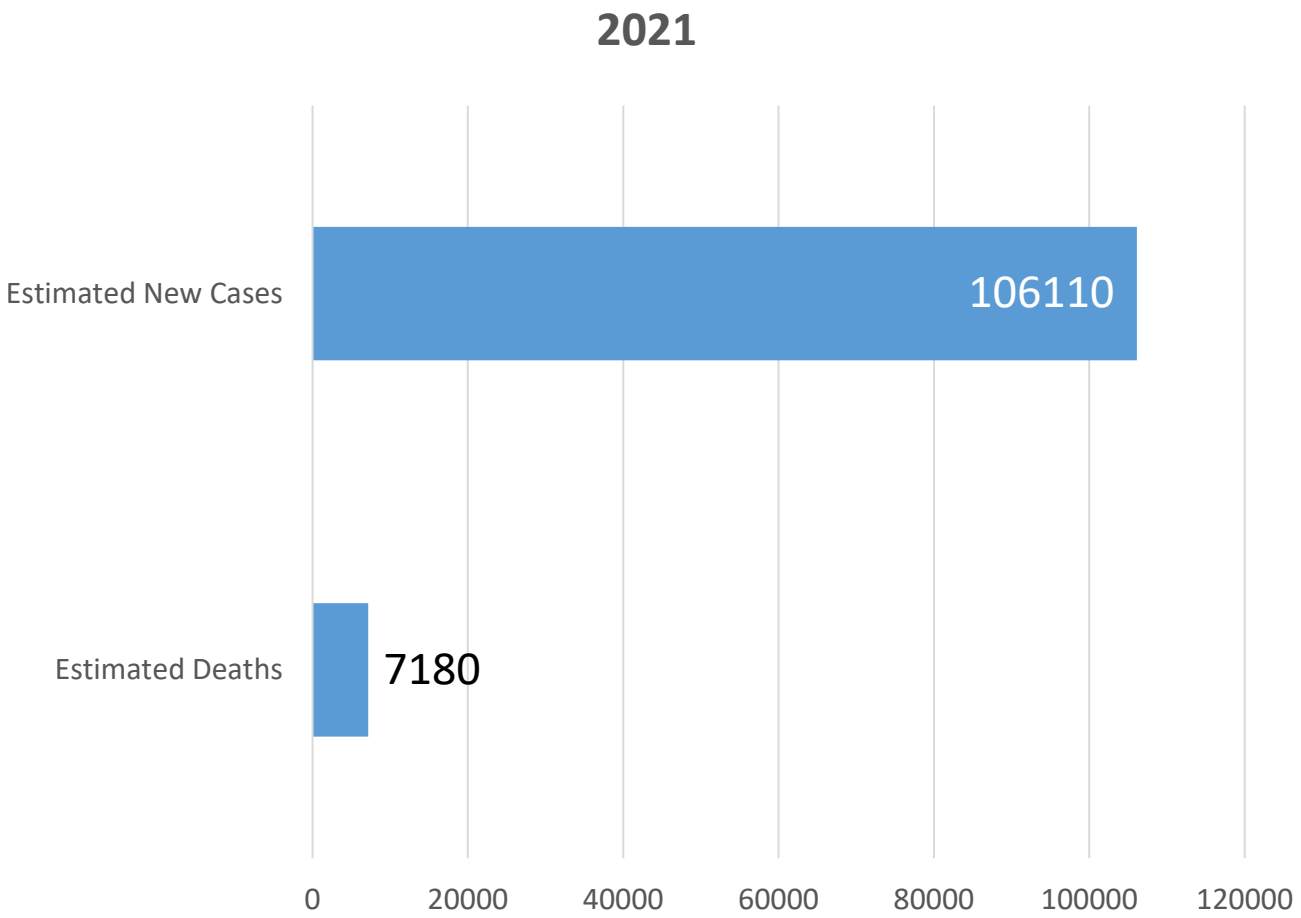
Frequently Asked Questions

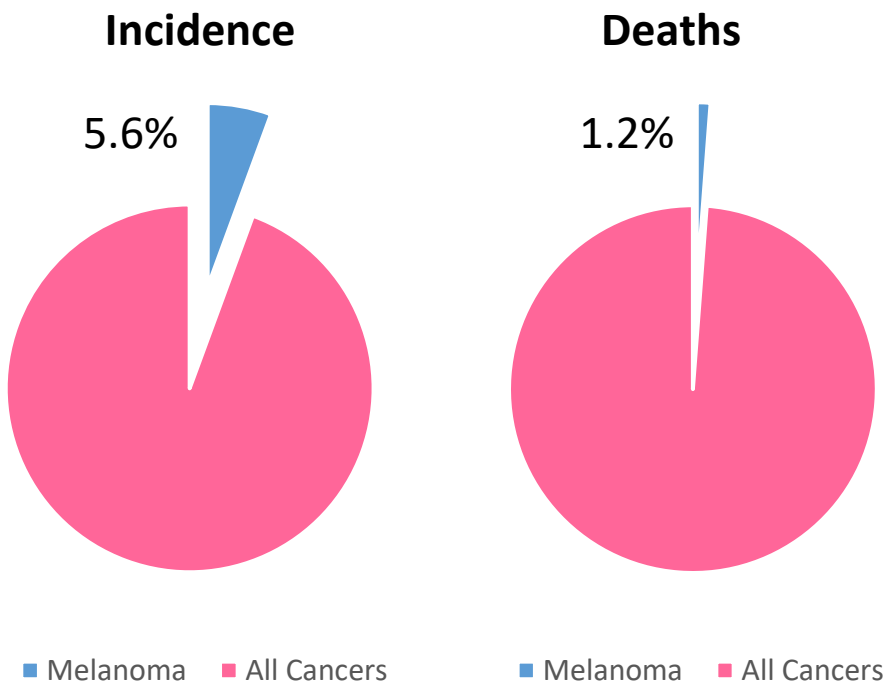
- Melanoma
  - BRAF-mutant Melanoma
- BRAF-MEK Inhibitor Treatment
- BRAF-MEK Inhibitor Toxicity and Management
- Pharmacist consideration



Melanoma

Statistics



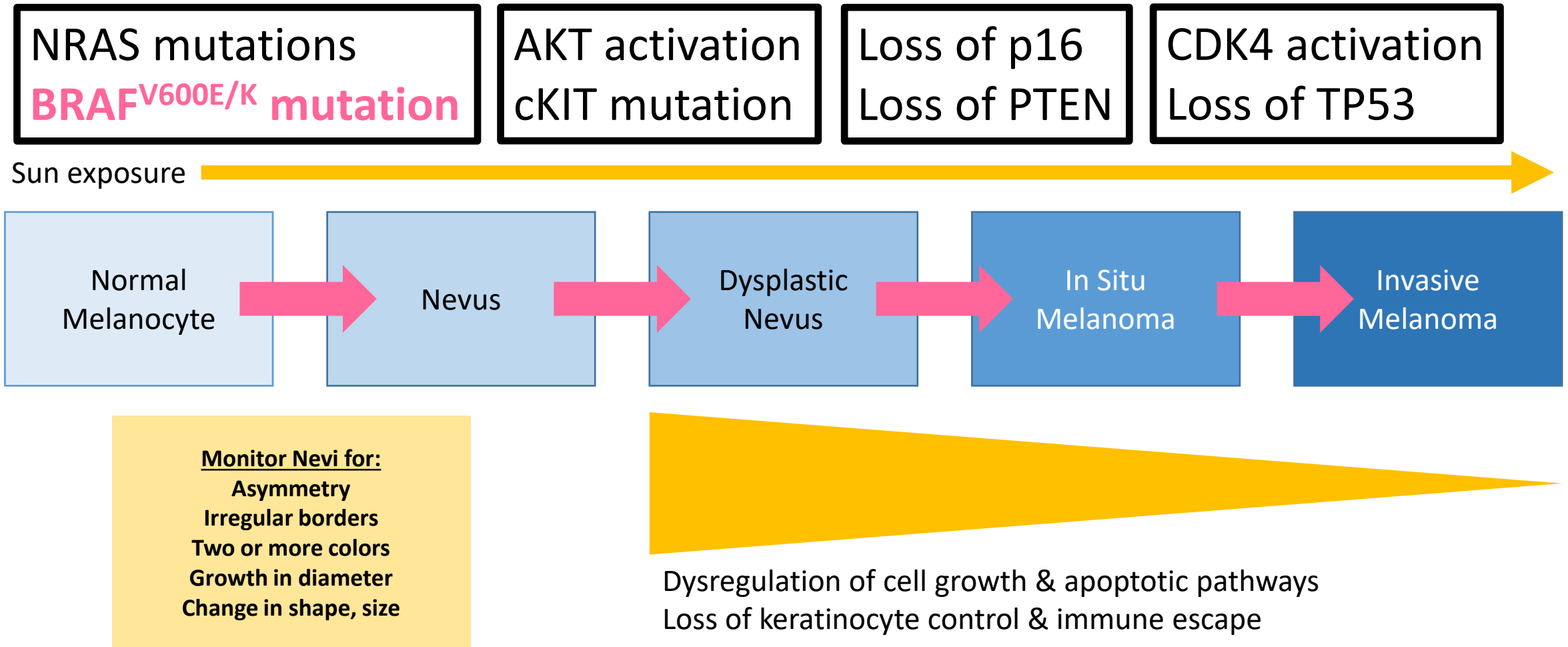


Cancer Stat Facts: Melanoma of the Skin. https://seer.cancer.gov/statfacts/html/melan.html Accessed 9/17/2021

Risk Factors

- Light skin
- Skin that burns, freckles, and/or reddens easily
- Blue/green eyes
- Blonde/red hair
- Large number of moles
- Exposure to ultraviolet rays
- Family or personal history of skin cancer
- Older age

Pathogenesis



Shain AH, Bastian BC. *Nature Reviews Cancer* 2016;16(6):345-358.

Staging Overview

Stage I

- Localized

Stage II

- Early, locally advanced

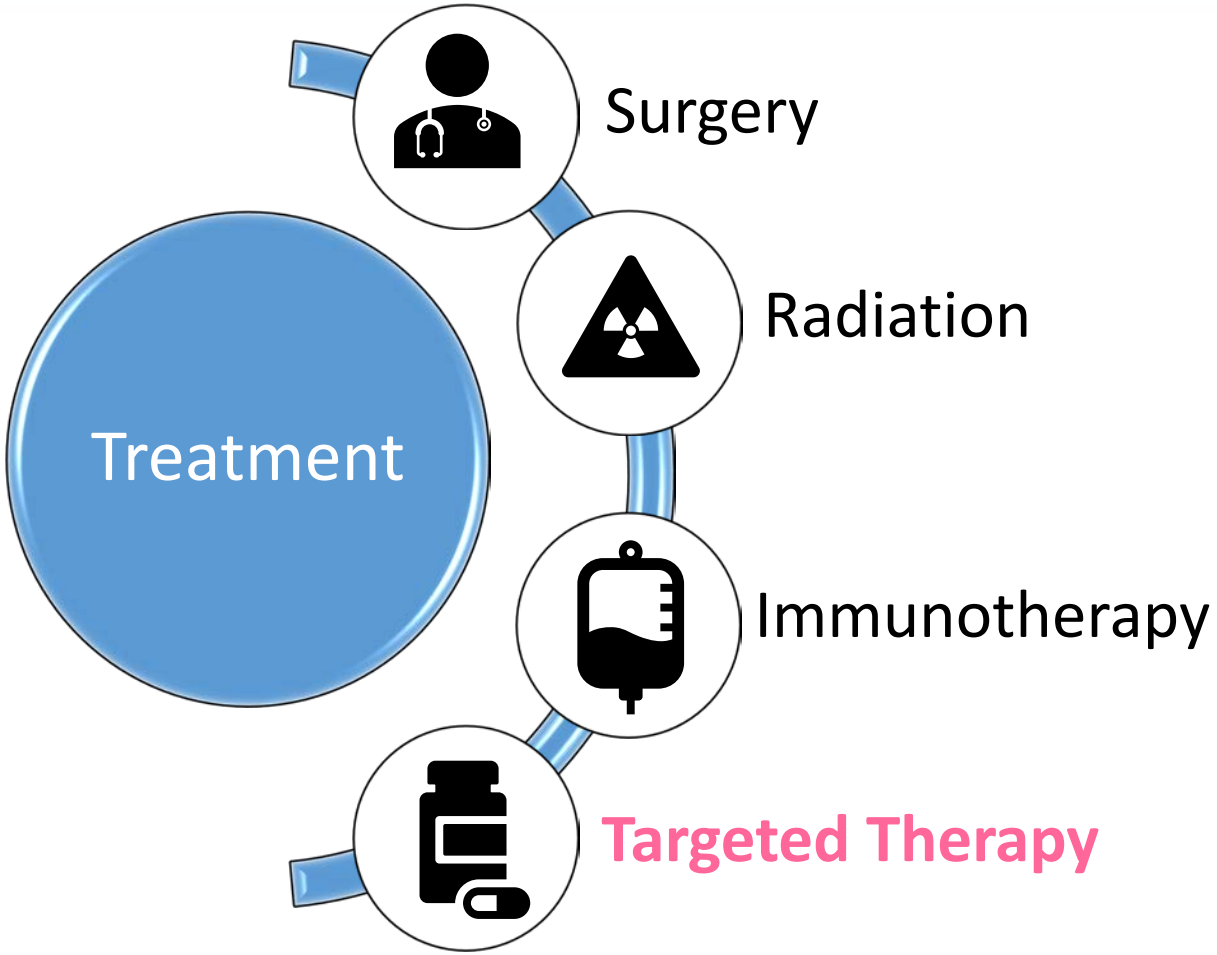
Stage III

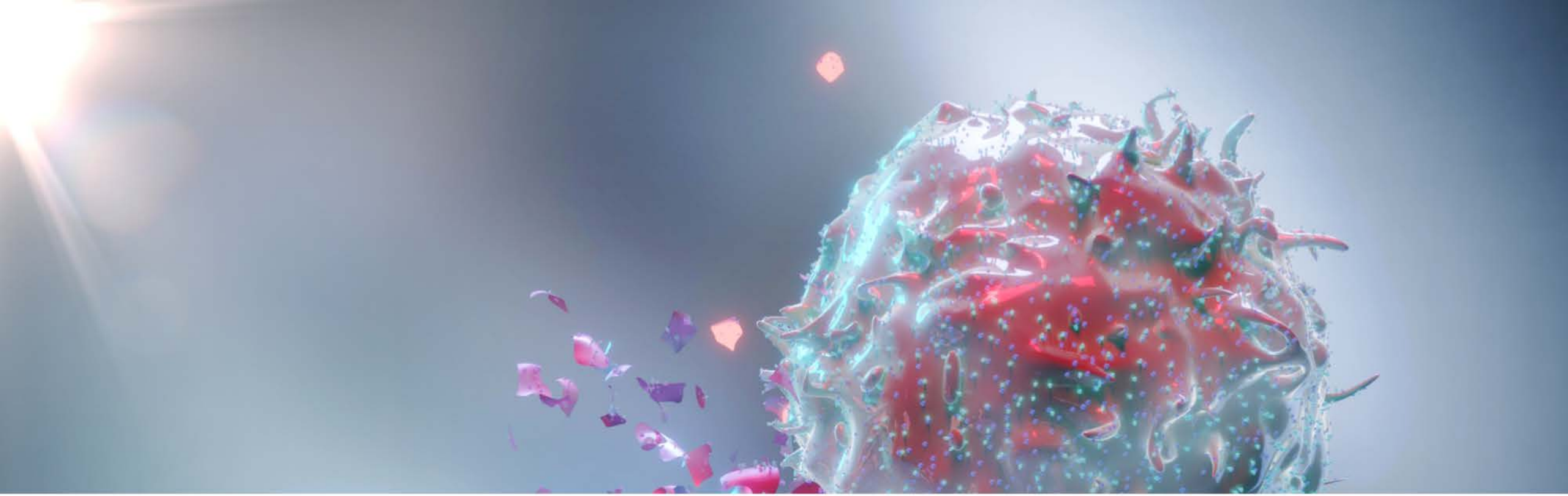
- Late, locally advanced

Stage IV

- Metastatic

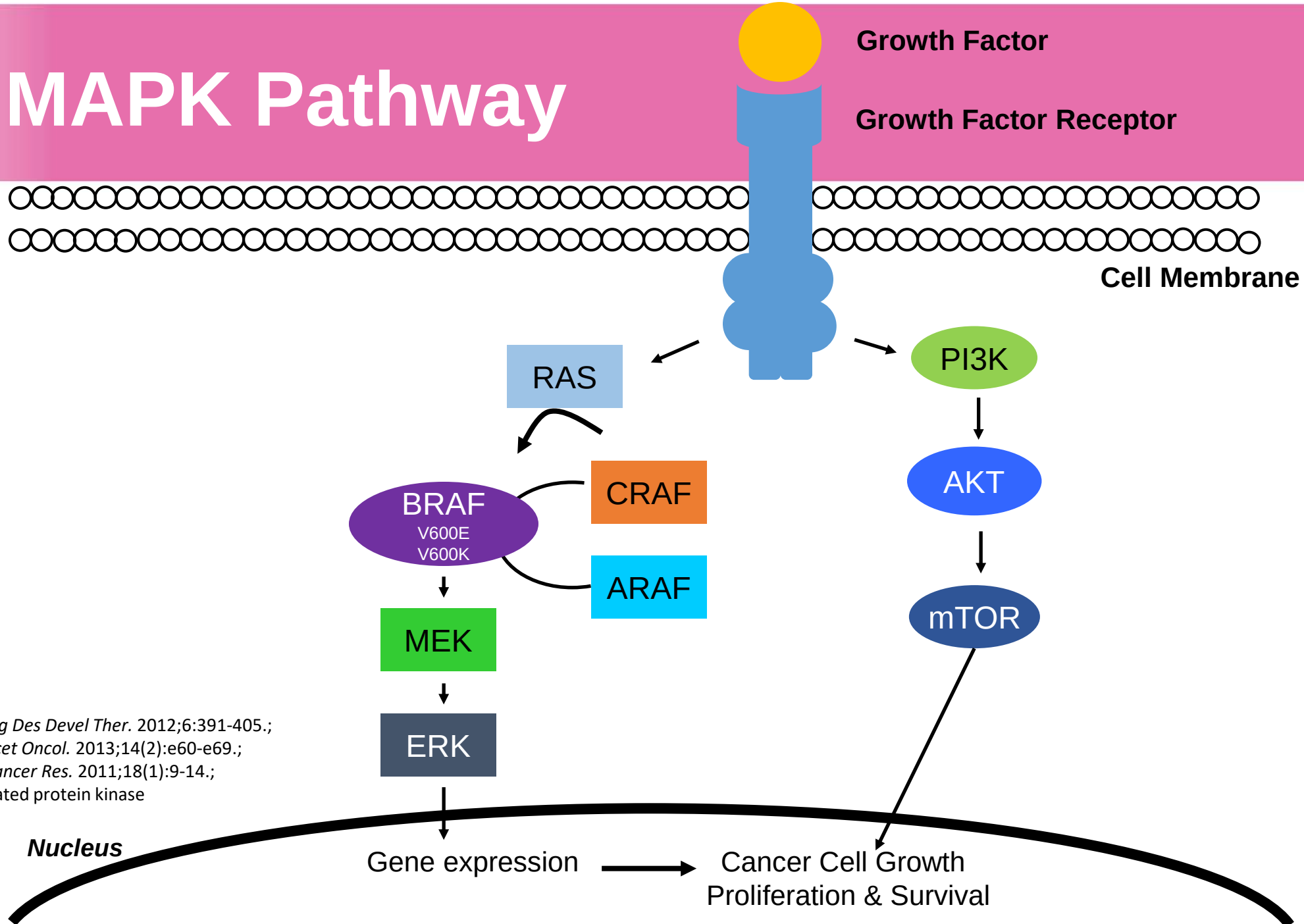
Treatment Overview





BRAF-Mutant Melanoma

MAPK Pathway



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Menzies AM, et al. *Drug Des Devel Ther.* 2012;6:391-405.;
Jang S, Atkins MB. *Lancet Oncol.* 2013;14(2):e60-e69.;
Luke JJ, Hodi FS. *Clin Cancer Res.* 2011;18(1):9-14.;
MAPK = mitogen-activated protein kinase

Mutations in BRAF

- Proto-oncogene
- Most common driver mutation in melanoma
- Present in ~50% of melanoma cases
  - $BRAF^{V600E}$ ~85%
  - $BRAFV^{600K}$ ~8%
- Younger patients
- May be associated with decreased survival

Patel H, et al. *Cancers (Basel).* 2020;12(2):482.;
Bhatia P, et al. *Ann Transl Med.* 2015;3(2):24.

BRAF Companion Diagnostics

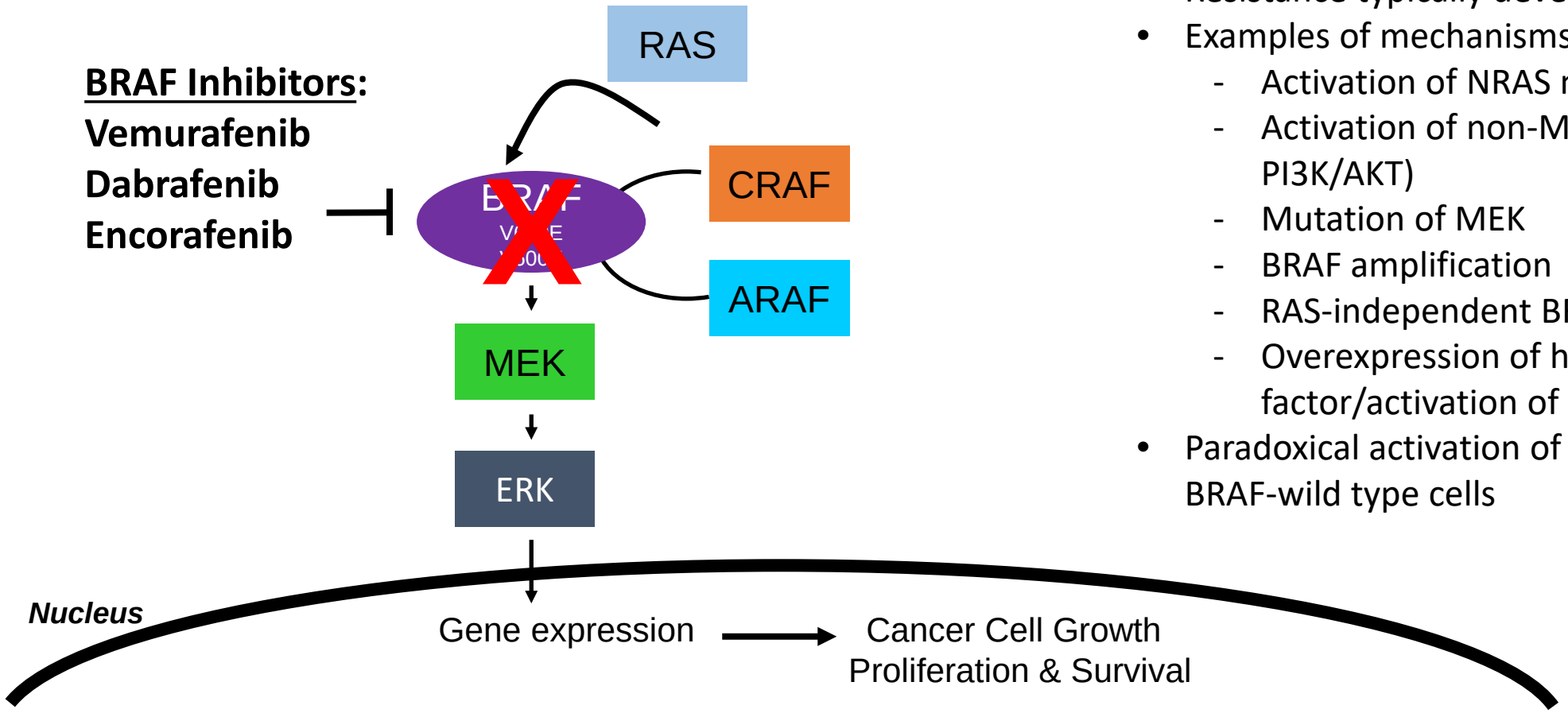
- Several methods to detect BRAF mutations
  - Sanger sequencing
  - Pyrosequencing
  - Next generation sequencing (NGS)
  - Immunohistochemistry (IHC)
  - Polymerase chain reaction (PCR)

FDA-Approved Diagnostics	Test Method	BRAF/MEK Inhibitors Included
FoundationOne CDx	NGS	Vemurafenib Dabrafenib Trametinib Vemurafenib + Cobimetinib
THXID BRAF Kit	PCR	Dabrafenib Trametinib Encorafenib + Binimetinib
Cobas 4800 BRAF V600 mutation test	PCR	Vemurafenib Vemurafenib + Cobimetinib

Vanni I, et al. *Front Mol Biosci.* 2020;7:113.; Cheng L, et al. *Mod Pathol.* 2018;31(1):24-38.
List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools).
https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. Accessed 9/27/2021

MAPK Pathway

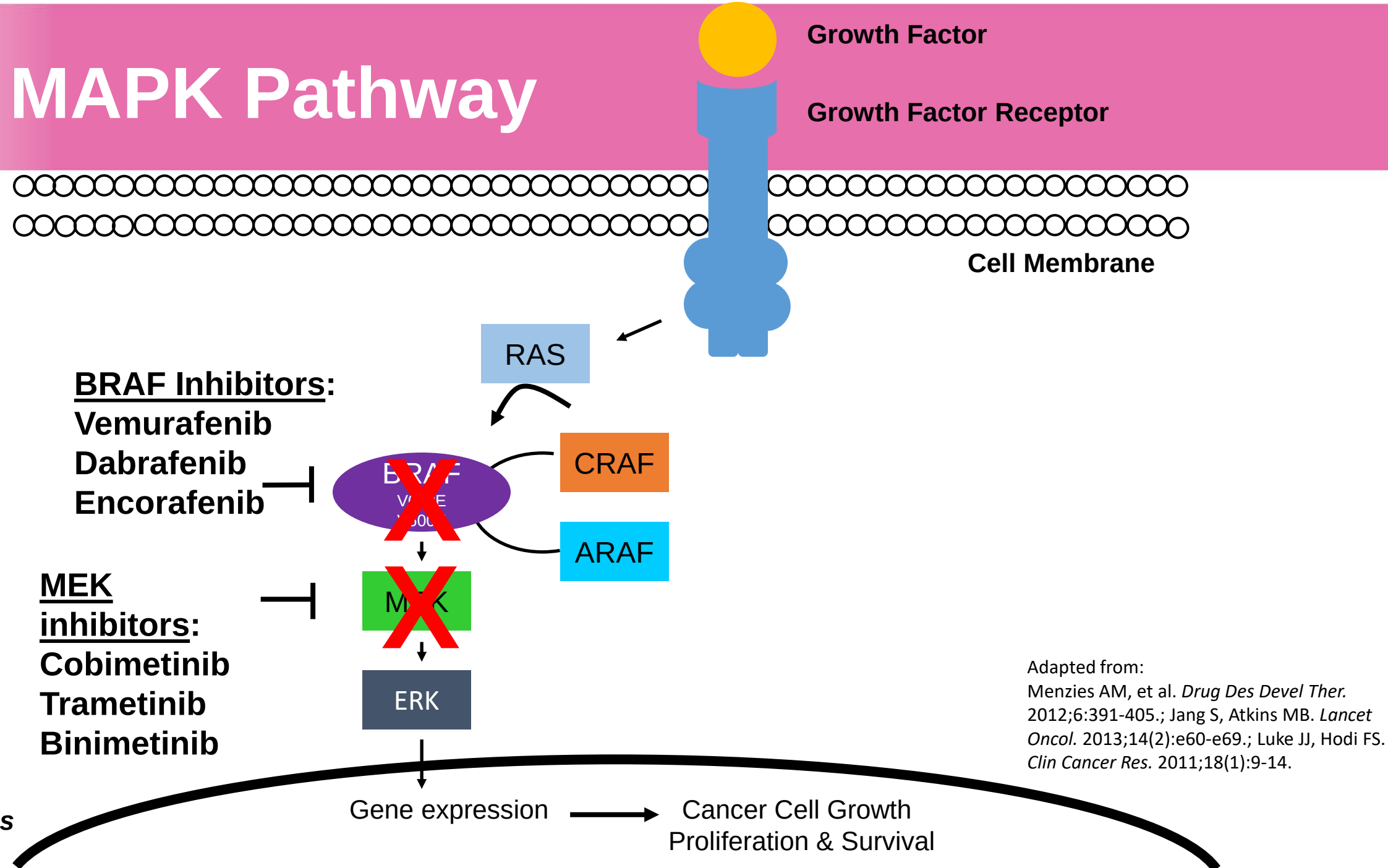
<u>BRAF Inhibitors</u>:
Vemurafenib
Dabrafenib
Encorafenib



- Resistance typically develops after 5-7 months
- Examples of mechanisms of resistance:
  - Activation of NRAS mutations
  - Activation of non-MAPK growth pathways (e.g., PI3K/AKT)
  - Mutation of MEK
  - BRAF amplification
  - RAS-independent BRAF isoform splice variants
  - Overexpression of hepatocyte growth factor/activation of MET
- Paradoxical activation of the MAPK pathway in BRAF-wild type cells

Broman KK, et al. *Expert Opin Drug Saf.* 2019;18(5):381-392.

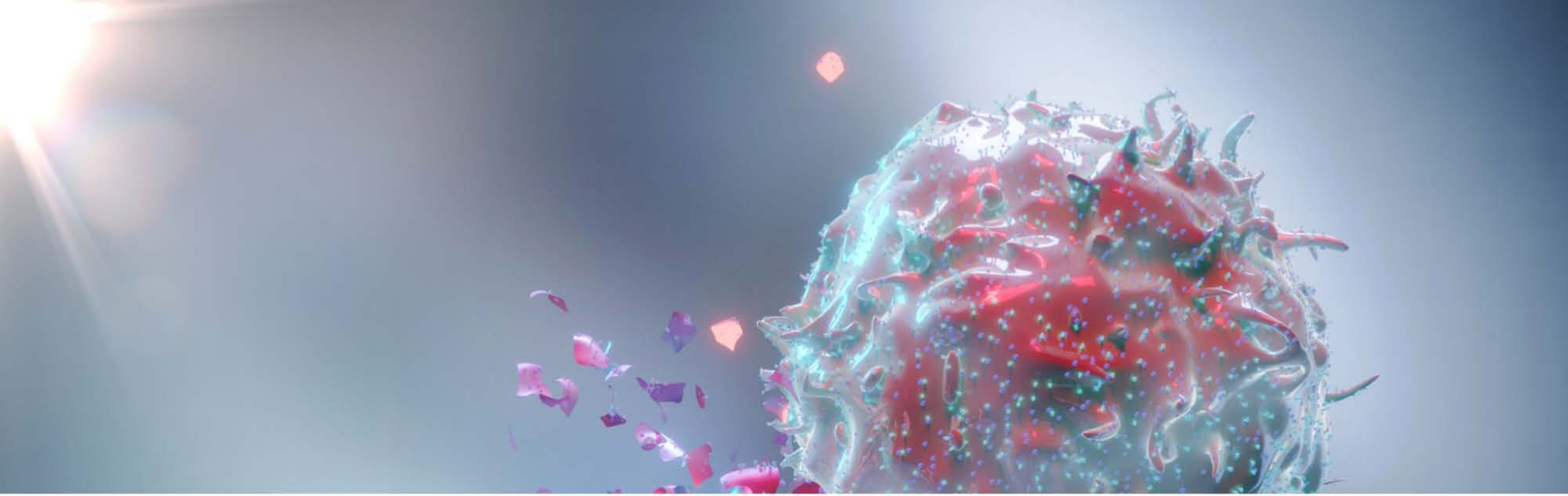
MAPK Pathway



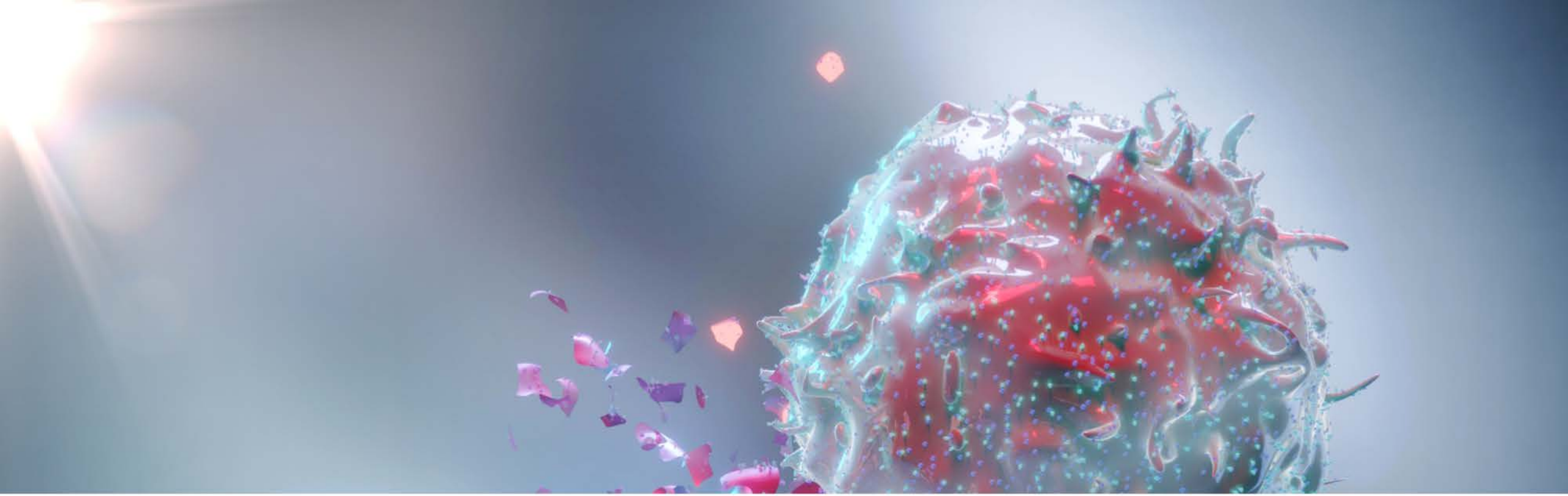
BRAF Inhibitors:
Vemurafenib
Dabrafenib
Encorafenib

MEK inhibitors:
Cobimetinib
Trametinib
Binimetinib

Adapted from:
Menzies AM, et al. *Drug Des Devel Ther.* 2012;6:391-405.; Jang S, Atkins MB. *Lancet Oncol.* 2013;14(2):e60-e69.; Luke JJ, Hodi FS. *Clin Cancer Res.* 2011;18(1):9-14.



Melanoma
Question & Answer



BRAF-MEK Inhibitor Treatment in Melanoma

Adjuvant Treatment of BRAF V600-Mutated Melanoma: Overview

Stage I and II: Observation

Stage III (sentinel lymph node positive or clinically positive nodes):

Dabrafenib + Trametinib x 1 year

PD-1 inhibitor x 1 year:
- Nivolumab
- Pembrolizumab

Observation

PD-1 = programmed cell death protein 1

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

Adjuvant BRAF + MEK Inhibitor

COMBI-AD: Phase III, double-blind, randomized controlled trial

- N = 870 patients with stage IIIA (> 1 mm metastasis diameter), IIIB – C
- Patients had BRAF V600E/K mutations
- Dabrafenib 150 mg PO BID + trametinib 2 mg PO daily vs. 2 matched placebos

Primary objective

- Relapse-free survival (RFS)

Results

- RFS: 52% for dabrafenib + trametinib vs. 36% with placebo (HR 0.51; 95% CI, 0.42 – 0.61)
- Distant metastasis-free survival at 5 years: 65% vs. 54% (HR 0.55; 95% CI, 0.44 – 0.70)

BID = twice daily; PO = by mouth

Dummer R, et al. *N Eng J Med.* 2020;383(12):1139-1148.

Adjuvant BRAF Inhibitor Monotherapy

BRIM8: Phase III, double-blind, randomized controlled trial

- N = 498 patients with stage IIC, IIIA, IIIB (cohort 1; n = 314) or stage IIIC (cohort 2; n = 93)
- Patients had BRAF V600E/K mutation that was fully resected
- Vemurafenib 960 mg PO BID vs. placebo

Primary objective

- Disease-free survival (DFS) in the intent-to-treat population

Results

- Cohort 2: DFS 23.1 months for vemurafenib vs. 15.4 months for placebo (HR 0.8, 95% CI, 0.54 – 1.18; p = 0.026)
- Cohort 1: DFS not reached in vemurafenib group vs. 36.9 months in placebo group (HR 0.54, 95% CI 0.37 – 0.78; p = 0.0010)
- DFS results not statistically significant (analysis of cohort 1 considered exploratory only due to statistical design)
- Grade 3 – 4 adverse events: 57% in vemurafenib group vs. 15% in placebo group

Maio M, et al. *Lancet Oncol.* 2018;19(4):510-520.

Bottom Line: Adjuvant Treatment with BRAF and MEK Inhibitors

- Dabrafenib + trametinib x 1 year is an option for adjuvant treatment of stage III melanoma based on COMBI-AD
- Other BRAF + MEK inhibitors have not been adequately studied in the adjuvant setting
  - Consider other combinations for patients with unacceptable toxicity to dabrafenib + trametinib
- Vemurafenib monotherapy is not recommended as adjuvant treatment
- Immunotherapy (nivolumab or pembrolizumab) is also an acceptable adjuvant treatment option
  - No direct trial comparison between immunotherapy and BRAF + MEK inhibitors

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

Options for the 1st Line Treatment of BRAF V600-Mutated Metastatic Melanoma

PD-1 inhibitor monotherapy*
- Nivolumab
- Pembrolizumab

BRAF + MEK inhibitor*
- Dabrafenib + trametinib
- Vemurafenib + cobimetinib
- Encorafenib + binimetinib

Nivolumab + ipilimumab*

Pembrolizumab + low-dose ipilimumab

Targeted therapy + immunotherapy
- Vemurafenib + cobimetinib + atezolizumab
- Dabrafenib + trametinib + pembrolizumab

* Preferred by NCCN Guidelines

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

COMBI-d and COMBI-v

Dabrafenib + Trametinib for BRAF-Mutated Metastatic Melanoma

	COMBI-d	COMBI-v
Trial Design	Phase III, double-blind, randomized	Phase III, open-label, randomized
N	423	704
Treatment Arms	Dabrafenib + Trametinib vs. Dabrafenib + Placebo	Dabrafenib + Trametinib vs. Vemurafenib
Median PFS (months)	9.3 vs. 8.8 in favor of combination therapy (HR 0.75; p=0.035)	11.4 vs. 7.4 in favor of combination therapy (HR 0.56; P<0.001)
ORR	67% vs. 51% (p=0.0015)	64% vs. 51% in favor of combination therapy (P<0.001)
Pooled 5-year Analysis	PFS: 21% at 4 years and 19% at 5 years OS: 37% at 4 years and 34% at 5 years	

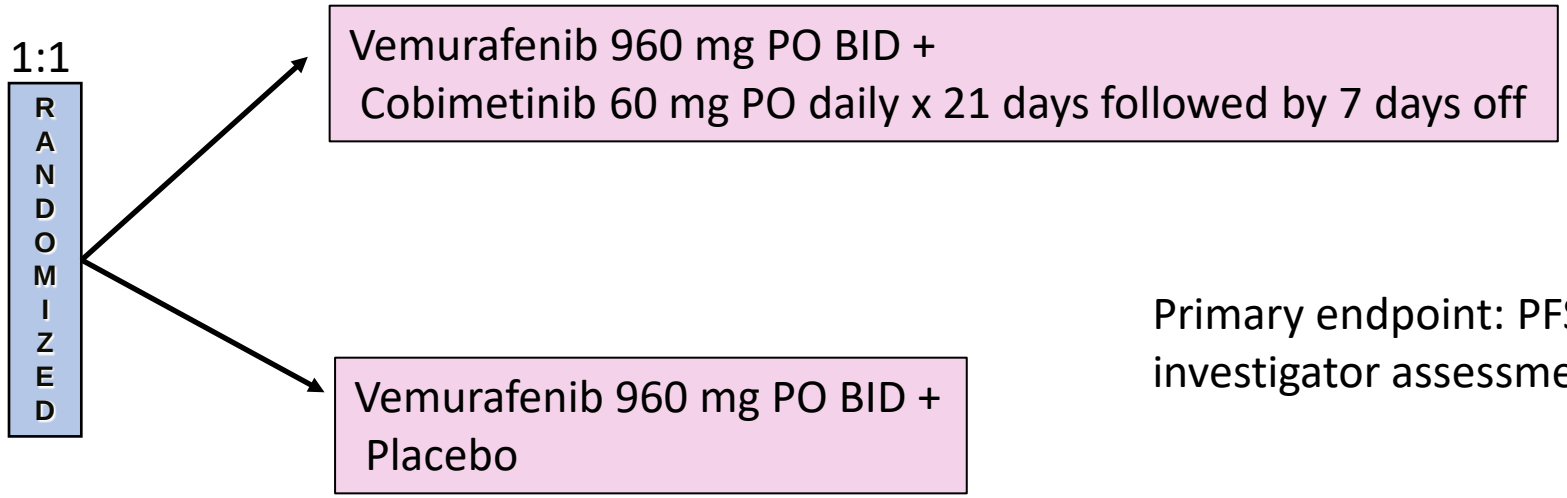
ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.;
Long GV, et al. *Ann Oncol.* 2017;28(7):1631-1639.

CoBRIM

Vemurafenib + Cobimetinib for BRAF-Mutated Metastatic Melanoma

Phase III RCT
N= 495
Previously untreated
Unresectable locally advanced (stage IIIC) or metastatic BRAF V600E/K mutated cutaneous melanoma



Primary endpoint: PFS by investigator assessment

- Median PFS significantly prolonged in the combination group (12.3 months vs. 7.2 months, HR 0.58, 95% CI 0.46 – 0.72; P<0.0001)
- Median OS significantly prolonged in the combination group (22.3 months vs. 17.4 months, HR 0.70, 95% CI 0.55 – 0.90; P=0.005)

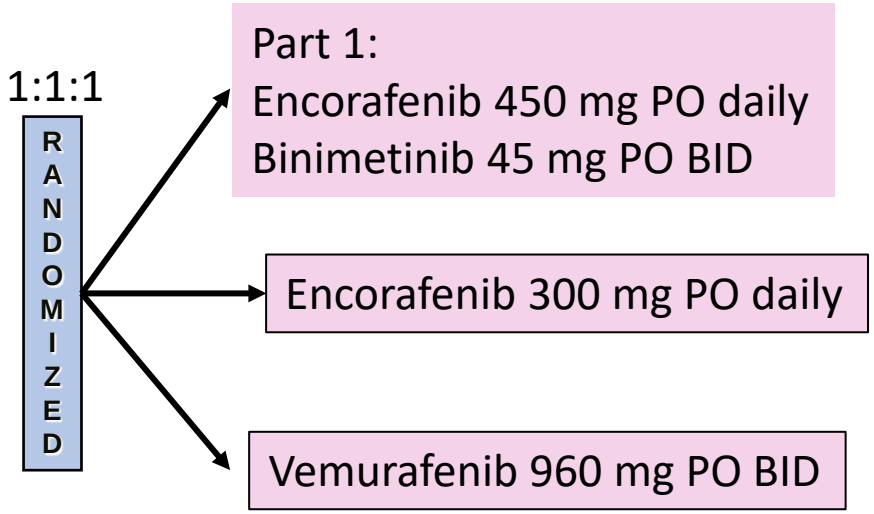
RCT = randomized controlled trial

Larkin J, et al. *N Engl J Med.* 2014;371(20):1867-1876.
Ascierto PA, et al. *Lancet Oncol.* 2016;17(9):1248-1260.

COLUMBUS
Encorafenib + Binimetinib for BRAF-Mutated Metastatic Melanoma

Phase III, open-label, randomized, two-part trial
N= 577

- Locally advanced (stage IIIB, IIIC), unresectable, or metastatic melanoma
- BRAF V600E/K mutated
- Treatment naïve or progressed on or after 1st line immunotherapy



Part 2:
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO BID

Primary endpoint: PFS by blinded independent review for combination vs. vemurafenib

	Median PFS (months)	Median OS (months)
Encorafenib + Binimetinib	14.9	33.6
Encorafenib	9.6	-
Vemurafenib	7.3	16.9

PFS comparisons:
Combination vs. vemurafenib: HR 0.54 (95% CI 0.41 – 0.71, two sided p<0.001)
Combination vs. encorafenib: HR 0.75 (95% CI 0.56 – 1.00, two sided p=0.051)

Dummer R, et al. *Lancet Oncol.* 2018;19(5):603-615.

Bottom Line: Metastatic Treatment with BRAF + MEK Inhibitors

- All 3 combination regimens are considered equally efficacious
- PFS and OS are improved with combination BRAF + MEK inhibitors compared to BRAF monotherapy
- Combination BRAF + MEK inhibitors preferred
  - Consider BRAF inhibitor monotherapy in patients with contraindications to MEK inhibitors
- Immunotherapy (monotherapy or combination) is also an acceptable treatment option

Options for the 1st Line Treatment of BRAF V600-Mutated Metastatic Melanoma

PD-1 inhibitor monotherapy*
- Nivolumab
- Pembrolizumab

BRAF + MEK inhibitor*
- Dabrafenib + trametinib
- Vemurafenib + cobimetinib
- Encorafenib + binimetinib

Nivolumab + ipilimumab*

Pembrolizumab + low-dose ipilimumab

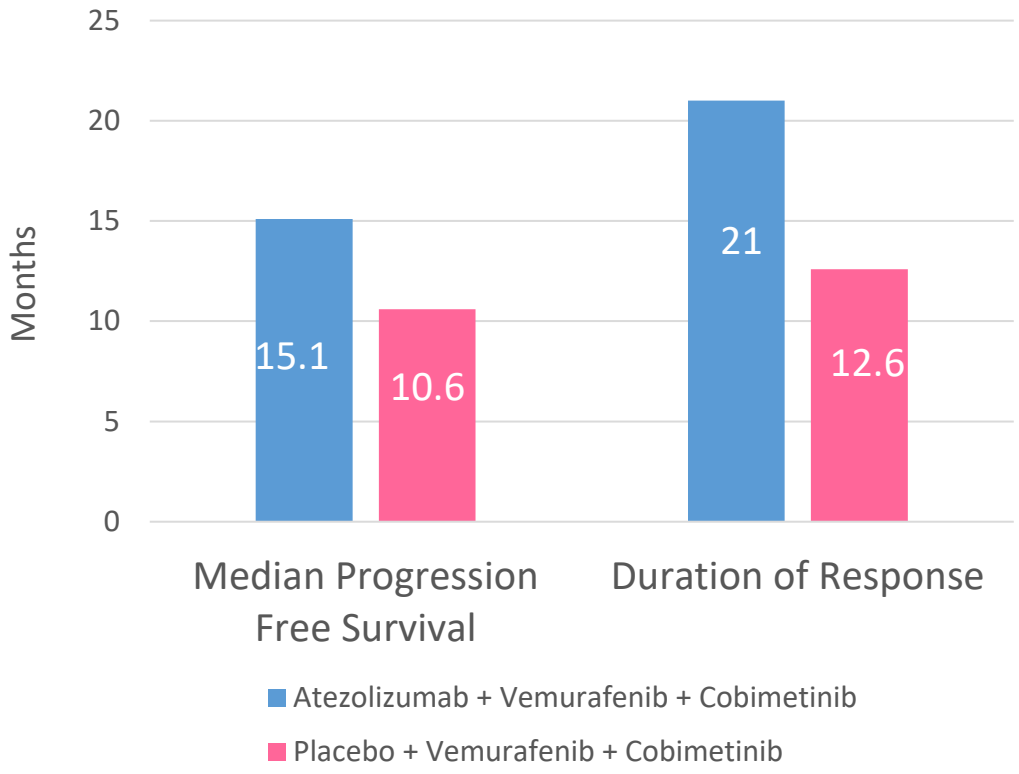
Targeted therapy + immunotherapy
- Vemurafenib + cobimetinib + atezolizumab
- Dabrafenib + trametinib + pembrolizumab

* Preferred by NCCN Guidelines

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

IMspire150
Atezolizumab + Vemurafenib + Cobimetinib

- Phase III double-blind, randomized, placebo-controlled trial
- Randomized to vemurafenib + cobimetinib + atezolizumab (n=256) or placebo (n=258)
- Primary endpoint: investigator-assessed PFS
- Guidelines include this triplet combination as a 1st-line recommended regimen for BRAF V600-mutated metastatic or unresectable melanoma
- Not preferred over the double combinations as mature overall survival data has not yet been reported



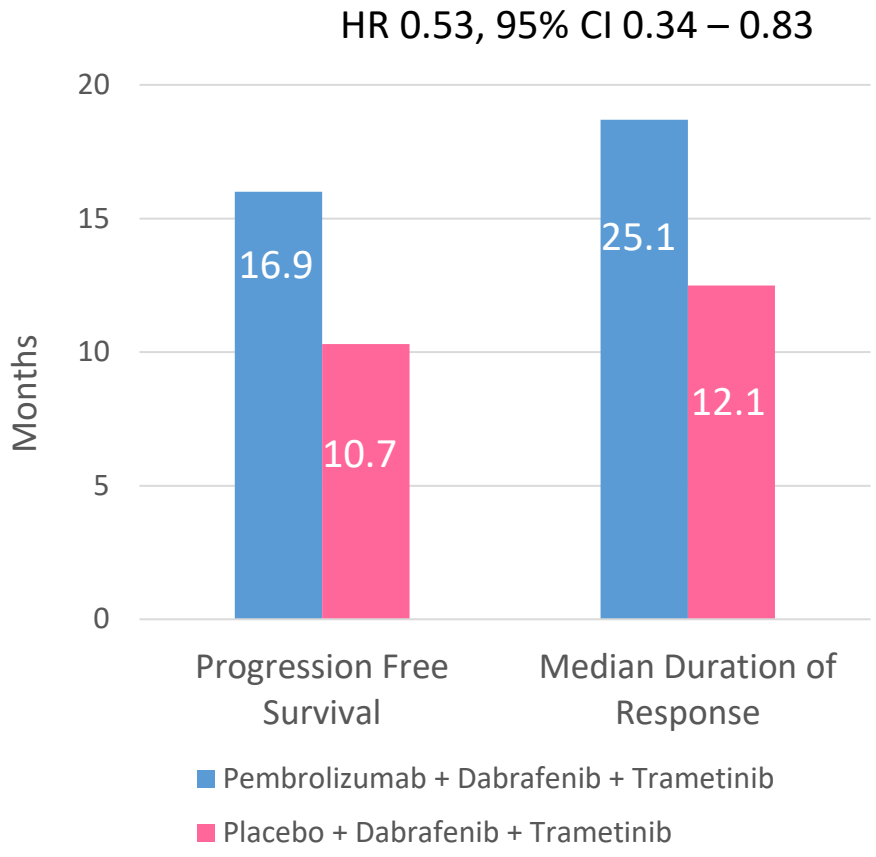
PFS HR 0.78 95% CI 0.63 – 0.97; p=0.025

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21;

Gutzmer R, et al. *Lancet.* 2020;395(10240):1835-1844.

KEYNOTE-022 Part 3
Pembrolizumab + Dabrafenib + Trametinib

- Phase II double-blind trial
- Randomized to dabrafenib + trametinib + pembrolizumab (n=60) or placebo (n=60)
- Primary endpoint: PFS
- Grade 3-5 toxicity was 58% (triplet) vs. 25% (doublet)
- Guidelines include this triplet combination as another 1st-line recommended regimen for BRAF V600-mutated metastatic or unresectable melanoma with a **lower category of evidence (2B)**



Ferrucci PF, et al. *J Immunother Cancer.* 2020;8(2):e001806.

Bottom Line: Metastatic Treatment with Triple Therapy (Immunotherapy + BRAF + MEK Inhibitors)

- Option for 1st line treatment of BRAF V600-mutated metastatic melanoma
  - Not considered a preferred option at this time
- Improved PFS and duration of response compared to BRAF + MEK inhibitor
  - Has not been compared to immunotherapy alone
- Increased risk of toxicity with triple therapy

Principles of Treatment Sequencing

- BRAF + MEK inhibition may be preferred for patients who require a rapid treatment response
- PD-1 / PD-L1 / CTLA-4 have a prolonged duration of response
- Ongoing trials are comparing 1st line BRAF + MEK inhibitors to immune therapy

PD-L1 = programmed cell death-ligand 1

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

Treatment After Progression for Patients with BRAF V600 Mutation

Options following progression on immune therapy:

- BRAF + MEK inhibitor combination
- Combination immune therapy
  - Anti-PD-1 + ipilimumab (preferred)
  - T-VEC + ipilimumab (for low burden of disease and injectable lesions)
- Ipilimumab
  - Consider if progression on single-agent anti-PD-1 therapy
- Clinical trial

Options following progression on BRAF + MEK Inhibitors:

- Combination immune therapy
  - Anti-PD-1 + ipilimumab
  - T-VEC + ipilimumab (for low burden of disease and injectable lesions)
- Single-agent anti-PD-1
- Consider rechallenge with BRAF + MEK inhibitors for patients who previously demonstrated clinical benefit
- Clinical trial

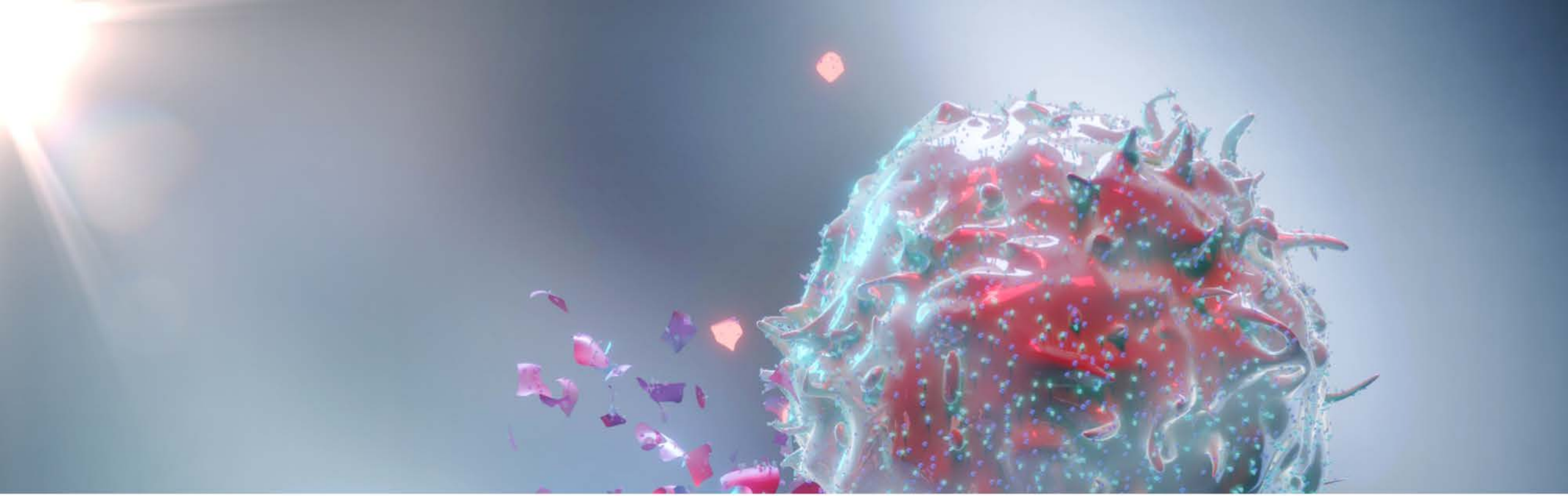
NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

T-VEC = talimogene laherparepvec

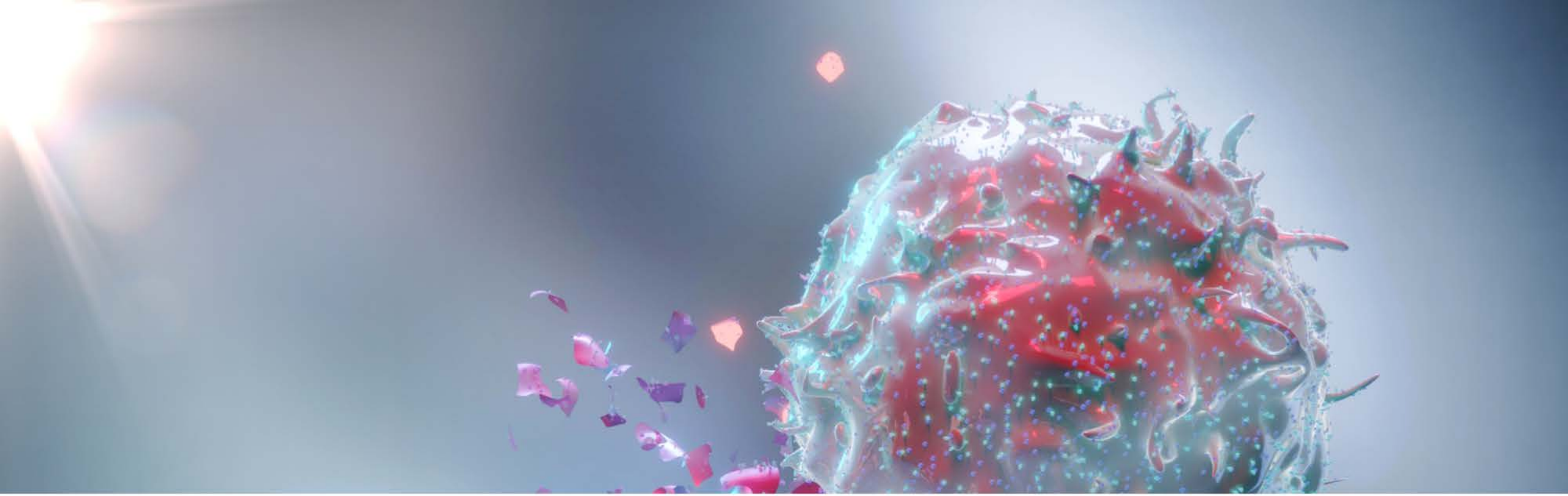
Treatment of Patients with Brain Metastases

- Most patients with brain metastases need systemic therapy and local brain-directed therapy (i.e., surgery or radiation)
- Local management generally required for patients with high burden of intracranial disease
- Initial course of systemic therapy may be preferred:
  - Lower volume, asymptomatic brain metastases
  - Extensive extracranial disease
- BRAF + MEK inhibitors have high intracranial response rate but PFS shorter for intracranial than extracranial disease
- Combination anti-PD-1 + ipilimumab is preferred for asymptomatic brain metastasis not requiring corticosteroids

NCCN Guidelines. Cutaneous Melanoma v. 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 09/29/21

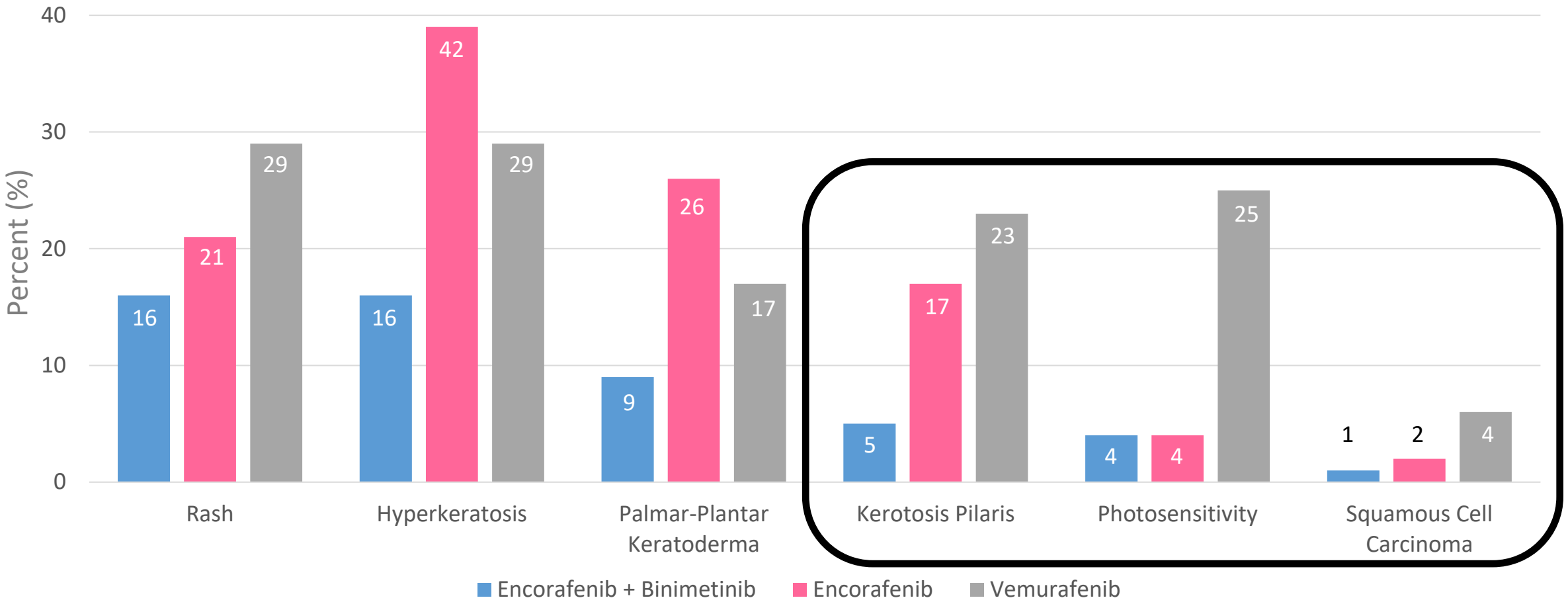


BRAF-MEK Inhibitor Treatment Question & Answer



BRAF-MEK Inhibitor Toxicity and Management

Higher Incidence Dermatologic Toxicities with BRAF Inhibitors Versus Combination



Drummer R, et al. *Lancet Oncol.* 2018;19(10):1315-1327.

Toxicity of BRAF-MEK Combinations

Toxicity	Vemurafenib + Cobimetinib N = 254		Dabrafenib + Trametinib N = 350		Encorafenib + Binimetinib N = 192	
	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4
Any toxicity, %	95	62	98	48	NR	64
Diarrhea, %	56	6	32	1	38	3
Nausea, %	40	1	35	1	44	2
Fatigue, %	32	4	34	1	29	2
Rash, %	21	1	22	1	16	2
Hyperkeratosis, %	10	0	4	0	16	1
Photosensitivity, %	28	2	4	0	3	1
Pyrexia, %	26	2	53	4	20	4
Arthralgia, %	32	2	24	1	28	1
SCC, %	3	2	1	1	1	0
Chorioretinopathy, %	13	1	1	0	16	0
↓ EF, %	8	1	8	4	7	2
QT prolongation, %	4	1	0	0	1	0

Larkin J, et al. *N Engl J Med.* 2014;371(20):1867-1876.; Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.; Robert C, et al. *N Engl J Med.* 2019;381(7):626-636.; Drummer R, et al. *Lancet Oncol.* 2018;19(5):603-615.; Drummer R, et al. *Lancet Oncol.* 2018;19(10):1315-1327.; EF = ejection fraction; SCC = squamous-cell carcinoma

Dose Modification for Toxicity

Agent	Standard Dosing	Dose Reduction 1st Toxicity Occurrence	Dose Reduction 2nd Toxicity Occurrence	Dose Reduction 3rd Toxicity Occurrence
BRAF Inhibitors				
Vemurafenib	960 mg twice daily	720 mg twice daily	480 mg twice daily	Discontinue
Dabrafenib	150 mg twice daily	100 mg twice daily	75 mg twice daily	50 mg twice daily
Encorafenib	450 mg once daily	300 mg once daily	225 mg once daily	Discontinue
MEK Inhibitors				
Cobimetinib	60 mg once daily days 1-21	40 mg once daily days 1-21	20 mg once daily days 1-21	Discontinue
Trametinib	2 mg once daily	1.5 mg once daily	1 mg once daily	Discontinue
Binimetinib	45 mg twice daily	30 mg twice daily	Discontinue	

Zelboraf [package insert]. Genentech USA, Inc.;2020.; Taflinar [package insert). Novartis Pharmaceuticals Corporation;2020.; Braftovi [package insert]. Array BioPharma Inc.;2020.; Cotellic [package insert]. Genentech USA, Inc.;2020.; Mekinist [package insert). Novartis Pharmaceuticals Corporation;2021.; Mektovi [package insert]. Array BioPharma Inc.;2020.

Management of Rash

Grade 1	• No symptoms • **Topical emollients**, observe
Grade 2	• Itching, soreness, rash < 50% of skin surface • Antihistamines, emollients, **topical steroids**
Grade 3	• Itching, soreness, rash ≥ 50% of skin surface • **Hold TKI until < Grade 1**, antihistamines, topical steroids, consider starting **oral prednisone 0.5 mg/kg/day**
Grade 4	• SJS, TEN, blisters, peeling, or mucosal • DC TKIs, consider alternate, consult derm

DC = discontinue; SJS = Stevens-Johnson Syndrome; TENS = Toxic Epidermal Necrolysis; TKI = tyrosine kinase inhibitor

Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7(2):122-136.; Zelboraf [package insert]. Genentech USA, Inc.;2020.; Taflinar [package insert). Novartis Pharmaceuticals Corporation;2020.; Braftovi [package insert]. Array BioPharma Inc.;2020.; Cotellic [package insert]. Genentech USA, Inc.;2020.; Mekinist [package insert). Novartis Pharmaceuticals Corporation;2021.; Mektovi [package insert]. Array BioPharma Inc.;2020.

Management of Other Dermatologic Toxicities

Dermatologic Toxicity	Symptoms	Management
Dry skin	Flaky skin including scalp May be associated with pruritis	Soap substitutes Moisturizers
Keratosis pilaris	Hyperkeratotic/cystic follicular eruption (folliculocentric papules) on head-neck region, torso, extremities	Moisturizers, topical steroids, antihistamines, prednisone, acitretin
Keratocanthoma/Squamous Cell Carcinoma	Rapidly growing nodule with crusty, erythematous base	Excision, acitretin, photodynamic light therapy, intralesional fluorouracil
Panniculitis	Tender skin nodules with or without arthralgias	Non-steroidal anti-inflammatory agents and analgesics
Plantar hyperkeratosis	Lesions only at points of pressure or friction (hands rarely involved)	Urea creams, avoid friction to area
Photosensitivity reactions	Painful burning sensation up to 10 minutes after UV light exposure	Sunscreen SPF > 30 (UVA+UVB), avoid sun

SPF = sun protection factor; UV = ultraviolet light; UVA = ultraviolet light A; UVB = ultraviolet light B. Sinha R, et al. *Br J Dermatol.* 2012;167(5):987-994.; Anforth R, et al. *Lancet Oncol.* 2013;14(1):e11-e18.; Ma L, et al. *Arch Dermatol.* 2012;148(12):1428-1429.; Zimmer L, et al. *Arch Dermatol.* 2012;148(3):357-361.; Anforth R, et al. *J Clin Oncol.* 2012;30(19):e165-e167.; Alloo A, et al. *Arch Dermatol.* 2012;148(3):363-366.; Novoa RA, et al. *J Am Acad Dermatol.* 2012;67(6):e271-e272.; van der Kooi K, et al. *J Am Acad Dermatol.* 2012;67(6):e286-e287.; LaPresto L, et al. *JAMA Dermatol.* 2013;149(3):279-281.

Management of Diarrhea

Grade 1	• ↑ 4 stools over baseline or mild ostomy output over baseline • **Loperamide**, dietary modifications, rule out infection
Grade 2	• ↑ 4-6 stools over baseline or moderate ostomy output over baseline • **Hold TKI until < Grade 1, loperamide**, dietary modification, rule out infection
Grade 3	• ↑ 7 stools over baseline, incontinence; severe ↑ ostomy output • **Hold TKI until < Grade 1, loperamide, codeine, hospitalization, fluids, rule out infection, quinolone antibiotic if fever or neutropenic**
Grade 4	• Life-threatening, urgent action needed • **DC TKIs, hospitalization, fluids, consider colonoscopy, antibiotics**

Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7(2):122-136.; Zelboraf [package insert]. Genentech USA, Inc.;2020.; Taflinar [package insert). Novartis Pharmaceuticals Corporation;2020.; Braftovi [package insert]. Array BioPharma Inc.;2020.; Cotellic [package insert]. Genentech USA, Inc.;2020.; Mekinist [package insert). Novartis Pharmaceuticals Corporation;2021.; Mektovi [package insert]. Array BioPharma Inc.;2020.

Management of Pyrexia

Grade 1	• Fever 38 to 39°C (100.4 to 102.2°F) • Continue TKI. Check CBC with differential, rule out infection. If negative, **acetaminophen 1000 mg every 6 hours**. **If fever persists, alternate NSAID with acetaminophen.**
Grade 2	• Fever > 39 to 40°C (102.3 to 104°F) • **Hold TKI.** Check CBC with differential, rule out infection. Acetaminophen 1000 mg every 6 hours; alternate NSAID. **Consider low-dose prednisone or switching BRAF inhibitors.**
Grade 3 or 4	• Fever > 40°C (> 104°F) ≤ 24 hours (Grade 3) or > 24 hours (Grade 4) • **DC TKI.** Check CBC with differential, rule out infection. Acetaminophen 1000 mg every 6 hours; alternate NSAID. **Consider low-dose prednisone or switching BRAF inhibitors.**

CBC = complete blood count; NSAID, non-steroidal anti-inflammatory drug.

Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7(2):122-136.; Zelboraf [package insert]. Genentech USA, Inc.;2020.; Taflinar [package insert). Novartis Pharmaceuticals Corporation;2020.; Braftovi [package insert]. Array BioPharma Inc.;2020.; Cotellic [package insert]. Genentech USA, Inc.;2020.; Mekinist [package insert). Novartis Pharmaceuticals Corporation;2021.; Mektovi [package insert]. Array BioPharma Inc.;2020.

Colchicine for Pyrexia with D/T

	Prior to Colchicine			After Colchicine			
Case	Treatment of Pyrexia	Days D/T Held	D/T Dose Reductions	Colchicine Dose	Days Pyrexia	Days D/T Held	D/T Dose Reductions
1	HC 5 mg BID, APAP PRN, Ibuprofen PRN	5/13	D: ↓50%	1.2 mg BID	1	2/0	0
2	APAP Q6H, Prednisone 20 mg/day	10/70	D: ↓50%	0.6 mg BID	1	0/0	0
3	APAP Q8H, Prednisone 20 mg/day	3/3	None	0.6 mg BID	0	0/0	0
4	APAP PRN	11/11	D: ↓50%	1.2 mg BID	2	0/0	0
5	Ibuprofen PRN	5/5	D: ↓50% T: ↓ 50%	1.2 mg BID	1	2/2	0

APAP = acetaminophen; BID = twice daily; D = dabrafenib; D/T = dabrafenib + trametinib; H = hours; HC = hydrocortisone; PRN = as needed; Q = every; T = trametinib

Vera J, et al. *Support Care Cancer.* 2019;27(10):3869-3875.

Management of Cardiomyopathy

Grade 1 or 2	• Asymptomatic ↓ LVEF < 10% (Grade 1) or ≥ 10 to < 20% (Grade 2) from baseline • **Hold TKI.** Remeasure LVEF. If improved, **restart at one dose level lower.**
Grade 3	• Symptomatic ↓ LVEF > 20% from baseline • **DC TKI.** Treat symptomatically.
Grade 4	• Refractory, poorly controlled heart failure requiring hospitalization, ventricular assist device, vasopressor support or transplant • **DC TKI.** Treat symptomatically.

LVEF = left ventricular ejection fraction

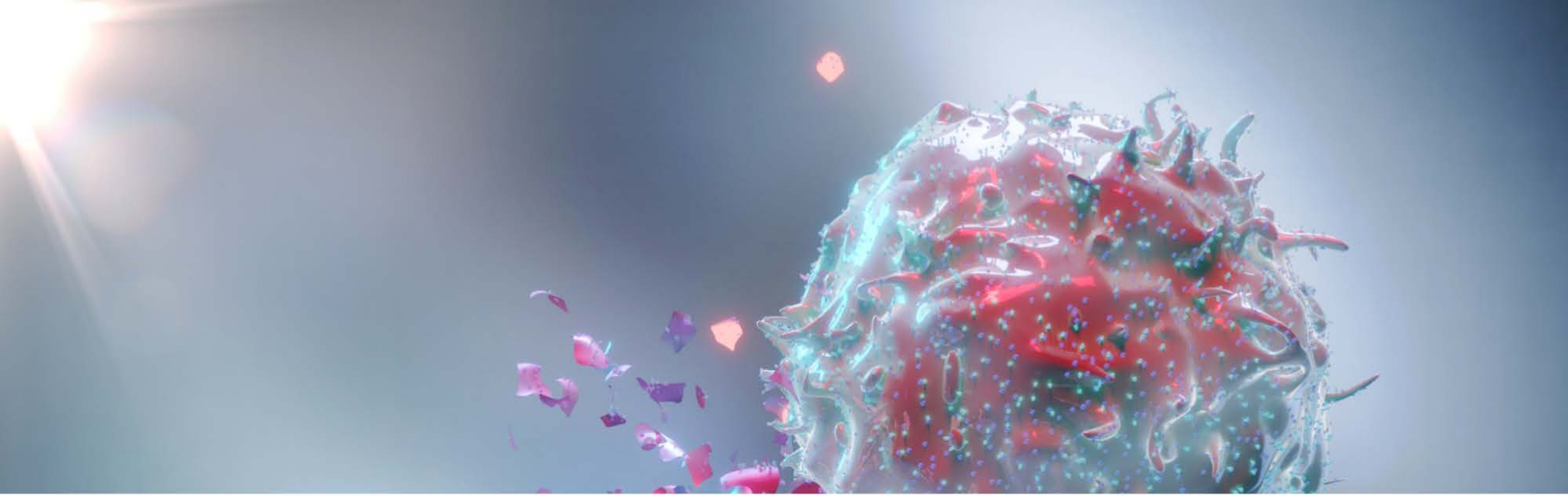
Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7(2):122-136.; Zelboraf [package insert]. Genentech USA, Inc.;2020.; Taflinar [package insert). Novartis Pharmaceuticals Corporation;2020.; Braftovi [package insert]. Array BioPharma Inc.;2020.; Cotellic [package insert]. Genentech USA, Inc.;2020.; Mekinist [package insert). Novartis Pharmaceuticals Corporation;2021.; Mektovi [package insert]. Array BioPharma Inc.;2020.

Management of Ocular Toxicities

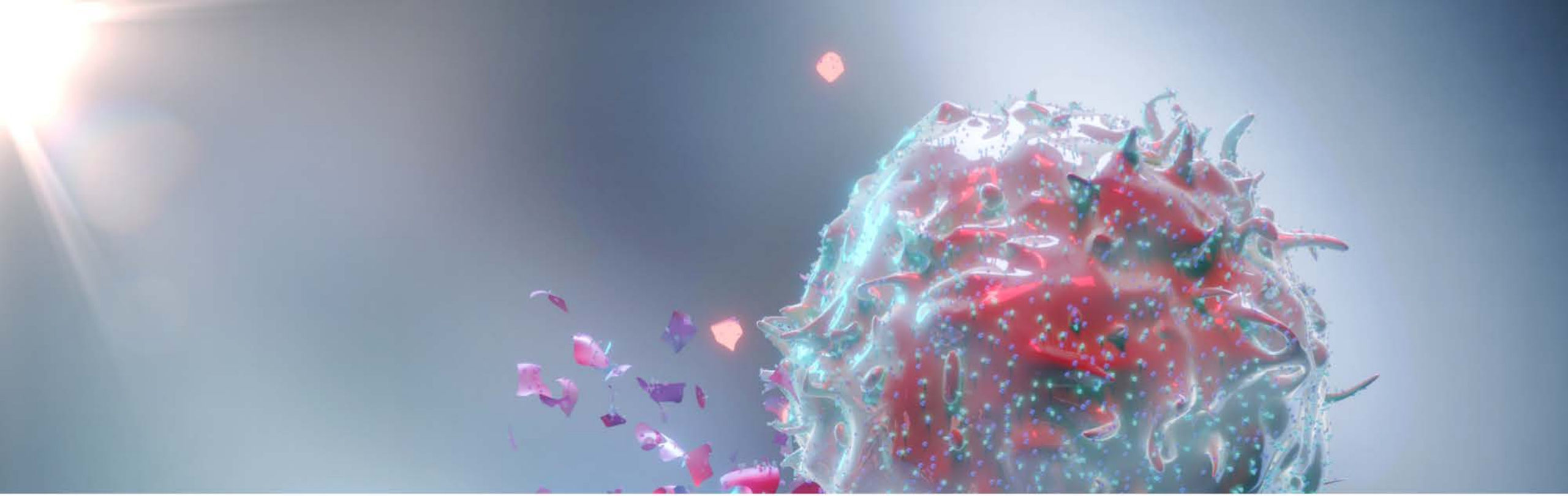
Grade 1	• Asymptomatic, no limit to activities of daily living • **Hold TKI.** Refer to Ophthalmology. **If uveitis, treat with corticosteroid eye drops. Restart MEK inhibitor at reduced dose.**
Grade 2	• Symptomatic, visual acuity ↓ to 20/40 or better in affected eye(s), limiting activities of daily living. • **Hold TKI.** Refer to Ophthalmology. **As above uveitis. If RVO, DC TKI.**
Grade 3	• Symptomatic, marked ↓ visual acuity to 20/40 or worse in affected eye(s), limiting self-care. • **DC TKI, urgent ophthalmology management.**
Grade 4	• Blindness, visual acuity worse than 20/200 in affected eye(s) • **DC TKI, urgent ophthalmology management.**

RVO = retinal vein occlusion

Welsh SJ, Corrie PG. *Ther Adv Med Oncol.* 2015;7(2):122-136. Sarny S, et al. *BMC Ophthalmol.* 2017;17(1):146.



Toxicity and Management Question & Answer



Considerations for Oncology Pharmacists

Case 1

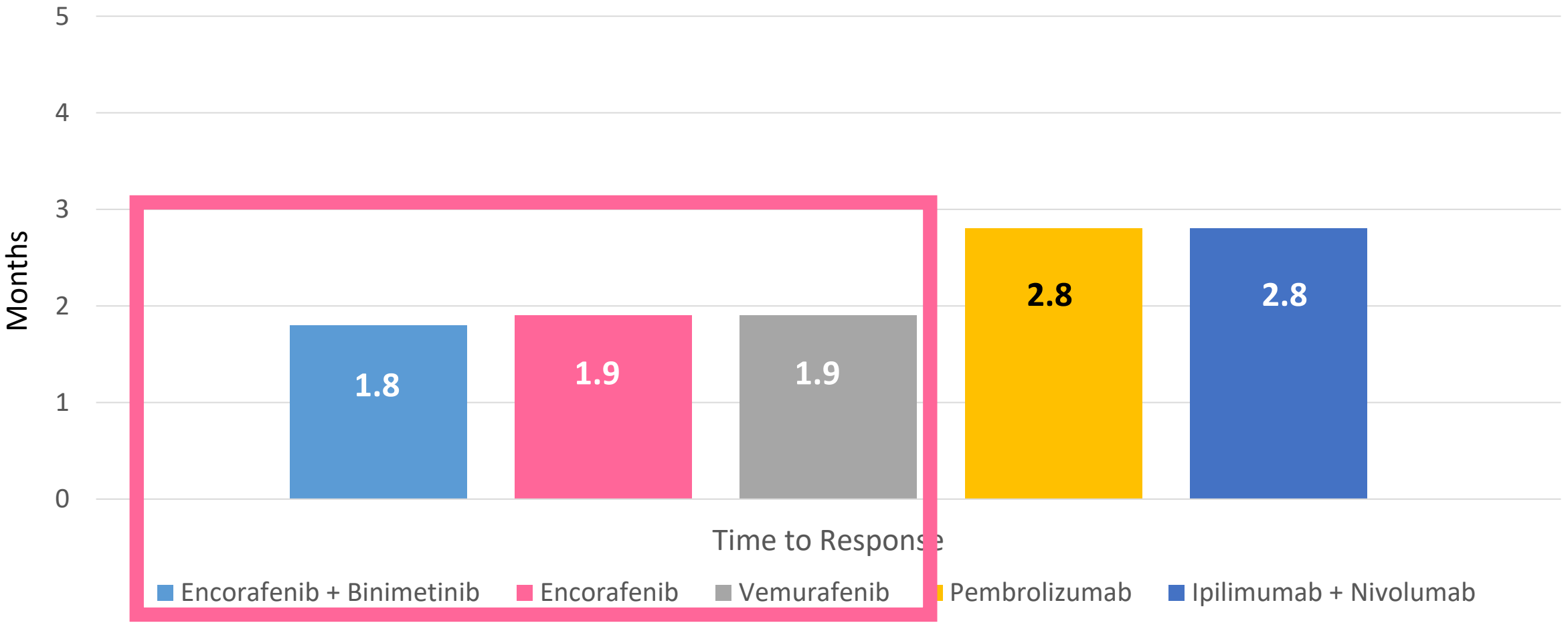
JS is a 48-year-old male with newly diagnosed $BRAF^{V600E}$ mutation-positive melanoma of the neck. PET/CT imaging reveals FDG-avid lymph nodes in the neck surrounding the windpipe. The patient's melanoma is considered aggressive with a mitotic rate of > 10/mm^2. He is admitted to the hospital for emergent treatment.

Which of the following would be an appropriate first-line regimen to treat JS's $BRAF^{V600E}$ mutation positive melanoma?

A. Encorafenib 450 mg PO once daily + binimetinib 45 mg PO twice daily
B. Ipilimumab 3 mg/kg IV on Day 1 + nivolumab 1 mg/kg IV on Day 1 every 3 weeks
C. Pembrolizumab 200 mg IV on Day 1 + dabrafenib 150 mg PO twice daily + trametinib 2 mg once daily

FDG = fluorodeoxyglucose

Time to Response BRAF vs. Immunotherapy



Dummer R, et al. *Lancet Oncol.* 2018;19(5):603-615.; Hamid O, et al. *Ann Oncol.* 2019;30(4):582-588.; Lebbe C, et al. *J Clin Oncol.* 2019;37(11):867-875.

Case 2

VF is a 72-year-old female with recurrent BRAF^{V600E} mutation-positive cutaneous melanoma with metastases to her lungs. She previously received therapy with nivolumab 480 mg IV on Day 1 every 4 weeks x 8 cycles.

Past medical history:

- Atrial fibrillation
- Hypothyroidism
- Recent pneumonia

Current medications:

- Metoprolol 50 mg twice daily
- Apixaban 5 mg twice daily
- Levothyroxine 75 mcg once daily before breakfast
- Clarithromycin 500 mg twice daily

The patient feels breathless & exhausted. An ECG returns with a QTc of 520 msec.

Which of the following is the best treatment for VF?

A. Vemurafenib + Cobimetinib, continue all current medications

B. Dabrafenib + Trametinib, switch apixaban to low molecular weight heparin and hold clarithromycin

C. Encorafenib + binimetinib, switch apixaban to low molecular weight heparin and hold clarithromycin

ECG = electrocardiogram

Drug Interactions with BRAF/MEK Inhibitors

BRAF Inhibitor	Vemurafenib	Dabrafenib	Encorafenib
Administration	960 mg orally twice daily **with or without food**	150 mg orally twice daily **at least 1 hour before or 2 hours after a meal**	450 mg once daily **with or without food**
Drug interactions	CYP3A4 substrate CYP1A2, CYP2D6, CYP2C9 inhibitor CYP3A4 inducer QTc prolonging medications	CYP3A4, CYP2C8 substrate CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2B6 inhibitor	CYP3A4, P-glycoprotein substrate CYP3A4 inhibitor, P-glycoprotein, BCRP, OCT2, OATP1B1, OATP1B3 QT prolonging medications

MEK Inhibitor	Cobimetinib	Trametinib	Binimetinib
Administration	60 mg once daily Days 1-21 **with or without food**	2 mg once daily **at least 1 hour before or 2 hours after a meal**	45 mg twice daily **with or without food**
Drug interactions	CYP3A4, P-glycoprotein substrate Avoid strong/moderate inhibitors, inducers CYP3A4 or reduce to 20 mg/day	CYP2C8 inhibitor (in vitro)	P-glycoprotein, BCRP substrate UGT1A1 inhibitors (smoking) do not have clinically relevant effect

BCRP = breast cancer resistance protein; CYP = cytochrome P450; UGT = UDP-glucuronosyltransferase

Zelboraf [package insert]. Genentech USA, Inc.;2020.; Taflinar [package insert). Novartis Pharmaceuticals Corporation;2020.; Braftovi [package insert]. Array BioPharma Inc.;2020.; Cotellic [package insert]. Genentech USA, Inc.;2020.; Mekinist [package insert). Novartis Pharmaceuticals Corporation;2021.; Mektovi [package insert]. Array BioPharma Inc.;2020.

Case 3

CE is a 68-year-old male with metastatic $BRAF^{V600E}$ mutated melanoma of the right ear. He is seeing you in clinic today prior to his 4th cycle of dabrafenib (D) 150 mg PO twice daily + trametinib (T) 2 mg PO once daily. He states he has a hard time sleeping at night as he develops fevers > 39ºC with accompanying chills and rigors.

Past Medical History: Hypertension, ESRD with CrCl = 20 mL/min

Which of the following is the best recommendation for CE?

A. Start colchicine 1.2 mg PO twice daily; continue DT
B. Give acetaminophen 1000 mg PO every 6 hours as needed
C. Switch to encorafenib 450 mg PO once daily + binimetinib 45 mg twice daily

CrCl = creatinine clearance; ESRD = end-stage renal disease

Treatment of DT-Induced Pyrexia in ESRD

Around the clock acetaminophen 1000 mg PO every 6 hours, avoid ibuprofen in ESRD; consider low-dose prednisone

Avoid colchicine in ESRD

Case 4

You receive a call at your specialty pharmacy from a community oncologist who is treating a $BRAF^{V600E}$ mutation-positive cutaneous melanoma patient with dabrafenib + trametinib. The patient will begin concomitant radiation therapy for a metastasis to the lung.

Which of the following is your best response?

A. It is not necessary to hold BRAF/MEK inhibitors while receiving concurrent radiation therapy.

B. I recommend holding the BRAF/MEK inhibitor while radiation therapy is ongoing due to concerns for increased BRAF/MEK inhibitor toxicity.

C. I have no idea how to answer this question. Help!

Severe Toxicity With Concurrent BRAF/MEK Inhibitors + Radiation Therapy (RT)

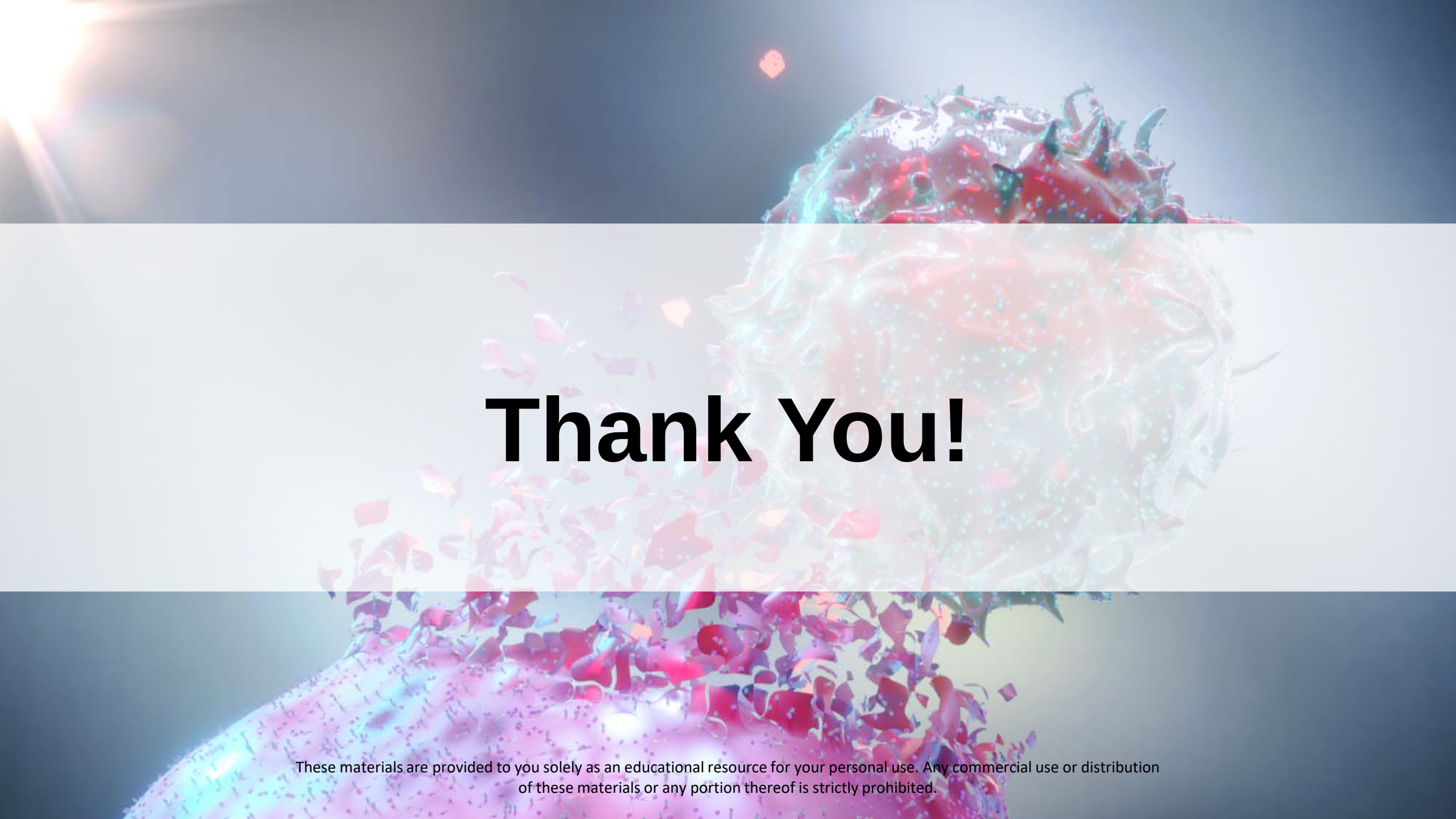
- BRAF inhibitors ↑ risk of grade 2 and 3 dermatitis with RT
- May result in painful or disfiguring keratosis pilaris & cutis furrowing of scalp
- Mucosal toxicity
- Pneumonitis

Consensus Recommendations

Treatment Modality	Recommendation
BRAF/MEK inhibitor	Hold ≥ 3 days before & after RT Hold ≥ 1 day prior to stereotactic radiosurgery
Radiation therapy	Consider < 4 Gy per fraction Adjuvant nodal basin RT, consider ≤ 48 to 50 Gy in 20 fractions For spinal metastases, consider posterior oblique RT

Anker CJ, et al. *Int J Radiat Oncol Biol Phys.* 2016;95(2):632-646.

Questions & Answers



Thank You!