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SUGAR FALL INPATIENT CARE FOR DIABETES

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Alpelisib – What you need to know as a diabetes specialist

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Overview

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- What is this?
- Context and current guidance in UK
- Data + Cases
- Management options
- Summary
- Questions

Background

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- Around 20% of people with cancer have pre-existing diabetes
- Those with diabetes have increased risk of hospitalisation, morbidity and toxicity.
- Anticancer treatment may be less efficacious due to dose reductions or cessation.
- Hyperglycaemia linked with worse overall survival and increased risk of recurrence.
- Both historic and novel therapies can cause hyperglycaemia

Problem solved

https://abcd.care/sites/default/files/site_uploads/JBDS_Guidelines_Current/JBDS_17_Oncology_Guideline_with_QR_code_January_2023.pdf

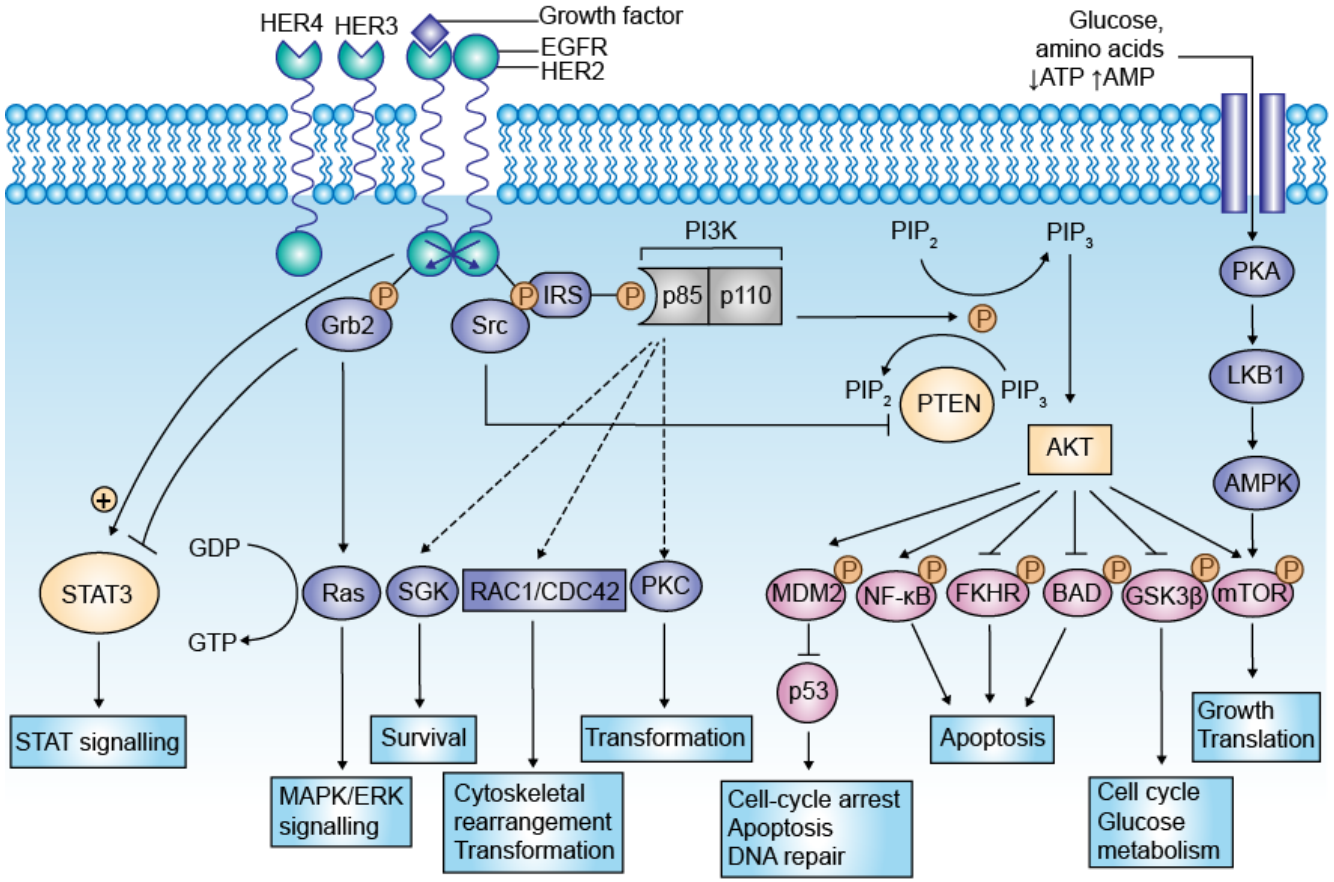
WHAT IS ALPELISIB

Alpelisib – (PI3K inhibitor) (Phosphatidylinositol-3-kinase)

- Advanced breast cancer (hormone receptor-positive / Human epidermal growth factor receptor 2-negative, PIK3CA mutated) (HR+/HER2-/PIK3CA-mutated)
- Locally advanced or metastatic disease
- Advanced breast cancer is incurable with aim of treatment to delay progression and extend survival
- Suggested by NICE after a CDK4/6 inhibitor + aromatase inhibitor
  - Palbociclib
  - Abemaciclib
  - Ribociclib

~40% of Patients With HR+, HER2– ABC Harbor a Mutation in *PIK3CA* in Their Tumors and Face a Poor Prognosis[1-5]

The PI3K Pathway[6]



PI3K signaling regulates diverse cellular functions including cell proliferation, survival, glucose metabolism, cell migration, and angiogenesis, and is often deregulated in cancers[6,7]

Patients from the SAFIR-02 study with *PIK3CA*-mutated ABC had 44% higher risk of death than patients without the mutation when treated with chemotherapy (HR multivariate: 1.44; 95% CI, 1.02-2.03; *P*=0.04)[5]

[a]In this systematic literature review, patients treated with PI3K-targeted therapies were excluded; allowed treatment included endocrine therapy, non-PI3K targeted therapy, and other treatment.

1. Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70; 2. Fritsch C, et al. AACR 2018. Abstract 3934 (poster); 3. Rajadurai P, et al. SABCS 2021. Abstract P5-13-25 (poster); 4. Fillbrunn M, et al. ASCO 2020. Poster 154; 5. Mosele F, et al. *Ann Oncol.* 2020;31(3):377-386; 6. Hennessy BT, et al. *Nat Rev Drug Discov*. 2005;4(12):988-1004; 7. Samuels Y. *Cell Cycle*. 2004;3(10):1221-1224.

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CONTEXT AND CURRENT GUIDANCE IN UK

Treatment related complications

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Type of SACT	Drug Examples	Risk of Diabetes Hyperglycaemia (Range of any grade)	Type of Diabetes
Targeted therapy			
mTOR inhibitors	Everolimus (32, 33)	12-50%	T2DM
	Temsirolimus (33)	26%	
PI3K inhibitors	Alpelisib (34)	37%	T2DM
	Idelialisib (31)	28/30%	
EGFR inhibitor	Osimertinib (35)	2%	T2DM
	Panitumumab (36, 37)	1-10%	
Multikinase inhibitor	Sunitinib (38-40)	0-8% Risk of hypoglycaemia	Reverses T1DM & T2DM, but also leads to hyperglycaemia
	Pazopanib (40)		
Tyrosine Kinase inhibitor (TKI)	Nilotinib (41)	6%	T2DM
	Ponatinib (42)	3%	
ALK Inhibitor	Ceritinib (43)	49%	T2DM
FLT3 inhibitor	Midostaurin (44, 45)	7-20%	T2DM
	Gilteritinib (46)	13%	
Monoclonal antibody	Gemtuzumab (anti-CD33) *inpatient use (47)	10%	T2DM
Somatostatin Analogues	Octreotide, Lanreotide(48)	Up to 30%	T2DM Risk of hypoglycaemia

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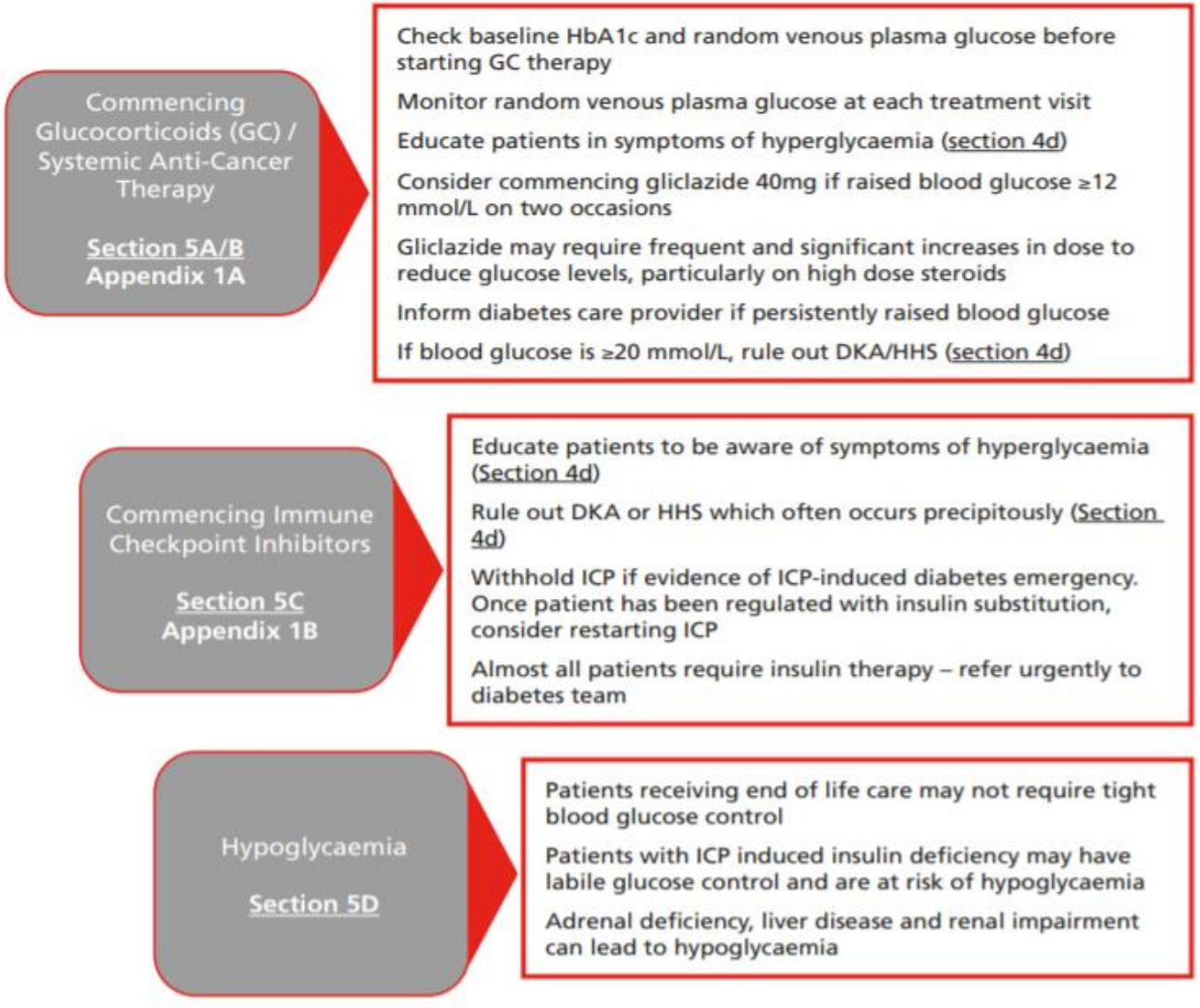
Treatment related complications

Chemotherapy			
Anti-metabolite	5-fluorouracil (49, 50)	Up to 10%	T2DM
	Pemetrexed (51, 52)	4%	
	Decitadine/Azacitidine (53)	6-33%	
Alkylating agents	Busulfan (54)	66-67%	
Platinum based	Oxaliplatin (55, 56)	4%	
Anthracyclines	Doxorubicin (50, 57)	Up to 10%	
Other	Arsenic trioxide (ATO) (58)	45%	
Immune Checkpoint Inhibitors			
PD-1	Nivolumab (59)	<1%	T1DM
	Pembrolizumab (60)	1-2.2%	
CTLA-4	Ipilumumab (59)	0.02%	
	Combination ICP (61)	4%	
Hormone Therapy			
Hormone Treatment	ADT (31, 62)	Risk ratio 1.39 (95% CI 1.27 1.53) n=65,595 cases	T2DM
	Tamoxifen (63)	Diabetes risk adj. odds ratio 1.24 (95% CI 1.08-1.42)	

https://abcd.care/sites/default/files/site_uploads/JBDS_Guidelines_Current/JBDS_17_Oncology_Guideline_with_QR_code_January_2023.pdf

Commencing therapy without previous diabetes



https://abcd.care/sites/default/files/site_uploads/JBDS_Guidelines_Current/JBDS_17_Oncology_Guideline_with_QR_code_January_2023.pdf

Commencing therapy with pre-existing diabetes

Managing Nausea and Vomiting

Section 6A

- PWD should be made aware of likely exacerbation of hyperglycaemia whilst on antiemetic therapy
- PWD receiving emetogenic chemotherapy should be offered an NK1 antagonist (e.g. aprepitant) with a long acting 5HT3 inhibitor (e.g. ondansetron)
- Consider the use of a GC in the first cycle and reduce doses or withdraw completely based on the PWD's emetic control and on blood glucose management

Managing a person with diabetes

Section 6B
Appendix 1C/D

- Ensure PWD has been supplied with a blood glucometer
- Individuals with known diabetes should undertake regular CBG monitoring upon commencing SACT
- Monitor HbA1c 3 monthly whilst receiving SACT
- Rapid antidiabetic therapy changes may be required when commencing high dose GCs /SACT to maintain CBG between 6-12 mmol/L
- Modifications to antidiabetic therapy may be necessary if CBG is found to be ≥12mmol/L. See appendix 1C/D for advice on titrating glucose lowering agents

https://abcd.care/sites/default/files/site_uploads/JBDS_Guidelines_Current/JBDS_17_Oncology_Guideline_with_QR_code_January_2023.pdf

NICE Guidance (Technology Appraisal TA)

Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer

Technology appraisal guidance
Published: 10 August 2022

www.nice.org.uk/guidance/ta816

1 Recommendations

1.1 Alpelisib plus fulvestrant is recommended as an option for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in adults, only if:

- their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor and
- the company provides alpelisib according to the commercial arrangement).

https://www.nice.org.uk/guidance/ta816

NICE impact statement (often governs comms)

Resource impact statement

NICE has recommended alpelisib with fulvestrant as an option for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in adults, only if:

- their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor and
- the company provides alpelisib according to the commercial arrangement (see section 2 of guidance).

This recommendation is not intended to affect treatment with alpelisib plus fulvestrant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

We expect the resource impact of implementing the recommendations in England will be less than £5 million per year (or approximately £9,000 per 100,000 population, based on a population for England of 56.3m people).

This is because the technology is a further treatment option and the overall cost of treatment will be similar. The genetic testing is part of the National Genomic Test Directory for cancer and is funded by NHS England.

https://www.nice.org.uk/guidance/ta816/resources/resource-impact-statement-11189746909

However…..was updated to:

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However the summary of product characteristics states that:

- all people having treatment with alpelisib should have their fasting plasma blood glucose and HbA1c monitored
- fasting glucose should be monitored at weeks 1,2,4,6 and 8 after treatment starts and then monthly for the remainder of the treatment
- HbA1c should be monitored after 4 weeks of treatment and every 4 weeks thereafter
- people with existing diabetes, pre-diabetes, BMI of 35 or higher or age 75 or older should have more frequent monitoring of fasting glucose.

This means that for the population who do not meet the requirements for increased frequency testing, the average number of fasting plasma glucose tests required for a course of treatment with alpelisib with fulvestrant is 14 and the average number of HbA1c tests would be 4. Fasting plasma glucose monitoring in people who meet the criteria for increased monitoring would be at least 28 tests, higher if required.

Feedback from experts has indicated that in some areas oncology teams will not have systems in place to set-up glucose monitoring for people having treatment with alpelisib with fulvestrant and there could be challenges in creating these links to diabetes services or primary care for HbA1c monitoring to be carried out.

https://www.nice.org.uk/guidance/ta816/resources/resource-impact-statement-11189746909

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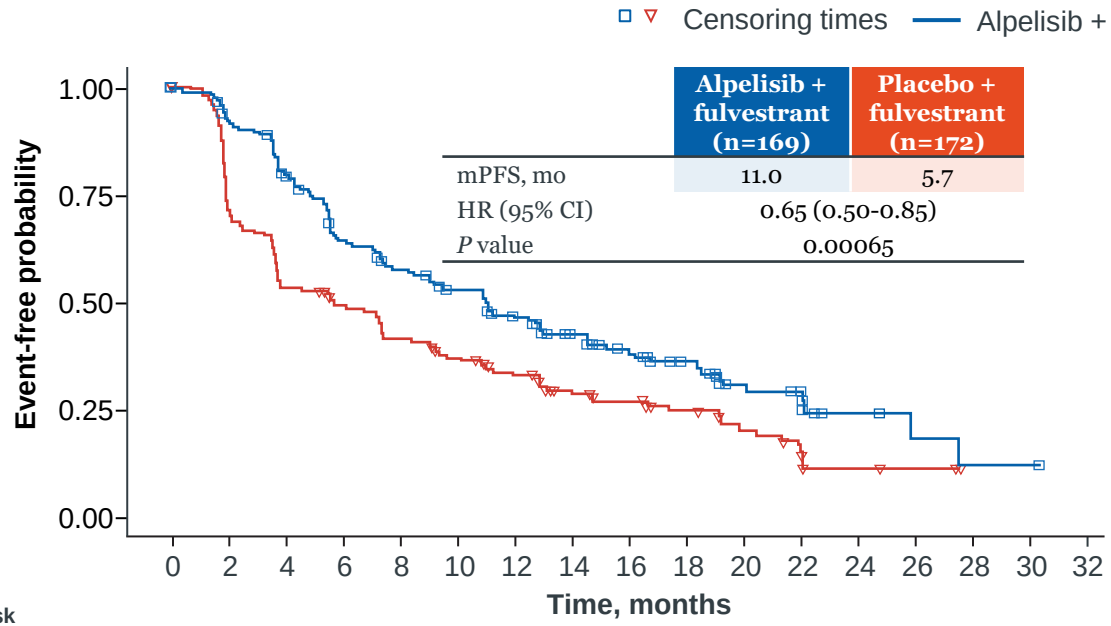
DATA + CASES

SOLAR-1: Alpelisib Significantly Prolonged PFS for Patients in the *PIK3CA*-mutant Cohort[1-3]

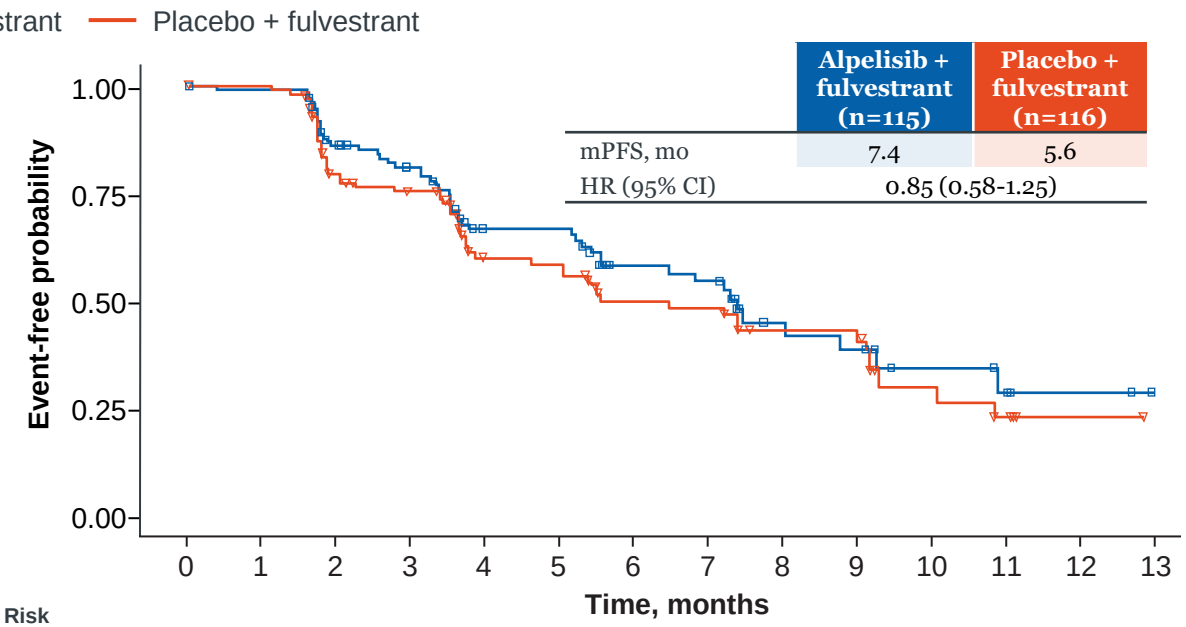
- SOLAR-1 met its primary endpoint; a statistically significant and clinically meaningful prolongation of PFS was observed with the addition of alpelisib to fulvestrant in patients with *PIK3CA*-mutant disease, but was not observed in those without *PIK3CA* mutations[1,2]

PFS in the *PIK3CA*-Mutant Cohort[1]



No. at Risk																	
Alpelisib + fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo + fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

PFS in the *PIK3CA*-Non-Mutant Cohort[1]



No. at Risk															
Alpelisib + fulvestrant	115	110	86	76	48	48	31	29	14	12	7	5	3	0
Placebo + fulvestrant	116	110	79	72	43	42	31	30	20	20	8	5	1	0

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940. Figures reprinted from André F, et al. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. Copyright © 2019 Massachusetts Medical Society. Reproduced with permission from the Massachusetts Medical Society; 2. André F, et al. ESMO 2018. Abstract LBA3 (oral); 3. André F, et al. *Ann Oncol* 2021;32(2):208-217.

NB – exclusion criteria

- Patients with an established diagnosis of diabetes mellitus Type I Diabetes or not controlled Type II Diabetes

- “not controlled” deemed as – HbA1c 48mmol/mol or FPG 7.8mmol/L

Alpelisib + Fulvestrant Has a Well-Characterized Safety Profile in Patients With HR+, HER2−, PIK3CA-mutated ABC

Most common AEs (all grades ≥25%), by Preferred Term, %	SOLAR-1 ALP + FUL (n=284)[1]		BYLieve Cohort A ALP + FUL (n=127)[2,3]		BYLieve Cohort C ALP + FUL (n=127)[5]	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hyperglycemia	63.7	36.6	58.3	28.3	65.1	23.8
Diarrhea	57.7	6.7	59.8	5.5	52.4	3.2
Nausea	44.7	2.5	45.7	0.0	40.5	2.4
Decreased appetite	35.6	0.7	28.3	0.8	32.5	6.3
Rash	35.6	9.9	28.3	9.4	38.9	13.5
Vomiting	27.1	0.7	23.6	1.6	24.6	1.6
Stomatitis	24.6	2.5	26.8	1.6	29.4	0.8
Fatigue	24.3	3.5	29.1	0.8	34.1	4.0

Hyperglycemia, diarrhea, and rash were the 3 most common grade ≥3 AEs with alpelisib + fulvestrant in SOLAR-1 and BYLieve Cohort A[1,2]

Hyperglycemia and rash were also the top grade ≥3 AEs with alpelisib + fulvestrant in Cohort C[4]

- Safety after 6 months of follow-up was consistent with that observed in the earlier-phase studies with alpelisib and there were no new or unexpected safety signals reported[1]
- Safety of alpelisib + letrozole was consistent with that observed for alpelisib + fulvestrant[5]
- No new safety signals or cumulative toxicities were observed in patients who achieved approximately 18 months' follow-up[6,7]

1. André F, et al. N Engl J Med. 2019;380(20):1929-1940; 2. Rugo HS, et al. Lancet Oncol. 2021;22(4):489-498; 3. Rugo HS, et al. ASCO 2020. Abstract 1006. 4. Rugo HS, et al. SABCS 2021. Abstract PD13-05 (poster). 5. Rugo HS, et al. SABCS 2020. Abstract PD2-07 (poster); 6. Ciruelos EM, et al. SABCS 2021. Abstract P1-18-03 (poster); 7. Rugo HS, et al. Ann Oncol. 2020;31(8):1001-1010.

These data are summarizing results from different studies and cannot be directly compared

Dose adjustment and classification of hyperglycaemia

	Fasting glucose (FG) values[1]	Recommendation
	Dose modification and management should only be based on fasting glucose (plasma/blood) values.	
Grade 1	>ULN-160 mg/dl or >ULN-8.9 mmol/l	No Piqray dose adjustment required. Initiate or intensify oral antidiabetic treatment[2].
Grade 2	>160-250 mg/dl or >8.9-13.9 mmol/l	No Piqray dose adjustment required. Initiate or intensify oral antidiabetic treatment[2]. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days with appropriate oral antidiabetic treatment[2,3], reduce Piqray dose by 1 dose level and follow FG-value-specific recommendations.
Grade 3	>250-500 mg/dl or >13.9-27.8 mmol/l	Interrupt Piqray. Initiate or intensify oral antidiabetic treatment[2] and consider additional antidiabetic medicinal products such as insulin[3] for 1-2 days until hyperglycaemia resolves, as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances). If FG decreases to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Piqray at next lower dose level. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, consultation with a healthcare professional with expertise in the treatment of hyperglycaemia is recommended. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days following appropriate antidiabetic treatment[2,3], permanently discontinue Piqray treatment.

Piqray 150 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Dose adjustment and classification of hyperglycaemia

Grade 4

>500 mg/dl or >27.8 mmol/l	Interrupt Piqray. Initiate or intensify appropriate antidiabetic treatment[2,3] (administer intravenous hydration and consider appropriate treatment [e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances]), re-check within 24 hours and as clinically indicated. If FG decreases to ≤500 mg/dl or ≤27.8 mmol/l, then follow FG-value-specific recommendations for <500 mg/dl. If FG is confirmed at >500 mg/dl or >27.8 mmol/l after 24 hours, permanently discontinue Piqray treatment.

[1] Fasting glucose levels reflect hyperglycaemia grading according to CTCAE Version 4.03 CTCAE = Common Terminology Criteria for Adverse Events.

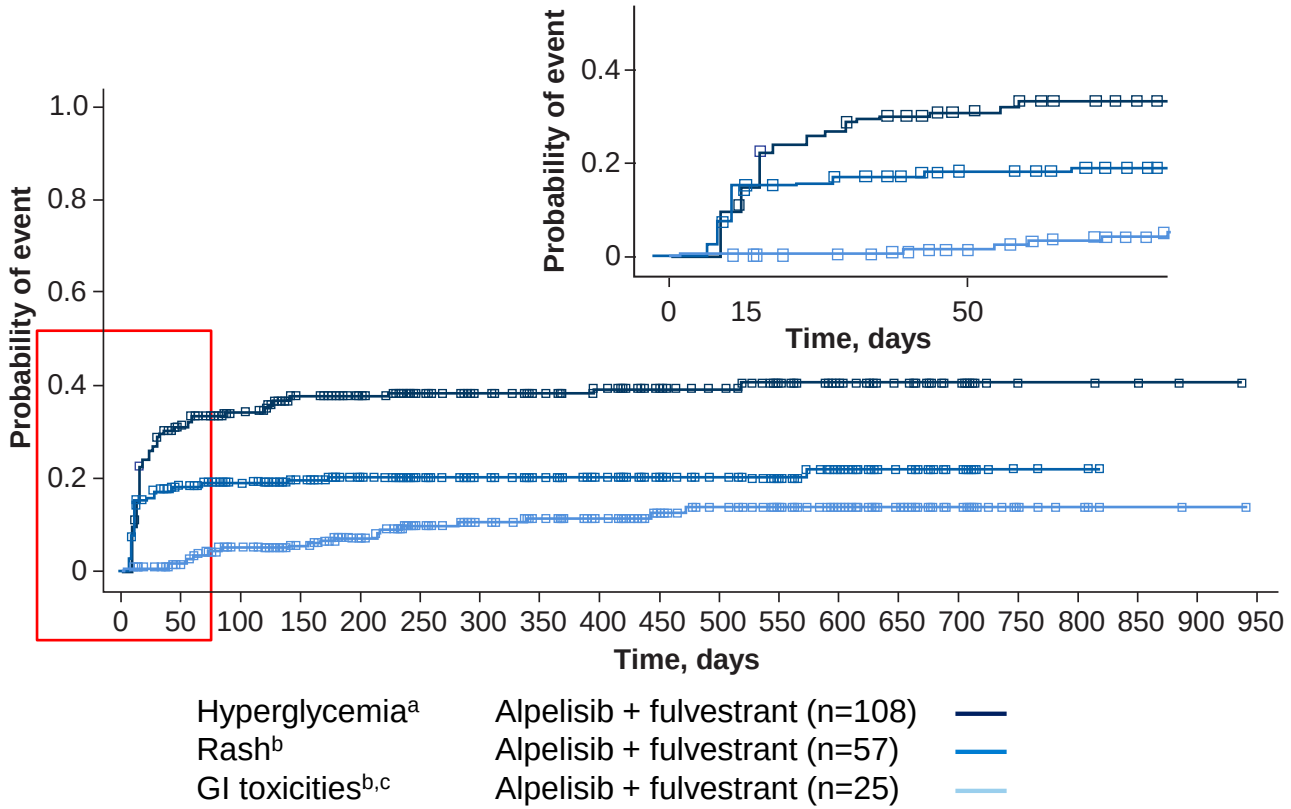
[2] Applicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the phase III clinical study with the following guidance: Metformin should be initiated at 500 mg once daily. Based on tolerability, the metformin dose may be increased to 500 mg twice daily, followed by 500 mg with breakfast, and 1000 mg with the evening meal, followed by further increase to 1000 mg twice daily if needed (see section 4.4).

[3] As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycaemia resolves. However, this may not be necessary in the majority of cases of alpelisib-induced hyperglycaemia, given the short half-life of alpelisib and the expectation that glucose levels will normalise following interruption of Piqray.

Piqray 150 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

SOLAR-1: Hyperglycemia and Rash Occur Early in the Treatment With Alpelisib, Whereas Diarrhea May Occur Over the Course of Treatment1,2

Probability of First Occurrence of Grade ≥3 AESI[1]



Time to Onset and Time to Improvement of Grade ≥3 AESIs[1,2]

	Median time to onset, days	Median time to improvement by ≥1 grade, days
Hyperglycemia	15	6
Rash	13	11
Diarrhea	139	18

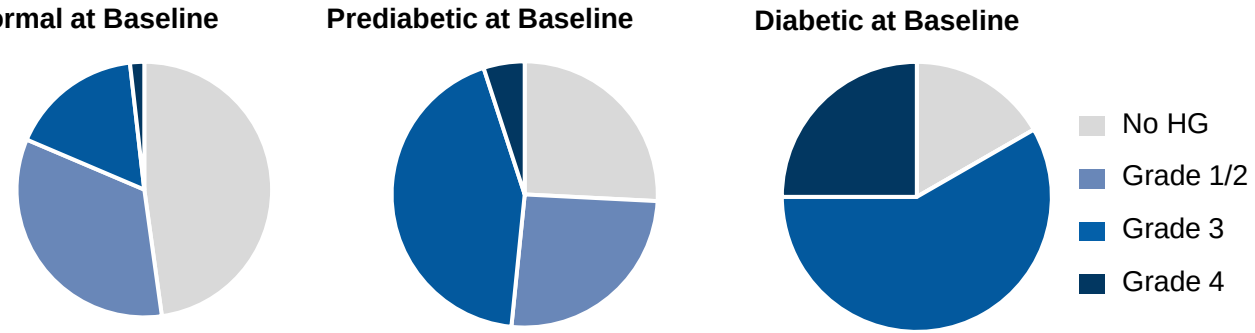
- 96% of patients who continued fulvestrant after discontinuing alpelisib due to hyperglycemia in SOLAR-1 had FPG return to baseline levels[3]

aBased on laboratory values rather than single preferred term. bBased on grouped terms. cOf the grade ≥3 GI toxicities, 76% of them were grade ≥3 diarrhea.

1. Rugo HS, et al. ESMO 2019. Abstract 324P (poster) ; 2. Rugo HS, et al. Ann Oncol. 2020;31(8):1001-1010; 3. Piqray (alpelisib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021.

Early Identification of Patients at Risk for Hyperglycemia Is Key to Providing Appropriate and Timely Interventions1

Hyperglycemia by Baseline Glycemic Status in SOLAR-1[1,2]



	Normal at Baseline	Prediabetic at Baseline	Diabetic at Baseline
	n=113	n=159	n=12
Leading to discontinuation of alpelisib:	3.5%	7.5%	25.0%

All-grade and grade 3/4 hyperglycemia was more frequent in patients who were prediabetic/diabetic compared with those who had normal glycemic status at baseline[1]

- A risk-factor model combining data from the Phase I FIH X2101 and Phase III SOLAR-1 studies identified baseline FPG, BMI, HbA1c, monocytes, and age as risk factors for developing grade 3/4 hyperglycemia during treatment with alpelisib[3]

Screen for prediabetes or diabetes at baseline[1]
Prediabetes: 5.6 to <7.0 mmol/L, HbA1c 5.7% to <6.5%
Diabetes: ≥7.0 mmol/L, HbA1c ≥6.5%

Identify baseline risk factors[4]
FPG ≥5.6 mmol/L BMI ≥30 Age ≥75 years

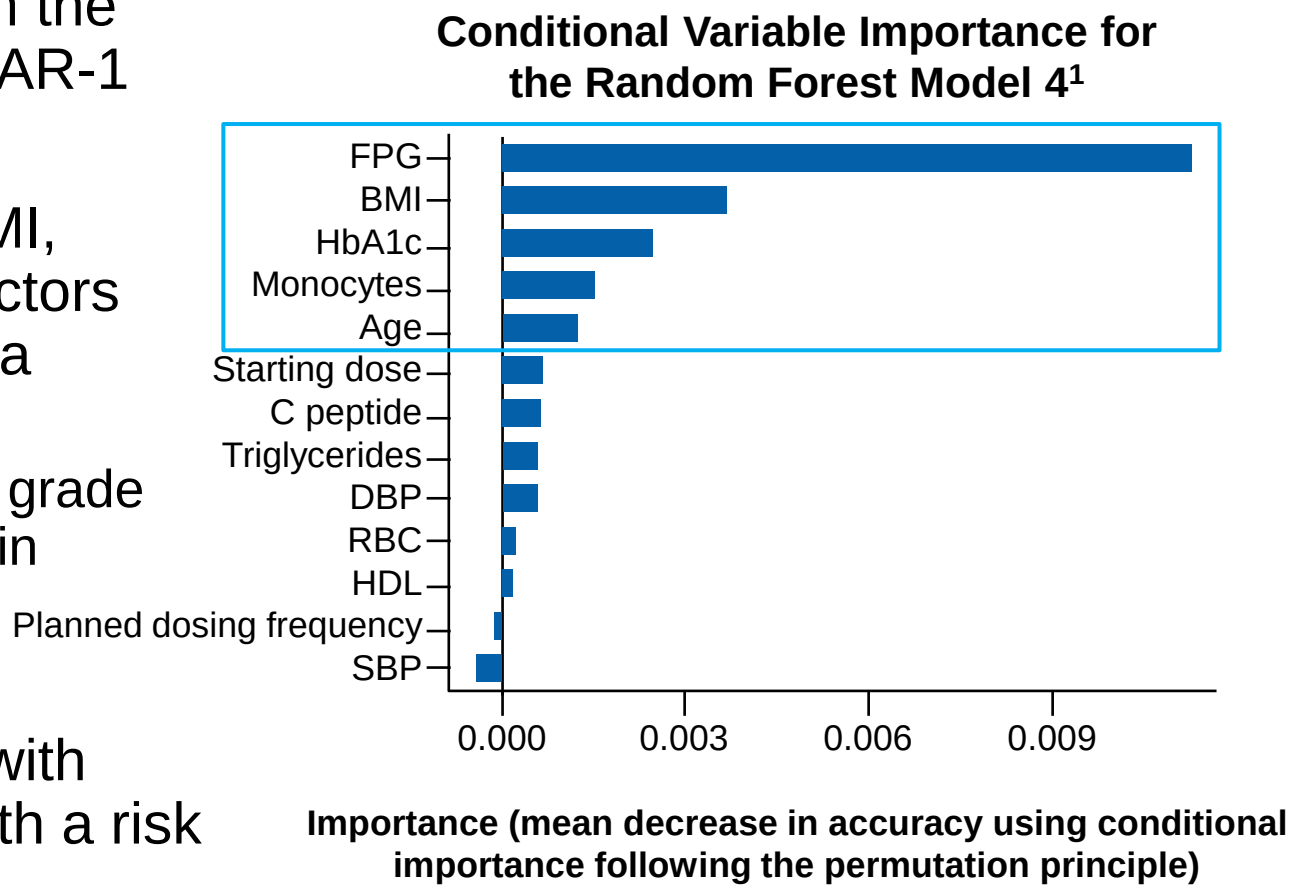
- If screening and risk factors indicate higher risk, manage before starting alpelisib
- Consider consultation with diabetologist
- Recommend lifestyle changes such as dietary advice and physical activity

After initiating alpelisib, advise patients to contact their HCP immediately for any symptoms of hyperglycemia (eg, excessive thirst, frequent urination, increased appetite with weight loss)

1. Rugo HS, et al. Ann Oncol. 2020;31(8):1001-1010; 2. Data on file; 3. Rodon J, et al. ESMO BC 2021. Abstract 96MO (oral); 4. Piqray (alpelisib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021.

A Risk Factor Model Identified Top Risk Factors for Developing Grade 3/4 Hyperglycemia During Treatment With Alpelisib

- This pooled model combined data from the Phase I FIH X2101 and Phase III SOLAR-1 studies1
- The model identified baseline FPG, BMI, HbA1c, monocytes, and age as risk factors for developing grade 3/4 hyperglycemia during treatment with alpelisib1
  - Most patients (86%) with all-grade and grade 3/4 hyperglycemia were able to maintain alpelisib treatment
- 74.7% of patients with all-grade hyperglycemia and 86.2% of patients with grade 3/4 hyperglycemia presented with a risk factor at baseline2



Both high- and low-risk patients with *PIK3CA*-mutated tumors achieved a similar benefit from alpelisib[1]

1. Rodon J, et al. ESMO BC 2021 Abstract 96MO (oral); 2. Piqray [summary of product characteristics]. Ireland: Novartis Europharm Limited; 2020.

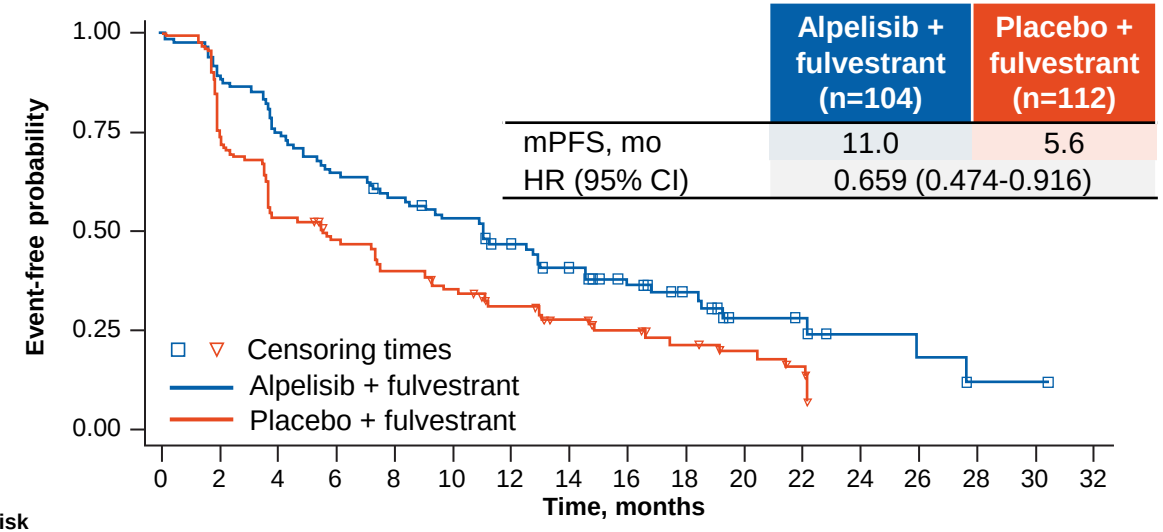
Schedule of fasting glucose monitoring suggested

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with Piqray	Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with Piqray
At screening, before initiating treatment with Piqray	Test for fasting plasma glucose (FPG), HbA1c, and optimise the patient's level of blood glucose (see Table 2).	
After initiating treatment with Piqray	Monitor fasting glucose at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter.	
	Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.	Monitor/self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.
	HbA1c should be monitored after 4 weeks of treatment and every 3 months thereafter.	
If hyperglycaemia develops after initiating treatment with Piqray	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.	
	During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycaemia.	
* All glucose monitoring should be performed at the physician's discretion as clinically indicated.		

Piqray 150 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

SOLAR-1: Baseline Glucose Levels Did Not Impact Alpelisib Efficacy[1,a]

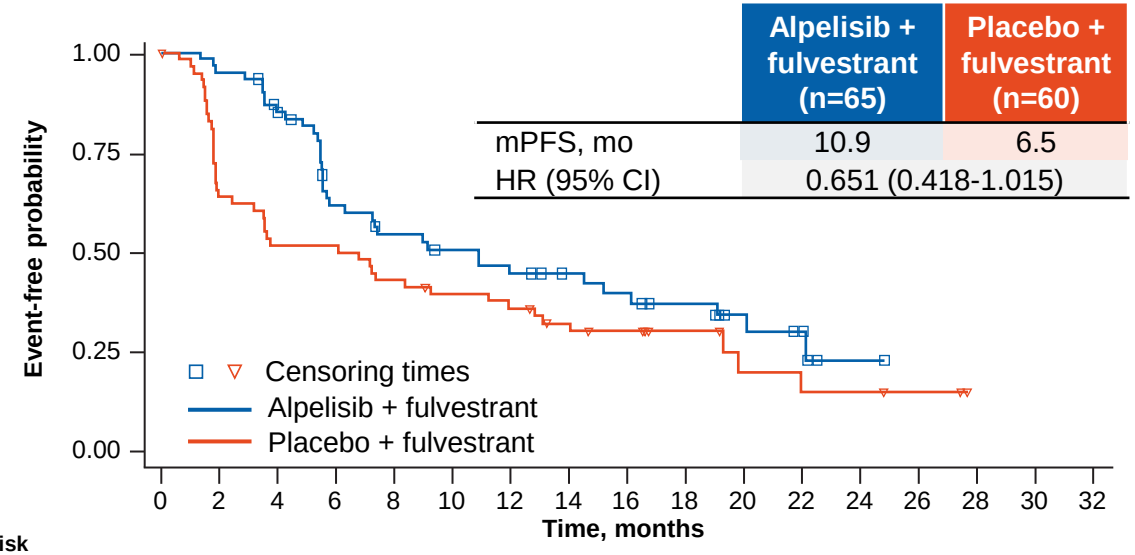
Prediabetic/Diabetic at Baseline[1]



No. at Risk

Alpelisib + fulvestrant	104	99	98	98	98	98	97	97	97	97	97	97	97	97	97	97	97
Placebo + fulvestrant	112	110	110	110	110	110	110	110	110	110	110	110	110	110	110	110	110

Normal Glycemic Status at Baseline[1]



No. at Risk

Alpelisib + fulvestrant	65	61	61	61	61	61	61	61	61	61	61	61	61	61	61	61	61
Placebo + fulvestrant	60	58	58	58	58	58	58	58	58	58	57	57	57	57	57	57	56

PFS advantage was consistent across the different glycemic status values in patients with *PIK3CA* mutations treated with alpelisib versus placebo[1]

[a]Glycemic status was evaluated prior to alpelisib dosing (before randomization) and was based on ADA guidelines: normal: FPG <5.6 mmol/L (<100 mg/dL) or HbA1c <5.7%; prediabetic: FPG 5.6-6.9 mmol/L (100-125 mg/dL) or HbA1c 5.7%-6.4%; diabetic: FPG ≥7.0 mmol/L (≥126 mg/dL) or HbA1c ≥6.5%.[1,2]

1. Rugo HS, et al. *Ann Oncol*. 2020;31(8):1001-1010; 2. American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S17-S38.

Case 1 – Type 2 Diabetes

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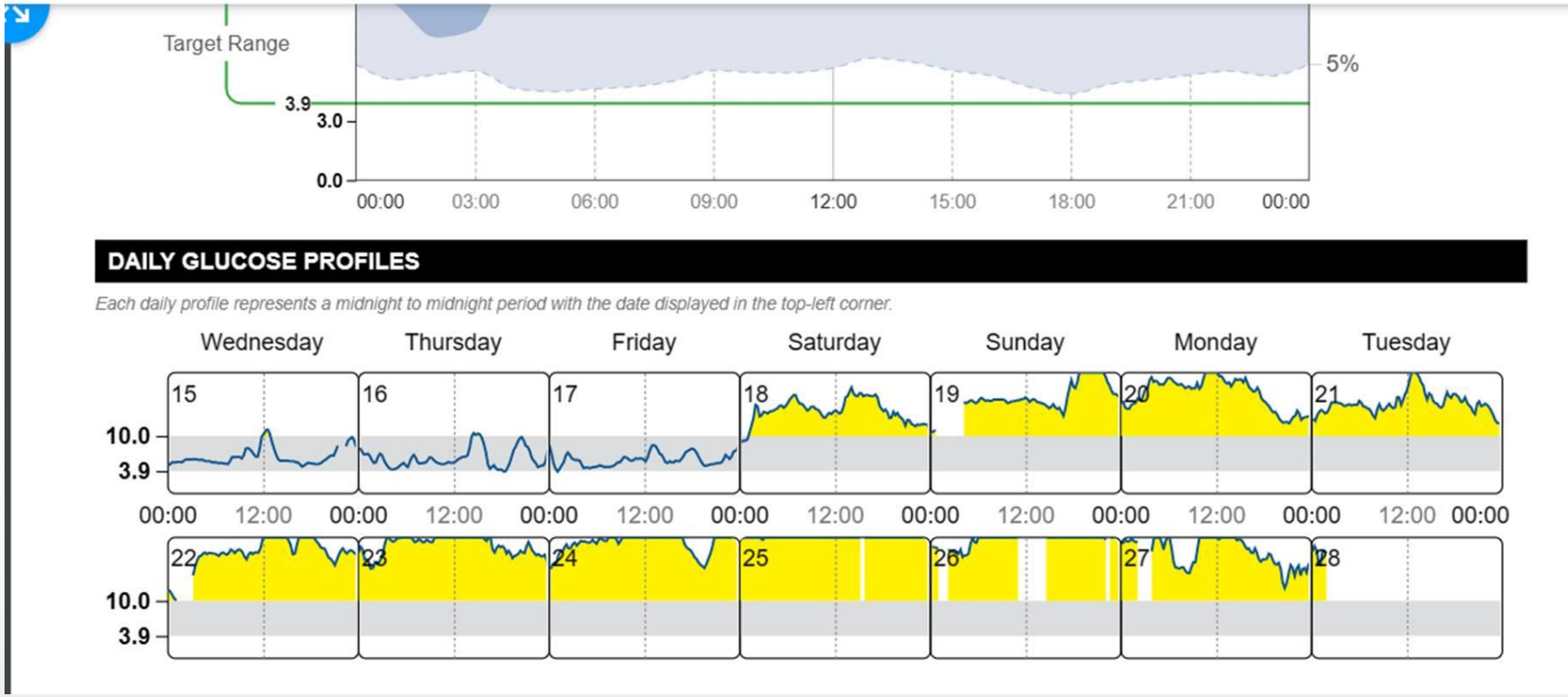
- Starting HbA1c 53mmol/mol (new Dx)
- No medications
- Metformin and Lantus 10 units started 7 days prior to alpelisib
- Ended up on 48units Lantus / Novorapid 22/16/16 + Metformin
- Eventually had to stop Alpelisib in line with SPC



Case and data used with permission, courtesy of A. Epps

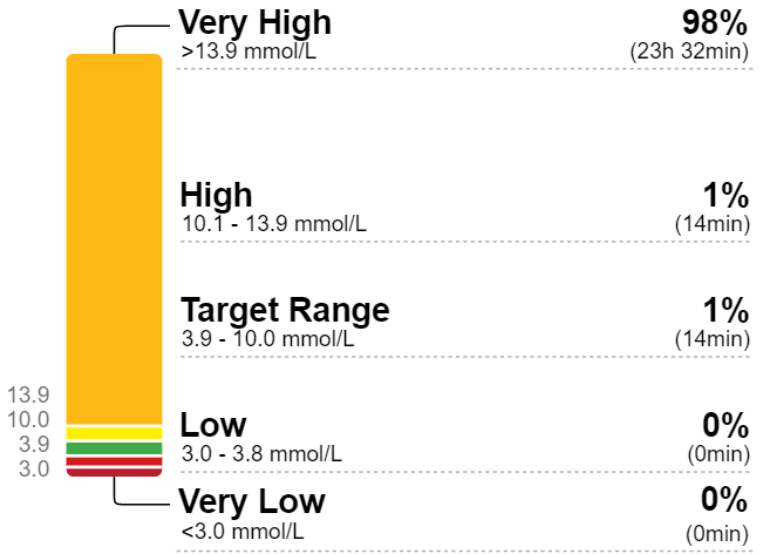
Case 2 - 8 days after starting

- On Abasaglar 10units with Libre device for monitoring
- No diabetes beforehand (HbA1c 38mmol/mol)

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 3.9-10.0 mmol/L	Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)
Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.	

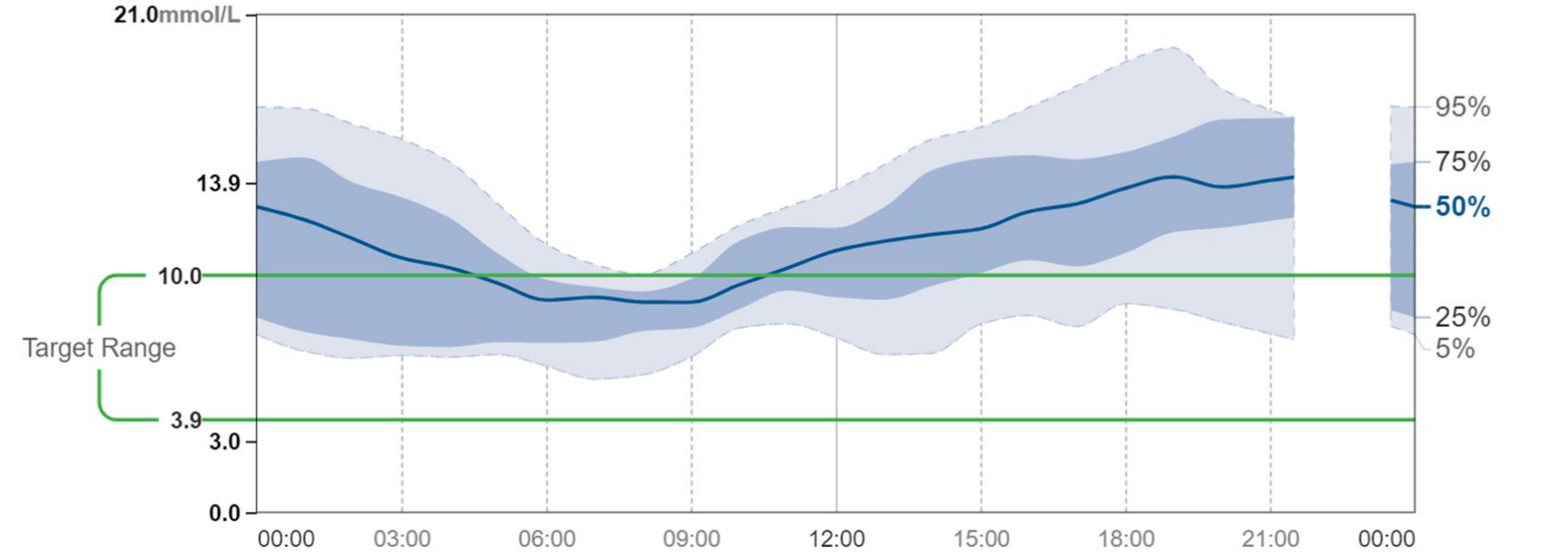
Average Glucose	**26.6** mmol/L
Glucose Management Indicator (GMI)	**14.8% or 138 mmol/mol**
Glucose Variability	**11.9%**

Defined as percent coefficient of variation (%CV); target ≤36%



Started on basal bolus

- Novo Rapid: 14:18:18units
- Absaglar 45 units



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On basal bolus therapy

Novo Rapid: 20:22:22units
Abasaglar 75 units

Time sensor active: **49%**

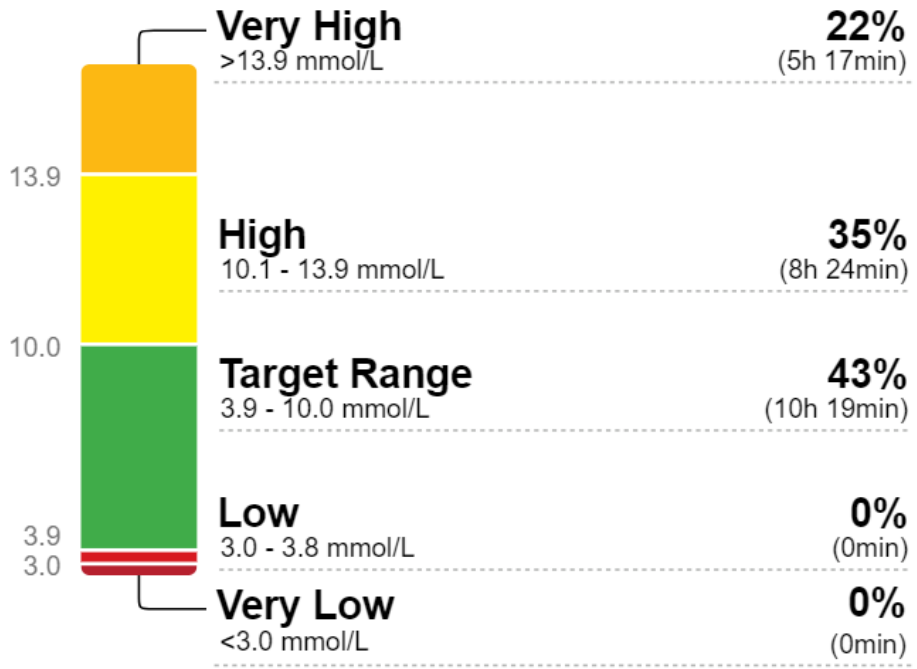
Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges Target Range 3.9-10.0 mmol/L	**Targets** % of Readings (Time/Day) Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)
Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.	

Average Glucose **11.2** mmol/L

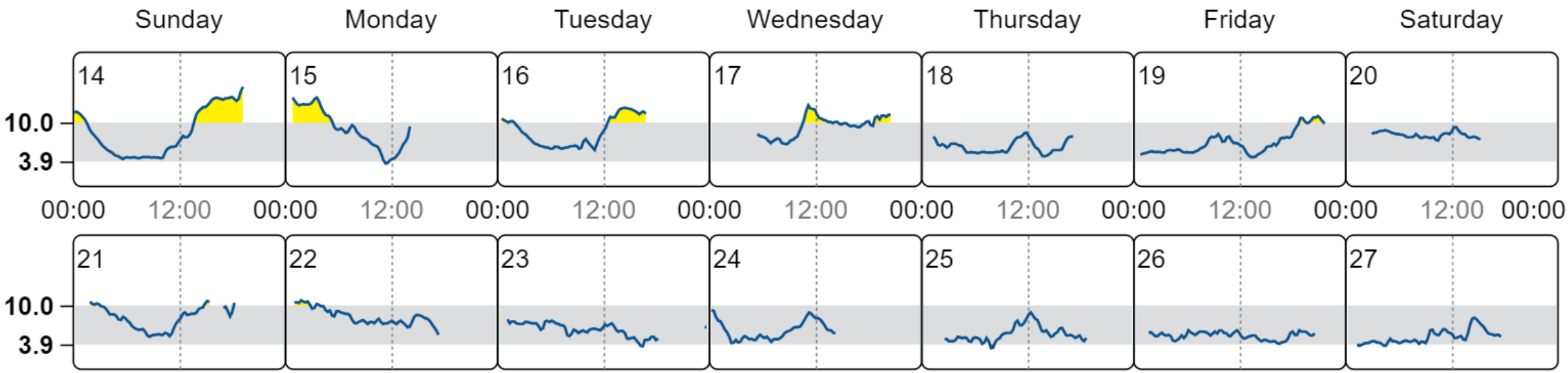
Glucose Management Indicator (GMI) **8.1% or 65 mmol/mol**

Glucose Variability **29.3%**

Defined as percent coefficient of variation (%CV); target ≤36%



Decision to stop Alpelisib on 17th of month



2 weeks data post stopping Apelisib (remained on steroids for separate issue)

Time sensor active: **71%**

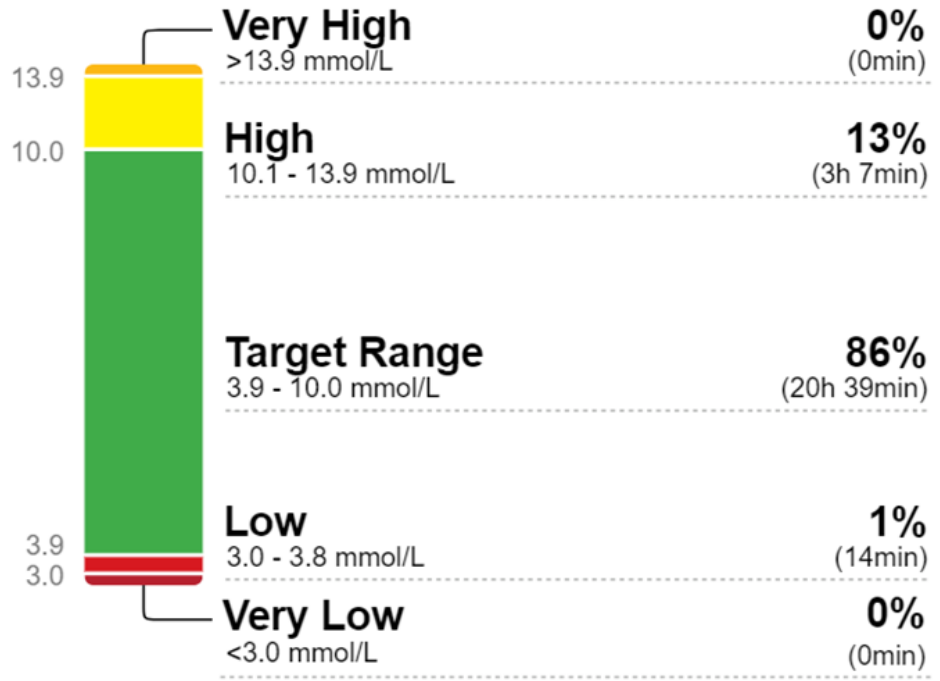
Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges Target Range 3.9-10.0 mmol/L	**Targets** % of Readings (Time/Day) Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)
Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.	

Average Glucose **7.2** mmol/L

Glucose Management Indicator (GMI) **-**

Glucose Variability **32.4%**

Defined as percent coefficient of variation (%CV); target ≤36%



1 month after stopping Apelisib

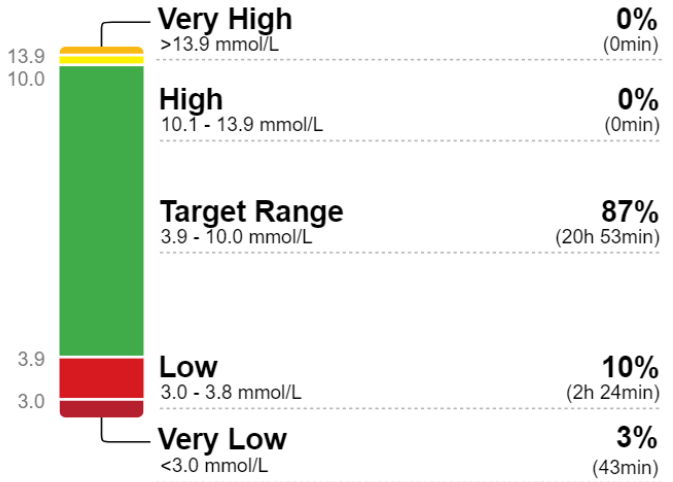
- No longer on insulin or any diabetes meds
- Venous Hba1c 33
- Stopped all cancer meds – for palliative therapies

Time sensor active: 71%

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges Target Range 3.9-10.0 mmol/L	**Targets** % of Readings (Time/Day) Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)
Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.	

Average Glucose	**4.8** mmol/L
Glucose Management Indicator (GMI)	**5.4% or 35 mmol/mol**
Glucose Variability	**18.7%**

Defined as percent coefficient of variation (%CV); target ≤36%



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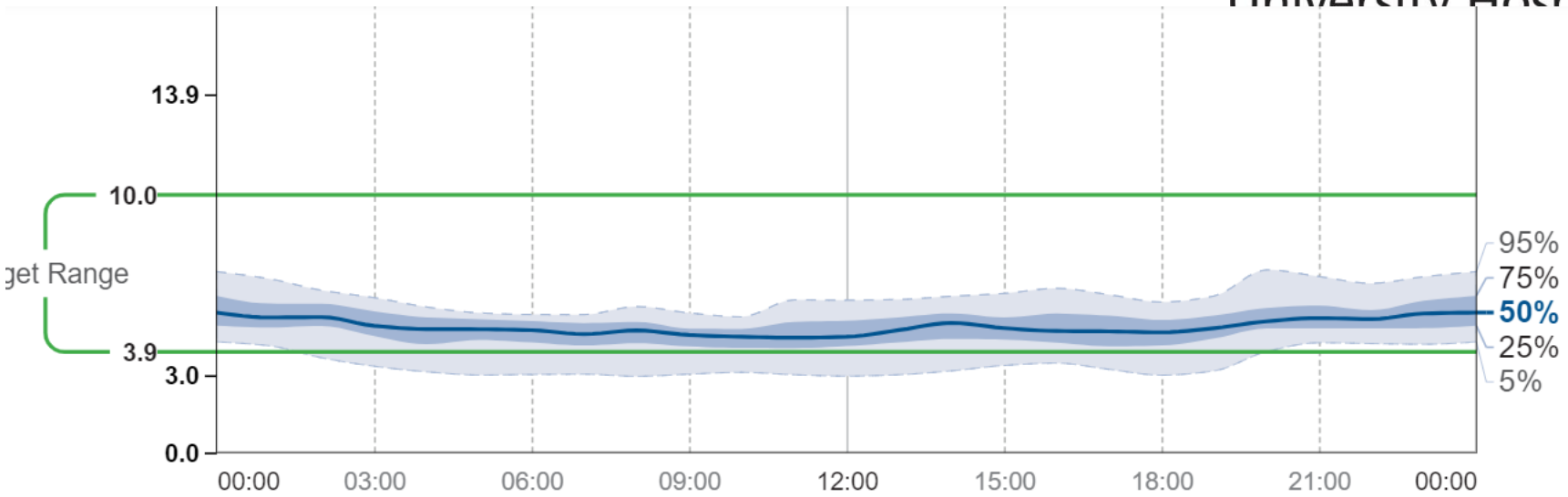
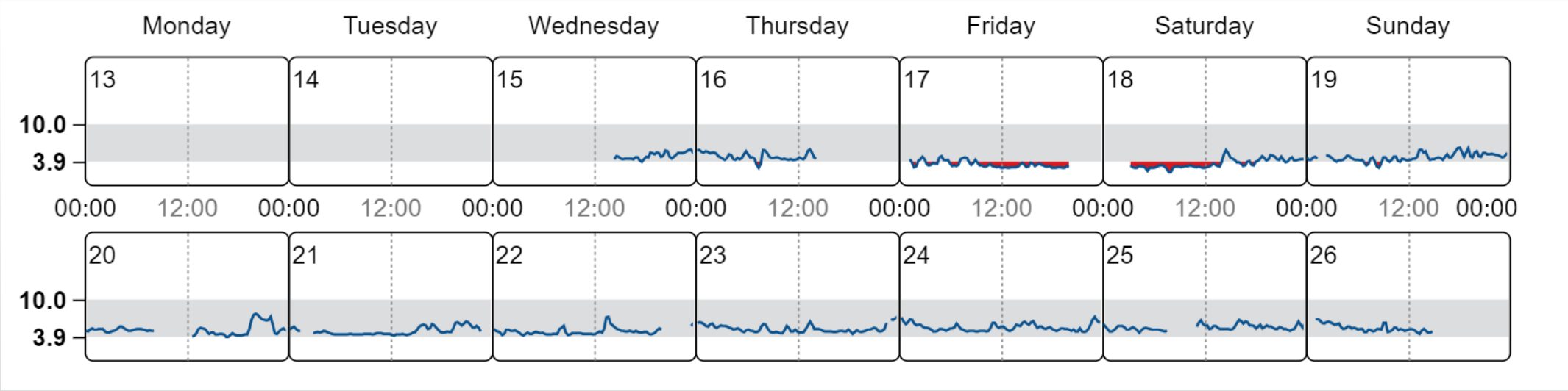




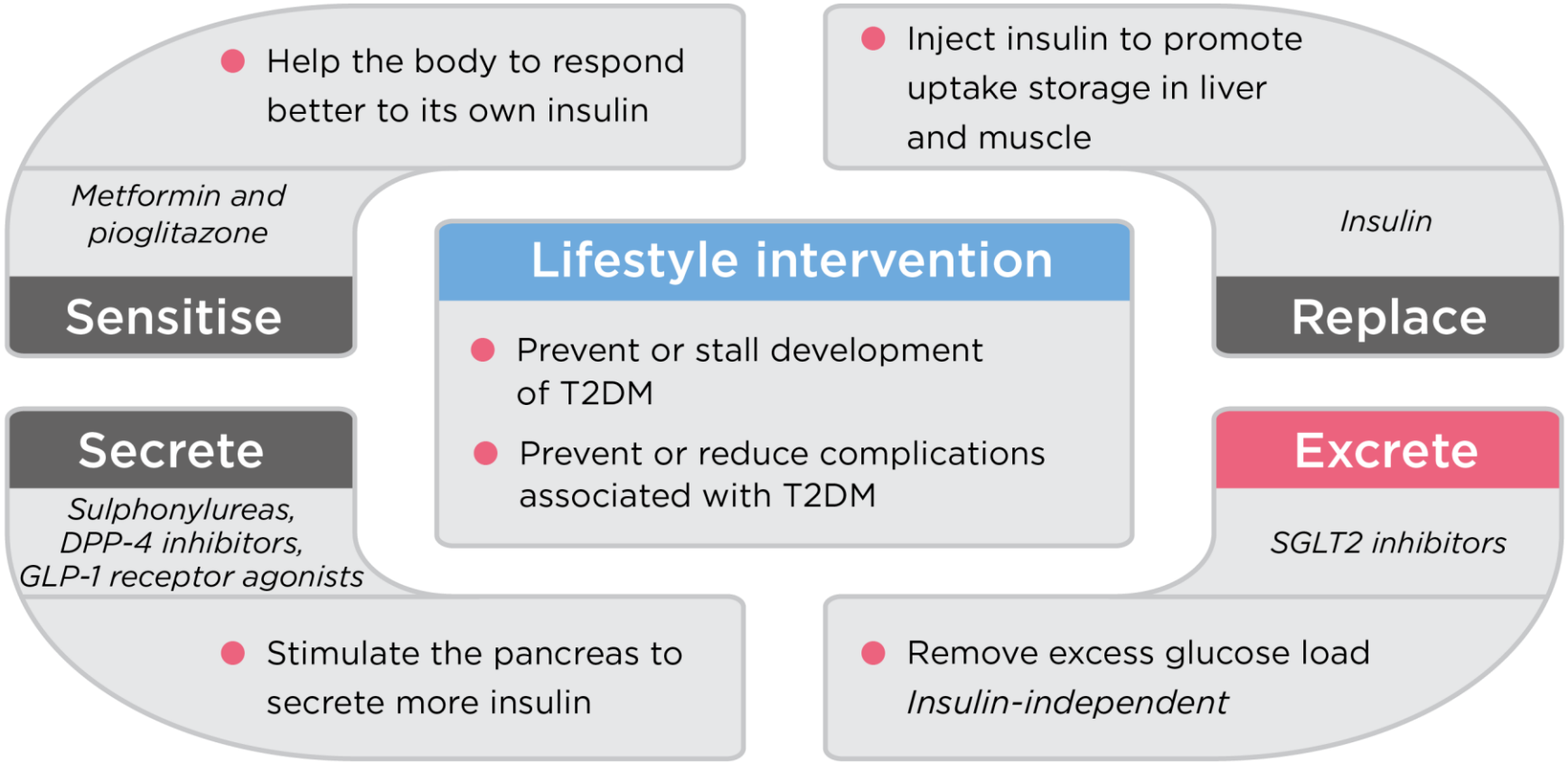
MANAGEMENT OPTIONS

NB – Treatment options

- Aim of treatment is to prolong survival
- Often this may be an increase of months rather than years
- All treatment suggestions need to balance:

» **Benefit vs Burden**

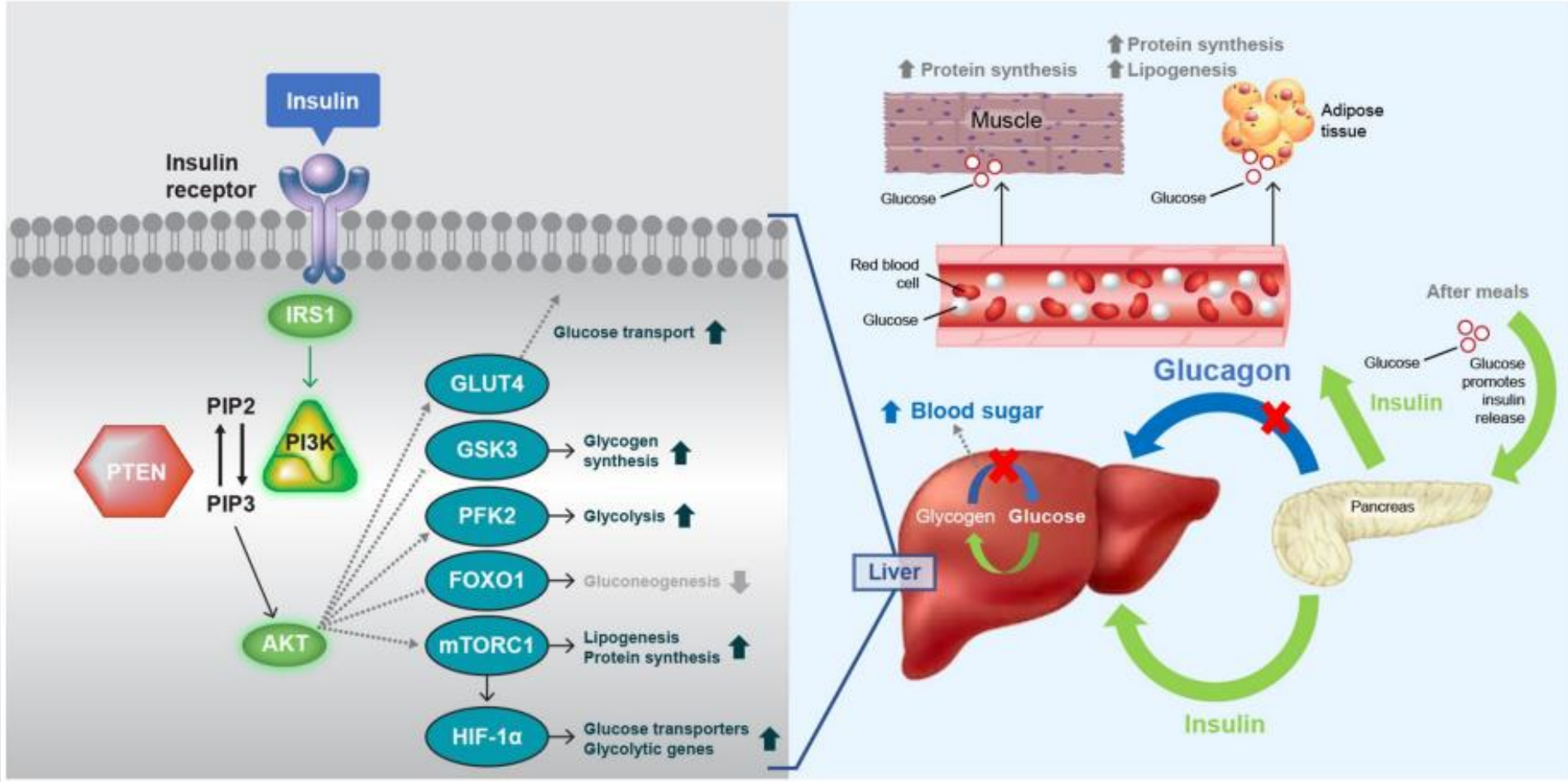
Treatment options for controlling excess blood glucose in type 2 diabetes



Adapted from Invokana SmPC,[2] NICE guideline NG28,[3] Bailey CJ, 2011,[4] and Patient.info.[5] DPP-4i dipeptidyl peptidase-4 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist; SGLT2i: sodium-glucose co-transporter 2 inhibitor.

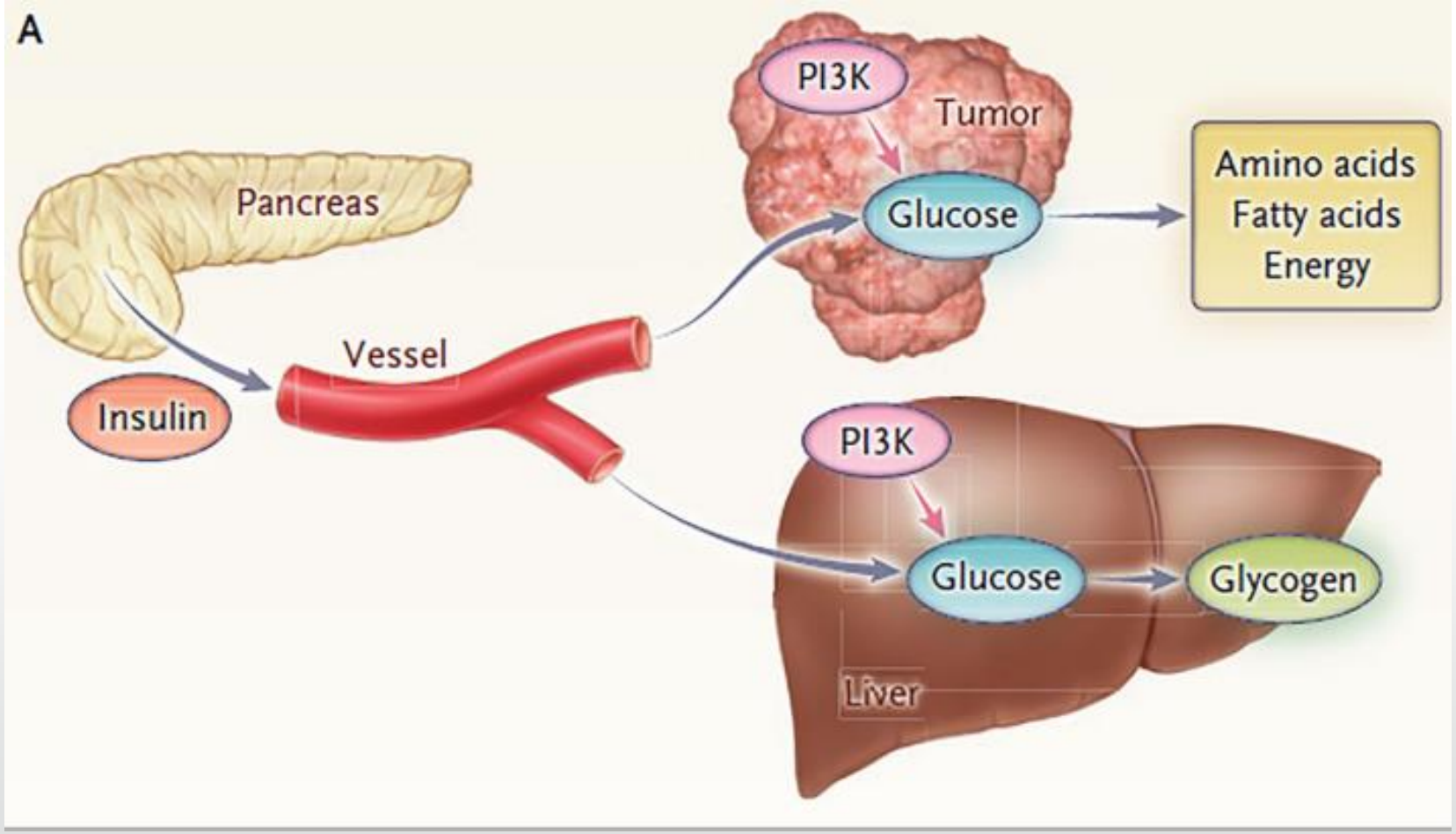
1. Bailey CJ, et al. BMC Med 2013;11:43.
2. Invokana 100 mg and 300 mg film-coated tablets. Summary of Product Characteristics. [Accessed August 2020]. www.medicines.org.uk/emc/product/8855
3. NICE guideline NG28. December2015. [Accessed July 2020]. www.nice.org.uk/guidance/ng28
4. Bailey CJ. Trends Pharmacol Sci 2011;32:63-71.
5. Patient.info. Type 2 diabetes treatment. [Accessed July 2020]. https://patient.info/health/type-2-diabetes

Role of insulin in the PI3K pathway



Goncalves MD, Farooki A. Management of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia. Integrative Cancer Therapies. 2022;21. doi:10.1177/15347354211073163

Increasing insulin may counter the effects of the PI3K inhibitor



Goncalves MD, Farooki A. Management of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia. Integrative Cancer Therapies. 2022;21. doi:10.1177/15347354211073163

Diabetes Medicines – do they affect the PIK pathway?

Evidence that reduction in insulin enhances efficacy of PI3K inhibitors[1]

- **Don't affect the PIK pathway**
  - Metformin
  - SGLT2i
  - Pioglitazone
  - Acarbose

- **Affect the PIK pathway**
  - Sulfonylureas
  - Meglitinides
  - DPP4i
  - GLP-1 RA
  - Insulin

1. Hopkins BD, Pauli C, Du X, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature. 2018;560:499-503. doi:10.1038/s41586-41018-40343-41584

Hyperglycemia Can Be Managed With Medical Intervention1

In SOLAR-1, **metformin** was most frequently used to manage hyperglycemia

Management of Hyperglycemia in SOLAR-1, % (n/N)[1-2]	
Managed with antihyperglycemic medication	87% (163/187)
Use of metformin (either as single agent or in combination with other antihyperglycemic medication[a,b])	76% (142/187)

Number of Secondary Antidiabetic Medications Received by Patients Managed With Antihyperglycemia Medication in the Alpelisib Group, N=163, n (%)[1]	
1	67 (41.1%)
2	49 (30.1%)
3	27 (16.6%)
4+	20 (12.3%)

Metformin dosing guidance[2,3]

Risks associated with metformin include GI effects (eg, diarrhea)[5]

- In SOLAR-1, the incidence and severity of diarrhea were similar in patients who did or did not receive metformin[1]

[a]Less frequently used antihyperglycemic medications in SOLAR-1 included various types of insulin, DPP4 inhibitors, sulfonylureas, and others.[2]

[b]With grade ≥3, SOLAR-1 protocol advised that insulin could be used for 1-2 days until hyperglycemia resolved; however, may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib.[3]

*Based on tolerability. Increase dose if needed for glycemic control. Refer to the full prescribing information for metformin.[2,3]

1. Rugo HS, et al. *Ann Oncol*. 2020;31(8):1001-1010; 2. Piqray (alpelisib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021; 3. CBYL719C2301 Clinical Protocol. Novartis Pharmaceuticals Corp; 2018; 4. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940; 5. American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S125-143.

Management of Hyperglycemia with SGLT2i in SOLAR-1

In SOLAR-1, 6 patients (2.1%) received an **SGLT2 inhibitor**[1]

- SGLT2 inhibitors produce a reduction in blood glucose without stimulating insulin release[2]

SGLT2 inhibitors used in SOLAR-1

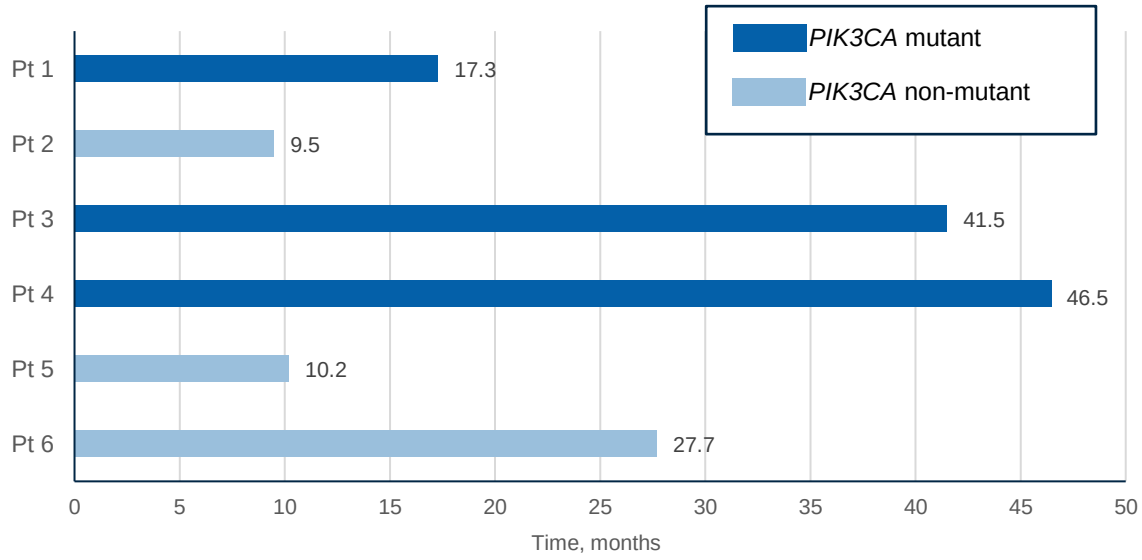
- **Empagliflozin**
- **Ipragliflozin**
- **Dapagliflozin**

Mostly used as 3rd-4th hypoglycemic agent, in combination with metformin and other agents (DPP4i, sulfonylureas, thiazolidinediones, etc)

Risks associated with SGLT2 inhibitors include diabetic ketoacidosis, genitourinary infections, volume depletion, and hypotension[3]

- After initiating an SGLT2 inhibitor, all subsequent hyperglycemia events were grade 1/2, except one grade 3 event with steroids as a confounding factor
- Despite all 6 patients presenting baseline risk factors (4 prediabetic, 2 diabetic, 2 obese [BMI ≥30], and 2 overweight [BMI 25-29.9]), none of these patients discontinued due to hyperglycemia
- A longer duration of treatment was observed in these 6 patients compared with the median observed in SOLAR-1

Duration of Treatment in Patients Receiving an SGLT2 Inhibitor[1,a]

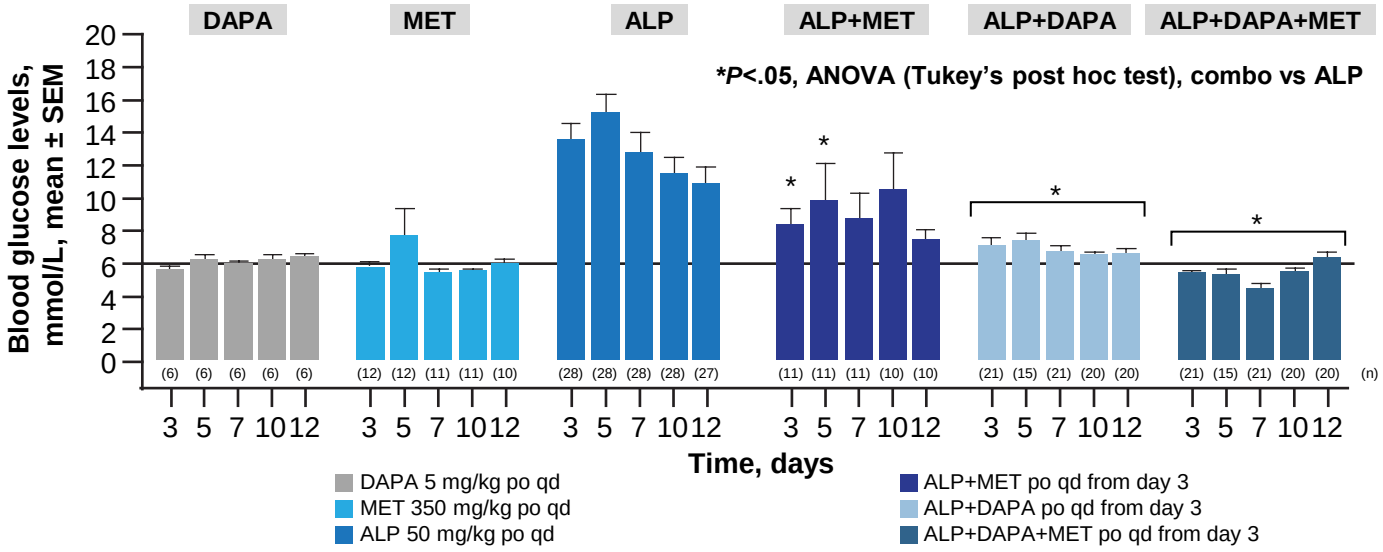


[a]Patients 3 and 4 were still receiving alpelisib at data cutoff.

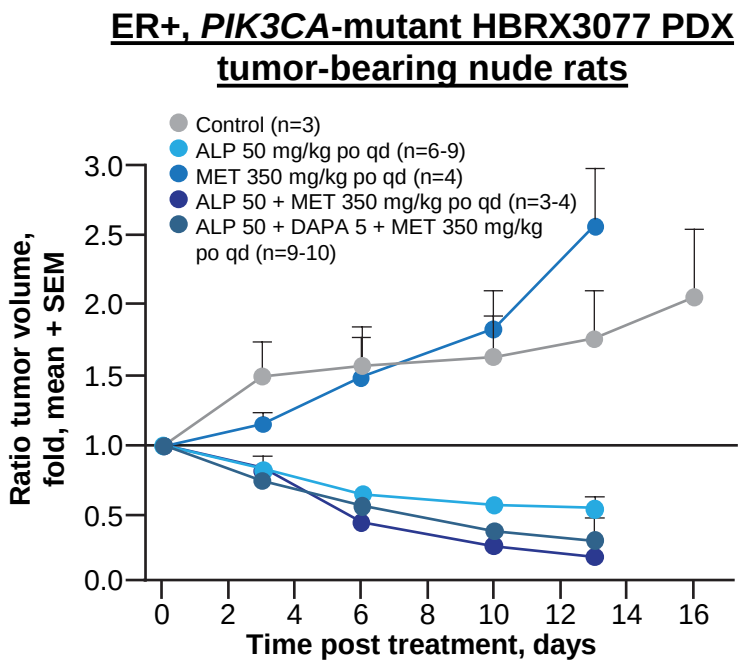
1. Lu Y-S, et al. ESMO 2020. Abstract 301P (poster); 2. Hsia DS, et al. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79; 3. American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S125-143.

Blood Glucose and Insulin Levels Were Reduced With Alpelisib and Dapagliflozin +/– Metformin While Maintaining Antitumor Efficacy

- In the Brown Norway rat model, the addition of dapagliflozin, an SGLT2 inhibitor, to alpelisib significantly reduced blood glucose levels with no evidence of drug-drug interaction
  - The addition of metformin to this combination further reduced blood glucose levels



- In tumor-bearing nude rat models, the antitumor efficacy of alpelisib was maintained or improved upon combination with DAPA or MET +/– DAPA



Schnell C, et al. AACR-NCI-EORTC 2021. Abstract P137 (poster).

EPIK-B4 Explores Prophylactic Metformin XR +/– Dapagliflozin for Patients at High Risk of Developing Severe Hyperglycemia Upon Treatment With Alpelisib + Fulvestrant1,2

There remains an unmet need for management strategies that offer earlier and more sustained improvement of hyperglycemia than what is achieved with metformin as initial therapy

Patient population:

- HR+, HER2– ABC with *PIK3CA* mutation and progression on or after endocrine-based therapy
- At least one risk factor for severe hyperglycemia based on baseline diabetic status (diabetes or prediabetes)[a], BMI ≥30, and age ≥75 years

N=132

R 1:1

Randomization will be stratified by diabetic status at baseline

All patients: Alpelisib (300 mg; oral; once daily starting at C1D8) with **fulvestrant** (500 mg; IM on C1D1 and C1D15 (if applicable), and then Day 1 of each subsequent cycle

(A) Dapagliflozin + metformin XR starting at C1D1 (n=66)

(B) Metformin XR starting at C1D1 (n=66)

Primary endpoint:
Occurrence of severe hyperglycemia (grade ≥3) over the first 8 weeks of treatment with alpelisib (C1D8 to C3D8)

Secondary endpoints:
PFS, ORR, CBR, safety and tolerability

- Estimated Start Date: February 28, 2022

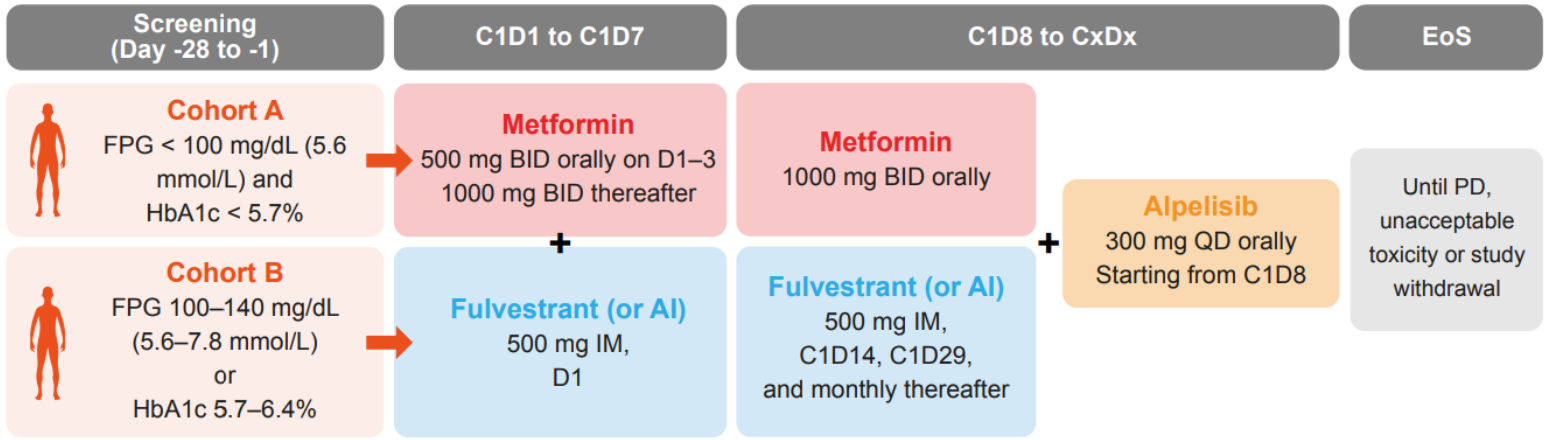
aDiabetes is defined as FPG ≥126 mg/dL (7.0 mmol/L) and/or HbA1c ≥6.5%; prediabetes is defined as FPG ≥100 mg/dL (5.6 mmol/L) and <126 mg/dL (7.0 mmol/L), and/or HbA1c ≥5.7% and <6.5%.

1. EPIK-B4. https://clinicaltrials.gov/ct2/show/record/NCT04899349. As accessed on 17 Feb 2022; 2. Data on file, EPIK-B4 protocol (v1), August 06, 2021.

OBJECTIVE

- METALLICA [NCT04300790] is a prospective, multicenter, open-label, two-cohort, Simon's two-stage design, phase II trial of ALP in combination with fulvestrant (or AI) plus MET as a treatment for preventing HG in pts with PIK3CA-mutated, HR[+]/HER2[–] ABC.

Study design



Primary Endpoint

Incidence rate of G3–4 HG by CTCAE criteria 4.03 over the first two cycles of treatment with ALP (8 weeks).

Secondary Endpoints

Rate of any grade and G3–4 HG, rate of treatment-emergent adverse events (TEAEs) by CTCAE criteria 4.03, rate of treatment discontinuations, objective response rate (ORR), duration of response (DoR) for responders, clinical benefit rate (CBR), and PFS defined per RECIST 1.1.

Llombart-Cussac A et al. Metformin (MET) for the prevention of Alpelisib (ALP)-related Hyperglycemia (HG) in PIK3CA-mutated, Hormone . Antonio Breast Cancer Symposium - December 6-10, 2022. Abstract # 1308377 – PD8-02

Results

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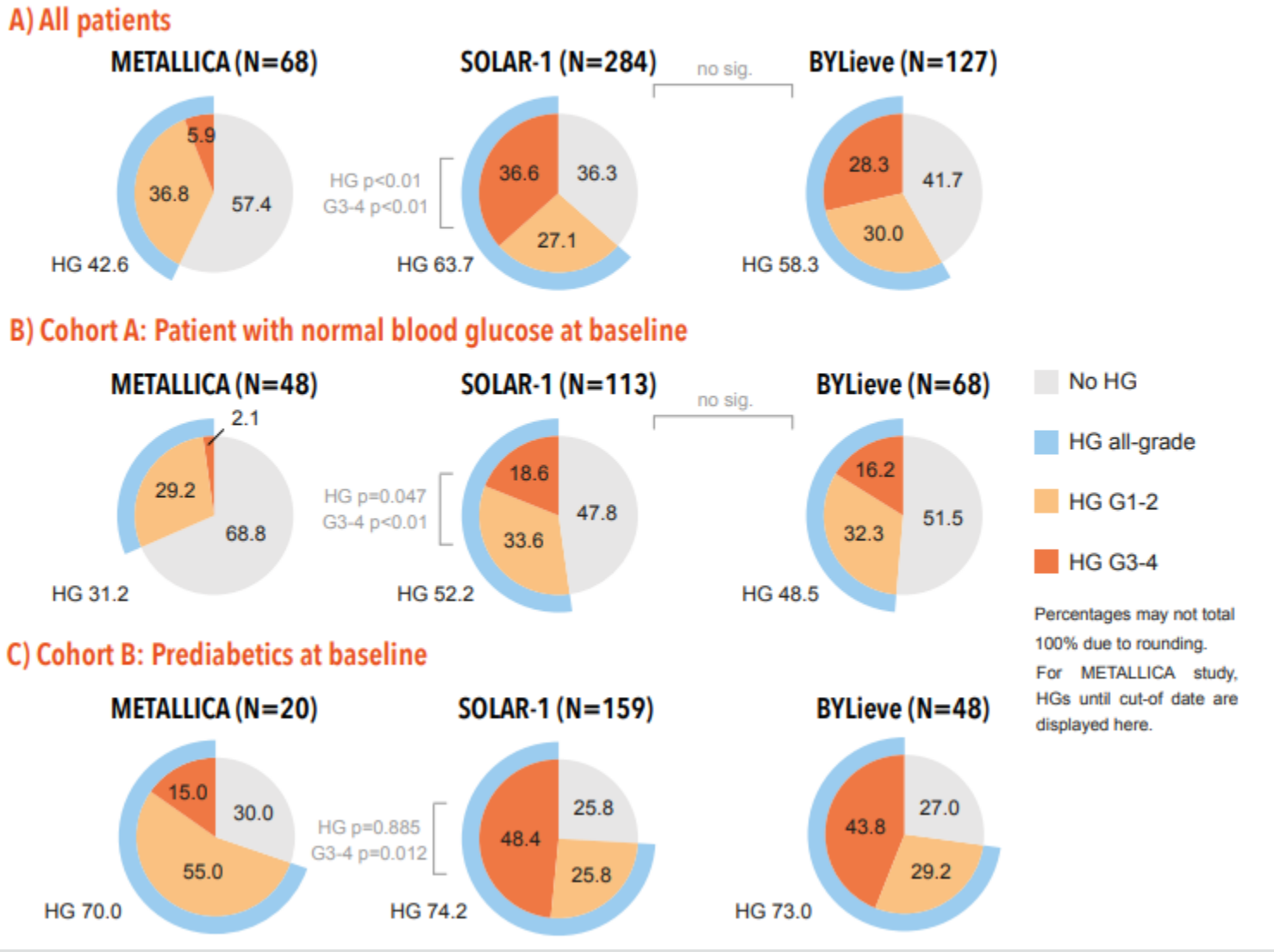
Figure 1. Rate of HG reported in METALLICA, SOLAR-1, and BYLieve (Cohort A) (%)



Llombart-Cussac A et al. Metformin (MET) for the prevention of Alpelisib (ALP)-related Hyperglycemia (HG) in PIK3CA-mutated, Hormone . Antonio Breast Cancer Symposium - December 6-10, 2022. Abstract # 1308377 – PD8-02

SGLT2i and DKA

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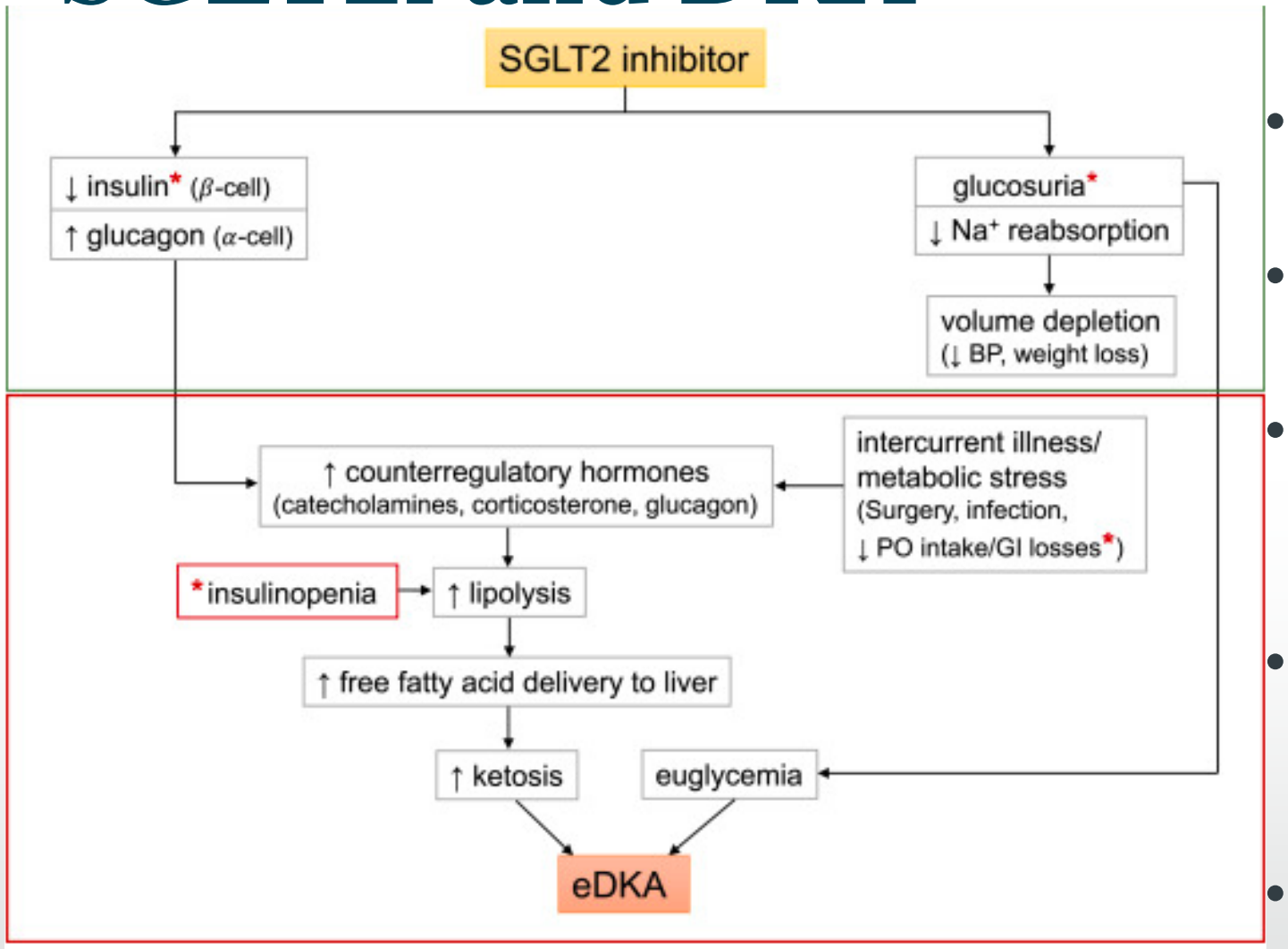
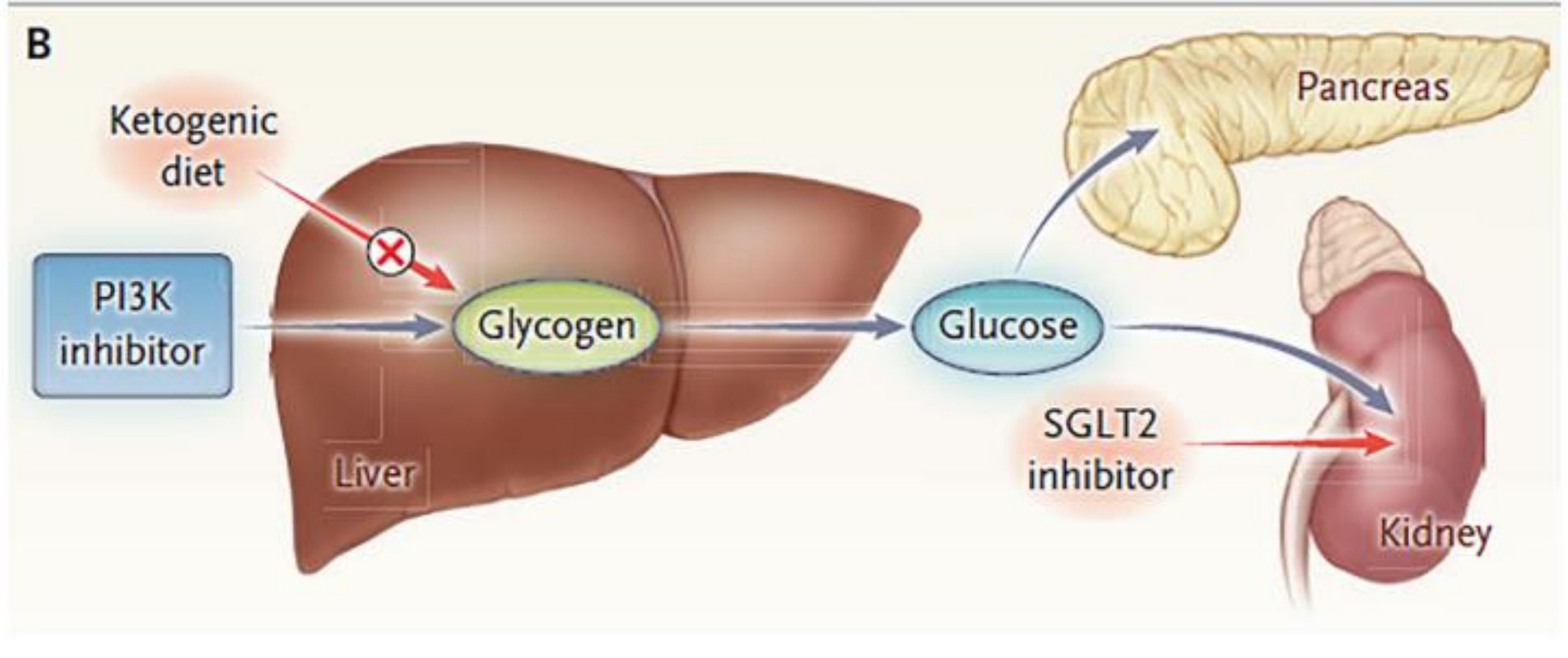


- "Pseudo-fasted" state
- Starvation ketosis
- Dehydration and concentration of ketones
- Increased Ketone resorption in Kindeys
- Relative insulinopenia

1. Wang KM, Isom RT. SGLT2 Inhibitor–Induced Euglycemic Diabetic Ketoacidosis: A Case Report. Kidney Med [Internet]. 2020 Mar;2(2):218–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2590059520300315

Role of SGLT2i and Ketogenic Diet



Goncalves MD, Farooki A. Management of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia. Integrative Cancer Therapies. 2022;21. doi:10.1177/15347354211073163

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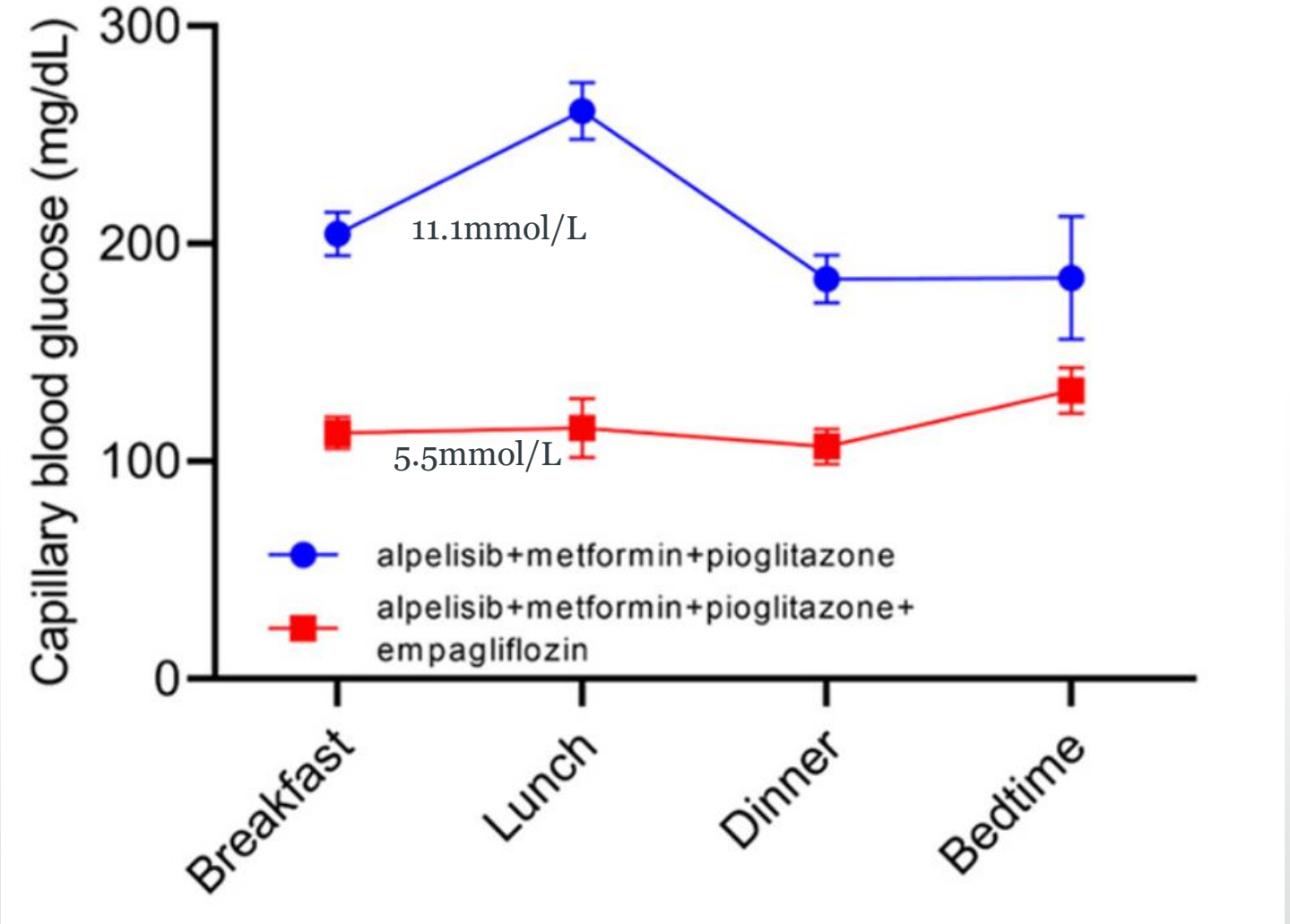
Case 3 - Type 2 Diabetes

- Type 2 Diabetes 80's
- Pre-diabetes prior to treatment (no medication)
- Day 14 developed Hyperglcyaemia (>27.7mmol/L)
- Blue = 4 days prior to Empagliflozin start
- Red = 9 days after Empagliflozin start



Blow T, Hyde PN, Falcone JN, et al. Treating Alpelisib-Induced Hyperglycemia with Very Low Carbohydrate Diets and Sodium-Glucose Co-Transporter 2 Inhibitors: A Case Series. Integrative Cancer Therapies. 2021;20. doi:10.1177/15347354211032283

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Low carbohydrate Diets

- Some evidence that tumour growth can be inhibited by lower carbohydrate diets (metabolise glucose by anaerobic respiration)
- Mice models of breast cancer – ketogenic diets resulted in smaller tumour volumes, reduced metastasis and prolonged survival (not all cancers)
- Pilot study has shown as long as no calorie deficit ketosis corresponds with reduced insulin levels reducing growth of glucose dependent cancers

Goncalves MD, Farooki A. Management of Phosphatidylinositol-3-Kinase Inhibitor-Associated Hyperglycemia. Integrative Cancer Therapies. 2022;21. doi:10.1177/15347354211073163

Blow T, Hyde PN, Falcone JN, et al. Treating Alpelisib-Induced Hyperglycemia with Very Low Carbohydrate Diets and Sodium-Glucose Co-Transporter 2 Inhibitors: A Case Series. Integrative Cancer Therapies. 2021;20. doi:10.1177/15347354211032283

Hopkins BD, Pauli C, Du X, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature. 2018;560:499-503. doi:10.1038/s41586-41018-40343-41584

Case 4- using low carbohydrate diet

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- Type 1 Diabetes 30's
- BMI 36
- On insulin pump +CGM
- Initially CHO <100g/day
- Eventually CHO <50g/day

Blow T, Hyde PN, Falcone JN, et al. Treating Alpelisib-Induced Hyperglycemia with Very Low Carbohydrate Diets and Sodium-Glucose Co-Transporter 2 Inhibitors: A Case Series. Integrative Cancer Therapies. 2021;20. doi:10.1177/15347354211032283

Summary

- Alpelisib causes hyperglcyaemia in >50% of patient taking the medication in those with HbA1c <48mmol/mol (not all will need intervention)
- Ensure pre-screening for diabetes with fasting plasma glucose
- Identify those at higher risk for development of grade >3 hyperglcyaemia (Age >75 / BMI >30 / Diabetes or pre-diabetes
- Decide on monitoring plan

Summary

- Consider low carbohydrate diets <150g to <100g as per patient preference to reduce insulin
- Maximise use of medications that don't increase insulin
  - Metformin
  - SGLT2i
  - Pioglitazone
- Continue insulin sparing agents where possible if forced to start insulin

QUESTIONS?