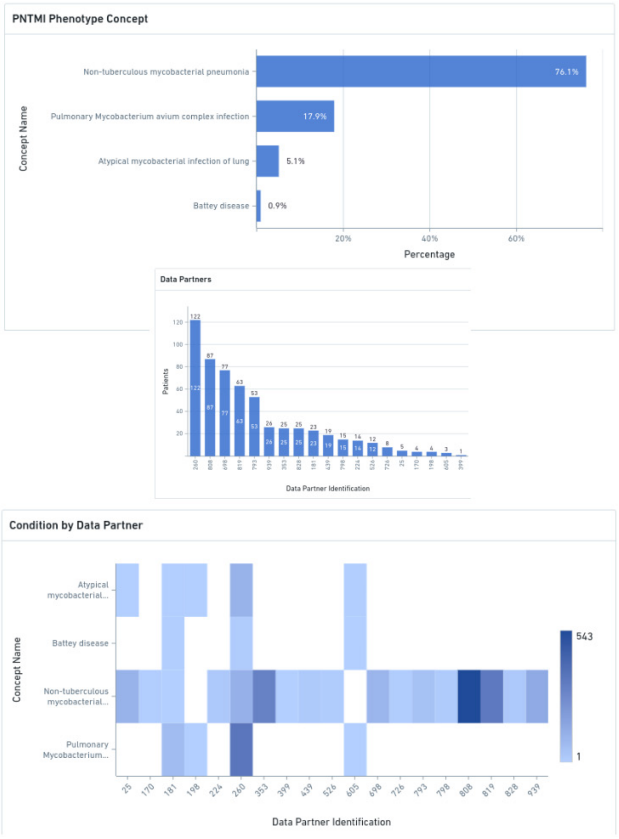

Figure 3. Concepts and data sources of pulmonary non-tuberculous Mycobacterium infection phenotype in N3C

Table 1:Baseline Characteristics of Pulmonary non-tuberculous *Mycobacterium* infection cohort

Characteristic	Total (n=555)		COVID-19 Positive (n=24)		COVID-19 Negative (n=531)		p
Age, years							0.1384
Mean (SD)	66.9 (14.2)		65.6 (14.4)		70 (14.2)		
Median (range)	69 (21-89)		65.6 (36-89)		69 (21-89)		
18-29	< 20		< 20		< 20		
30-49	58	10.5%	< 20		56	10.5%	
50-69	223	40.2%	< 20		210	39.5%	
70 and more	266	47.9%	< 20		257	48.4%	
Sex							0.0656
Female	340	61.3%	< 20		321	60.5%	
Male	215	38.7%	< 20		210	39.5%	
Unknown or missing							
Race							0.0218
White	447	80.5%	< 20		428	80.6%	
Black or African American	70	12.6%	< 20		66	12.4%	
Asian	< 20		< 20		< 20		
Native Hawaiian or Other Pacific islander	< 20		< 20		< 20		
Other	< 20		< 20		< 20		
Unknown or missing	< 20		< 20		< 20		
Ethnicity							0.7582
Not Hispanic or Latino	508	91.5%	23	95.8%	485	91.3%	
Hispanic	30	5.4%	< 20		29	5.5%	
Unknown or missing	< 20		< 20		< 20		
Geographical Location							0.0002
US Northeast	< 20		< 20		< 20		
US Midwest	125	22.5%	< 20		111	20.9%	
US South	114	20.5%	< 20		107	20.2%	
US Mountain	< 20		< 20		< 20		
US West	< 20		< 20		< 20		
Unknown or missing	302	54.4%	< 20		302	56.9%	
Deaths							0.94
No	511	92.1%	22	91.7%	489	92.1%	
Yes	44	7.9%	< 20		42	7.9%	

SD, standard deviation. Geographical locations based on US Census tract regions. Per N3C policy, exact counts that are 20 or less were not reported to protect the privacy of individuals.

Conclusion. In N3C, the PNTMI cohort has a lower proportion of COVID-19 infection than the general population, and it was not a cause of mortality. Further analysis to study impact of comorbidities, and differences in race and geographical location are warranted. N3C is a powerful research platform to study the impact of COVID-19 in special populations with low prevalence, and it can be used to study other populations of interest.

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1410. Isoniazid Therapy for Latent Tuberculosis Infection in Patients with Cancer Treated with Checkpoint Inhibitors Immunotherapy

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Session: P-80. Tuberculosis and other Mycobacterial Infections

Background. Data on the efficacy and tolerability of latent tuberculosis infection (LTBI) treatment in cancer patients receiving checkpoint inhibitor immunotherapy (CPI) is limited. We sought to assess LTBI therapy and its adverse events and outcomes in patients treated with CPI.

Methods. We performed a retrospective cohort study at MD Anderson Cancer Center of adult patients, between April 2016 and May 2021, who were receiving CPI and were diagnosed with LTBI based on positive T-SPOT TB test. We then compared those patients treated with isoniazid (INH) 5mg/kg daily versus those that did not receive INH therapy.

Results. We identified 35 patients treated with CPI who had a diagnosis of LTBI. Patients were divided into 2 groups: CPI alone (23 patients, 65.7%) and CPI+INH (12 patients, 34.3%). The majority of patients in both groups had renal cell carcinoma (34.3%) and melanoma (17.1%). Nivolumab as monotherapy was the most commonly used CPI agent in both groups (37.1%), whereas nivolumab and ipilimumab combination was mainly used in the CPI group (34.7%) compared to CPI+INH group (8.3%). In the CPI+INH group, 7 patients (58.3%) developed moderate to severe hepatoxicity that led to discontinuation of INH and CPI therapy versus none in the CPI group (p= 0.001). There was no statistically significant difference in the alanine aminotransferase (ALT) at baseline between both groups (p=0.117), whereas the median ALT level was significantly higher during CPI+INH therapy compared to CPI alone (135 U/L vs 24 U/L respectively, p=0.025. Furthermore, immune-related adverse events were reported in a total of 12 of 35 patients (34.2%). None of the patients in either group developed tuberculosis reactivation during a follow up period of up to 1148 days.

Conclusion. Our data suggest that latent tuberculosis reactivation is rare in cancer patients on CPI immunotherapy. Hepatotoxicity remains a concern in this patient population with LTBI treated with CPI and INH. With the widespread use of CPI, close laboratory and clinical monitoring is required to avoid life-threatening drug-induced liver injury and interruption of LTBI therapy and immunotherapy. Further clinical studies are warranted to determine the optimal management of LTBI during CPI therapy.

Disclosures. **Pablo C. Okhuysen, MD, FACP, FIDSA**, **Deinove Pharmaceuticals** (Grant/Research Support)**Ferring Pharmaceuticals** (Consultant)**Melinta Therapeutics** (Grant/Research Support)**Merck & Co.** (Grant/Research Support)**Napo Pharmaceuticals** (Consultant, Scientific Research Study Investigator, Research Grant or Support)**Singulex** (Consultant)**Summit Therapeutics** (Grant/Research Support) **Dimitrios P. Kontoyiannis, MD**, **Astellas** (Consultant)**Cidara Therapeutics** (Advisor or Review Panel member)**Gilead Sciences** (Consultant, Grant/Research Support, Other Financial or Material Support, Honoraria)

1411. Noninvasive Assessment of Intralesional Antimicrobial Concentration-Time Profiles in Pulmonary and Central Nervous System Tuberculosis using Dynamic ^{18}F-Pretomanid Positron Emission Tomography

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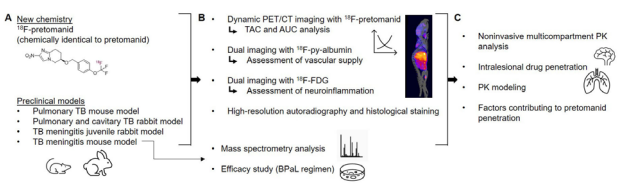
Session: P-80. Tuberculosis and other Mycobacterial Infections

Background. Pretomanid is used in combination with bedaquiline and linezolid (BPaL regimen) in the treatment of multidrug-resistant tuberculosis (MDR-TB). However, the penetration of pretomanid in privileged sites remain unknown. Antimicrobial pharmacokinetic (PK) parameters are traditionally derived from clinical samples (blood and cerebrospinal fluid), which may not accurately represent the intralesional tissue PK, affected by drug properties, vascular supply, barrier permeability, and the microenvironment.

Methods. We developed ^{18}F-pretomanid (chemically identical to pretomanid) for *in vivo* multi-compartment PK by positron emission tomography (PET). Dynamic ^{18}F-pretomanid PET was used to obtain cross species pretomanid concentration-time profiles in animal models of TB (mice and rabbits) to quantify penetration into pulmonary and brain lesions. A subset of animals underwent PET/CT imaging with ^{18}F-py-albumin and ^{18}F-FDG to assess vascular supply and inflammation. Postmortem ^{18}F-pretomanid autoradiography (high-resolution) and mass spectrometry were performed in infected tissues. A mouse model of TB meningitis was used to evaluate the bactericidal activity of the BPaL regimen (Figure 1).

Figure 1. Experimental schematics.

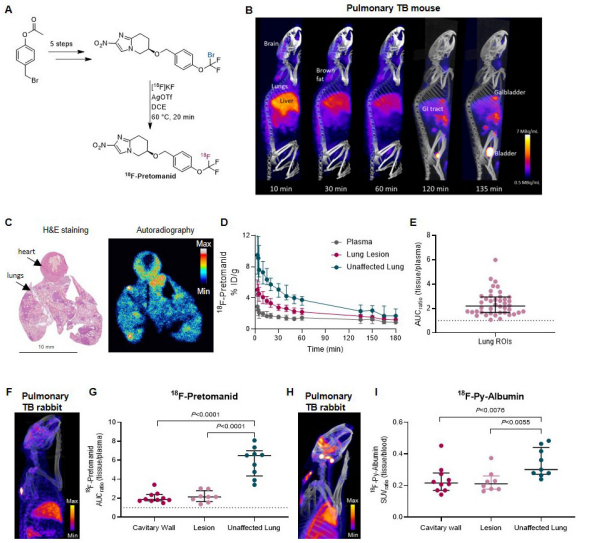


(A) A new synthetic approach was developed to obtain radiofluorinated pretomanid (18F-pretomanid), which is chemically identical to pretomanid and therefore

undergoes identical PK and metabolism in vivo. Dynamic 18F-pretomanid PET/CT imaging was performed in validated preclinical models of tuberculosis following intravenous administration of 18F-pretomanid. (B) PET signal was quantified in multiple compartments to generate time activity curves (TACs) used to calculate area under the curve (AUC) over 0-60 minutes. A subset of animals also underwent PET/CT imaging of 18F-py-albumin to assess vascular supply to lung and brain lesions, and with 18F-FDG to confirm the presence of neuroinflammation in the mouse and rabbit models of TB meningitis. Tissue resection post-mortem was used to visualize the intralesional retention of 18F-pretomanid using high-resolution (10 µm) autoradiography. The efficacy of the BPaL regimen in TB meningitis was compared to that of standard treatment with rifampin, isoniazid, and pyrazinamide in the mouse model. Mass spectrometry was performed following oral administration of BPaL to determine brain drug levels. (C) These data provide multicompartment PK analysis, intralesional levels of pretomanid, and insights into the mechanism that govern pretomanid tissue distribution.

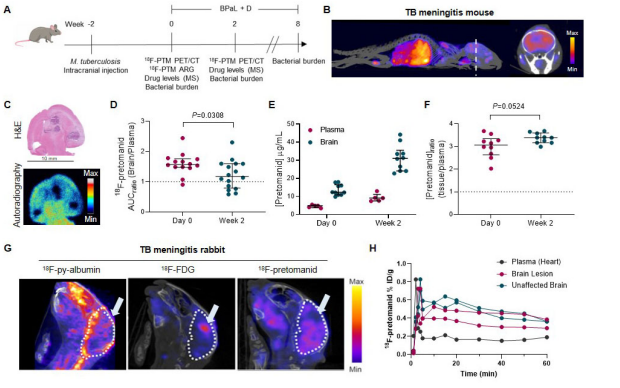
Results. ^{18}F-Pretomanid PET provided detailed concentration-time profiles in infected tissues demonstrating excellent lung and brain tissue penetration (AUC ratio to plasma > 1) in both animal species, which was spatially compartmentalized, likely due to differential vascular supply (^{18}F-py-albumin PET) (Figure 2). Brain lesions (identified by ^{18}F-FDG PET) demonstrated localized leakiness on ^{18}F-py-albumin PET. Autoradiography and mass spectrometry corroborated the imaging findings. The efficacy of the BPaL regimen in TB meningitis was substantially lower than standard TB treatment (Figure 3), likely due to restricted penetration of bedaquiline and linezolid into the brain parenchyma.

Figure 2. Spatial heterogeneity of 18F-Pretomanid penetration and vascular supply to pulmonary TB lesions.



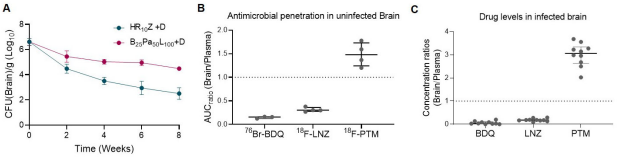
(A) A novel synthetic was devised to obtain 18F-pretomanid, which is chemically identical to pretomanid. (B) Maximum intensity projection (MIP) of 18F-Pretomanid PET/CT in M.tb.-infected mice over 3 hrs shows hepatobiliary and renal excretion, high uptake into brown fat, brain, and lungs. (C) Resection of infected lungs 30 minutes post intravenous administration of 18F-pretomanid shows heterogenous distribution of 18F-pretomanid into the lungs visible by high resolution autoradiography. Areas of pneumonia are identifiable by hematoxylin and eosin (H&E) staining of the same tissue section used for autoradiography. (D) Time-activity curves of 18F-Pretomanid in infected mouse lung (0-3 hours) and derived area under the curve (AUC) ratios to plasma (E) in infected mouse lung. Representative MIP of 18F-pretomanid (F) and 18F-py-albumin (H) PET/CT in a rabbit with cavitary TB and quantification of the AUC ratios to plasma show reduced penetration into lung lesions and cavitary wall compared to areas of unaffected lung (G and I). Data are represented as median ± interquartile range, n=3-4 group.

Figure 3. Exposure levels of 18/19F-pretomanid in models of TB meningitis.



(A) Experimental timeline used to assess the penetration of pretomanid into infected mouse brain before and during treatment with antimicrobials bedaquiline (B), pretomanid (Pa), and linezolid (L), and corticosteroid dexamethasone (D). (B) Representative three-dimensional MIP of 18F-pretomanid PET/CT in the CNS-TB model, 10 min post-injection, and transverse section showing high and heterogeneous brain uptake. (C) High-resolution autoradiography was performed to confirm heterogeneous penetration of 18F-pretomanid into infected brain lesions in the mouse. (D). 8F-pretomanid AUC ratios of tissue to plasma in mouse brain before (day 0) and two weeks into treatment show a reduction in penetration at week 2. (E). Pretomanid concentrations (µg/mL) in mouse plasma and brain, at day 0 and two weeks into treatment, measured by mass spectrometry and derived concentration ratios of brain to plasma (F) suggest drug accumulation due to the long half-life. (G) While 18F-py-albumin and 18F-FDG PET/CT show vascular leakage and neuroinflammation in the rabbit model of TB meningitis, the penetration of 18F-pretomanid is heterogeneous and reduced at the lesion site (indicated by white arrow). (H) Quantification of the PET signal shows variability within the same animal. Data are represented as median ± interquartile range, n=3-5 group.

Figure 4. Evaluation of a pretomanid-containing regimen in TB meningitis.



(A) Mice with experimentally induced TB meningitis were treated with Bedaquiline (25 mg/day), Pretomanid (100 mg/day), Linezolid (100 mg/day), and Dexamethasone (2 mg/day) or Rifampin (10 mg/day), Isoniazid (10 mg/day), Pyrazinamide (150 mg/day) and Dexamethasone (2mg/day) for 8 weeks. Treatment efficacy was determined based on the brain bacterial burden after 2, 4, 6, and 8 weeks of treatment. (B) The penetration of 76Br-bedaquiline, 18F-linezolid, and 18F-pretomanid into the brain parenchyma was measured non-invasively by PET and revealed low penetration of 76Br-bedaquiline (AUC radio to plasma 0.15) and 18F-linezolid (AUC radio to plasma 0.3). (C) Mass spectrometry analysis was performed to confirm the brain penetration of bedaquiline, linezolid, and pretomanid following oral administration.

Conclusion. Dynamic ^{18}F-pretomanid PET provided holistic data on pretomanid exposures showing excellent penetration into infected lung and brain tissues. The BPaL regimen was inferior to standard TB treatment for TB meningitis. Thus, new pretomanid-containing regimens need to be developed for the treatment of MDR-TB meningitis.

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1412. Clinical Epidemiology and Characteristics of Pulmonary Nontuberculous Mycobacterial Isolates from a Large Academic Military Treatment Facility

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Session: P-80. Tuberculosis and other Mycobacterial Infections

Background. Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment and include pathogenic and nonpathogenic species. Although prevalence appears to be increasing in the US, diagnosis and treatment can be challenging. This study describes the epidemiology and clinical characteristics of pulmonary NTM (pNTM) isolates at Brooke Army Medical Center (BAMC).

Methods. BAMC pulmonary NTM isolates from 2012-2020 were included. Corresponding electronic health records were reviewed for epidemiologic, microbiologic, and clinical data. Pulmonary NTM infection (pNTMi) was defined using 2020 NTM guidelines and patients were divided into 2 groups based on whether guideline criteria for pNTMi were met. Demographic, microbiologic, and clinical characteristics were compared between groups.

Results. A total of 813 isolates from 225 patients were analyzed (median 2 [IQR 1-4] isolates per patient). Approximately half (49.7%) were female with a median age of 71 years (IQR 62-79, Table 1), and the majority were current or former smokers (57.3%). Compared to those not meeting criteria (n=116; 51.6%), pNTMi patients (n=109; 48.4%) more commonly had bronchiectasis (47.7% vs 27.6; p=0.002) but were less likely to have solid organ malignancy (11.9% vs 23.3%; p=0.036). A higher proportion of pNTMi patients were female (58% vs 42%; p=0.005) and had lower median Body Mass Index (BMI, 22.6 vs 25.1; p=0.001). *M. avium* complex (MAC) was more common among pNTMi patients (75.2% vs 35.3%; p=0.001). In contrast, *M. simiae* and *M. gordonae* were more likely to be isolated from those not meeting criteria (25.9% vs. 10.1%; p=0.003 and 16.4% vs. 1.8%; p=0.001, respectively). Among pNTMi patients, 60 (55%) were offered therapy and were more likely to be younger (70 [IQR 63-76] vs. 73 [IQR 65-82] years; p=0.049), have chronic obstructive pulmonary disease (COPD; 51.7% vs 24.5%; p=0.006) and MAC (88.3% vs. 59.2%; p=0.001) compared to untreated patients (Table 2).