

# 다제내성 결핵 신약의 임상경험

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# 신약과 재활용

- 신약(New Drugs)
  - ▣ Bedaquiline(Bdq): 서투러
  - ▣ Delamanid(DIm) : 델티바
- 재활용약(Re-Purposed Drugs)
  - ▣ Linezolid(Lzd): 자이복스
  - ▣ Clofazimine(Cfz)



# 내용

- 신약의 효과
  - ▣ 효과적인 약제의 구성(Optimal Regimen)
    - 살균, 멸균약제(Bactericidal, core drug)
  - ▣ 두가지 약제 병용 치료
    - Case
    - 신약제부작용 모니터링
      - QT prolongation
    - 6개월이상의 치료



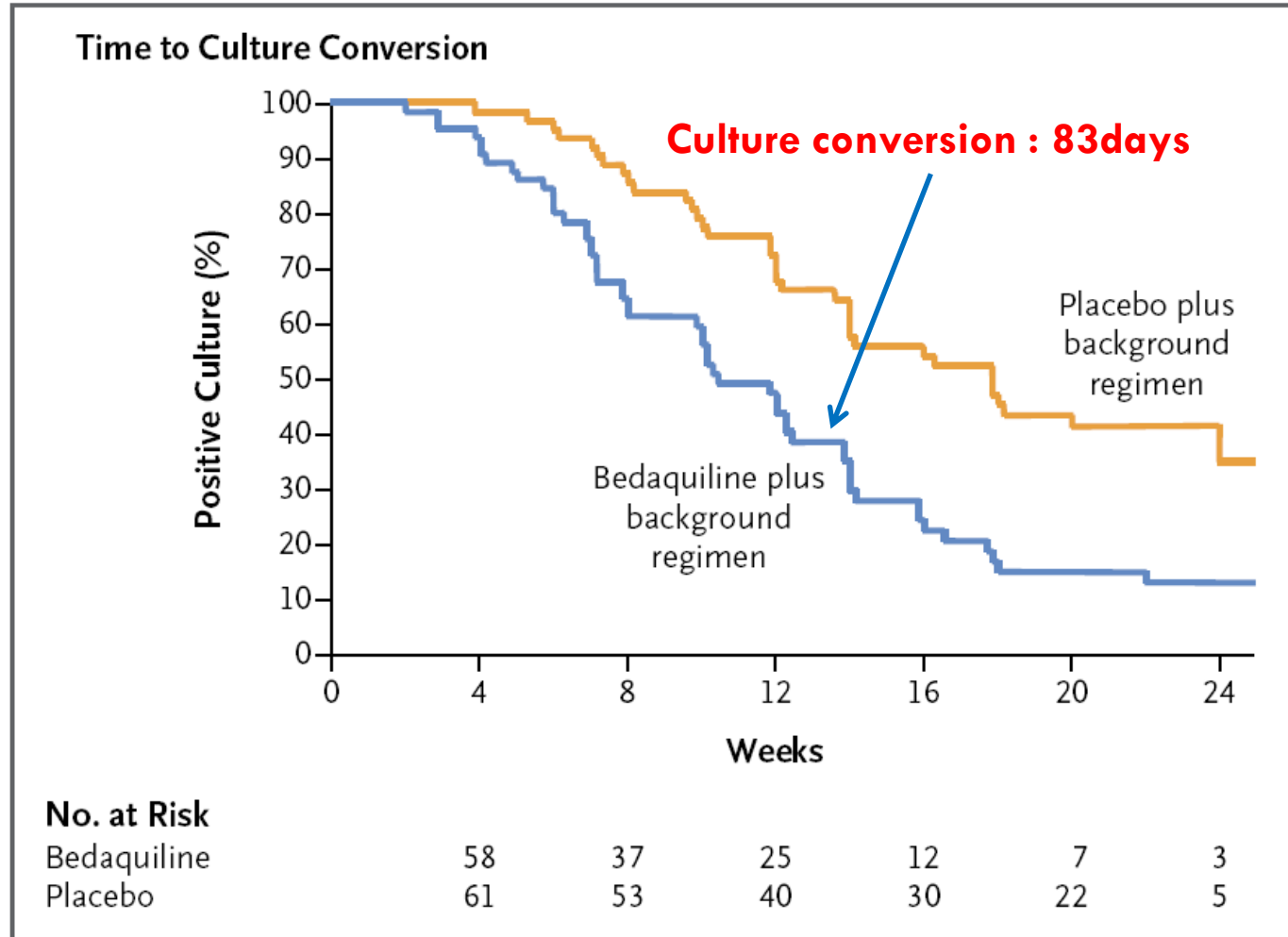
# Bedaquiline

- Absorption: increased with food
  - ▣ Half-life: 5.5month
- Metabolism: Hepatic via CYP3A4
  - ▣ Excretion: feces
- Dosing :
  - ▣ Weeks 1~2 : 400mg once daily
  - ▣ Weeks 3~24 : 200mg 3times weekly
- Resistance
  - ▣ Mutation: Rv0678, *atpE*
  - ▣ Cross Resistance: Cfz



# Bedaquiline

## 24주간 투여



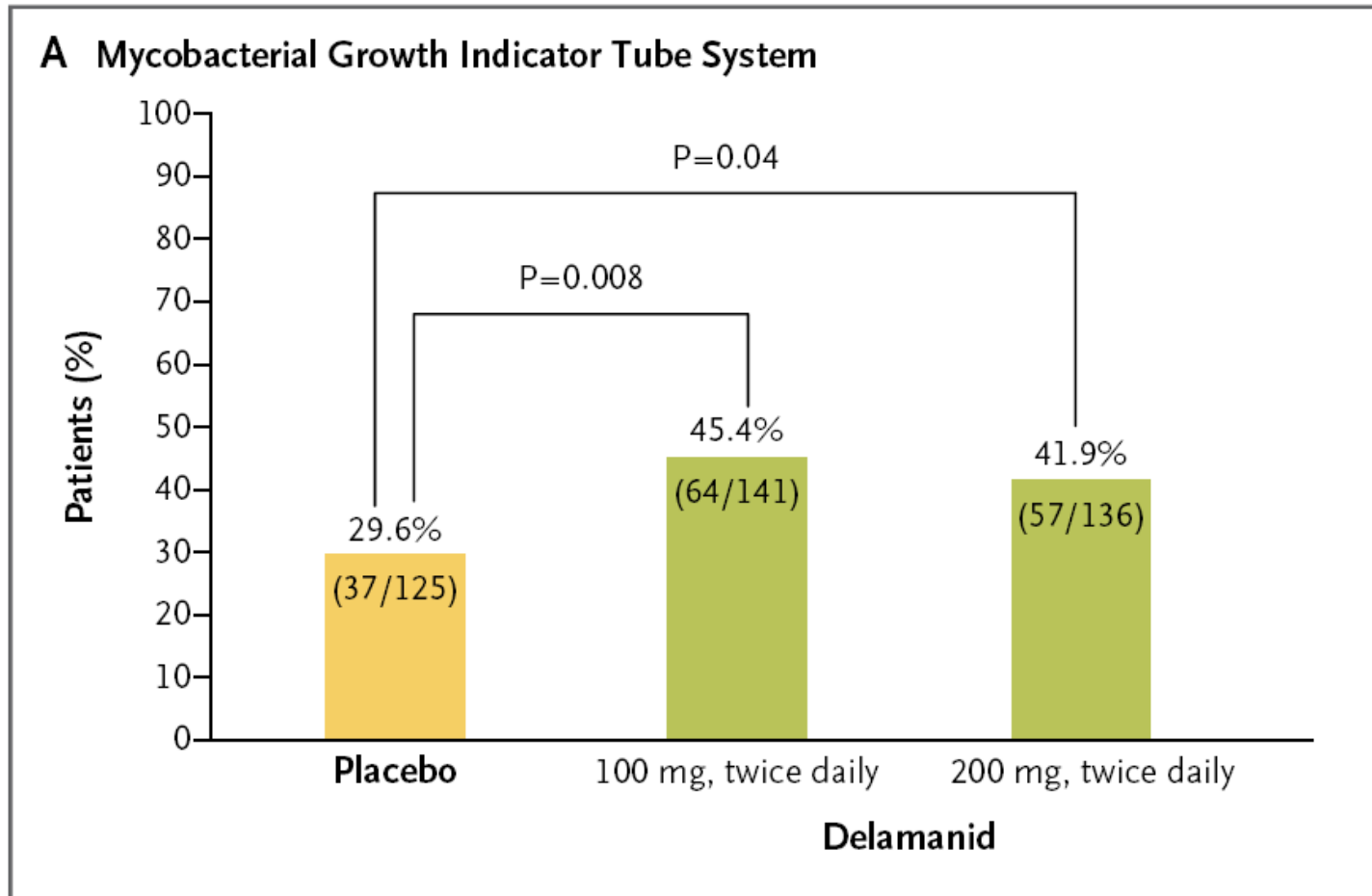
# Delamanid

- Bioavailability : 25~ 47%
  - ▣ Water solubility poor : with food
- Half-life: 30~ 38 hours
  - ▣ Excreted in stool(89%), in urine(<5%)
- 99% protein bound
  - ▣ Metabolized by albumin : 2.8g/dL
- Metabolites(M1 ~ M4) contribute to QT prolongation



# Delamanid

## 2개월 치료후 배양음전

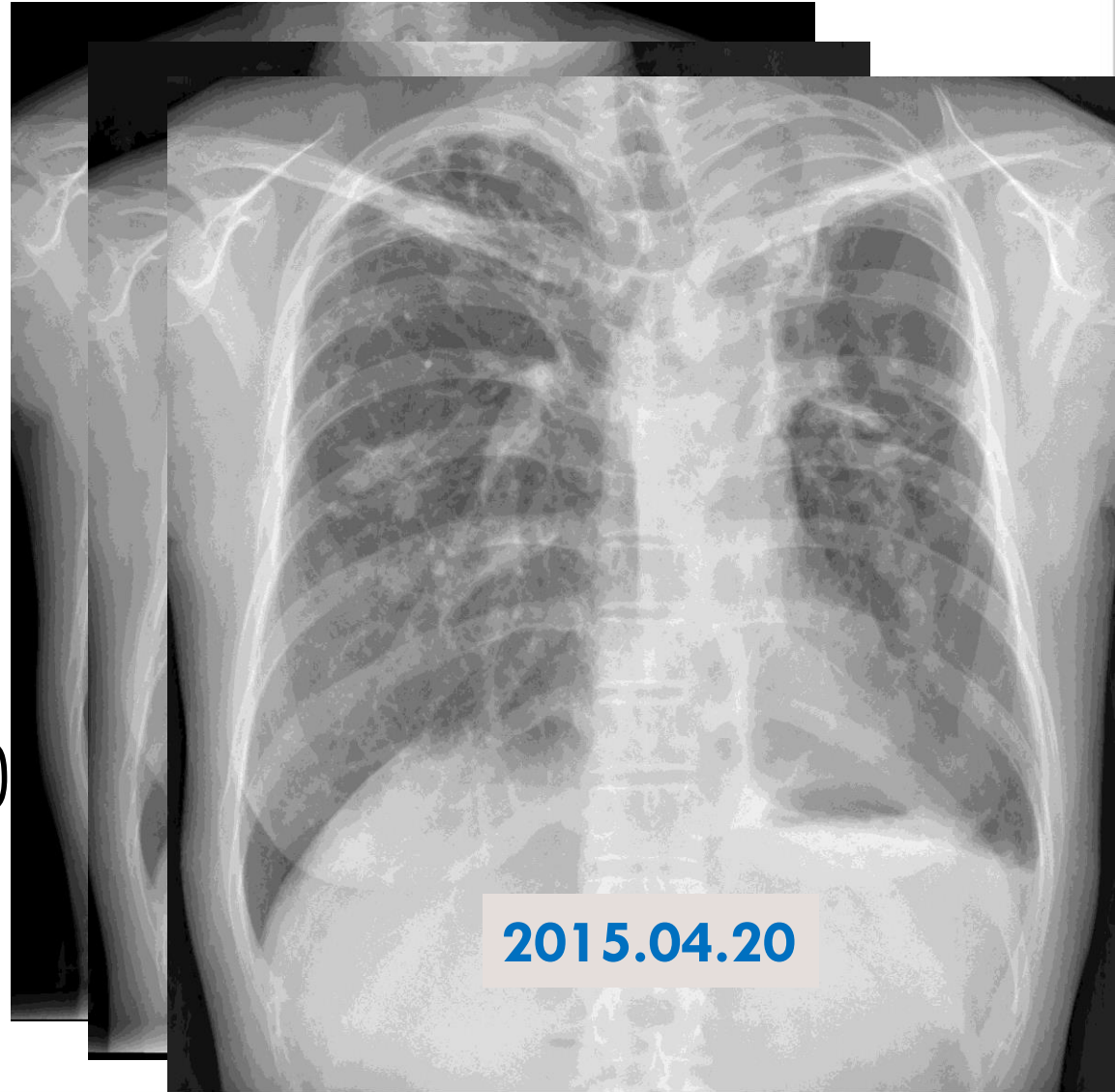


# 결핵약의 새로운 분류

A. Fluoroquinolones <sup>2</sup>	Levofloxacin Moxifloxacin Gatifloxacin		Lfx Mfx Gfx
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin) <sup>3</sup>		Am Cm Km (S)
C. Other core second-line agents <sup>2</sup>	Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine		Eto / Pto Cs / Trd <u>Lzd</u> Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	<b>D1</b>	Pyrazinamide Ethambutol High-dose isoniazid	Z E H <sup>h</sup>
	<b>D2</b>	Bedaquiline Delamanid	<u>Bdq</u> <u>Dlm</u>
	<b>D3</b>	<i>p</i> -aminosalicylic acid Imipenem-cilastatin <sup>4</sup> Meropenem <sup>4</sup> Amoxicillin-clavulanate <sup>4</sup> (Thioacetazone) <sup>5</sup>	PAS lpm Mpm Amx-Clv (T)

# 신약 사용(I)

- F/39
- 2003년 Pul. TB
- 2004년 MDR-TB
  - ▣ Cs, Pth, Emb
- 2012년
  - ▣ Cs, Pth, Emb + Agu. , CLari + Km(11/4- 12/10) + Pza (13/9 ~)
    - ▣ AFB: 1 ~ 2 +



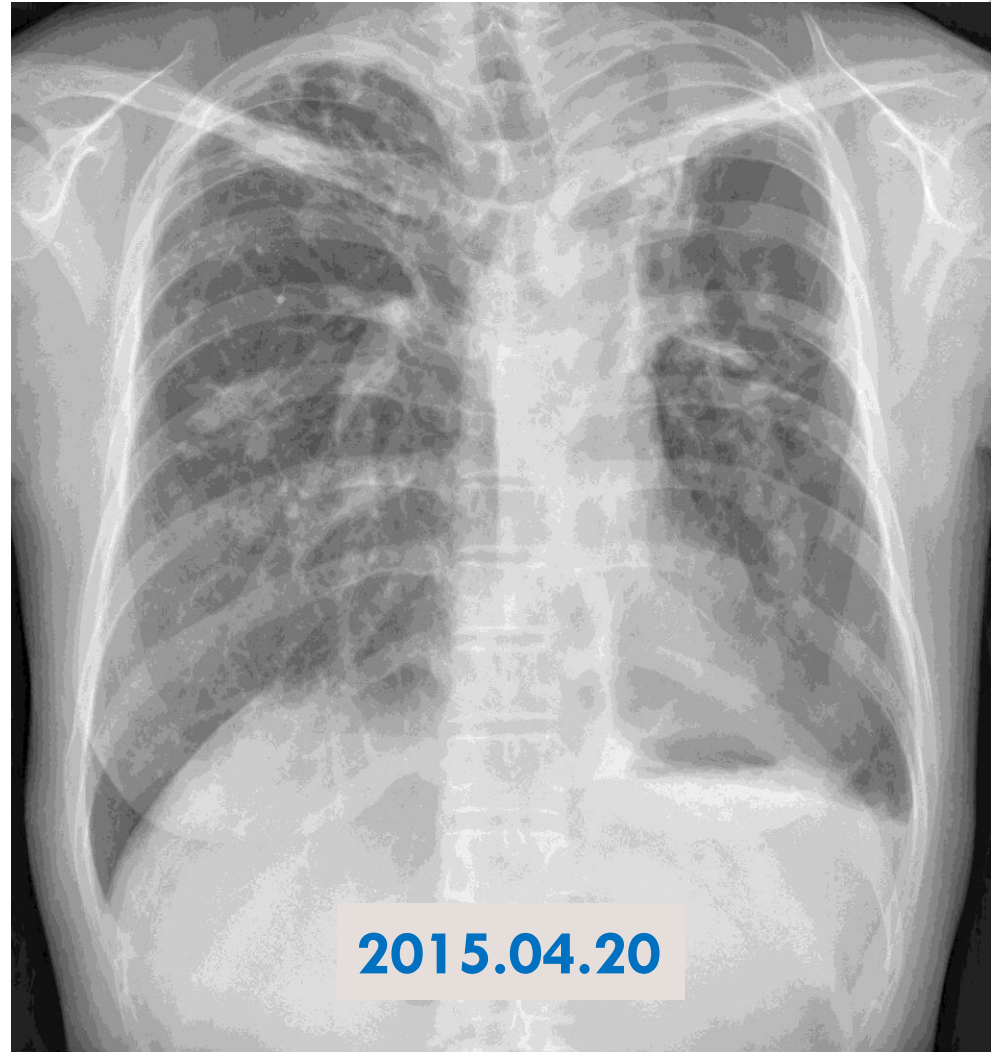
# 000 F/39

- 2015년 : Emb, Cs, Pth, Amox-cla, Clar, PZA (13/9 ~)
- DST
  - ▣ 2006년 S: Cs, Km, Cpm, Amk, Pth, Emb, Pas
  - ▣ 2008년 S: Cs, Cpm, Amk, Pth
  - ▣ 2010년 S: Cs, Km, Cpm, Amk
  - ▣ 2013년 S: Cs, Km, Cpm, Amk, Pth, Pza
  - ▣ 2014년 S: Cs, Km, Cpm, Amk, Pth
- 효과적인 약제:
  - ▣ Cs, Pth(오심,구토)
  - ▣ Km(11/4- 12/10) : 양쪽 다리 저림
  - ▣ Amx-Clv, Clar : 효과?
- 수술(X): 양측성 미만성 병변



# 000 F/39

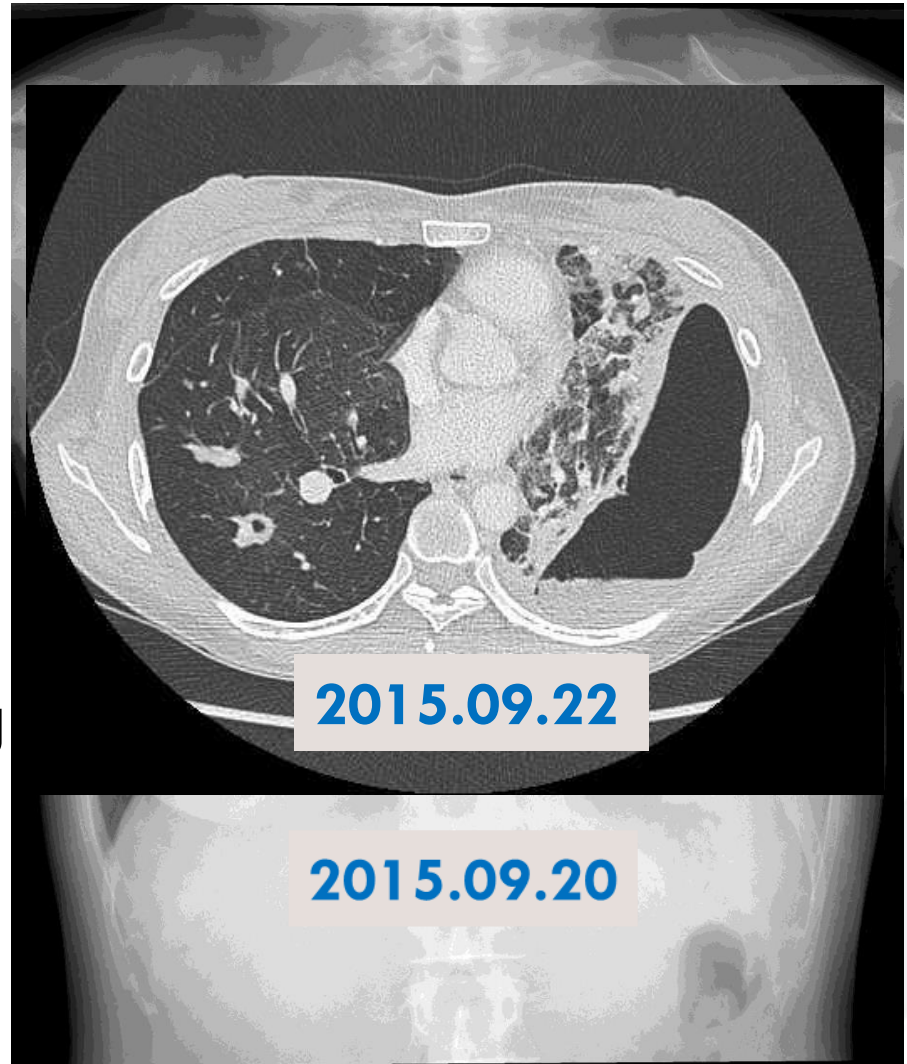
- 2014년
  - S: Cs, Pth, Km, Amk
  - Lzd :입원명령 거부
  - Km(11/4- 12/10)
  
- 2015년
  - Cs, Pth, Aug, Clar
  - PZA (13/9 ~)



2015.04.20

# 결핵 농흉

- 2015년 9월
  - Fever 39
  - AFB 4+,
  - Plueral fluid 1+
- 결핵성 농흉으로 진행
  - 10년간 사용약제
  - Cs, Pth, PZA, Clar, Aug



# 효과적인 약제구성

- Cs, Pth, PZA : 중단
  - 효과?, 내성
    - S: Cs, Pth : 10년간 사용
    - TB empyema (pre XDR)
- 새로운 약제구성
  - Lzd + Bdq(Dlm) + Cs + Pth + Amk
  - Lzd + Bdq + Amk + Imipenem(Ipm)
    - Dlm(15/11 ~ )
  - 2015/12/03 DST: S: Cs, KM, CPM, AMK, PZA
  - Cs, Pza(12/9 ~ )

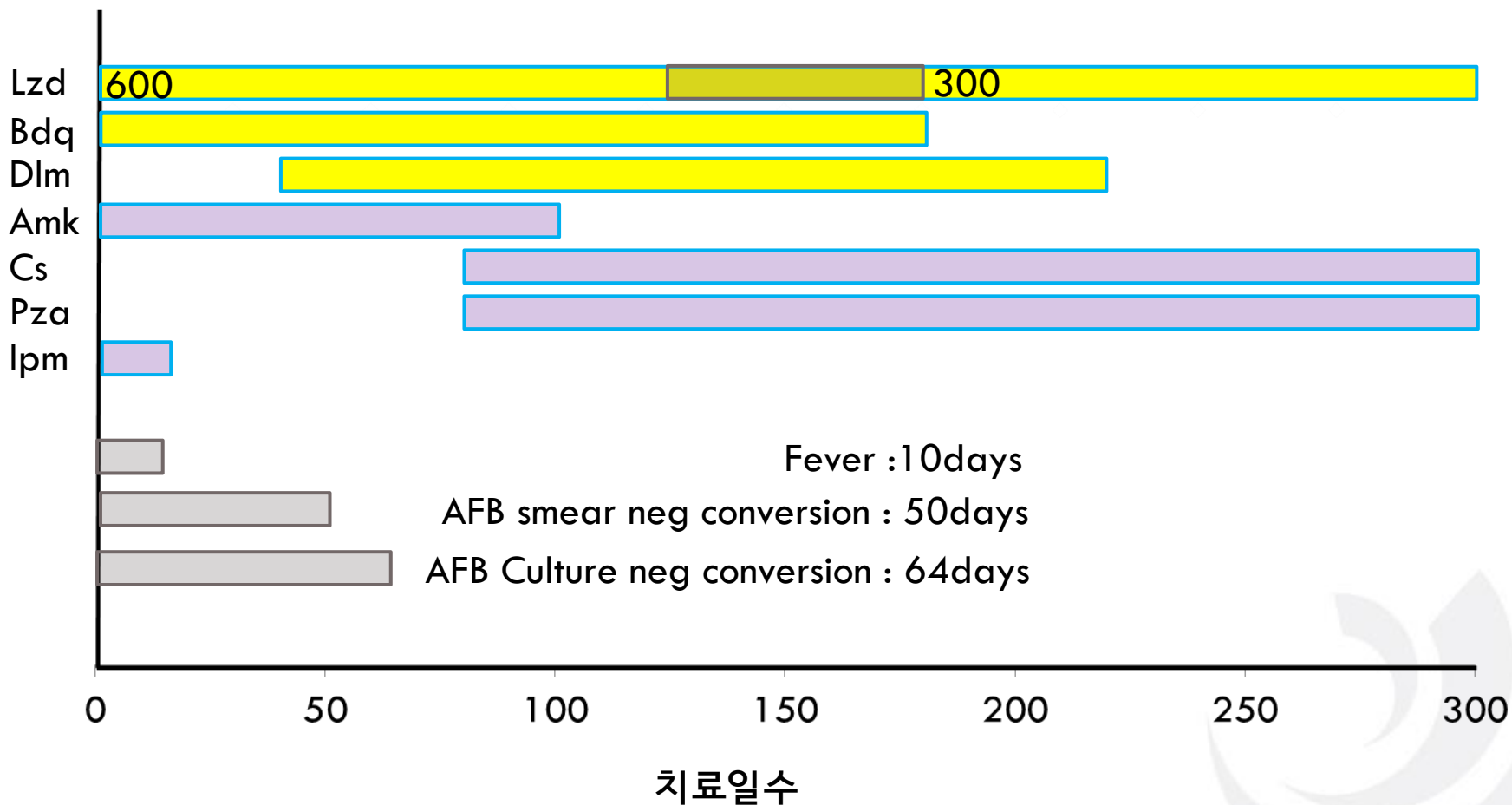


# 임상경과

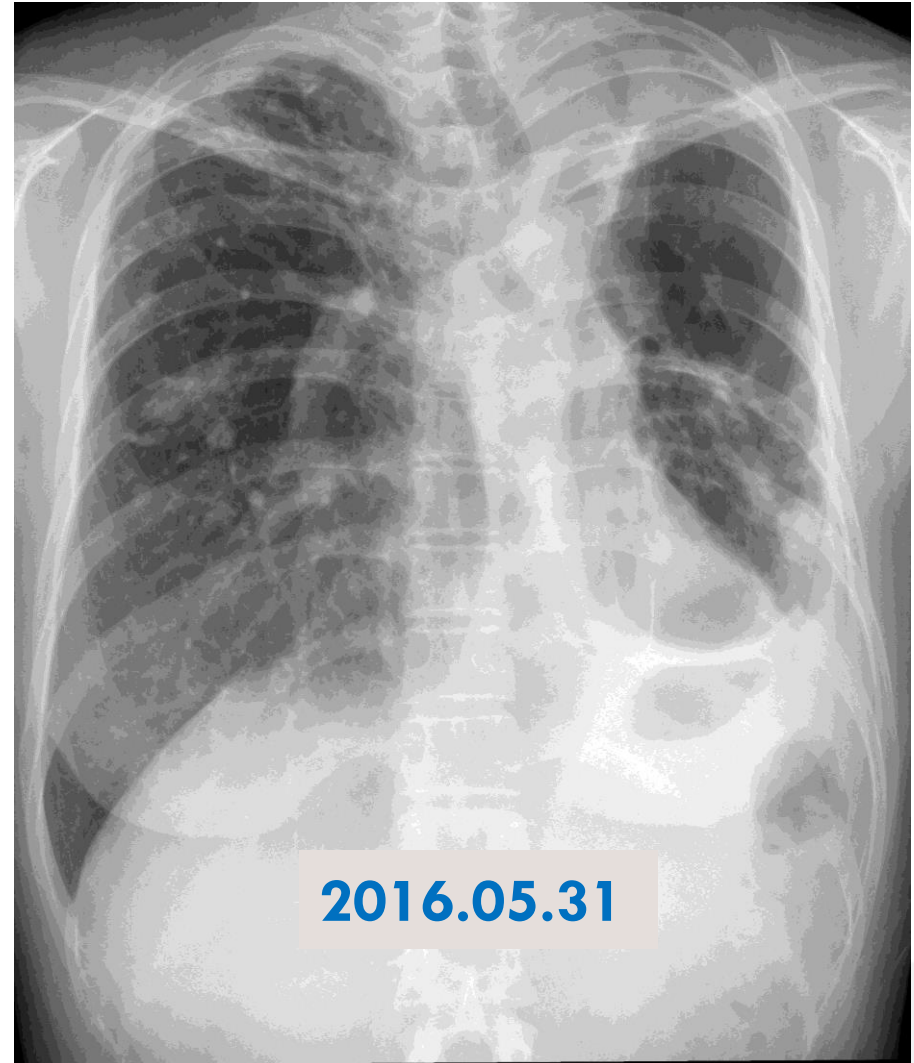
- Lz, Bdq, Amk, Ipm, (DIm)
  - ▣ 열 : 40도(10일: 09/22 ~ 10/01) →37도
  - ▣ 38도 (10/30, 11/06)
  
- PCD
  - ▣ 15/09/30 ~ 10/22, 11/10 ~ 12/02)
  
- AFB :
  - ▣ smear conversion(15/11/10) : HD 50day
  - ▣ culture conversion(15/12/4) : HD 64day



# 약제



# X-ray



# 부작용

- Bdq
  - ▣ QT 연장
  - ▣ 간기능 이상
  - ▣ 사망
- DIm
  - ▣ QT 연장
  - ▣ 오심(38%), 구역(33%), 졸음(30%)
- Bdq, DIm combinaton: 추천하지 않음

# 부작용(Bdq)

**Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.\***

Variable	Bedaquiline (N = 79)	Placebo (N = 81)
Median duration of overall treatment phase (range) — wk	91.7 (2.0–120.0)	94.1 (2.0–137.3)
Adverse event — no. (%)		
Any	78 (99)	79 (98)
Related to treatment	55 (70)	56 (69)
Grade 3 or 4†	34 (43)	29 (36)
Leading to discontinuation of treatment	4 (5)	5 (6)
Serious adverse events — no. (%)‡	18 (23)	15 (19)
Adverse event occurring in ≥20% of patients — no. (%)		
Nausea	32 (41)	30 (37)
Arthralgia	29 (37)	22 (27)
Vomiting	23 (29)	22 (27)
Headache	23 (29)	18 (22)
Hyperuricemia	20 (25)	27 (33)
Hemoptysis	16 (20)	14 (17)

# 부작용(Bdq, N=22)

Masan National Hospital

<b>AEs</b>	<b><i>Cutaneous</i></b>	<b>4</b>
	<b><i>Musculoskeletal</i></b>	<b>2</b>
	<b><i>hematologic</i></b>	<b>3</b>
	<b><i>Peripheral neuropathy</i></b>	<b>7</b>
	<b><i>ototoxicity</i></b>	<b>3</b>
	<b><i>psychiatric</i></b>	<b>3</b>
	<b><i>others</i></b>	<b>3(fatigue, etc.)</b>

Slide: Courtesy of HS Kang, MD

# Delamanid

- 흔한 부작용
  - ▣ Nausea(38%), vomiting(33%), dizziness(30%)
- 중단(204 study: 2개월치료)
  - ▣ 100mg bid: Psychiatric(2) dermatologic(1), thrombocytopenia(1),
  - ▣ 200mg bid: Leukopenia(1), Psychiatric(3), respiratory failure(1), dermatologic(2)
- QT 연장
  - ▣ Hypoalbuminemia(<2.8g/dL)
  - ▣ Initial 6-10 weeks of treatment



**Table 2. Incidence of Adverse Events (Occurring in  $\geq 10\%$  of Patients in Either Delamanid Group and with Greater Frequency Than in the Placebo Group).\***

Adverse Event	Delamanid, 100 mg Twice Daily (N = 161)	Delamanid, 200 mg Twice Daily (N = 160)	Placebo (N = 160)
	<i>number of patients (percent)</i>		
<b>Hematopoietic</b>			
Anemia	18 (11.2)	10 (6.2)	14 (8.8)
Reticulocytosis	19 (11.8)	20 (12.5)	17 (10.6)
<b>Gastrointestinal</b>			
Nausea	58 (36.0)	65 (40.6)	53 (33.1)
Vomiting	48 (29.8)	58 (36.2)	44 (27.5)
Upper abdominal pain	41 (25.5)	36 (22.5)	38 (23.8)
<b>Cardiovascular</b>			
Palpitations	13 (8.1)	20 (12.5)	10 (6.2)
Prolonged QT interval on ECG	16 (9.9)	21 (13.1)	6 (3.8)
Respiratory: hemoptysis	19 (11.8)	15 (9.4)	17 (10.6)
<b>Nervous system</b>			
Headache	36 (22.4)	41 (25.6)	30 (18.8)
Paresthesias	17 (10.6)	20 (12.5)	12 (7.5)
Tremor	19 (11.8)	16 (10.0)	13 (8.1)
Insomnia	42 (26.1)	51 (31.9)	42 (26.2)
<b>General</b>			
Tinnitus	16 (9.9)	22 (13.8)	12 (7.5)
Asthenia	20 (12.4)	27 (16.9)	20 (12.5)
Malaise	12 (7.5)	16 (10.0)	12 (7.5)
Anorexia	23 (14.3)	34 (21.2)	24 (15.0)
Hyperhidrosis	9 (5.6)	17 (10.6)	8 (5.0)
Hyperuricemia	31 (19.3)	38 (23.8)	35 (21.9)
Hypokalemia	20 (12.4)	31 (19.4)	24 (15.0)

# 부작용(DIm, N=11)

Masan National Hospital

<b>AEs</b>	<b><i>Gastrointestinal</i></b>	<b>3(1)</b> <b>Nausea, vomiting</b>
	<b><i>Cutaneous</i></b>	<b>1</b> <b>Exfoliative dermatitis</b>
	<b><i>hematologic</i></b>	<b>2</b> <b>anemia</b>
	<b><i>neuropathy</i></b>	<b>3(1)</b> <b>Paresthesia, severe pain and leg cramp</b>
	<b><i>QT prolongation</i></b>	<b>1(1)</b>
	<b><i>others</i></b>	<b>1(1)</b> <b>General weakness</b>

# QTc 모니터링

- ECG
  - ▣ QTc prolongation
  - ▣ 48회(98일 입원기간): Interval : 402 ~ 489
  - ▣ 508(15/11/21) : Delamanid 중단(11/21,22 ± 日)
- Electrolytes
  - ▣ K, Mg, Ca
- Albumin
  - ▣ Dlm toxicity 2.8 g/dL 미만시 QTc 증가
  - ▣ Interval : 2.5 ~ 4.4
- CBC, LFT.



# Torsade de Pointes (TdP)

- Risk factor
  - ▣ female sex, advanced age, extreme bradycardia, renal failure, long QT syndrome
  - ▣ Electrolytes(K, Mg, Ca)
- Anti-TB medication (associated with TdP)
  - ▣ Quinolone: Mf, Lf, Of
  - ▣ Bdq
  - ▣ Dlm
  - ▣ Cfz

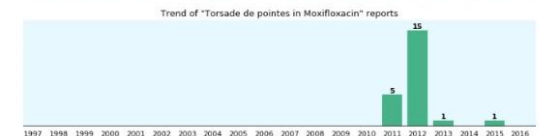


# 약제관련 TdP

## US FDA Adverse Event Reporting System 2004 ~ 2008년

Antimicrobial agent	Cases	Non-cases	Crude ROR (95% CI)	Cases without concomitant QT interval-prolonging drugs <sup>a</sup>
<b>β-Lactam antibacterials</b>				
ampicillin	1	254	2.42 (NA)	1
amoxicillin piperacillin/	3	2588	0.71 (NA)	
tazobactam cefazolin	4	1332	1.85 (0.59, 5.09)	2
ceftriaxone	5	2182	1.41 (0.52, 3.50)	3
<b>Carbapenems</b>				
meropenem	3	657	2.81 (0.72, 8.99)	
<b>Macrolides</b>				
erythromycin	7	653	6.60 (2.88, 14.34)	2
clarithromycin	22	2531	5.37 (3.44, 8.31)	10
azithromycin	16	2406	4.10 (2.42, 6.84)	11
telithromycin	6	1632	2.26 (0.92, 5.21)	5
<b>Aminoglycoside antibacterials</b>				
gentamicin	1	763	0.81 (NA)	1
amikacin	1	430	1.43 (NA)	
<b>Fluoroquinolones</b>				
ofloxacin	1	765	0.80 (NA)	
ciprofloxacin	35	3554	6.10 (4.30, 8.62)	20
levofloxacin	55	4990	6.86 (5.20, 9.04)	42
moxifloxacin	37	2912	7.88 (5.61, 11.03)	29
gatifloxacin	6	638	5.79 (2.34, 13.36)	4

Number of reports submitted per year:



Time on Moxifloxacin when people have Torsade De Pointes\*:

- < 1 month: 100 %
- 1 - 6 months: 0.0 %
- 6 - 12 months: 0.0 %
- 1 - 2 years: 0.0 %
- 2 - 5 years: 0.0 %
- 5 - 10 years: 0.0 %
- 10+ years: 0.0 %

22 case

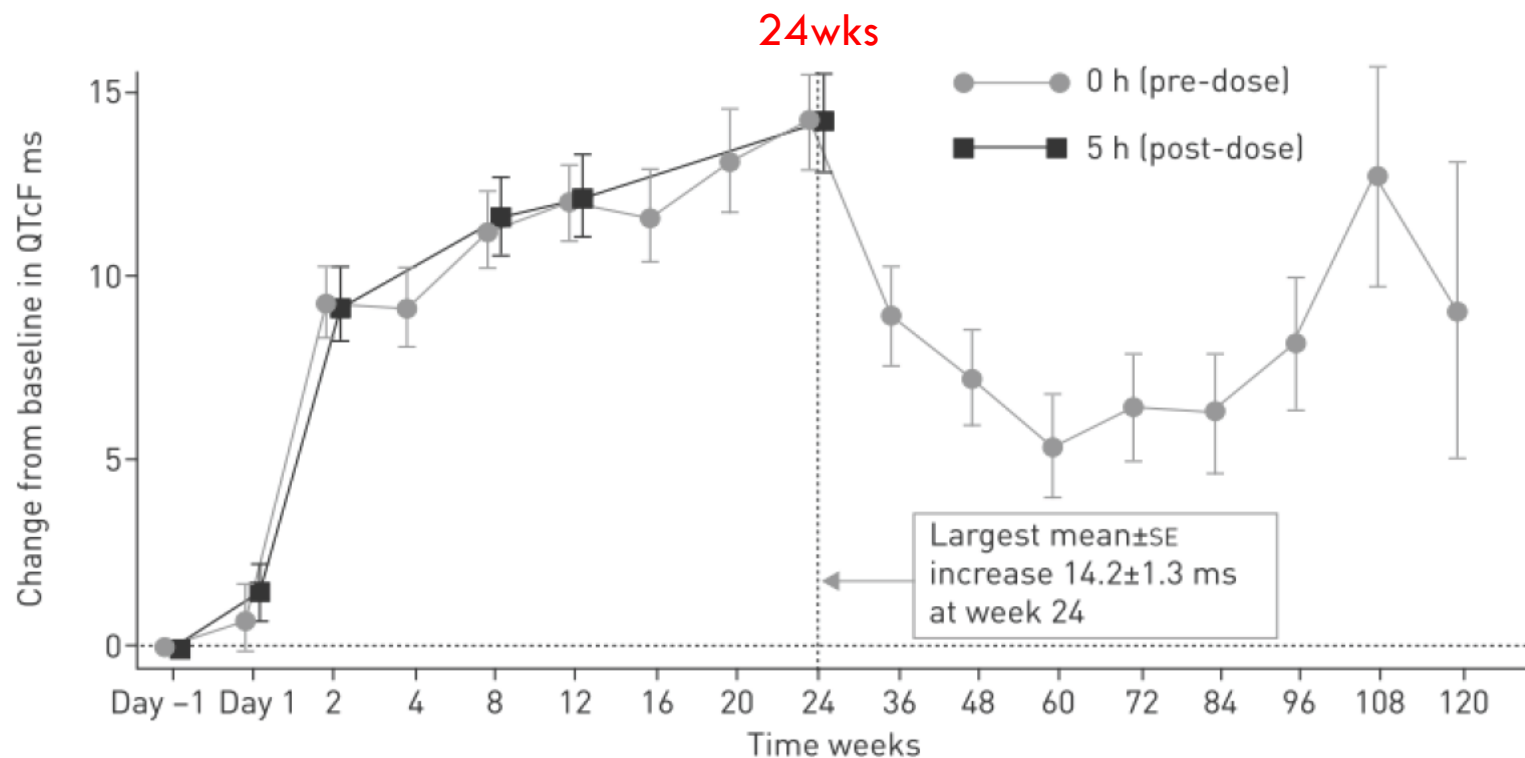
Gender of people who have Torsade De Pointes when taking Moxifloxacin\*:

- female: 90.48 %
- male: 9.52 %

Age of people who have Torsade De Pointes when taking Moxifloxacin\*:

- 0-1: 0.0 %
- 2-9: 0.0 %
- 10-19: 0.0 %
- 20-29: 4.76 %

# QTc Bdq



Patients n

0 h 228 227 220 221 218 216 209 204 200 203 189 193 183 151 108 48 30

5 h 226 226 217 214 212 191

# QTc :DIm

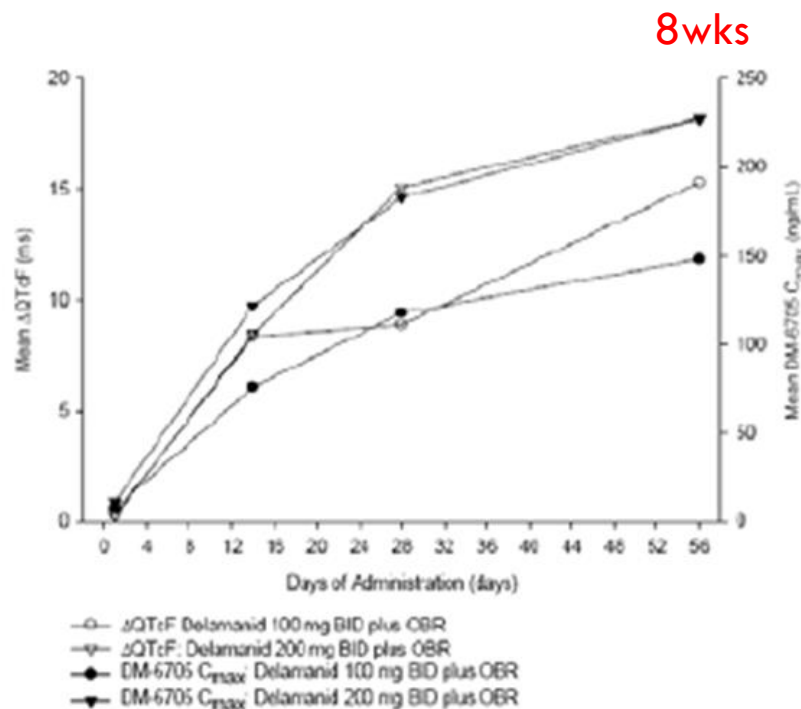


Figure 10.4.2-2 Mean QTcF Change From Baseline and Plasma DM-6705 C<sub>max</sub> Versus Time

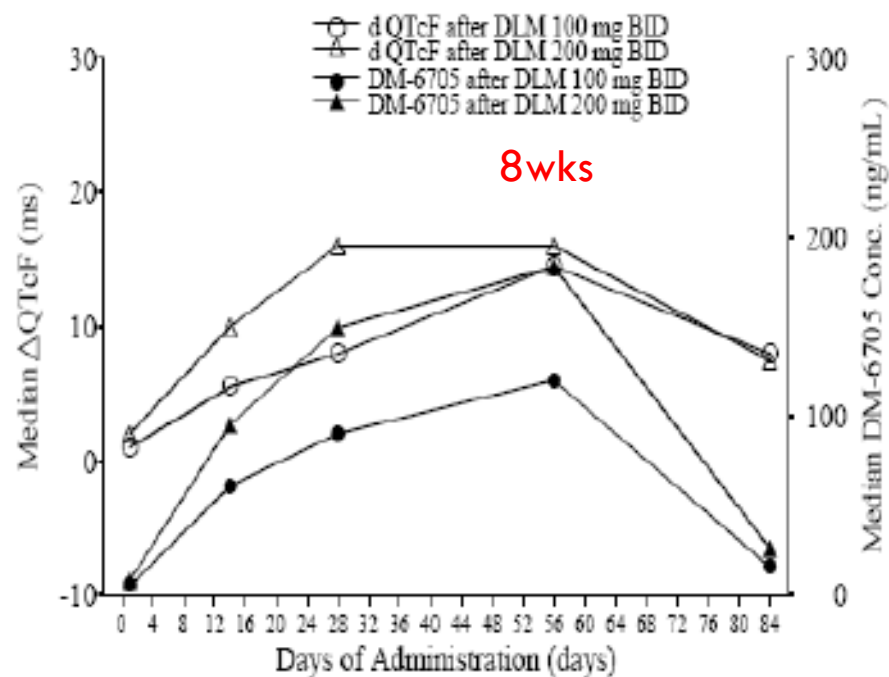
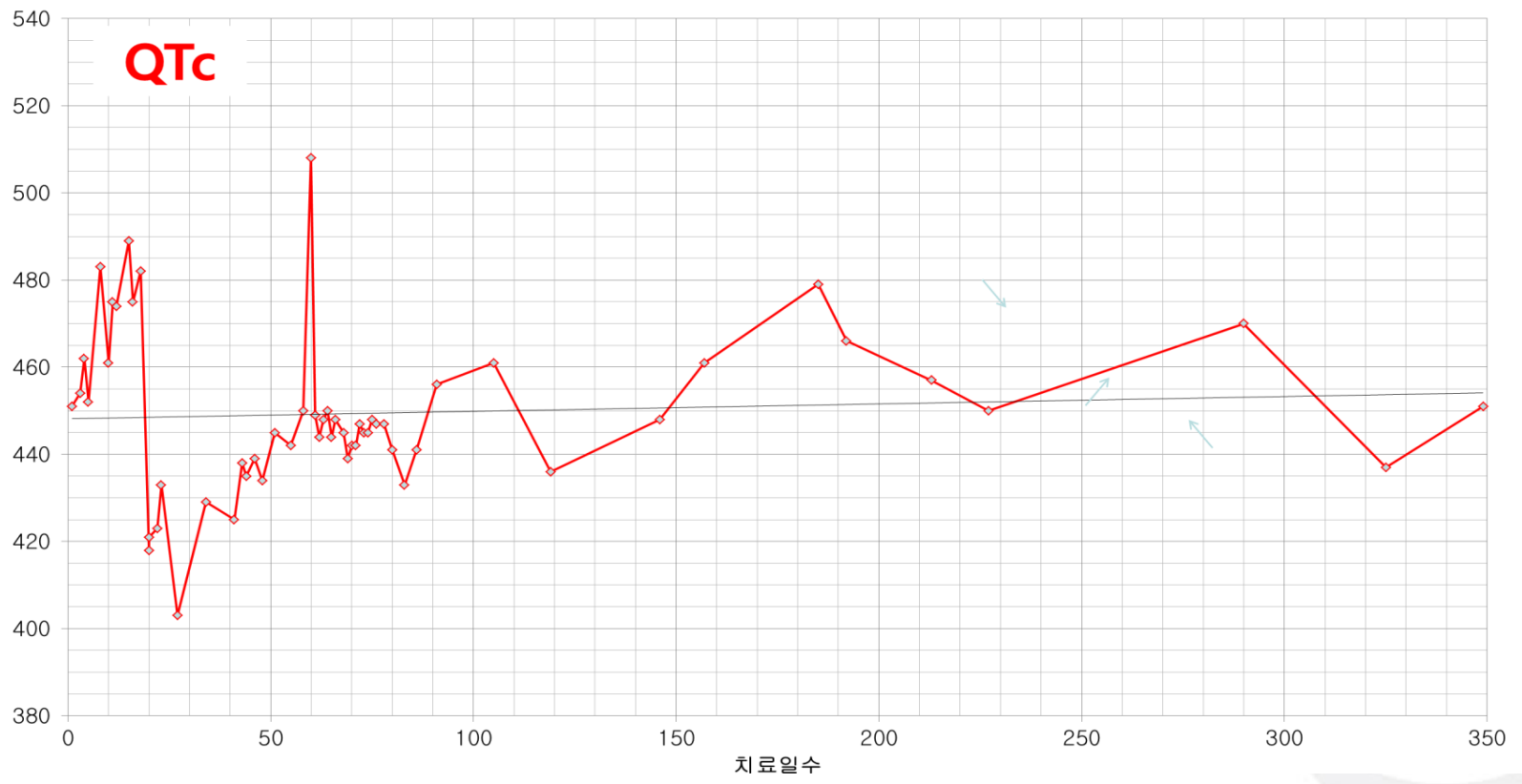
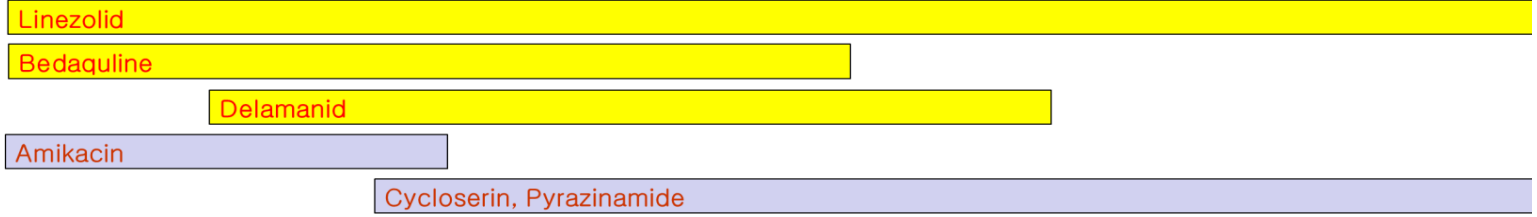


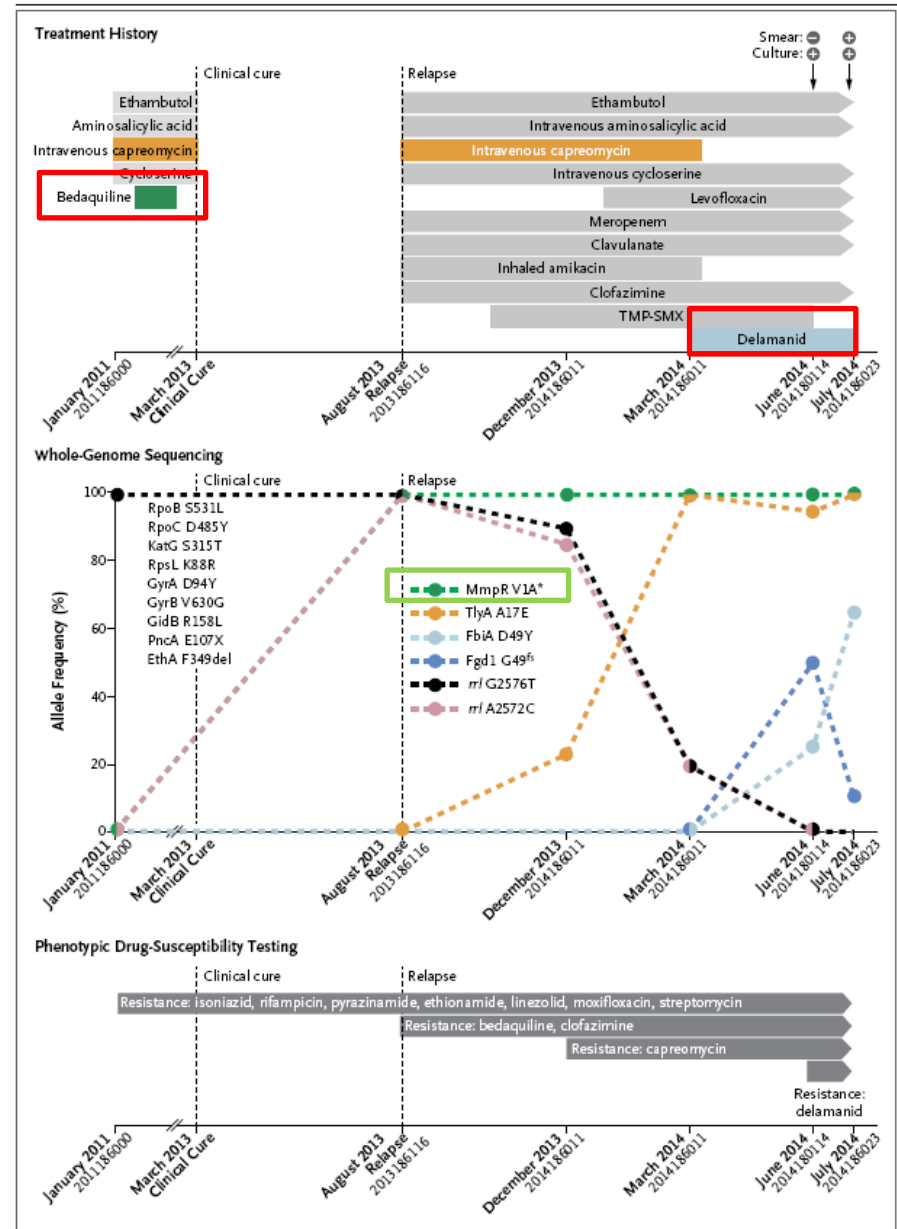
Figure 2.7.2.2.3.2.1-1 Median QTcF Change From Baseline and Plasma DM-6705 Concentration Versus Time

# QTc 모니터링



# 유지기의 약제

- 유지약제 :
  - ▣ Lz, Cs, Pza
- AFB 음전유지
- CXR 안정적

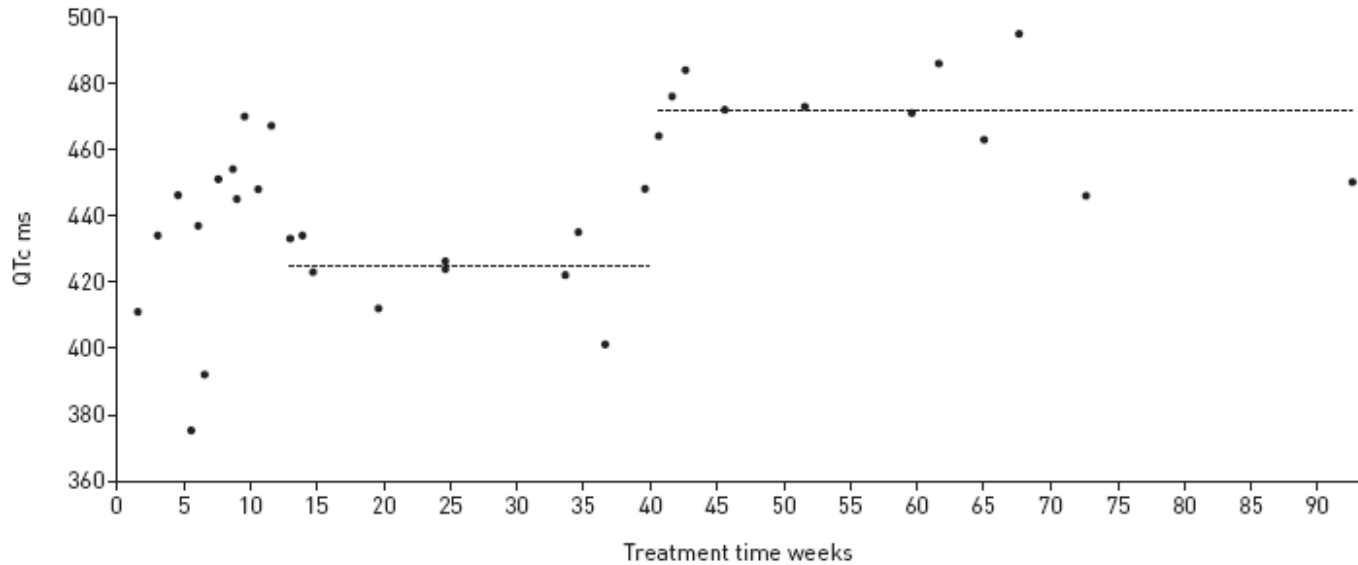


Sputum smear status P P P P P N N N N N N N N N N  
 Sputum culture status P P P P P N N N N N N N N N N

First-line treatment  
 MDR treatment  
 Second-line and group 5 drugs



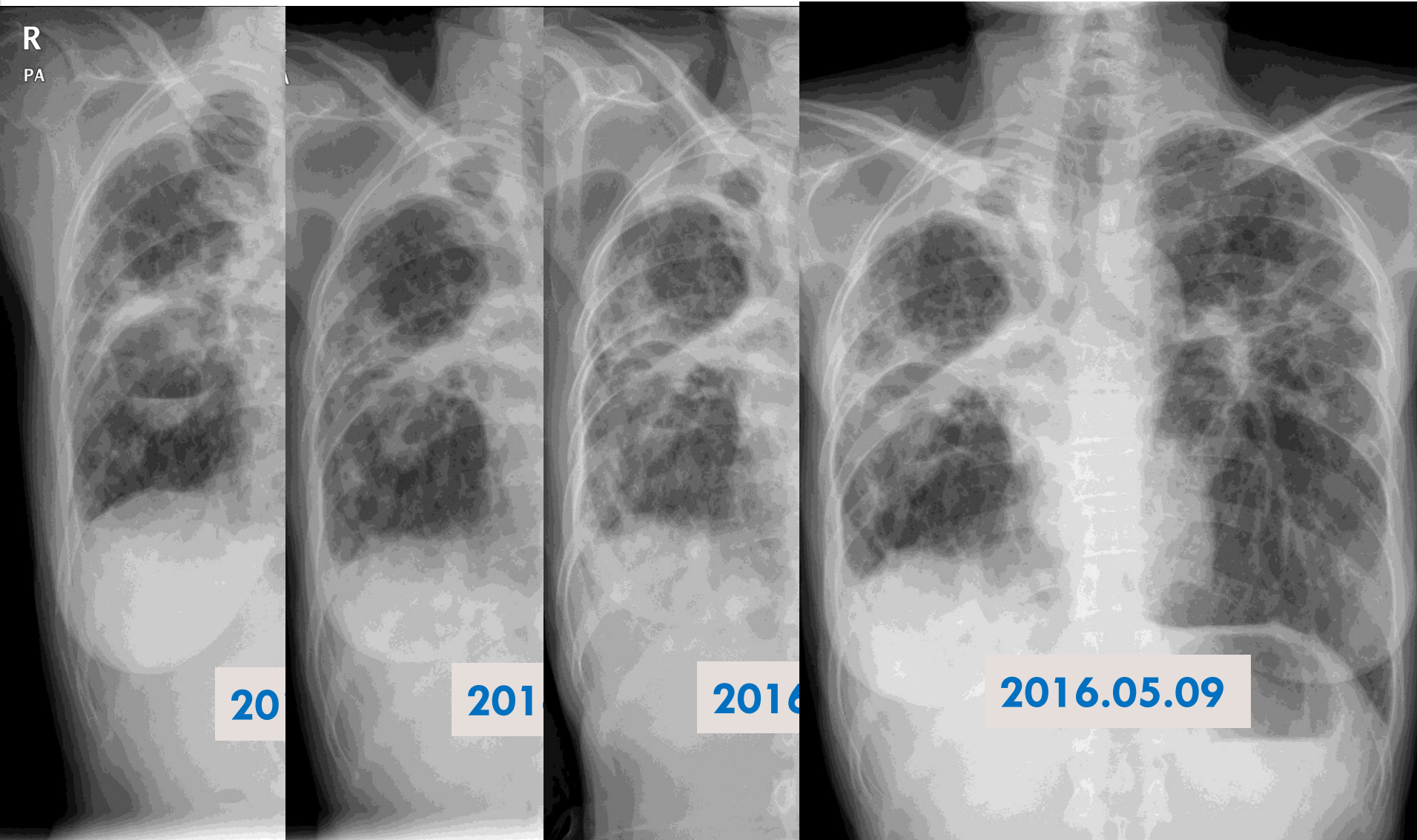
b)



# 신약사용(II)

- F/59
- 1999 TB, 2013 LZD resistance
- AFB 4+
- DST(14/10/07): S: onlySM
  - ▣ Meropenem : 15/11/10 ~16/05/11
  - ▣ BDQ: 15/11/10 ~ 16/05/07
  - ▣ DLM : 15/11/23 ~ 16/05/20
  - ▣ SM (3/wk) : 15/11/09 ~ 16/05/11
- DST(15/12/14): S: Sm, Pth
  - ▣ Pth : 15/12/15 ~
  - ▣ Clofazimine: 100mg qd(16/04/21~) 200qd(05/10~)

# X-ray



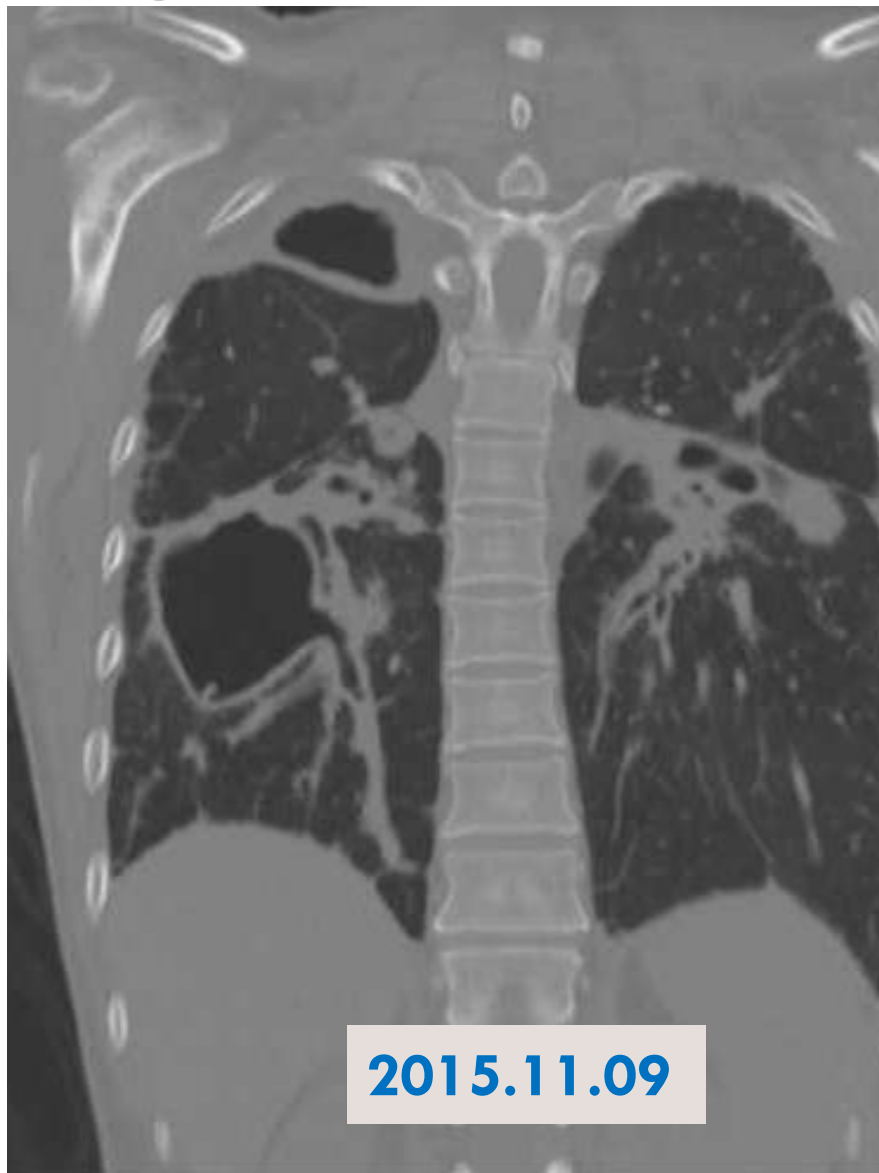
2011

2012

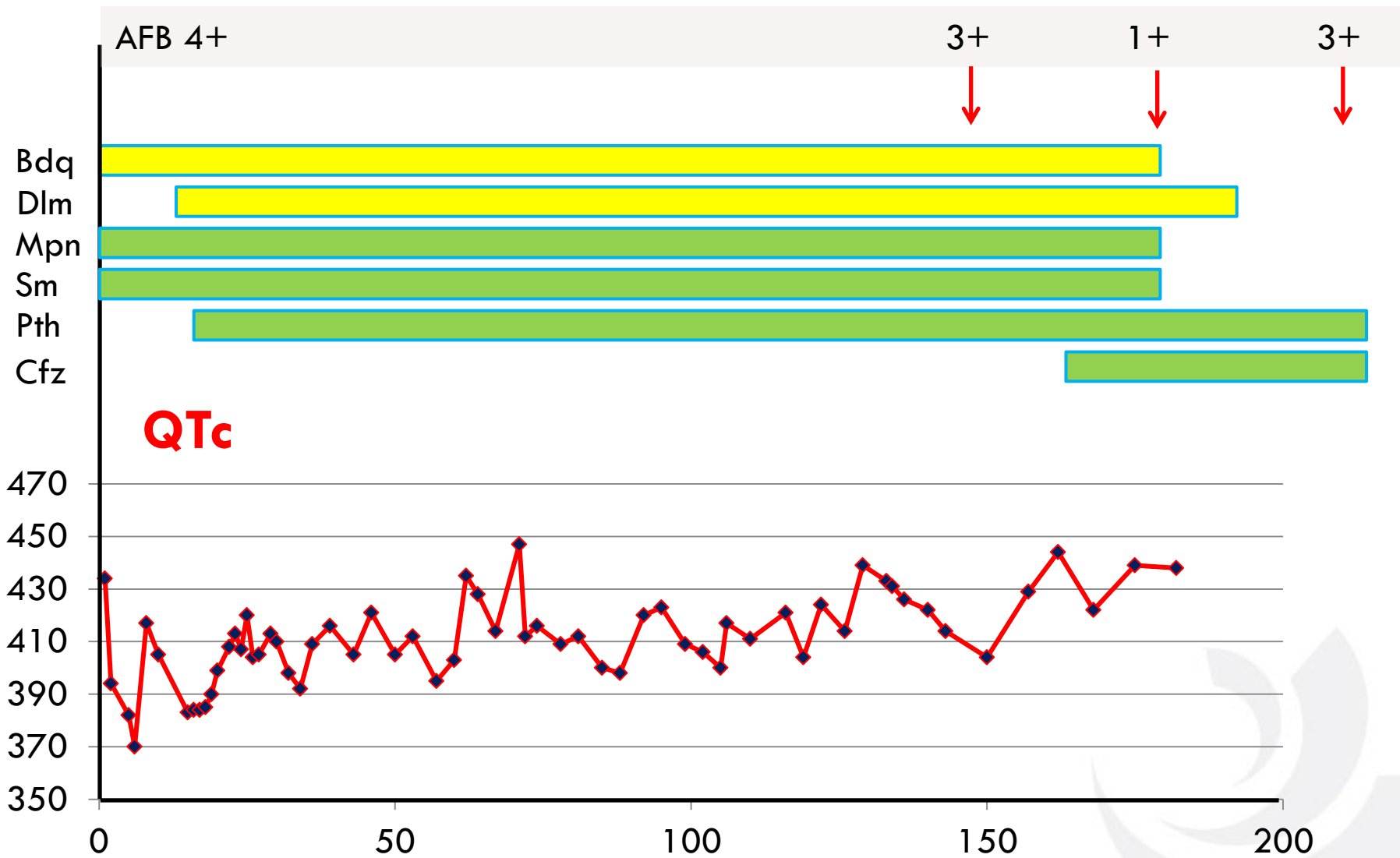
2016

2016.05.09

CT



# 경과



# 정리

- 신약: MDR-TB에서의 믿을만한 약제
  - ▣ 효과가 증명됨
  - ▣ 견딜만한 부작용(순응도 증가)
- 부작용 모니터링
  - ▣ QT prolong :
    - TdP, Monitoring (ECG, K, Ca, Mg, Albumin) 간격
    - Quinolone, Cfz, 신약 병용시
- 기대
  - ▣ 병용(Bdq, Dlm) 효과, 부작용: + Lz
  - ▣ Bdq, Dlm : 6개월만 사용 vs. 유지기의 사용
    - 내성 증가, 치료 실패
  - ▣ 교차내성: Bdq + Cfz
  - ▣ 추가약제 지침

