66 yo F with Hyperglycemia

Mizuho Mimoto
Endorama
June 30, 2016

CC: 66 F who presents with hyperglycemia

- HPI: Hx of metastatic NSCLC referred from for management of new onset diabetes.
- Meals:
  - B: Breakfast bar, Jell-O, Applesauce, Dry cereal
  - L: Bagel, coffee
  - D: Spaghetti, corn, chicken
  - Dessert: avoiding; No sugar-sweetened beverages
- Home BG Monitoring:
  - Fasting sugars 161-274
  - Post-prandial: up to 364
- Metformin →nausea, diarrhea
  - Low carb diet – limited by nausea

CC: 66 F who presents with hyperglycemia

- ROS: notable for fatigue and hyperglycemia otherwise unremarkable
- PMH: Lung Adenocarcinoma, osteoporosis
- PSH: RUL, LUL lobectomy, tonsillectomy, breast lumpectomy
- Soc: Former smoker 15 py (quit 2000); EtOH: 1-2 shots whiskey per day
- FH: Mother with DM2 (dx late, not on insulin until her 90s)
- Current meds: ibandronate 150 mg monthly, rociletinib (EGFR inhibitor - CO-1686), prochlorperazine

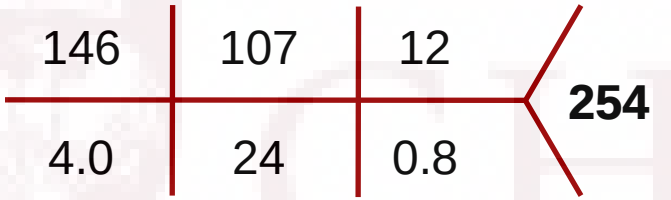
Physical Exam – generally unremarkable

- VS: T 98.6F, BP 153/88, P 71, RR 16, SpO2 97% RA, Ht 167.6 cm, Wt 145 lb, BMI 23.4 kg/m^2

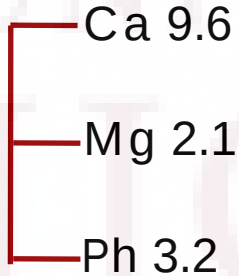
- Constitutional: She is oriented to person, place, and time. She appears well-developed and well-nourished.
- Head: Normocephalic and atraumatic.
- Eyes: Conjunctivae are normal. Pupils are equal, round, and reactive to light.
- Neck: Normal range of motion. Neck supple. No thyromegaly present.
- Cardiovascular: Normal rate and regular rhythm.
- Pulmonary/Chest: Effort normal and breath sounds normal.
- Abdominal: Soft. Bowel sounds are normal.
  Musculoskeletal: She exhibits no edema.
  Neurological: She is alert and oriented to person, place, and time.
- Skin: Skin is warm and dry.
  Psychiatric: She has a normal mood and affect. Her behavior is normal. Judgment and thought content normal.

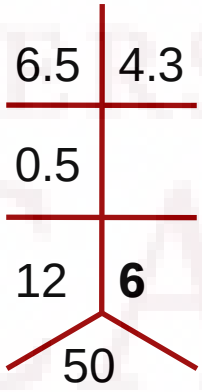
Labs from initial Endocrine visit:

7/17/15

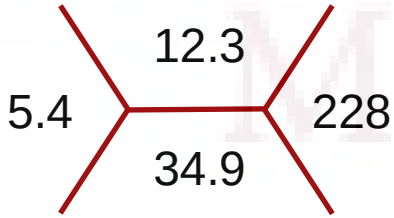


254



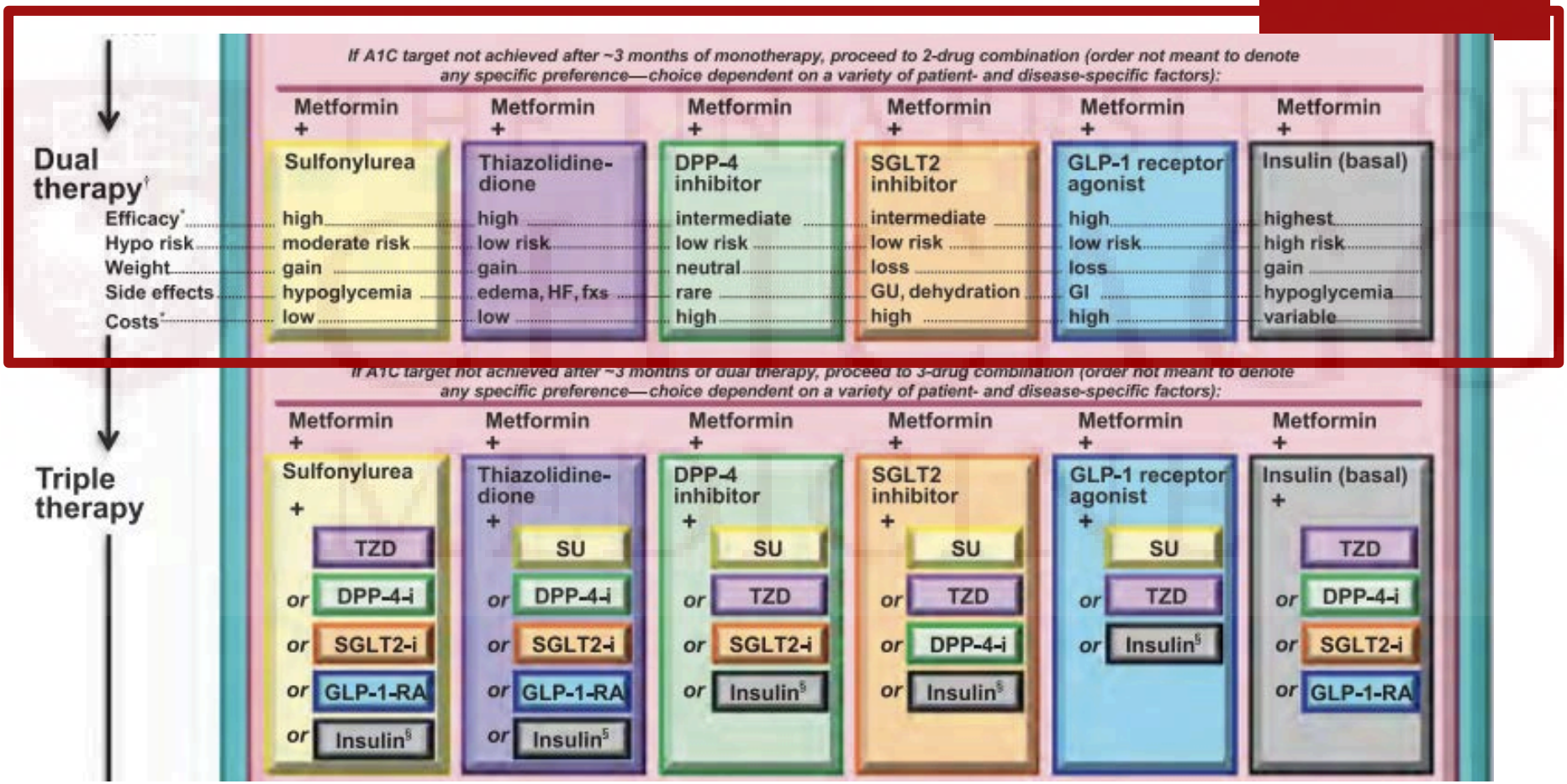


HbA1c: **9.3 %**
C-peptide: 2.08



What would you like to do?

Approach to glycemic treatment T2DM – A1c 9-10%



Standards of Medical Care in Diabetes 2016. Diabetes Care Volume 39, Supplement 1

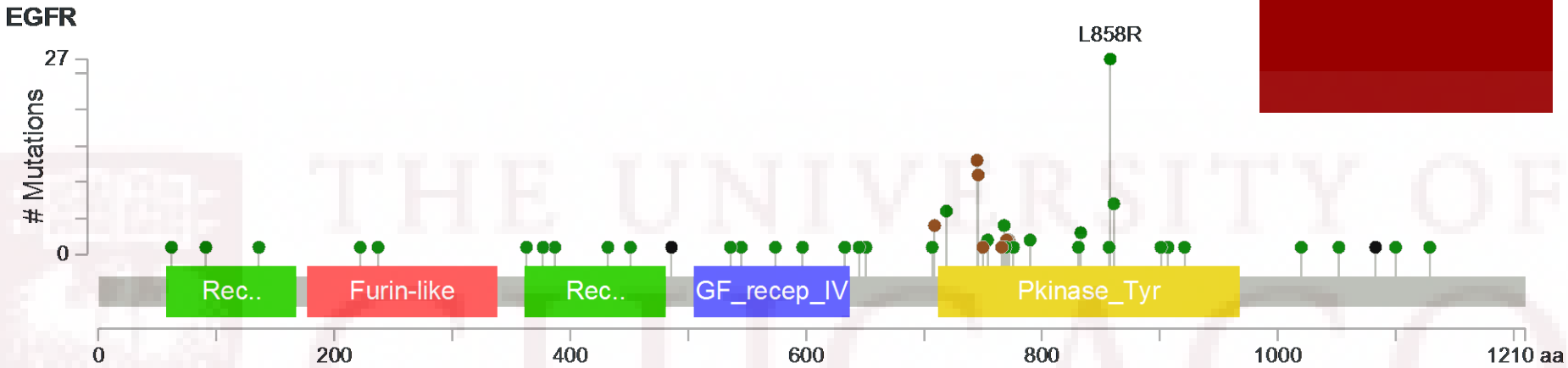
Our Plan:

- Start sitagliptin 50 mg daily, uptitrate to 100 mg daily
- Add canagliflozin if not at target
- Insulin as third line
- Avoid pioglitazone given hx of osteoporosis and increased risk of fracture
- Monitor blood sugars fasting and HS and touch base in a week

Additional history:

- October 2011: presented with respiratory infection and incidentally noted RUL mass on imaging, differentiated adenocarcinoma.
- RUL Lobectomy, cisplatin/pemetrexed.
- March 2013 PD: LUL lobectomy
  - Sequencing of mass: EGFR exon 19 deletion, started on erlotinib (1st gen EGFR TKI)
- July 2014 PD: afatinib (2nd gen EGFR TKI)
- March 2015 PD: RLL biopsy with Foundation One testing revealed EGFR T790M mutation and enrolled in a clinical trial with rociletinib (3rd gen EGFR TKI)

EGFR in lung cancer



- EGFR mutations present in 17% of lung cancer
  - 10% caucasian, 50% asian patients (more common in non-smokers)
  - Mutation in the Kinase domain→constitutive activation which prevents normal apoptosis of cancer cells
  - 78% response rate to EGFR TKIs (erlotinib, gefitinib)
    - Compared to platinum-based chemotherapy, targeted EGFR inhibitors:
      - Better PFS
      - No change in OS
    - Acquired resistance due to EGFR T790M mutation in 60-70% of patients following initial therapy

Morgensztern et al. JAMA Oncol. 2015;1(2):146-148
Lee etal. JNCI. Vol. 105, Issue 9 | May 1, 2013

Rociletinib is a 3rd generation TKI that specifically targets T790M

ORIGINAL ARTICLE

Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

L.V. Sequist, J.-C. Soria, J.W. Goldman, H.A. Wakelee, S.M. Gadgeel, A. Varga, V. Papadimitrakopoulou, B.J. Solomon, G.R. Oxnard, R. Dziadziuszko, D.L. Aisner, R.C. Doebele, C. Galasso, E.B. Garon, R.S. Heist, J. Logan, J.W. Neal, M.A. Mendenhall, S. Nichols, Z. Piotrowska, A.J. Wozniak, M. Raponi, C.A. Karlovich, S. Jaw-Tsai, J. Isaacson, D. Despain, S.L. Matheny, L. Rolfe, A.R. Allen, and D.R. Camidge

- T790M mutation
  - More common in patients with acquired resistance following prior EGFR inhibitor treatment
  - Located in the kinase domain of the protein

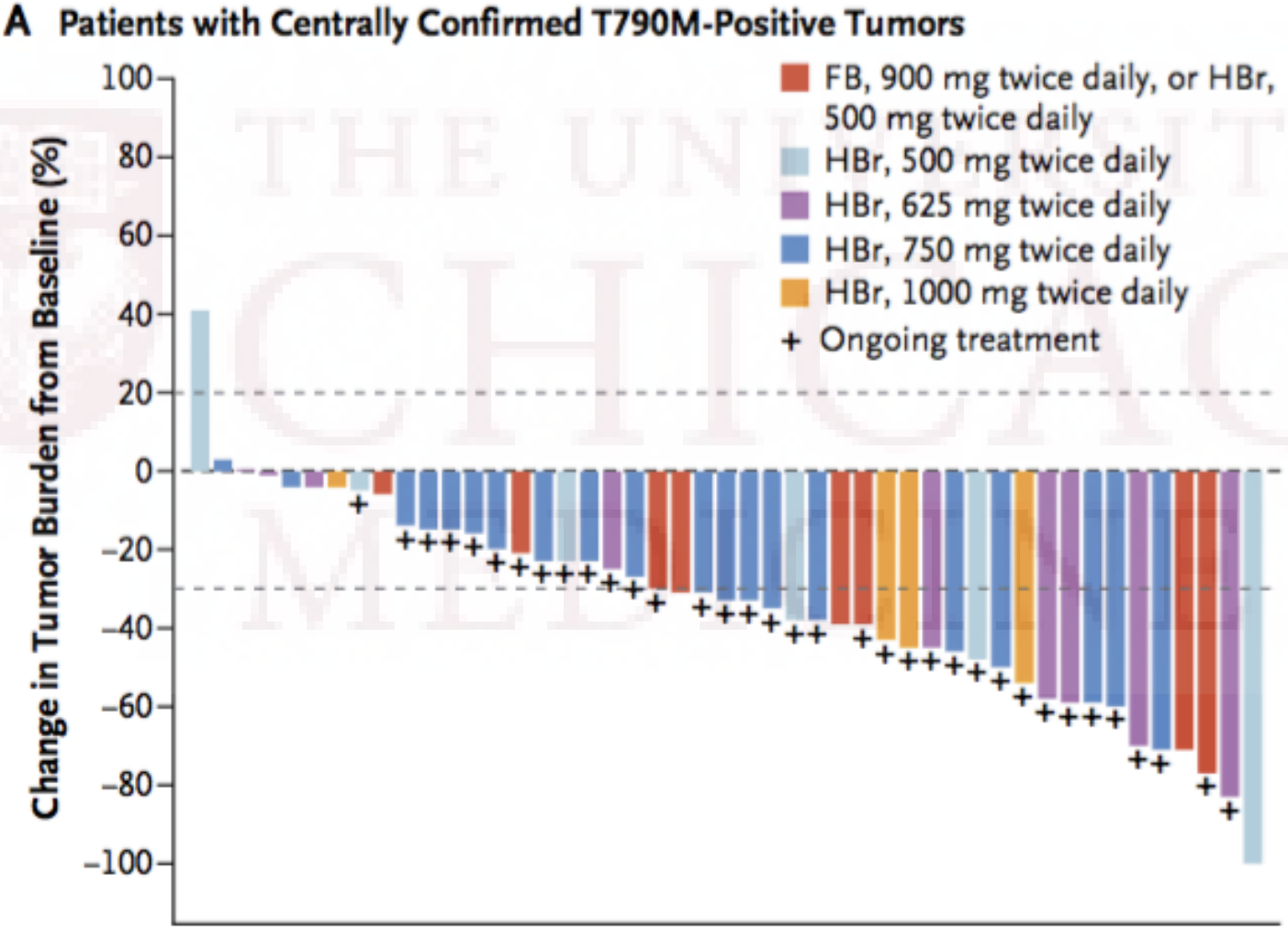
Sequist, L. V. *et al.*. *N Engl J Med* **372,** 1700–1709 (2015).

Rociletinib is active in EGFR T790M NSCLC

- Phase 1-2 dose finding study
  - Phase 1
    - Primary objectives: Safety, Side effect profile, Pharmacokinetics
    - Secondary objective: Response rate, duration of response, progression-free survival, QOL
  - Phase 2
    - Primary endpoints: Response rate, duration
    - Secondary endpoints: as above
- 130 patients with NSCLC
  - Previously treated with EGFR TKI
  - Median # of prior treatments tried: 4
  - 50% with metastatic disease (44% to brain)
- 78/172 patients screened for phase 2 → T790M positive.
  - Treated in 21 day cycles until PD, toxicity or withdrawal of consent
  - No maximum tolerated dose – **only dose limiting A.E. was hyperglycemia**

Sequist, L. V. *et al.*. *N Engl J Med* **372,** 1700–1709 (2015).

Rociletinib is active in EGFR T790M NSCLC

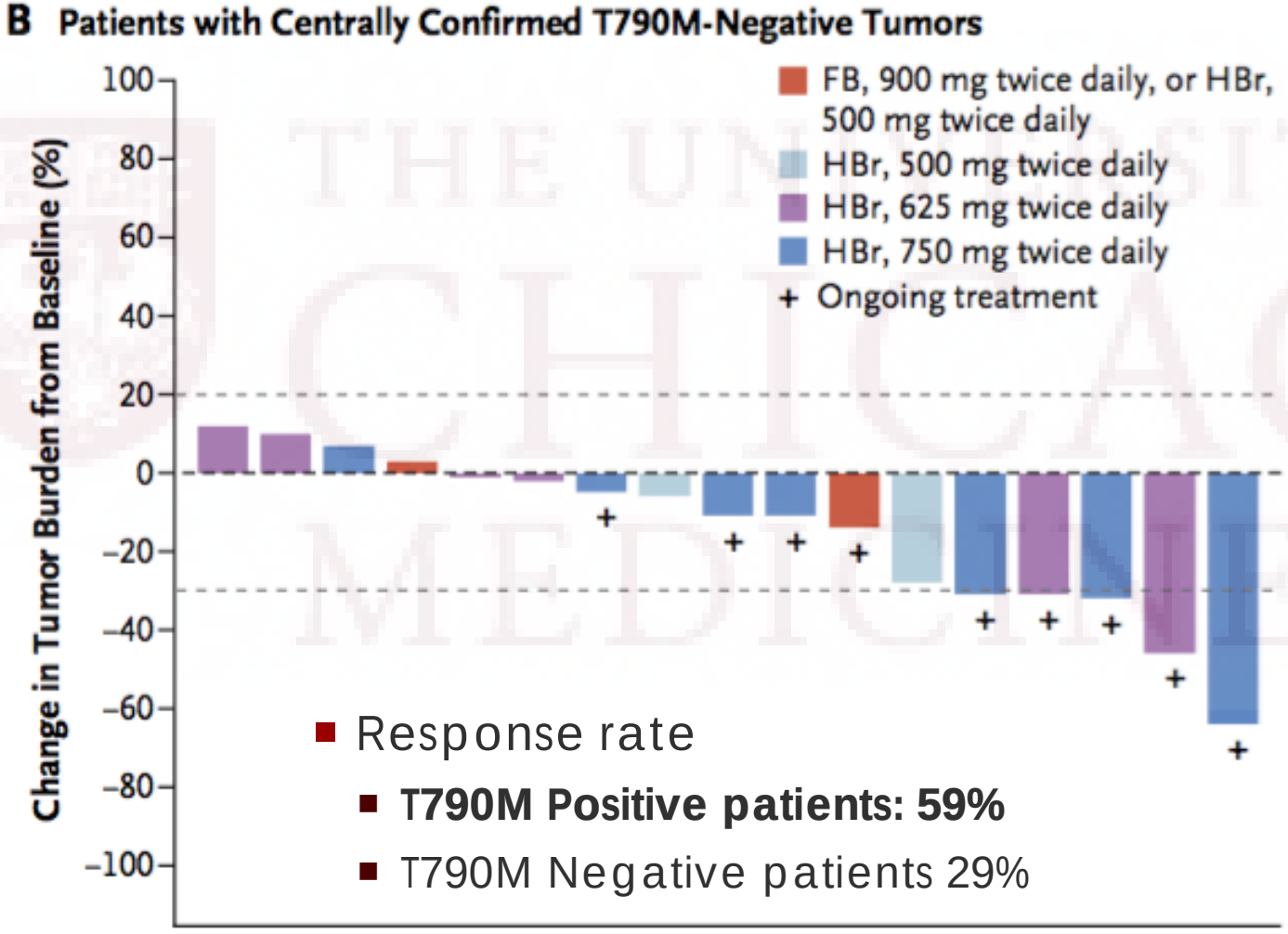


PD

Partial Response

Sequist, L. V. *et al.*. *N Engl J Med* **372,** 1700–1709 (2015).

Rociletinib is active in EGFR T790M NSCLC



Sequist, L. V. *et al.*. *N Engl J Med* **372,** 1700–1709 (2015).

Rociletinib: Hyperglycemia is the most common A.E.

Table 4. Treatment-Related Adverse Events in the 92 Patients Receiving Therapeutic Doses of Rociletinib, According to Event Grade.*

Event	Any Grade	Grade 1	Grade 2	Grade 3
	number (percent)			
Hyperglycemia†	43 (47)	14 (15)	9 (10)	20 (22)
Nausea	32 (35)	16 (17)	14 (15)	2 (2)
Fatigue	22 (24)	9 (10)	9 (10)	4 (4)
Diarrhea	20 (22)	16 (17)	4 (4)	0
Decreased appetite	18 (20)	10 (11)	7 (8)	1 (1)
Vomiting	13 (14)	9 (10)	2 (2)	2 (2)
QTc prolongation	11 (12)	3 (3)	3 (3)	5 (5)
Muscle spasms	10 (11)	9 (10)	0	1 (1)

Table 3. Treat

Event

Therapeutic Dose (N=92)†

Hyperglycemi 43 (47)
Nausea 32 (35)
Fatigue 22 (24)
Diarrhea 20 (22)
Decreased ap 18 (20)
Vomiting 13 (14)
Muscle spasn 10 (11)

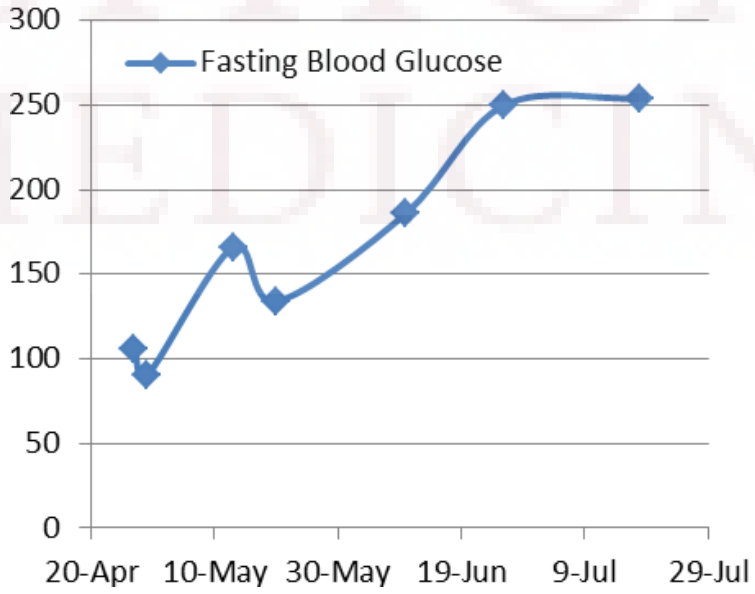
* Shown are ev
† Therapeutic d ...750 mg twice daily, and 1000 mg twice daily of the hydrogen bromide salt form.
‡ Hyperglycemia includes the combined terms of increased blood glucose level, glucose intolerance, impaired glucose tolerance, and hyperglycemia.

Returning to our patient: **Rewind** to review pre-treatment labs and initial monitoring

4/27/15 – pre treatment

146	107	12	106	Ca 9.6	6.5	4.3	
4.0	24	0.8		Mg 2.1	0.5		
				Ph 3.2	12	**6**	50

HbA1c: 5.7 %



Initial management strategy by oncology:

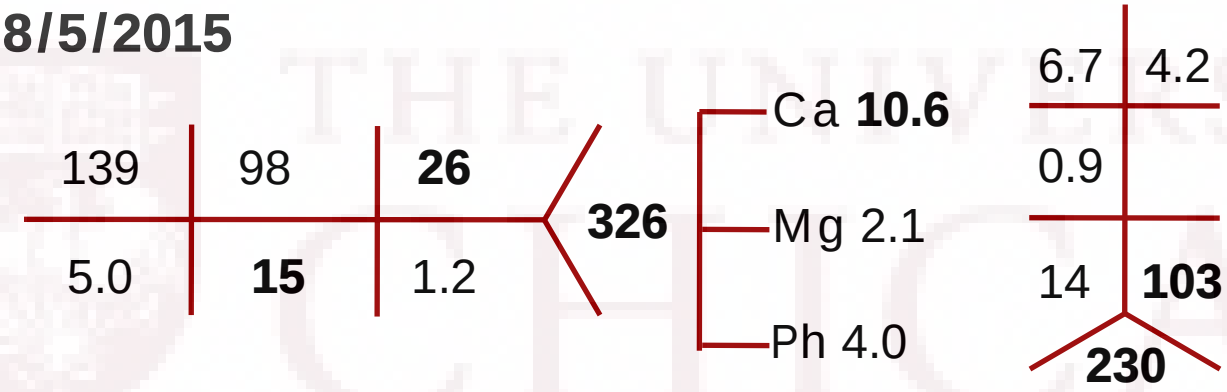
- Rociletinib held – also having transaminitis; confounded by EtOH and Tylenol use
- Resolution of Hyperglycemia
- Started on metformin but having issues with nausea and diarrhea
- Referral to Endocrinology

Our Plan:

- Start sitagliptin 50 mg daily, uptitrate to 100 mg daily
- Add canagliflozin if not at target
- Insulin as third line
- Avoid pioglitazone given hx of osteoporosis and increased risk of fracture
- **Monitor blood sugars fasting and HS and touch base in a week.**
- **Low carb diet**

Endo visit: 1 week follow up labs

8/5/2015



β-hydroxybutyrate: **6.94**

- What would you like to do now?
- Insulin start
- Home ketone monitoring

Home ketone monitoring

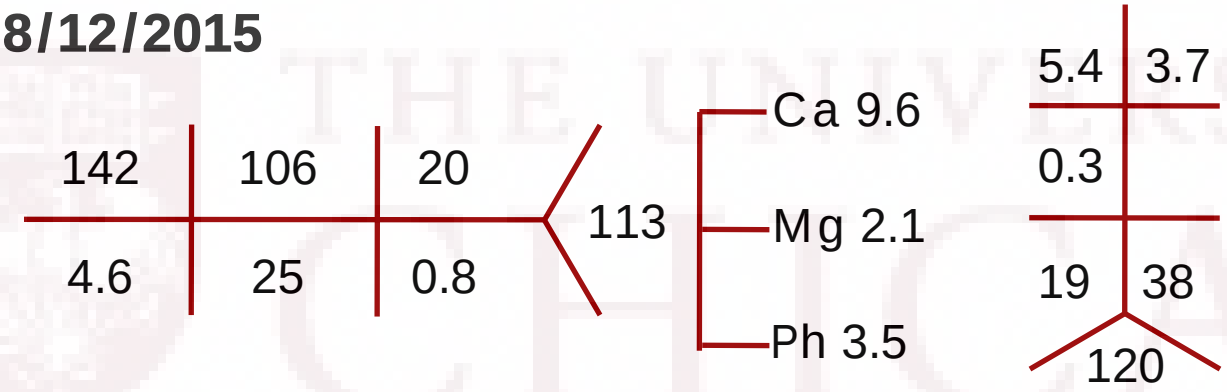
Urine Ketones	Blood Ketones	Give this much extra fast acting insulin:
Negative	under 0.6	No extra insulin; give correction every 3 hours.
Small	0.6 - 1.5	Increase correction by 5% and recheck BG in 3 hours.
Moderate	1.5 - 3	Increase correction by 10% and consult with the advice nurse or the MD on call and recheck BG in 3 hours.
Large	over 3	Increase correction by 20% and consult with the advice nurse or the MD on call. Check BG in 3 hours.

- Fluids to prevent dehydration
  - If blood sugars > 200 mg/dl, drink sugar-free fluids.
  - If blood sugars < 200 mg/dl, drink small amounts of sweetened fluids (sports drinks, Pedialyte, diluted juice)

https://diabetes.ucsf.edu/sites/diabetes.ucsf.edu/files/Sick%20Day%20Final%2011%2023%2009_0.pdf

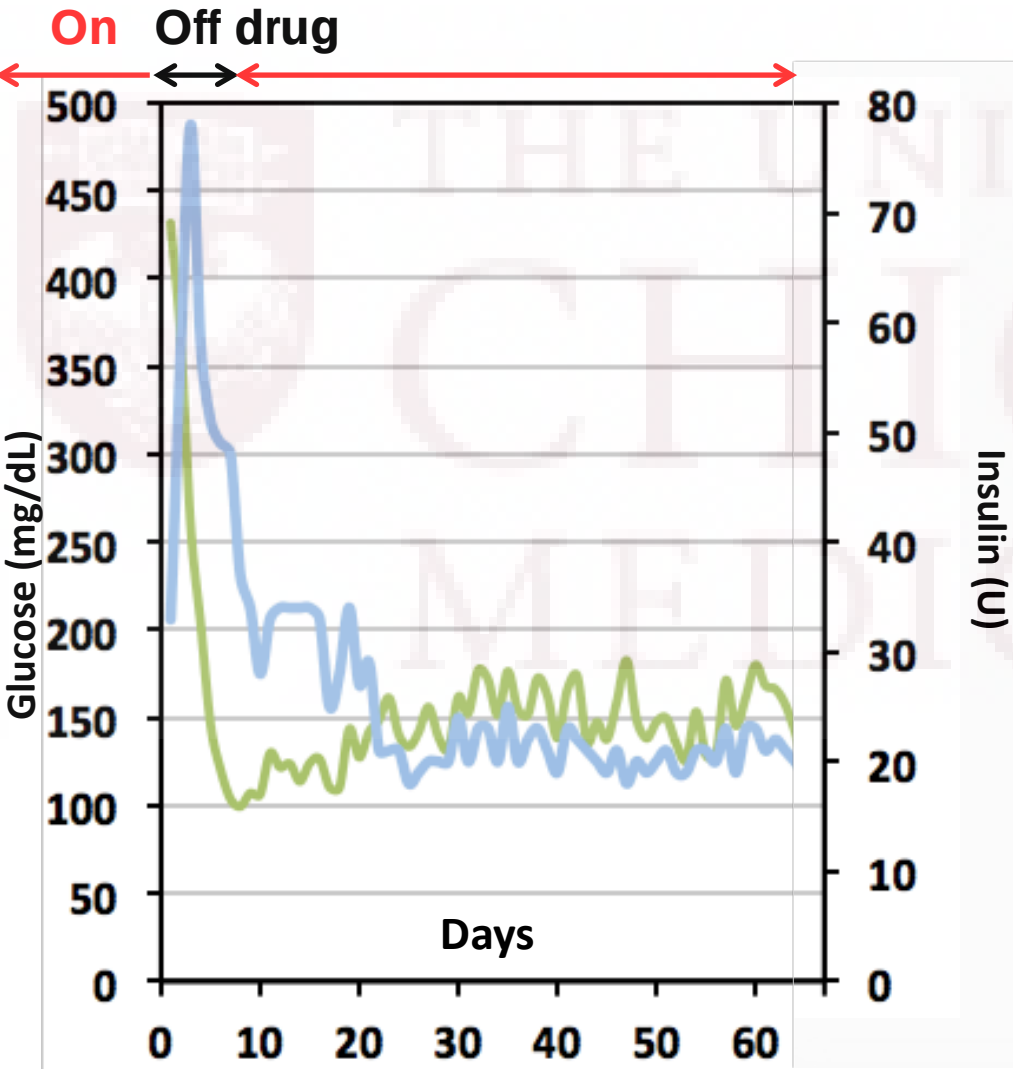
Repeat labs look better

8/12/2015

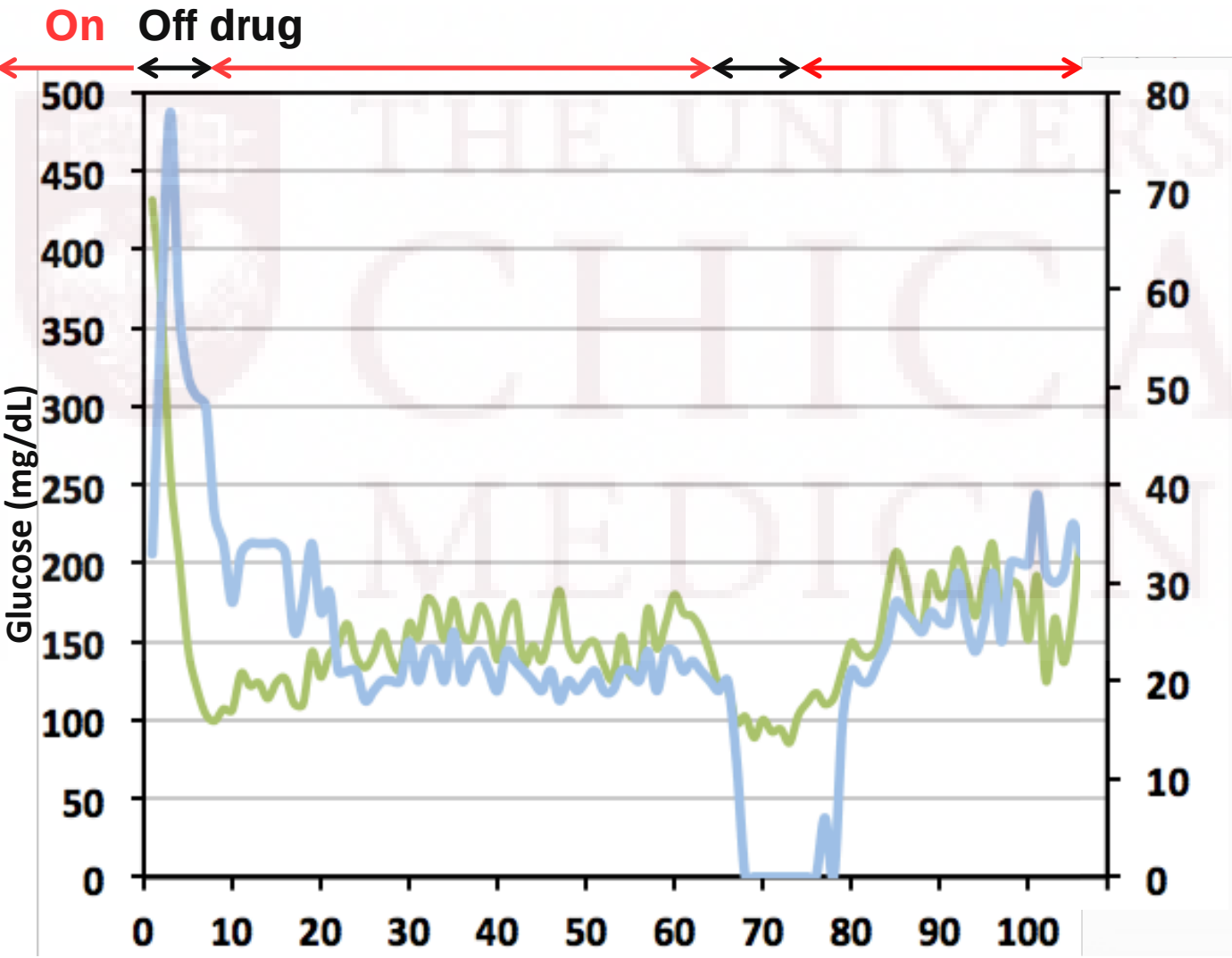


β-hydroxybutyrate: <0.10

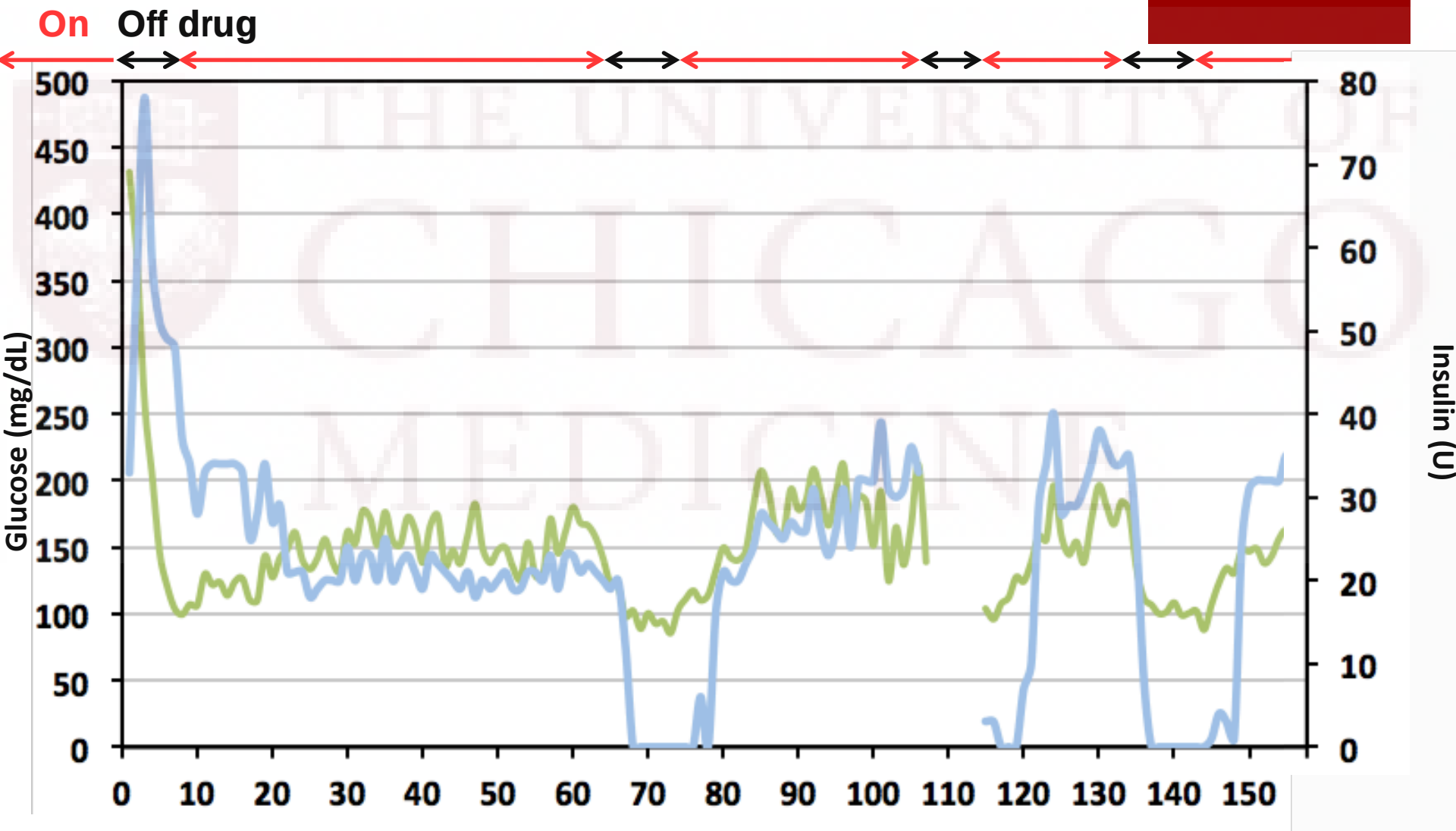
Blood sugars stably improved on insulin



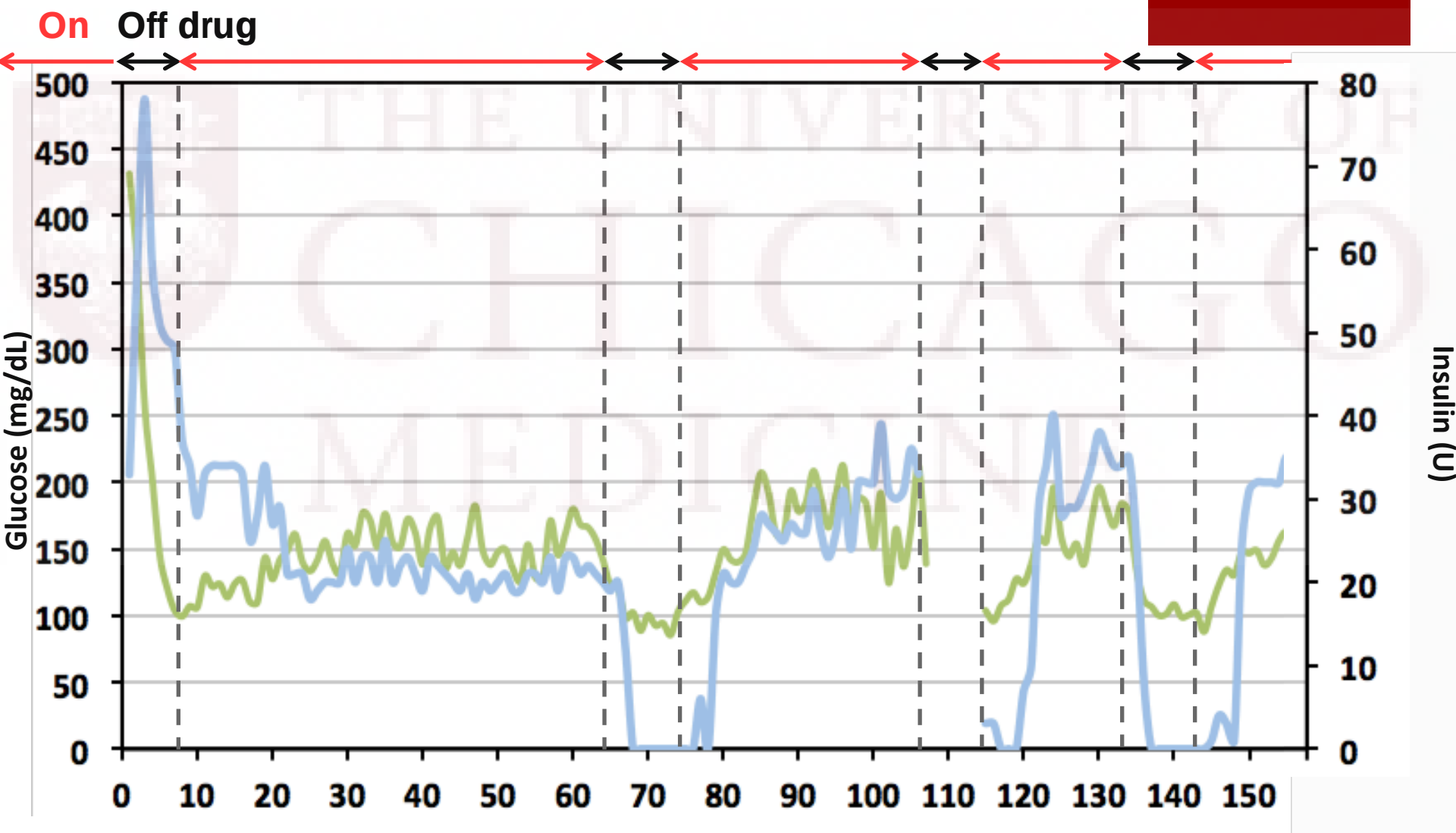
Continued course...



Continued course...



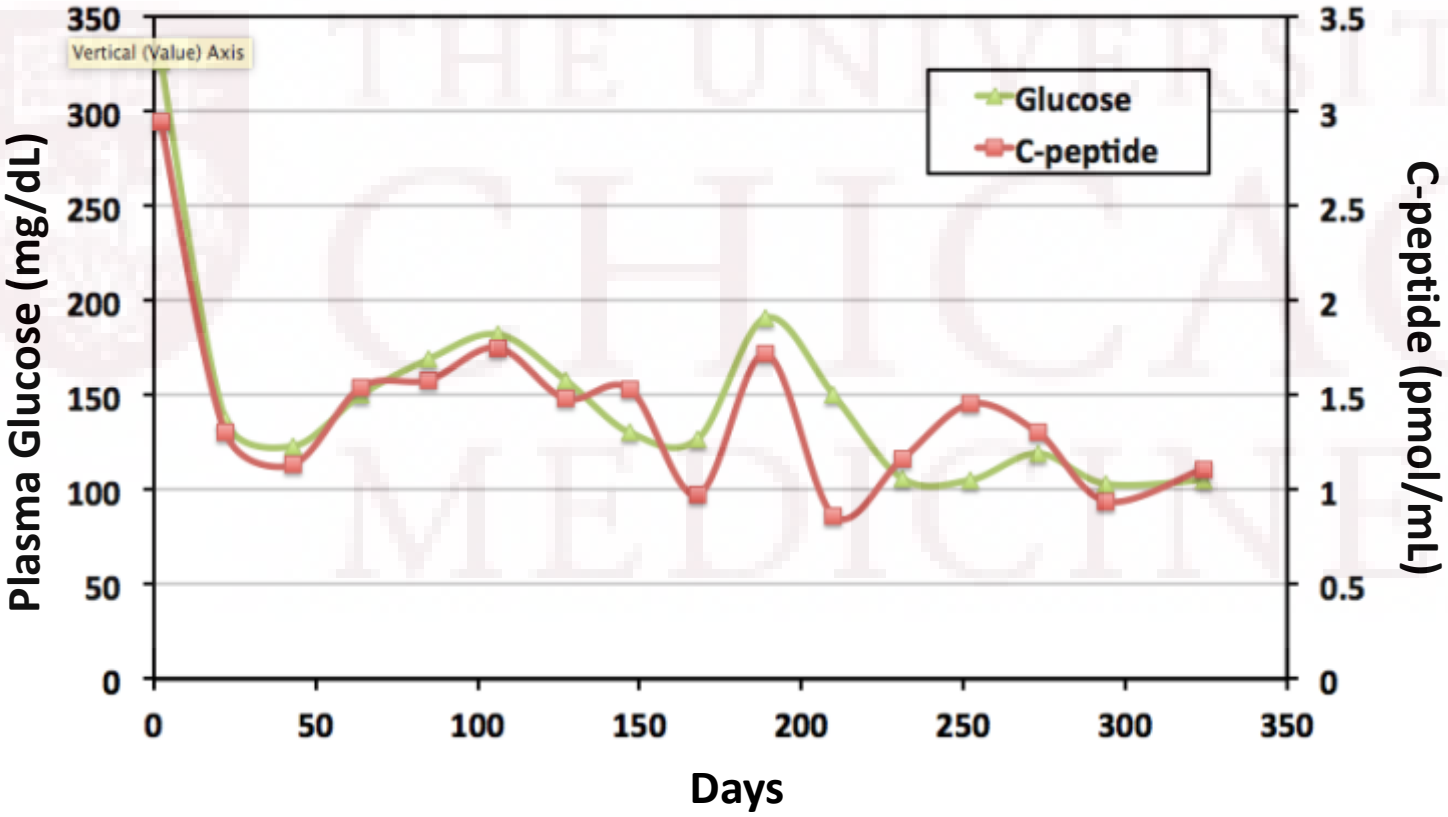
No insulin required when off drug



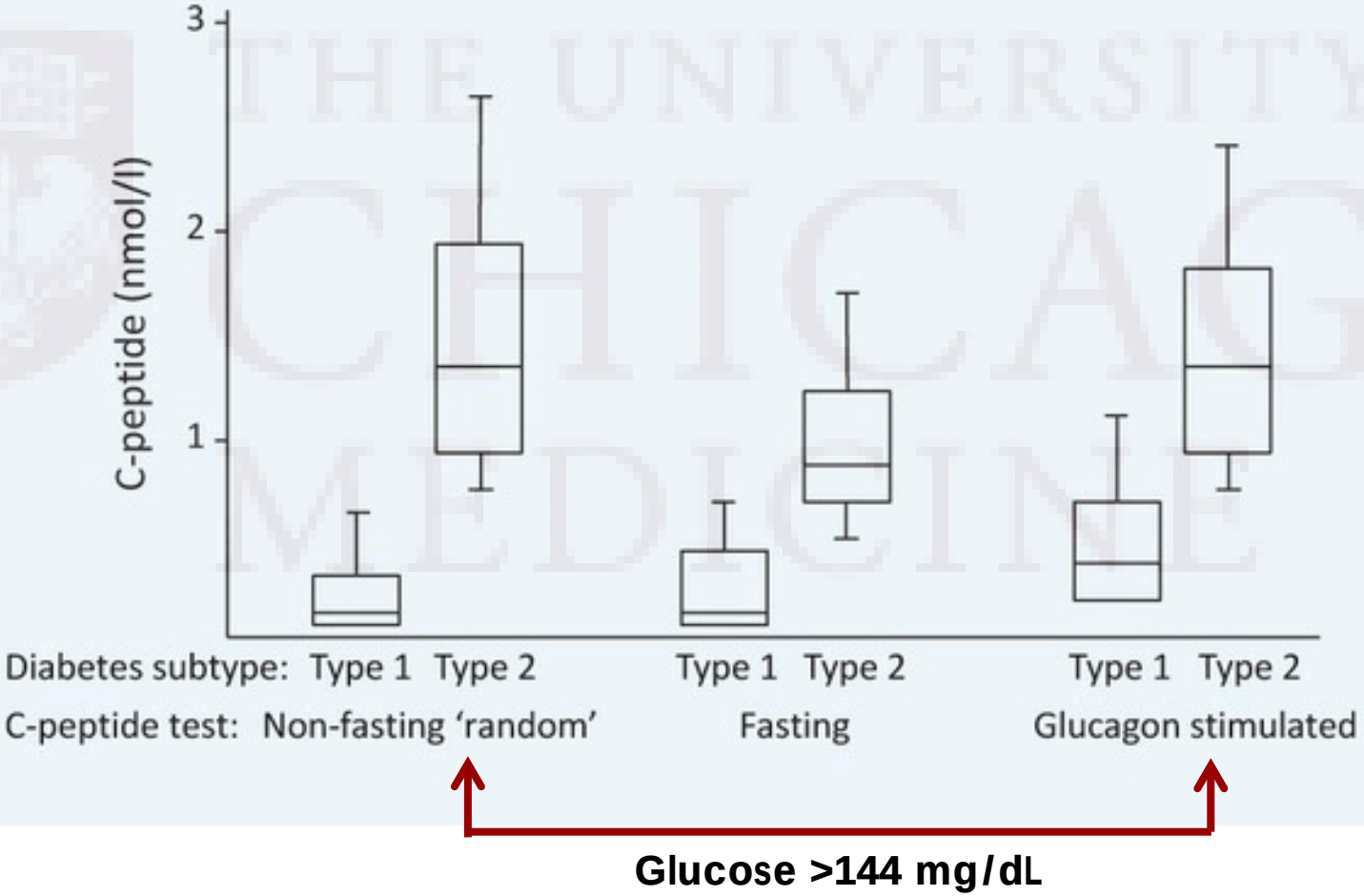
Insulin Insufficiency vs. Resistance?

- Transient and reversible beta-cell dysfunction with DKA
  - Suggests primary defect is insulin insufficiency rather than resistance
  - Normalization of blood sugars with minimal amounts of insulin (0.3-0.5 U/kg/d)

Back to our patient: Insulin secretion appears to be intact



Utility of C-peptide in predicting insulin secretion



Diabet Med. 2013 Jul; 30(7): 803–817.

Suggested C-peptide thresholds to guide clinical practice

Clinical role	Stimulated (non-fasting 'random'/post-glucagon/mixed-meal test) (nmol/l)	Fasting (nmol/l)
Absolute insulin deficiency/absolute insulin requirement [76]	< 0.2	< 0.08
Likely Type 1 diabetes/inability to achieve glycaemic control with non-insulin therapies [39,40,95]	< 0.6	< 0.25
Suggests Type 2 or monogenic (MODY) diabetes in a patient with presumed Type 1 diabetes > 3–5 years post-diagnosis [65,71]	> 0.2	> 0.08
Consider MODY/Type 2 diabetes in young onset diabetes at diagnosis [67]	> 1	> 0.4

Diabet Med. 2013 Jul; 30(7): 803–817.

Potential mechanisms for drug-induced hyperglycemia

- Pancreatic effects
  - Reduced beta-cell function/mass
  - Impaired insulin secretion –C-peptide levels suggest against this
    - DKA – suggests primary defect is insulin insufficiency rather than resistance
    - Normalization of blood sugars with minimal amounts of insulin (0.3-0.5 U/kg/d)
- Hepatic effects
  - Inhibition of glycogen synthesis/Increased gluconeogenesis
  - Increased glycogenolysis
- Peripheral effects
  - Reduced peripheral glucose uptake
- NEJM report alludes to preclinical data (rats) suggesting that drug metabolite inhibits IGF-1R and insulin R signaling
  - Increased hepatic gluconeogenesis
  - Reduced peripheral glucose uptake
  - Hyperglycemia-mediated beta cell impairment

Recommended monitoring

Fasting blood glucose (FBG) monitoring:

- Screening/baseline visit; cycle 1: day 1, 8, 15; cycle 2 and beyond: day 1; end of treatment visit

Initial home monitoring:

- Daily (alternate between fasting glucose and pre-dinner glucose)

General treatment goals:

- Fasting plasma glucose <160 mg/dL; random plasma glucose <200 mg/dL; HbA1c ≤8%
- Lifestyle modifications (refer to nutritionist or diabetes specialist if needed)[†]

Pre-existing diabetes:

- Continue current home glucose monitoring regimen; adjust frequency of monitoring and/or diabetic medication according to standard guidelines and grade of hyperglycemia

Provider should be contacted for:

- FBG >160 mg/dL
- Presence of hyperglycemia symptoms (polydipsia, polyuria, polyphagia, blurry vision)

NOTE: Hyperglycemia generally occurs within the first 3 weeks of treatment

Villadolid et al. *Translational Lung Cancer Research* **4,** 576–583

Recommended treatment

Grade 2 hyperglycemia
(FBG >160 to 250 mg/dL; >8.9 to 13.9 mmol/L)

- EGFR TKI targeting T790M may continue without interruption or dose reduction in asymptomatic patients
- Hold EGFR TKI targeting T790M for 48 to 72 hours if symptomatic
- Twice daily home monitoring (before breakfast and dinner)

→

Asymptomatic

- Repeat FBG within 1 week—if grade 2 results at least twice in 1 week, start antihyperglycemic agent (metformin 500 mg orally twice daily‡)
- Continue home monitoring—if worsens or no improvement, treat according to grade 3 or 4

Symptomatic

- Start antihyperglycemic agent (metformin 500 mg orally twice daily‡)
- Continue home monitoring—if worsens or no improvement, treat according to grade 3 or 4

- Hold drug until resolution (FBG <250)
- Increased home monitoring
- Second oral agent/insulin
- Fluids if signs/symptoms of dehydration

Villadolid et al. *Translational Lung Cancer Research* **4,** 576–583

References

- Standards of Medical Care in Diabetes 2016. Diabetes Care Volume 39, Supplement 1
- Morgensztern et al. JAMA Oncol. 2015;1(2):146-148
- Lee etal. JNCI. Vol. 105, Issue 9 | May 1, 2013
- Sequist, L. V. *et al.*. *N Engl J Med* **372,** 1700–1709 (2015).
- https://diabetes.ucsf.edu/sites/diabetes.ucsf.edu/files/Sick%20Day%20Final%2011%2023%2009_0.pdf
- Diabet Med. 2013 Jul; 30(7): 803–817.
- Villadolid et al. *Translational Lung Cancer Research* **4,** 576–583