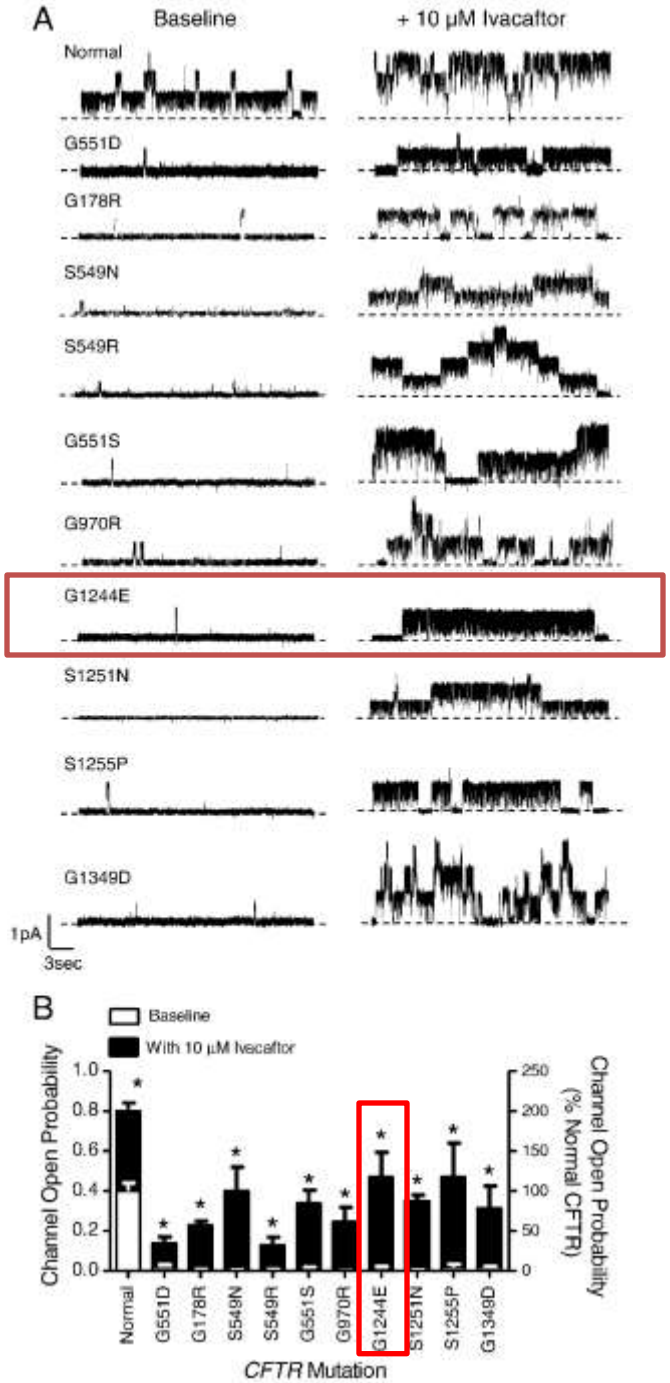
A Patient with advanced CF on Ivacaftor treatment questions and dilemmas

Michal Shteinberg, Reut Lutzky, Rachel Friedman, Galit Livnat- Levanon
Carmel Medical Center
Technion- Israel Institute of Technology
Haifa, Israel

- 37 year old, diagnosed with CF in early childhood
- G1244E/G1244E
- Pancreatic Insufficient
- Impaired Glucose tolerance
- Elevated liver enzymes w/o overt cirrhosis
- FMF- heterozygote
- Recurrent bowel obstruction (DIOS (+opiate induced?)), several laparotomies
- 2010- 20 cm terminal ileum resected with loop ileostomy in place 17 cm. prox. to ileocecal valve

- Chronic *Pseudomonas aeruginosa ;* MRSA infection
- Opiate abuse
- Partial adherence to medical recommendations
- Lung function- FEV_1- 35- 40 %
- Recommended medications: inh. rhDNase, inh. 6% HS , lung clearance, inhaled tobramycin/ colomycin, azithromycin, pancreatic and nutritional supplements, colchicine, UDCA

- Recent prolonged hospitalization- intestinal obstruction
- Pulmonary exacerbation
- Urine toxicology screen positive to opiates
- Prolonged time to relief obstruction
- Should we treat this patient with ivacaftor?



Journal of Cystic Fibrosis 2012 11, 237-245

Table 2
Efficacy results, stratified by genotype, raw means.

Mutation, *n*	Absolute change from baseline in % predicted FEV_1, % points, mean (min, max)			Absolute change from baseline in sweat chloride at week 8, mmol/L, mean (min, max)	Absolute change from baseline in BMI at week 8, kg/m^2, mean (min, max)	Absolute change from baseline in CFQ-R Score at week 8, points, mean 2(min, max)
	At week 2	At week 4	At week 8			
G1244E (5)	11.08 (−5.20, 25.41)	5.54 (−4.63, 12.95)	8.36 (−0.93, 18.37)	−55.10 (−75.0, −34.0)	0.63 (0.34, 1.32)	3.3 (−27.8, 22.2)
G1349D (2)	19.42 (5.49, 33.36)	18.48 (1.60, 35.37)	19.67 (2.97, 36.37)	−80.25 (−81.5, −79.0)	1.15 (1.07, 1.22)	16.7 (−11.1, 44.4)
G178R (5)	7.46 (1.42, 16.99)	10.23 (−2.31, 20.53)	8.37 (−0.77, 17.56)	−52.50 (−64.5, −35.0)	0.85 (0.33, 1.46)	20.0 (5.6, 50.0)
G551S (2)	−0.09 (−4.69, 4.51)	0.29 (−5.32, 5.89)	3.12 [a]	−68.0 [a]	0.16 [a]	16.7 [a]
G970R (4)	6.72 (0.52, 12.61)	6.76 (1.21, 14.23)	2.55 (−1.30, 4.52)	−6.25 (−16.0, −2.0)	0.48 (−0.38, 1.75)	1.4 (−16.7, 16.7)
S1251N (8)	2.14 (−23.28, 19.95)	7.66 (−13.20, 26.03)	8.70 (−19.57, 21.38)	−54.38 (−84.0, −7.0)	0.73 (0.08, 1.83)	23.3 (5.6, 50.0)
S1255P (2)	11.10 (8.25, 13.94)	8.73 (4.74, 12.73)	3.14 (−1.42, 7.70)	−77.75 (−82.0, −73.5)	1.62 (1.39, 1.84)	8.3 (5.6, 11.1)
S549N (6)	10.55 (5.11, 15.93)	8.06 (−9.29, 19.30)	11.31 (−2.40, 19.78)	−74.25 (−92.5, −53.0)	0.79 (0.00, 1.91)	8.8 (−8.3, 27.8)
S549R (4)	3.47 (−3.55, 7.59)	4.11 (−3.78, 10.00)	5.18 (−3.07, 12.74)	−60.67 (−70.5, −53.5)	0.53 (0.33, 0.80)	6.9 (0.0, 11.1)
Overall	7.23 (−23.28, 33.36) (n = 38)	7.55 (−13.20, 35.37) (n = 38)	8.13 (−19.57, 36.37) (n = 37)	−55.82 (−92.5, −2.0) (n = 36)	0.75 (−0.38, 1.91) (n = 37)	12.31 (−27.8, 50.0) (n = 37)

[a] Only one patient with the *G551S* mutation completed 8 weeks of ivacaftor treatment.

De Boeck, Kris, et al. "Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation." *Journal of Cystic Fibrosis* 13.6 (2014): 674-680.

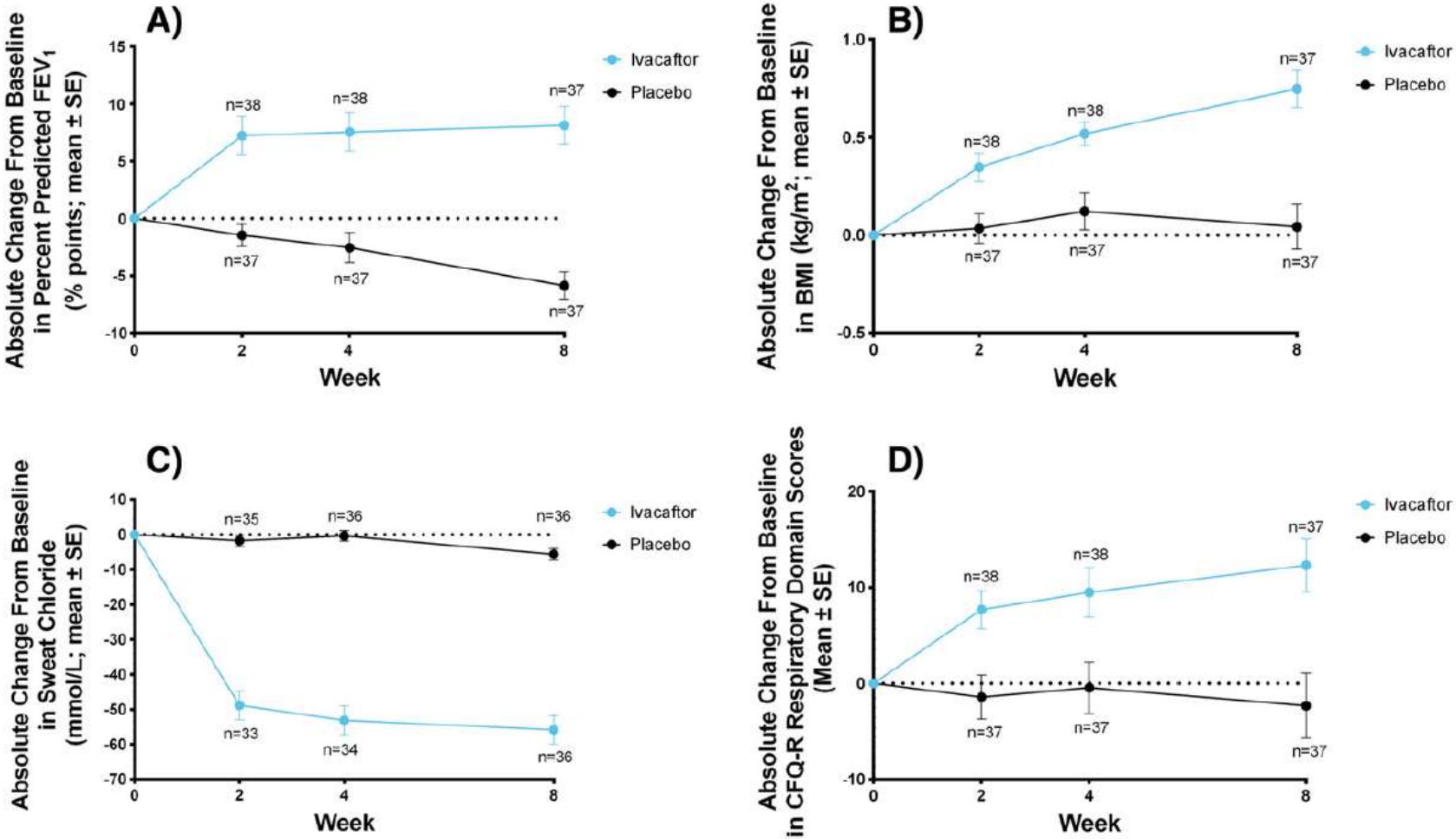


Fig. 1. Mean absolute change from baseline after 8 weeks of treatment in (A) percent predicted FEV_1; (B) BMI; (C) sweat chloride; and (D) CFQ-R respiratory domain score. BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised.

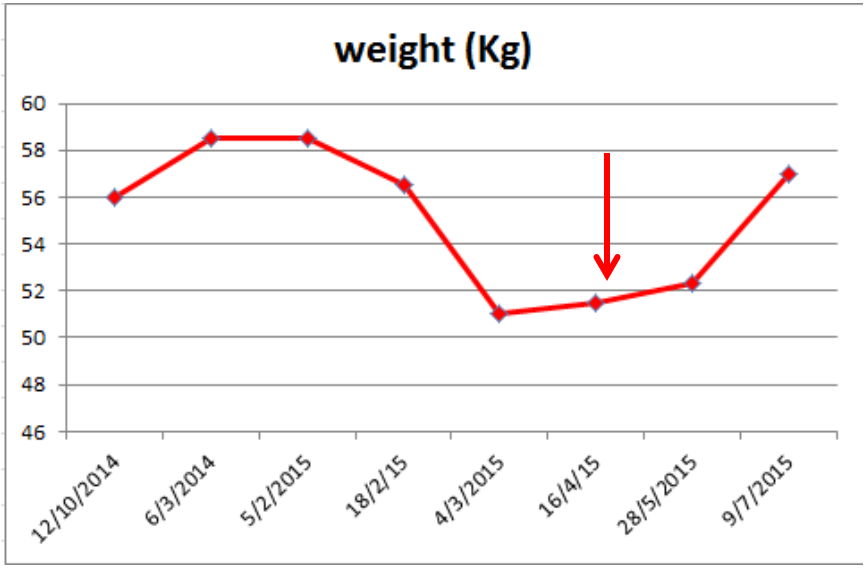
De Boeck, Kris, et al. "Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation." *Journal of Cystic Fibrosis* 13.6 (2014): 674-680.

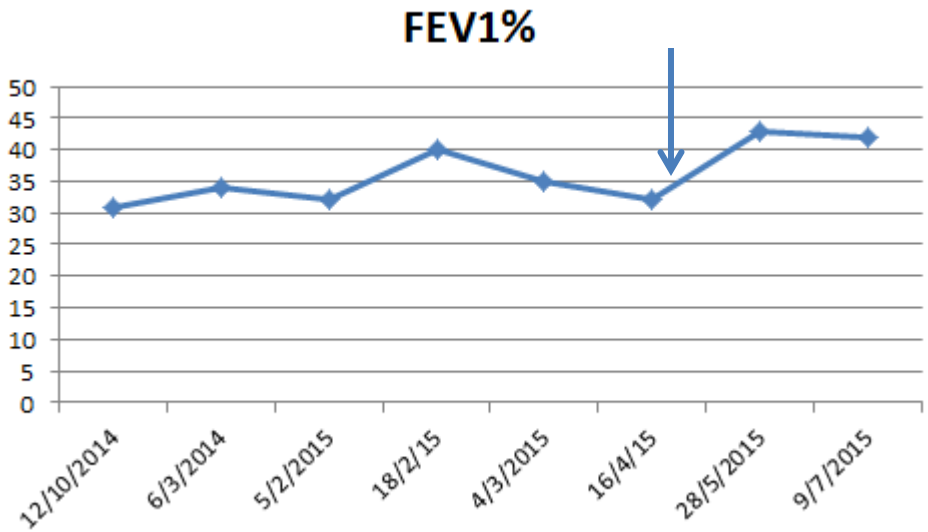
Questions and Dilemmas

- Would ivacaftor absorption be impaired due to ileal resection and existing ileostomy? Is there a way to monitor drug absorption?
- Would partial adherence (to ivacaftor, to other treatment recommendations) jeopardize ivacaftor effect?
- Would ivacaftor have the reported effect in advanced lung disease?
- Can ivacaftor improve bowel transit, reducing the risk for recurrent obstruction?
- Is cost justified in this patient?

Management

- Started Ivacaftor treatment 22/4/15
- Referred to an outpatient rehabilitation program
- 1 month on Ivacaftor- Spirometry 43% (last 39%), no change in weight
- 2 months on ivacaftor- lung function stable, gained 5 Kg
- Well being improved, started a phone technician course





Arrows indicate time of ivacaftor commencement

Effects of Ivacaftor in Patients With Cystic Fibrosis Who Carry the G551D Mutation and Have Severe Lung Disease

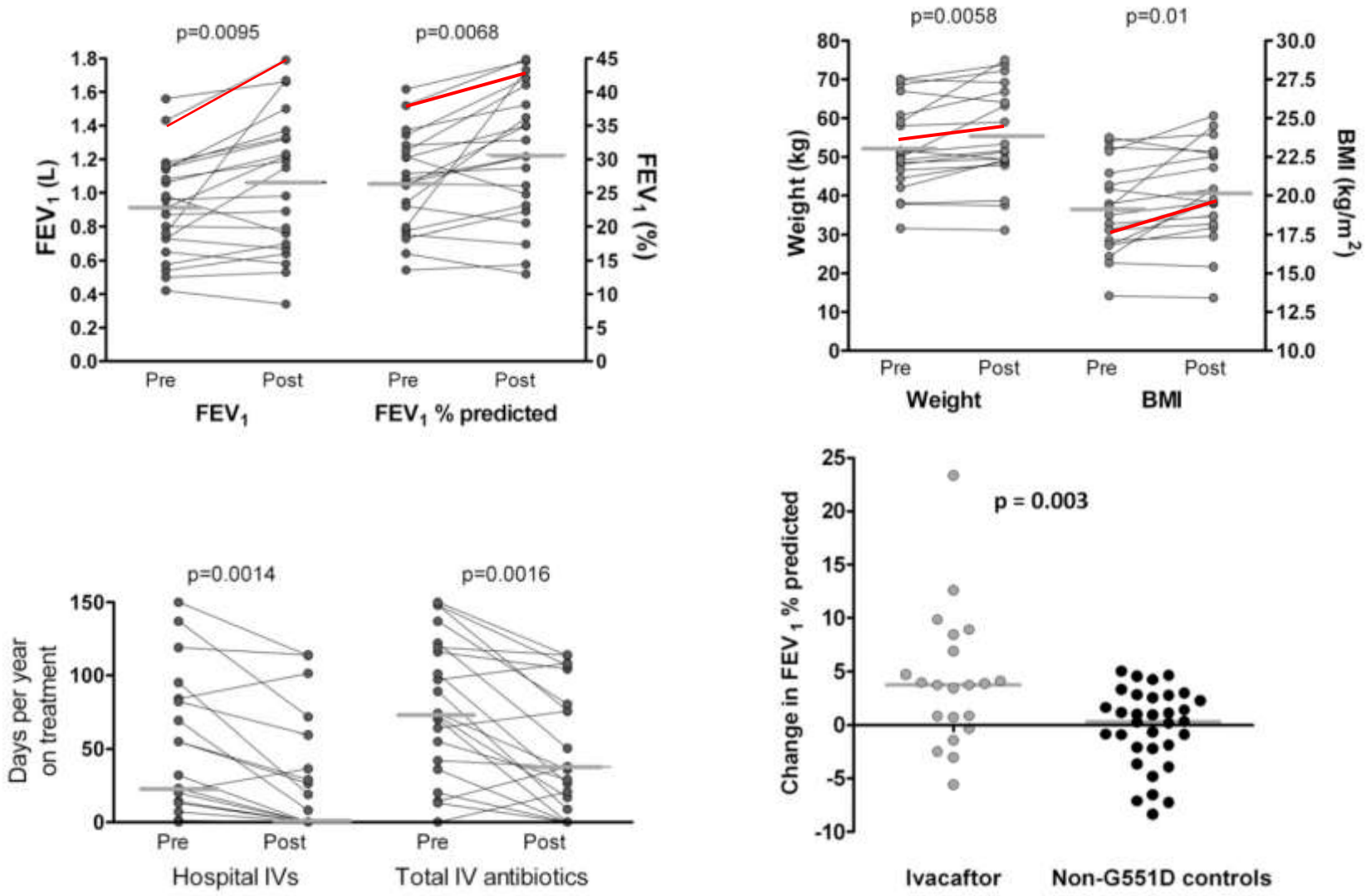
Peter J. Barry, MBBCh; Barry J. Plant, MD; Arjun Nair, MBChB; Stephen Bicknell, MBChB; Nicholas J. Simmonds, MD; Nicholas J. Bell, MBChB; Nadia T. Shafi, MD; Thomas Daniels, MD; Susan Shelmerdine, MBBS; Imogen Felton, MBBS; Cedric Gunaratnam MBBCh; Andrew M. Jones, MD; and Alex R. Horsley, PhD

TABLE 1] Baseline Demographics in Cases and Control Subjects

Demographic	Patients Treated With Ivacaftor	Control Subjects Without the G551D CF Mutation	*P* Value
Patients, No.	21	35	
Age, y	22 (20-31)	23 (21-27)	.85
Male sex, %	10 (48)	18(51)	.79
Diabetic, No. (%)	10 (48)	17 (49)	.945
CF-related liver disease, No. (%)	6 (29)	6 (17)	.31
Home oxygen, No. (%)	12 (57)	19 (54)	.83
Transplant list, No. (%)	0 (0)	2 (6)	.52
FEV_1, L	0.91 (0.30)	1.08 (0.29)	.05
FEV_1, %	26.5 (7.2)	30.3 (7.5)	.08
FVC, L	2.03 (0.87)	2.14 (0.78)	.6
Weight, kg	49.8 (44.4-60.7)	54.0 (49.0-62.4)	.2
BMI, kg/m^2	19.1 (2.9)	20.2 (5.2)	.37
HBA1C, mmol/mol	45 (42-58·5)	45.0 (40.0-61.0)	.9
Oral antibiotics, d/y	7 (0-20)	8 (0-28)	.5
Inpatient IV antibiotics, d/y	23 (14-83)	33 (2-55)	.7
Home IV antibiotics, d/y	20 (0-61)	14 (0-60)	.97
Total IV antibiotics, d/y	74 (39-121)	66 (29-112)	.4

Data are presented as mean (SD) or median (interquartile range) as appropriate, unless otherwise indicated. CF = cystic fibrosis; HBA1C = glycosylated hemoglobin A1C.

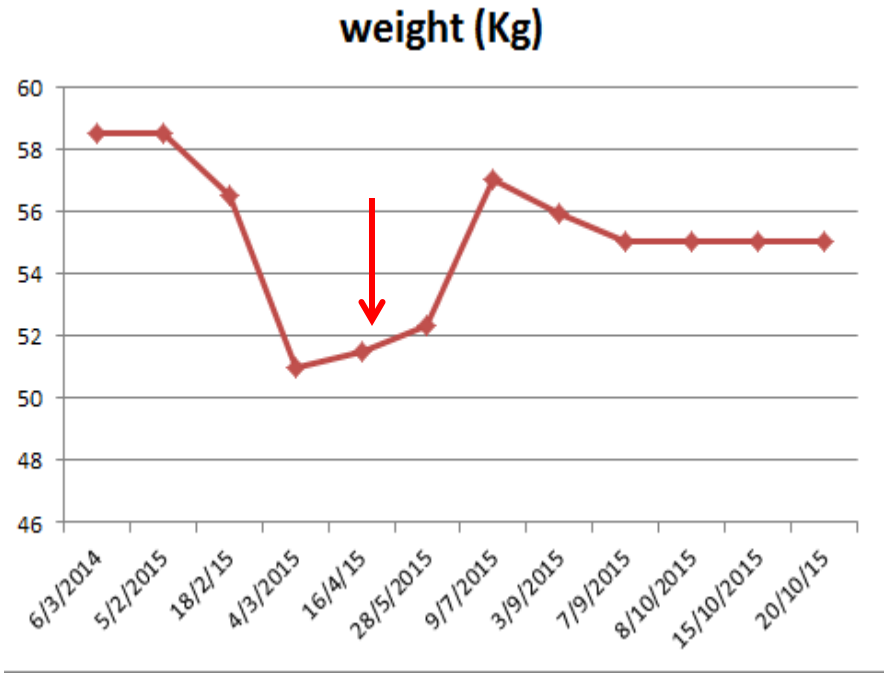
Barry, Peter J., et al. "Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease." *CHEST Journal* 146.1 (2014): 152-158.

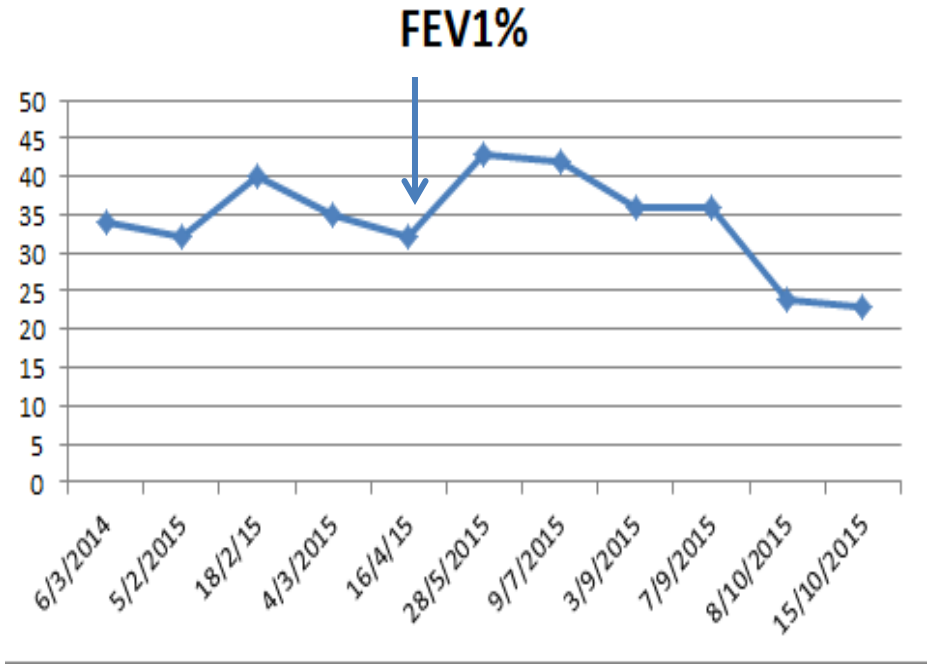


Barry, Peter J., et al. "Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease." *CHEST Journal* 146.1 (2014): 152-158.

Continued

- 5 months on ivacaftor- presented with an exacerbation (cough, SOB, hypoxemia, rales)
- Lost weight and lung function
- Admitted to not adhering to treatments (except ivacaftor)
- Does not comply with drug rehabilitation program
- Prolonged hospitalization, hypoxemia





Arrows indicate time of ivacaftor commencement

Testing ivacaftor effect

- How can we test for ivacaftor absorption and effect?
- Ivacaftor blood levels???
- mean (±SD) for AUC and Cmax were 10600 (5260) ng*hr/mL and 768 (233) ng/mL, respectively[1].
- Use sweat Cl?
- Non G551D: −49.2 mmol/L (95% CI: −57.0, −41.4), 5 pts G1244E: −55.10 (95% CI: −75.0, −34.0)[2]
- Sweat Cl: 110->94
- NPD- unchanged

1 Kalydeco prescribing information, ©2012 Vertex Pharmaceuticals Incorporated
2 De Boeck, Kris, et al. "Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation." *Journal of Cystic Fibrosis* 13.6 (2014): 674-680.

Summary

- G1244E homozygote with severe lung disease, bowel resection and ileostomy, opiate abuse, repeat bowel obstruction
- Initial improvement in lung function and weight gain- ivacaftor effect or IV antibiotics?
- Stopping all treatments expectedly led to an irreversible deterioration
- No change in sweat Cl, NPD!
- Is ivacaftor being absorbed and working?
- Stop ivacaftor treatment?

Acknowledgements

Carmel CF Center:

- Dr. Galit Livnat- Levanon- Pediatric Pulmonology
- Dr. Michal Shteinberg- Adult Pulmonology
- Dr. Reut Lutzky- Adult Gastroenterology
- Dr. Yigal Elenberg– Pediatric Gastroenterology
- Dr. Ilana Koren- Pediatric Endocrinology
- Nona Purits- Nurse
- Orit Brazlavsky- Nurse
- Dr. Rachel Friedman- Social worker
- Dr. Maram Salameh- Clinical pharmacist
- Ofra Tsuk- Physiotherapist
- Rivka Steinmitz- Nutritionist
- Hila Alterovitz- Nutritionist
- Michal Maoz- Katz- Nutritionist
- Iehudit Mandel- Administrative assistant
- Nursing and medical staff at Carmel pediatrics dept.

Hadassah Medical Center:
Prof. Michael Wilschanski
Vertex: Dr. Joe Healy
Dr. Cecile Lecamus
Medison: Dr. Yael Gruenbaum