JADPRO Clinical Case Series

Targeted Therapy Management in HR+ Metastatic Breast Cancer

Sponsored by AstraZeneca

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Program Agenda

- Treatment landscape in HR+ metastatic cancer
- Discuss role of NGS testing for second-line HR+ metastatic breast cancer
- Review FDA approvals for PI3K and AKT inhibitors for metastatic ER+ breast cancer
- Review of patient case studies and polling questions

NGS, next-generation sequencing.

Audience Response Question #1

PRE: Which of the following best reflects an appropriate proactive and early management strategy for diarrhea associated with AKT/PI3K-pathway targeted therapy (eg, capivasertib)?

a. Provide hydration and dietary counseling; use antidiarrheal agents only once diarrhea reaches grade ≥2
b. Offer early antidiarrheal guidance and withhold therapy until recovery to grade ≤1, resuming at the same or a reduced dose as indicated
c. Start all patients on prophylactic antidiarrheals and continue therapy uninterrupted unless diarrhea becomes grade ≥3
d. Emphasize non-pharmacologic measures; dose interruptions are rarely necessary for early diarrhea
e. Unsure

Audience Response Question #2

PRE: Which of the following best reflects an appropriate proactive strategy for managing hyperglycemia risk associated with glucose elevations when initiating therapy?

a. Focus primarily on lifestyle counseling and only check fasting glucose if patients report symptoms, as routine lab monitoring is not generally necessary early in therapy
b. Obtain baseline fasting glucose and hemoglobin A1c levels; consider early endocrinology involvement or metformin prophylaxis in patients with pre-diabetes
c. Check baseline fasting glucose only; routine A1c monitoring is typically unnecessary if initial values are normal
d. Defer endocrine consultation until hyperglycemia becomes persistent despite initial lifestyle modifications and dose adjustments
e. Unsure

Audience Response Question #3

PRE: Which of the following best characterizes a key difference in the adverse event profiles of alpelisib and capivasertib?

a. Hyperglycemia is substantially more common with capivasertib, while diarrhea is the predominant toxicity with alpelisib
b. Alpelisib has notably higher rates of hyperglycemia, whereas capivasertib more frequently causes diarrhea despite lower rates of metabolic toxicity
c. Both agents have nearly identical rates of hyperglycemia, diarrhea, and rash, but alpelisib has significantly lower rates of dose reduction
d. Capivasertib is associated with higher rates of hyperglycemia and has a higher discontinuation rate compared with alpelisib
e. Unsure

Treatment Landscape in HR+ Metastatic Breast Cancer

- **First-line:**
  - Recurrence >12 months after AI or no previous AI: CDK4/6 inhibitor + AI
  - Recurrence while on adjuvant AI or <12 months since AI completed: Fulvestrant + AI
    - If *PIK3CA* mutated: fulvestrant + palbociclib + inavolisib
- **Second-line—based on tumor genomics/mutational analysis:**
  - *PIK3CA* mutation: alpelisib or capivasertib combination with fulvestrant
  - *AKT* or *PTEN* alteration: capivasertib + fulvestrant
  - *ESR1* mutation: elacestrant or imlunestrant
  - *BRCA1/2* mutation: olaparib or talozaparib
  - No actionable mutation: everolimus + exemestane, fulvestrant monotherapy, abemaciclib + fulvestrant, tamoxifen monotherapy
- **Endocrine resistant/third-line and beyond—ADCs or chemotherapy:**
  - HER2-low or -ultralow: fam-trastuzumab deruxtecan
  - HER2-negative: sacituzumab govitecan or datopotamab deruxtecan
  - Chemotherapy options include capecitabine, paclitaxel, nab-paclitaxel, eribulin, gemcitabine, and doxorubicin liposomal

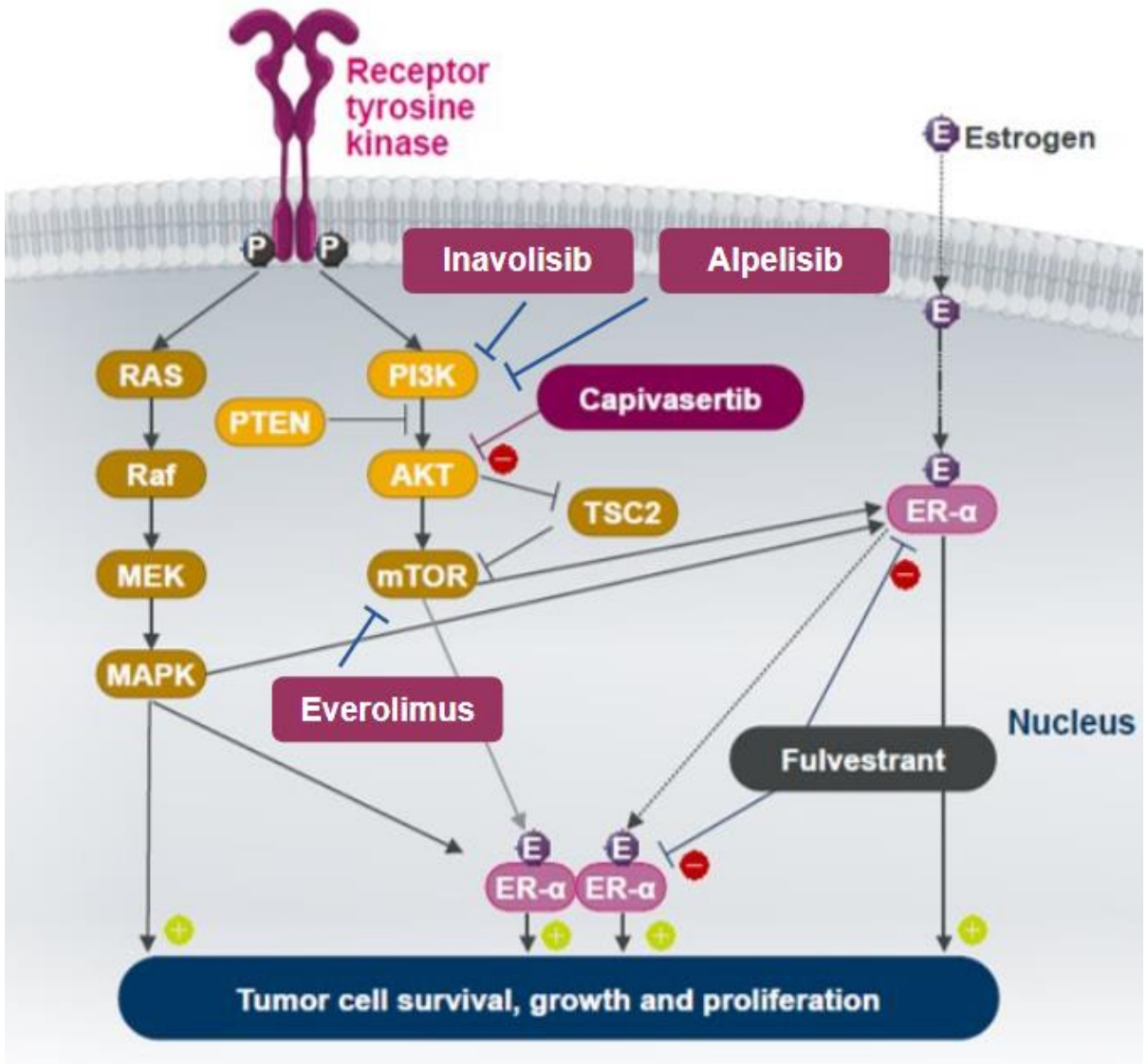
ADC, antibody-drug conjugate; AI, aromatase inhibition.
NCCN Guidelines: Breast Cancer v5.2025

NGS Testing/Molecular Profiling

- Should be considered after disease progression on first-line ET and at times of subsequent progressions to assess for actionable mutations that could guide targeted approach
  - Testing recommended at metastatic diagnosis in patients with relapse within 12 months of completing adjuvant ET due to latest FDA approval of inavolisib
- Liquid or tissue-based testing or combination of two through multiple FDA-approved assays (ie, Caris, Guardant 360, Tempus, Foundation One)
  - Liquid testing provides more insight into tumor heterogeneity, faster turnaround time, and less invasive—so, often preferred over tissue-based approach
- Key actionable mutations/alterations in this population include *BRCA*, AKT/PTEN/PI3K pathway mutations, *ESR1*, *ERBB2*, MSI-H or TMB-high

ET, endocrine therapy; MSI-H, microsatellite instability-high; TMB, tumor mutational burden.
NCCN Guidelines: Breast Cancer v5.2025

PI3K Pathway Often Aberrantly Activated in Breast Cancer



Breast Cancer	*PIK3CA/AKT/PTEN* alterations
HR+/HER2–	~50%
HER2+	~35–40%
TNBC	~25–30%

Everolimus – mTOR inhibitor

Alpelisib – PI3Kα inhibitor

Inavolisib – PI3Kα inhibitor

Capivasertib – AKT inhibitor

Turner N, *et al*. ESMO Breast 2023. Abstract 187O.

FDA Approvals in PI3K Pathway

- INAVO120 (phase III): Inavolisib + Palbociclib + Fulvestrant
  - FDA approval 2025
  - First-line with *PIK3CA* mutation if recurrence within 12 months of adjuvant ET
  - Inavolisib 9 mg PO QD w/ or w/o food + palbociclib + fulvestrant
  - Niche population
- SOLAR-1 (phase III): Alpelisib + Fulvestrant
  - FDA approval 2019
  - Second-line with *PIK3CA* mutation after PD w/ advanced or MBC on or after endocrine based regimen
  - Alpelisip 300 mg PO QD w/ food + fulvestrant
- CAPitello-291 (phase III): Capivasertib + Fulvestrant
  - FDA approval 2023
  - Second-line with *PIK3CA/AKT1/PTEN* alteration after PD on/after CDK4/6 + AI in metastatic setting or w/ recurrence on/within 12 months of adjuvant ET
  - Capivasertib 400 mg PO BID 4 days on/3 days off w/ or w/o food + fulvestrant

AI, aromatase inhibitor; BID, twice daily; ET, endocrine therapy; MBC, metastatic breast cancer; PD, progressive disease; PO, oral; QD, daily.

1. Jhaveri KL, et al. *N Engl J Med.* 2025;393(2):151-161. 2. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940. 3. Turner NC, et al. *N Engl J Med.* 2023;388:2058-2070.

Case 1: Treatment Selection Based on Molecular Profile

- A.M. is a 55-year-old female w/ right breast IDC, ER 95%, PR 75%, node positive
- Treated with bilateral MRM, adjuvant TAC for 6 cycles and adjuvant radiotherapy, followed by 5 years exemestane
- Recurs 3 years following AI completion w/ metastases to lungs and mediastinal nodes, remains ER+ 95%
- First-line treatment w/ letrozole + ribociclib for 18 months, at progression, liquid biopsy shows *PIK3CA* mutation, no other actionable mutations

AI, aromatase inhibition; ER, estrogen receptor; IDC, invasive ductal carcinoma; MRM, modified radical mastectomy; PR, progesterone receptor; TAC, Taxotere, Adriamycin, and cyclophosphamide.

Case 1 *continued*

- Second-line therapy selection is capivasertib + fulvestrant based on multiple variables:
  - *PIK3CA* mutation and known PFS and OS benefit in combination therapy approach based on SOLAR-1 and CAPitello-291 data[1,2]
  - Side effect profile considerations of both combination therapies and patient goals
  - Patient comorbidities: Type 1 DM (higher rate of hyperglycemia in SOLAR-1 w/ alpelisib 63%[1] vs CAPitello-291 rate 16%[2])
  - Patient's high health literacy and perceived ability to maintain oral adherence of unique dosing schedule and diarrhea management
- Patient Outcome
  - Continues capivasertib + fulvestrant with good tolerance after one dose reduction for diarrhea
  - Increased glucose monitoring w/ endocrinologist and increased insulin requirements but maintains well controlled glucose

DM, diabetes mellitus; OS, overall survival; PFS, progression-free survival.

1. André F, et al. *N Engl J Med.* 2019;380(20):1929-1940. 2. Turner NC, et al. *N Engl J Med.* 2023; 388:2058-2070.

Key Differences: Capivasertib vs Alpelisib

Alpelisib (PI3K Inhibitor)

- SOLAR-1[1,2]: mPFS 11 vs 5.7 months in placebo arm; mOS 39.3 vs 31.4 months in placebo arm
- Only approved for *PI3K* activating mutations
- Once daily dosing, with food
- Common AEs:
  - Hyperglycemia: 63%
  - Diarrhea: 57%
  - Nausea: 44%
  - Rash: 35%
  - Stomatitis: 24%
  - Fatigue: 24%
- Dose reductions: 63.9%
- Discontinuations: 25%

Capivasertib (AKT Inhibitor)

- CAPItello-291[3]: mPFS 7.3 vs 3.1 months in placebo arm; OS at 18 months 73.9% vs 65% in placebo arm
- Approved for *PIK3CA/AKT1/PTEN* alterations
- BID dosing, 4 days on of 7-day cycle, w/ or w/o food
- Common AEs:
  - Hyperglycemia: 16%
  - Diarrhea: 72%
  - Nausea: 34%
  - Rash: 38%
  - Stomatitis: 14%
  - Fatigue: 20%
- Dose reductions: 19.7%
- Discontinuations: 13%

AE, adverse event; BID, twice daily; OS, overall survival; PFS, progression-free survival.

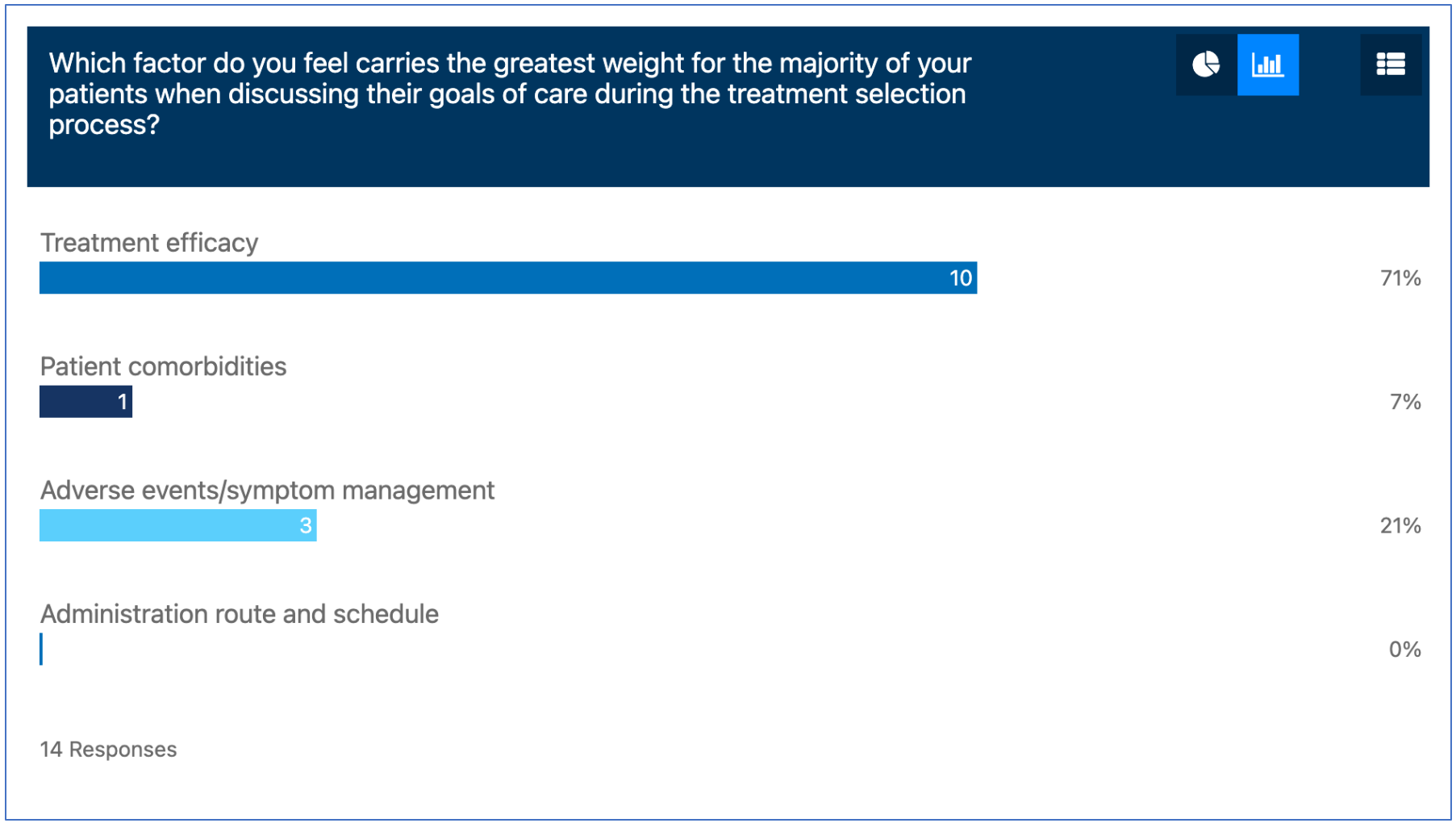
1. André F, et al. *N Engl J Med.* 2019;380(20):1929-1940. 2. André F, et al. *Ann Oncol.* 2021;32(2):208-217. 3. Turner NC, et al. *N Engl J Med*. 2023;388:2058-2070.

Case 1 Polling Question

Which factor do you feel carries the greatest weight for the majority of your patients when discussing their goals of care during the treatment selection process?

a. Treatment efficacy
b. Patient comorbidities
c. Adverse events/symptom management
d. Administration route and schedule

Case 1 Polling Results



Case 2: Dose Adjustments and Oral Adherence in a Patient on Capivasertib

- L.M. is 80-year-old female w/ right breast invasive micropapillary carcinoma with lobular features, node positive
- Received adjuvant TAC for 6 cycles and adjuvant anastrozole for 5 years
- Recurrence 4 years post adjuvant AI completion w/ bone metastases
- First-line treatment w/ letrozole + palbociclib (CDK4/6) with durable response for 6 years then progressive disease with new liver metastases
- NGS testing at progression: *CDH1, ESR1, CCND1, FGF3,* and *AKT1* alterations
- Second-line treatment w/ elacestrant for *ESR1* mutation w/ 13 months on therapy (still endocrine sensitive)
- Third-line ET is initiated w/ capivasertib + fulvestrant

AI, aromatase inhibition; ET, endocrine therapy; TAC, Taxotere, Adriamycin, and cyclophosphamide.

Case 2 *continued*

- Oral adherence concerns: patient is elderly w/ history of missed doses on prior oncolytic therapy and previous treatment with more simplified dosing schedule
  - Involvement of primary caregiver (daughter) and plan is developed to maintain dosing calendar at home

TABLE. Weekly Capivasertib Dosing Schedule

Day	1	2	3	4	5	6	7
Morning	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg	X	X	X
Evening	2 x 200 mg	2 x 200 mg	2 x 200 mg	2 x 200 mg	X	X	X

AstraZeneca. (2011). Truqap (capivasertib) package insert.

Case 2 *continued*

- L.M. experiences grade 2 diarrhea (6 episodes/day) in cycle 1 despite proper use of loperamide. Diphenoxylate/atropine is added and capivasertib dosing continues, 2 days later you call and check in and diarrhea has improved but is still grade 2. Capivasertib is held.
- You send 160-mg tablets to specialty pharmacy in preparation for dose reduction. She returns after 1 week hold w/ resolution of diarrhea.
- Capivasertib restarted at dose reduction w/ acceptable tolerance of grade 1 diarrhea and as-needed use of anti-diarrheal therapy.

TABLE. Recommended Dose Reductions of Capivasertib for Adverse Events

	Dose and Schedule
First dose reduction	320 mg twice daily for 4 days followed by 3 days off
Second dose reduction	200 mg twice daily for 4 days followed by 3 days off

AstraZeneca. (2011). Truqap (capivasertib) package insert.

Diarrhea Management Strategies

- Educate that diarrhea is seen commonly on this treatment, seen in 72% of patients
- Encourage to have loperamide on hand before starting first cycle
- At onset take loperamide promptly (two 2-mg tablets with first episode) then repeat 2-mg tablet w/ each subsequent episode, max 16 mg/day (8 tablets)
- Consider adding diphenoxylate/atropine if diarrhea not optimally managed on loperamide, can alternate with loperamide with each episode of diarrhea, max dose 20 mg/24 hr or 8 tablets/day
- Educate on signs/symptoms of dehydration and administer IVF or electrolyte repletion as needed
- If grade 2+ (increases to 4 stool/day over baseline), hold drug until resolves to grade 1 then refer to package insert regarding dose reduction

AstraZeneca. (2011). Truqap (capivasertib) package insert.

Dose Modifications of Capivasertib for Diarrhea

Severity	Capivasertib Dosage Modification
Grade 2	Withhold capivasertib until recovery to grade ≤1. If recovery occurs in ≤28 days, resume capivasertib at same dose or one dose lower as clinically indicated. If recovery occurs in >28 days, resume at one dose lower as clinically indicated. For recurrence, reduce capivasertib by one dose lower.
Grade 3	Withhold capivasertib until recovery to grade ≤1. If recovery occurs in ≤28 days, resume capivasertib at same dose or one dose lower as clinically indicated. If recovery occurs in >28 days, permanently discontinue capivasertib.
Grade 4	Permanently discontinue capivasertib.

1. AstraZeneca. (2011). Truqap (capivasertib) package insert. 2. CTCAE v5.0. NCI Division of Cancer Treatment & Diagnosis.

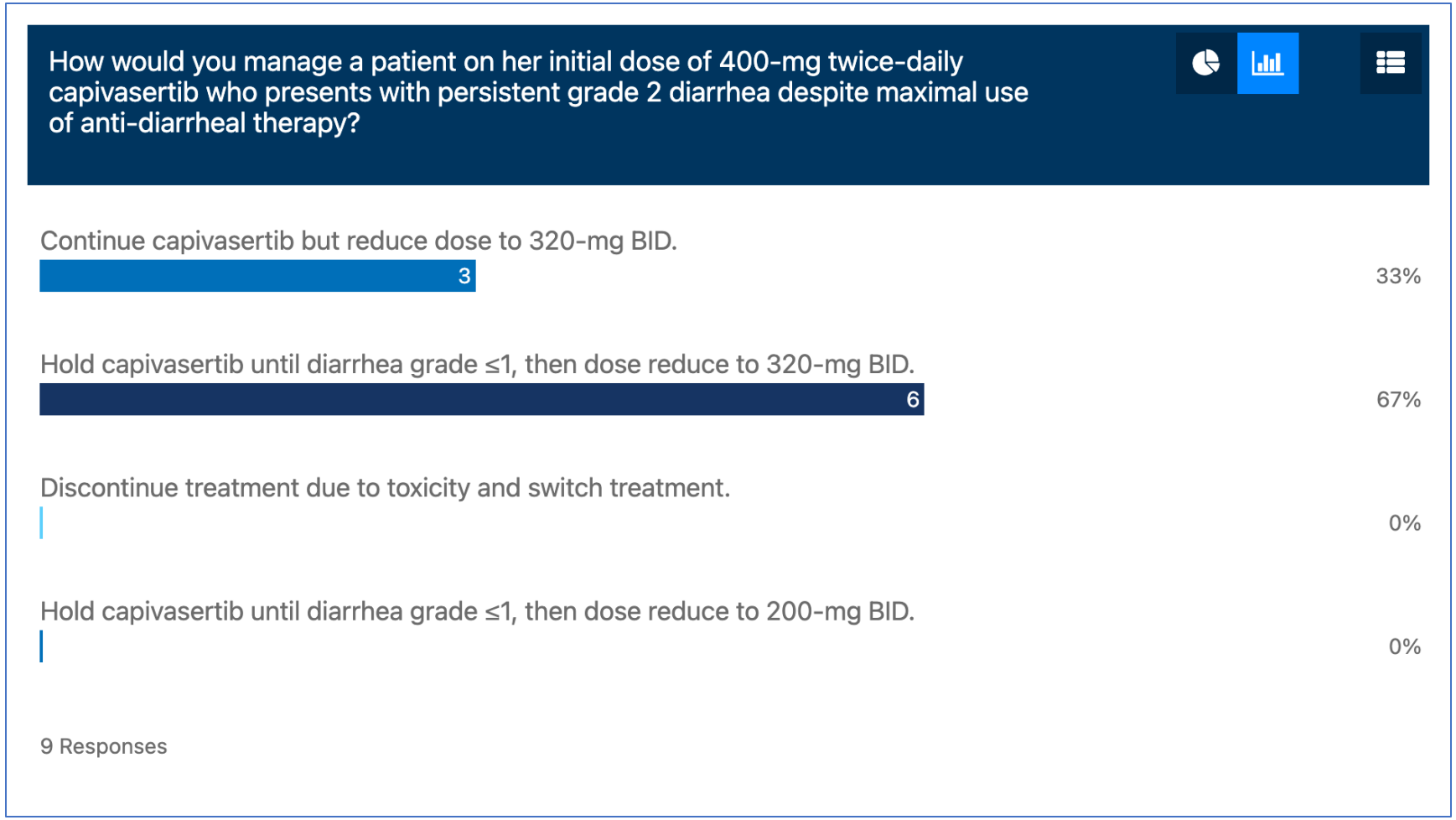
Case 2 Polling Question

How would you manage a patient on her initial dose of 400-mg twice-daily capivasertib who presents with persistent grade 2 diarrhea despite maximal use of anti-diarrheal therapy?

a. Continue capivasertib, but reduce dose to 320-mg BID.
b. Hold capivasertib until diarrhea resolves to grade ≤1, then dose reduce to 320-mg BID.
c. Discontinue treatment due to toxicity and switch treatment.
d. Hold capivasertib until diarrhea resolves to grade ≤1, then dose reduce to 200-mg BID.

BID, twice daily.

Case 2 Polling Results



BID, twice daily.

Case 3: Proactive Adverse Event Management With Capivasertib and Fulvestrant

- T.H. is a 48-year-old female w/ right breast IDC, ER 95%, PR 95% who undergoes bilateral MRM for a large 6-cm invasive component but node negative, low oncotype score
- Completes 5 years of adjuvant tamoxifen
- Recurrence 2 years after tamoxifen completion w/ bone and nodal involvement, biopsy of node w/ disease still ER 100%, PR 98%
- First-line letrozole, ribociclib + goserelin (premenopausal) and denosumab with progressive disease after 3 years
- NGS testing with liquid biopsy reveals *ESR1*, *PIK3CA*, *FGFR1* amplification, *EGFR1* amplification, and MSS

ER, estrogen receptor; IDC, invasive ductal carcinoma; MRM, moderated radical mastectomy; MSS, microsatellite stable; PR, progesterone receptor.

Case 3 *continued*

- Second-line ET started w/ capivasertib + fulvestrant due to *AKT1* and *PIK3CA* alterations
- Symptom management strategies implemented early due to patient's lifestyle needs: full-time employment and busy mom

ET, endocrine therapy.

Cutaneous AE Management Strategies

- Educate on potential for rash and to report at first signs
  - Rash is seen in 56% of patients on capivasertib in CAPItello-291,[1] 15% grade 3/4 events
- Consider prophylactic antihistamines (ie, loratadine, cetirizine, fexofenadine) during first 8 weeks
  - SOLAR-1[2] prophylactic antihistamines reduced rash by ~50%
- Discuss lifestyle changes: sunscreen, unscented skincare products, avoiding agents that can dry or irritate skin (ie, alcohol, salicylic acid, topical retinols)
- Follow dose modification guidelines

1. Turner NC, et al. *N Engl J Med*. 2023; 388:2058-2070. 2. André F, et al. *N Engl J Med.* 2019;380(20):1929-1940. 3. AstraZeneca. (2011). Truqap (capivasertib) package insert.

Hyperglycemia Management Strategies

- Educate that hyperglycemia is seen in 19% of patients
- Patients with diabetes or pre-diabetes at baseline should consider seeing endocrinologist for closer monitoring in first few months of treatment
- Consider starting metformin prophylactically in patients with pre-diabetes (weigh risk of added diarrhea) or endocrinology consult if not established
- Discuss lifestyle modifications (dietary changes and exercise), particularly in patients with higher BMI at baseline
- Monitor fasting blood glucose and hemoglobin A1c at baseline: continue fasting glucose monthly and hemoglobin A1c every 3 months while on treatment
- If fasting glucose >160 mg/dL or hemoglobin A1c >7%, consider initiation or increased dose of anti-diabetic medication and refer to package insert for dose modifications

AstraZeneca. (2011). Truqap (capivasertib) package insert.

Case 3 *continued*

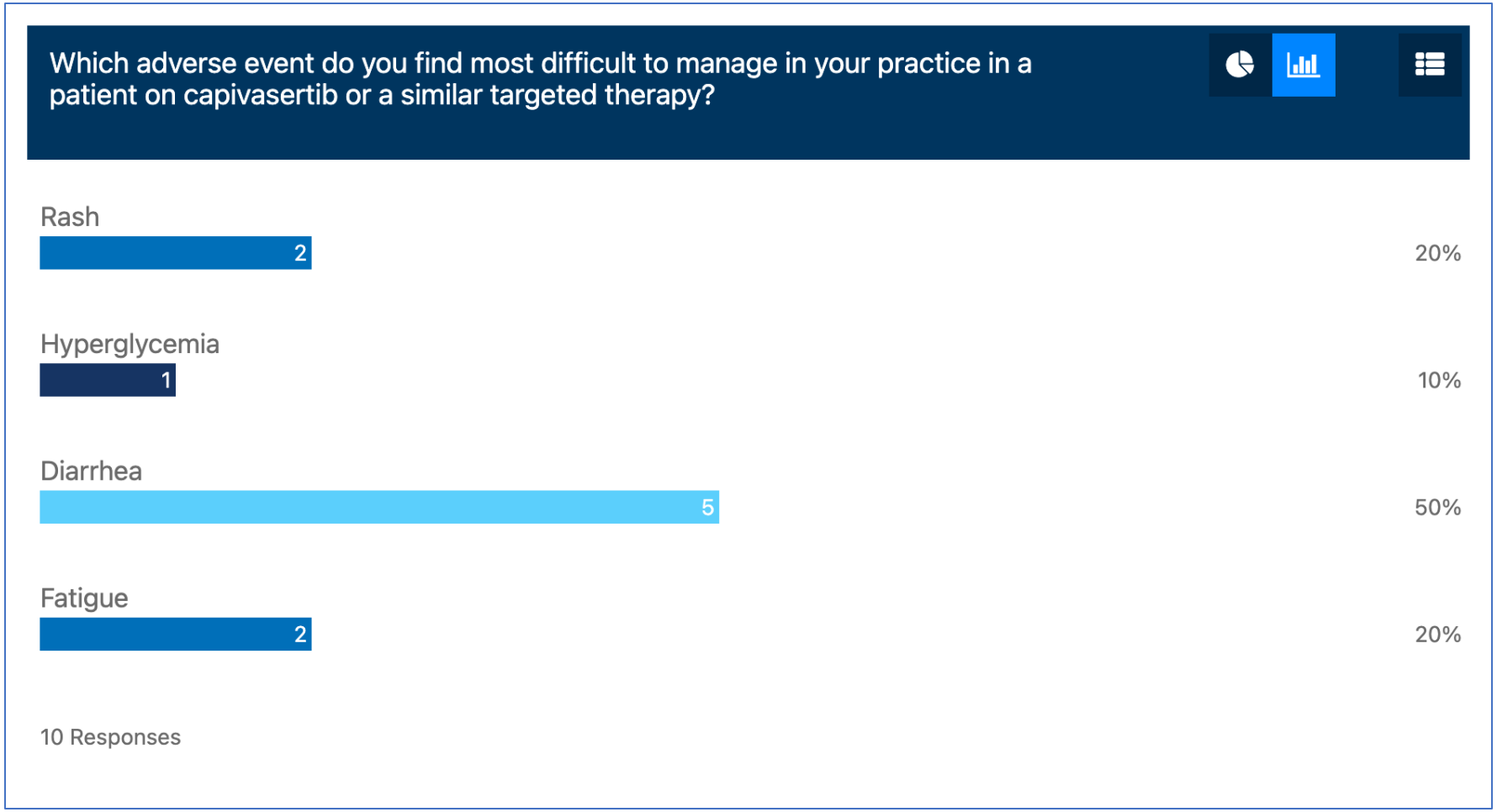
- T.H. initiates prophylactic loratadine for rash/cutaneous AE prevention, in addition to lifestyle changes for skin; has loperamide on hand before starting capivasertib
- Has baseline hemoglobin A1c that is consistent with pre-diabetes, so begins dietary modifications and is referred for endocrinology consult
- Comes in for cycle 2, day 1 visit with reports of loose stools and fatigue: labs reveal elevated fasting glucose 160 mg/dL, metformin 1,000-mg extended release initiated
- Fasting glucose improves within 1 week of endocrinology consult and glucose testing supplies provided; ongoing surveillance with every-3-month endocrinology visits
- In cycle 3, she has mild rash in <10% BSA after stopping her antihistamine, restarts loratadine and treats with topical corticosteroid to resolve rash
- T.H. goes on to have durable benefit with 11 months on capivasertib + fulvestrant before progressing
- Blood glucose returns to baseline after discontinuing capivasertib and she is able to stop metformin while still seeing endocrinologist annually for pre-diabetes

Case 3 Polling Question

Which adverse event do you find most difficult to manage in your practice for patients on capivasertib or a similar targeted therapy?

a. Rash
b. Hyperglycemia
c. Diarrhea
d. Fatigue

Case 3 Polling Results



Future Directions in PI3K/AKT Pathway

PI3K inhibitor	Company	Type	Status
CYH33	Haihe Biopharma	PI3Ka inhibitor	Phase 2
JS105	Junshi Biosciences	PI3Ka inhibitor	Phase 1/ 2
Serabelisib	Faeth Therapeutics	PI3Ka inhibitor	Phase 2
TOS-358	Totus Medicines	PI3Ka inhibitor	Phase 1
RLY-2608	Relay Therapeutics	Pan mutant selective PI3Ka inhibitor	Phase 3 planned
STX-478	Scorpion/Lilly	Allosteric mutant selective PI3Ka inhibitor	Phase 1/2
OKI-219	OnKure	*PI3Ka* H1047R mutant specific	Phase 1
LY4045004	Eli Lilly	*PI3Ka* H1047R and E545K mutant	Preclinical
BBO-1023	BridgeBio	PI3Ka:RAS interaction blocker	Phase 1
ALTA2618	Alterome	*AKT1* E17K mutation	Phase 1

Audience Response Question #4

POST: Which of the following best reflects an appropriate proactive and early management strategy for diarrhea associated with AKT/PI3K-pathway targeted therapy (eg, capivasertib)?

a. Provide hydration and dietary counseling; use antidiarrheal agents only once diarrhea reaches grade ≥2
b. Offer early antidiarrheal guidance and withhold therapy until recovery to grade ≤1, resuming at the same or a reduced dose as indicated
c. Start all patients on prophylactic antidiarrheals and continue therapy uninterrupted unless diarrhea becomes grade ≥3
d. Emphasize non-pharmacologic measures; dose interruptions are rarely necessary for early diarrhea
e. Unsure

Audience Response Question #5

POST: Which of the following best reflects an appropriate proactive strategy for managing hyperglycemia risk associated with glucose elevations when initiating therapy?

a. Focus primarily on lifestyle counseling and only check fasting glucose if patients report symptoms, as routine lab monitoring is not generally necessary early in therapy
b. Obtain baseline fasting glucose and hemoglobin A1c levels; consider early endocrinology involvement or metformin prophylaxis in patients with pre-diabetes
c. Check baseline fasting glucose only; routine A1c monitoring is typically unnecessary if initial values are normal
d. Defer endocrine consultation until hyperglycemia becomes persistent despite initial lifestyle modifications and dose adjustments
e. Unsure

Audience Response Question #6

POST: Which of the following best characterizes a key difference in the adverse event profiles of alpelisib and capivasertib?

a. Hyperglycemia is substantially more common with capivasertib, while diarrhea is the predominant toxicity with alpelisib
b. Alpelisib has notably higher rates of hyperglycemia, whereas capivasertib more frequently causes diarrhea despite lower rates of metabolic toxicity
c. Both agents have nearly identical rates of hyperglycemia, diarrhea, and rash, but alpelisib has significantly lower rates of dose reduction
d. Capivasertib is associated with higher rates of hyperglycemia and has a higher discontinuation rate compared with alpelisib
e. Unsure

Q & A

Please type your questions for **Melissa Rikal** into the **question box**.

Thank You

Please look out for a brief post-webinar survey coming in your email!