2023 분자폐암연구회 임상연구워크숍

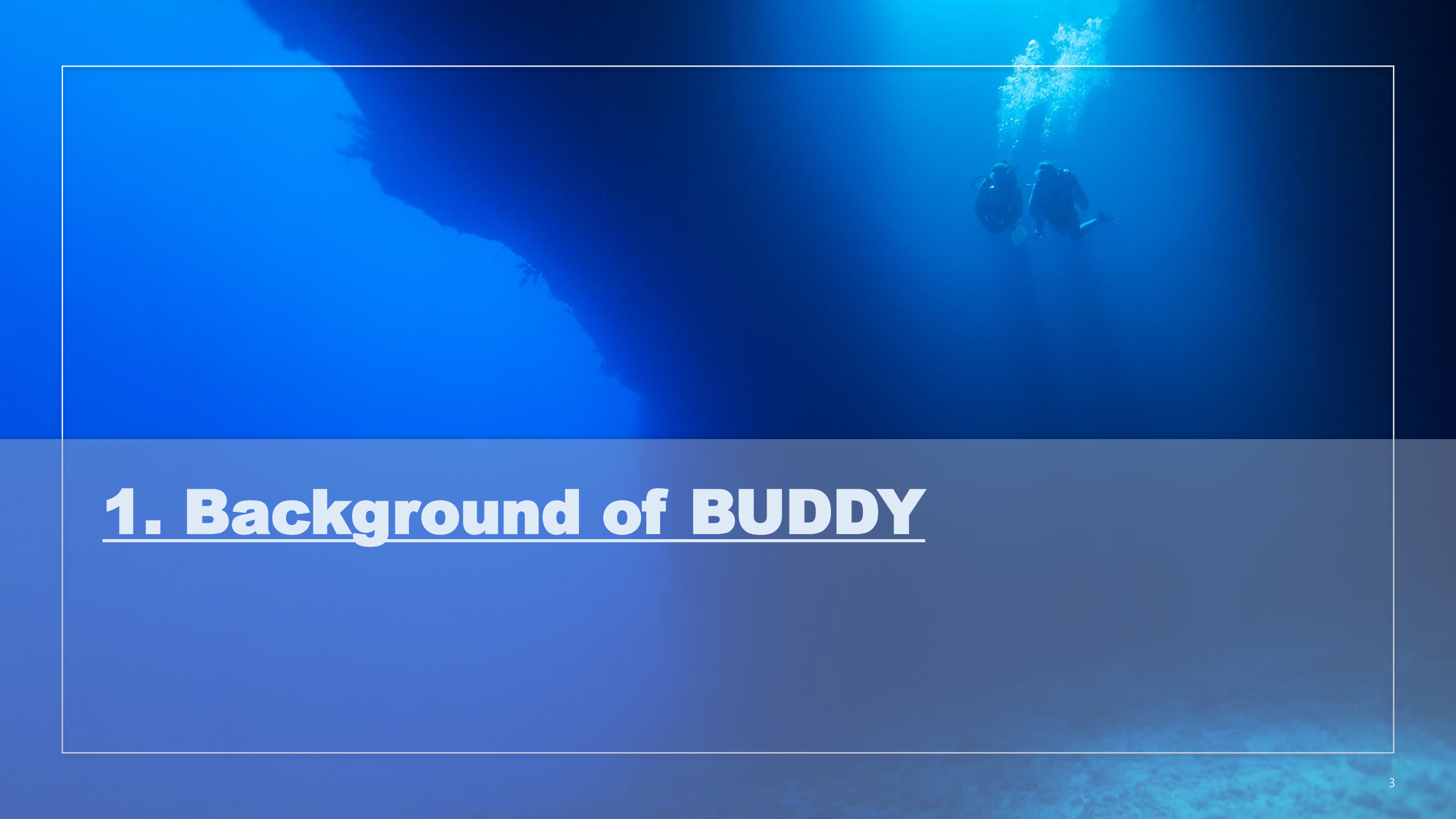
비소세포폐암 환자의 2차 이상 치료에서 아테졸리주맙의 유효성 향상 지표로서 BLOOD TUMOR MUTATION BURDEN (bTMB)의 평가

Evaluation of blood tumor mutation burden for improved efficacy of atezolizumab in 2L+ non-small cell lung cancer

- CI: 오인재(화순전남대병원)
- PI: 이재철(서울아산병원), 이승룡(고려대학교구로병원), 이신엽(칠곡경북대병원), 이정은(충남대병원), 윤성훈(양산부산대병원)

Agenda

1. Background of BUDDY
2. Protocol Development
3. Review of Protocol
4. Management of Samples
5. Results



1. Background of BUDDY

Background of BUDDY

Why we need biomarkers?

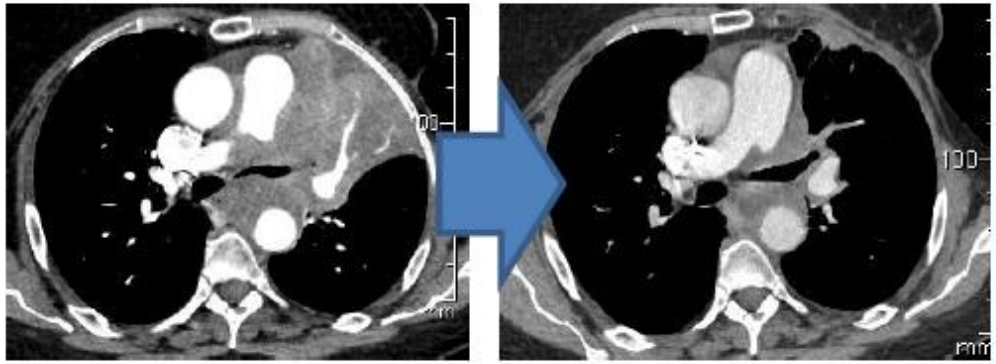
BENEFIT

PROVIDE DRUGS ONLY TO PATIENTS WHO COULD BENEFIT FROM THEM

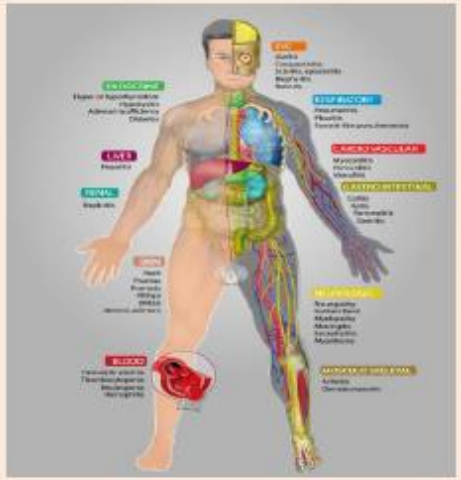
RISK

AVOID TO EXPOSE PATIENTS TO TOXICITY WHEN THERE ARE NO CHANCES OF EFFICACY

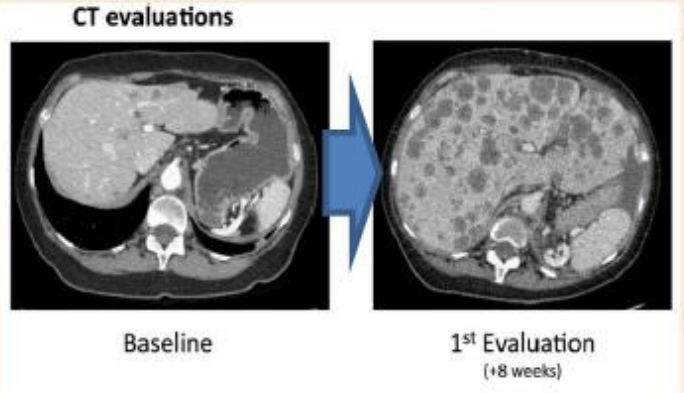
Efficacy with IO (PDL1 80%)



Toxicity



Hyperprogressive disease



Background of BUDDY

PD-L1 a good bioM ?

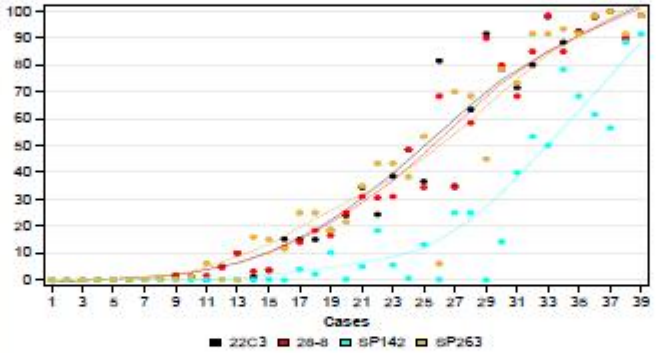
Comparison of PD-L1 assays in NSCLC

Immunotherapy (IO)	Nivolumab	Pembrolizumab	Durvalumab	Avelumab	Atezolizumab
Detection antibody	28-8	22C3	SP263	73-10	SP142
IHC platform	Dako	Dako	Ventana	Dako	Ventana
Cell types scored for NSCLC	TC	TC	TC	TC	TC & IC
Cut-off definitions for positivity (complementary vs companion)	>5%	First line: PD-L1+≥50% Late lines: PD-L1+≥1%	>25%	None	None

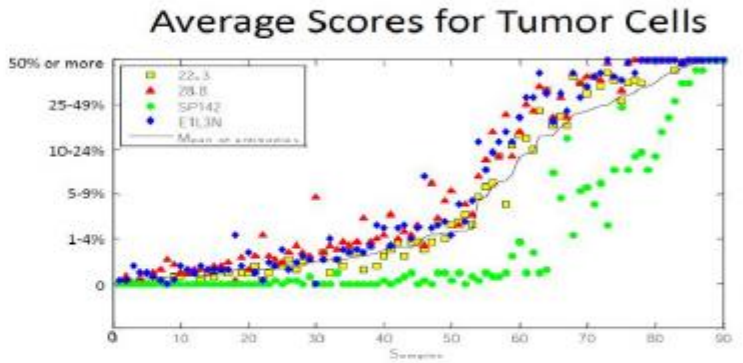
✓ **Comparables: 22C3, 28-8 and SP263**

✓ **Weaker: SP142** *lower sensitivity*

Blueprint phase 1[1]

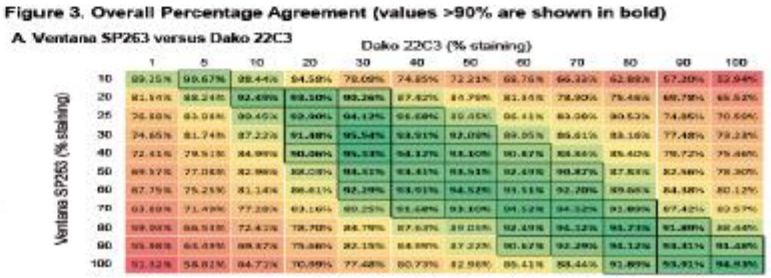


NCCN study[2]



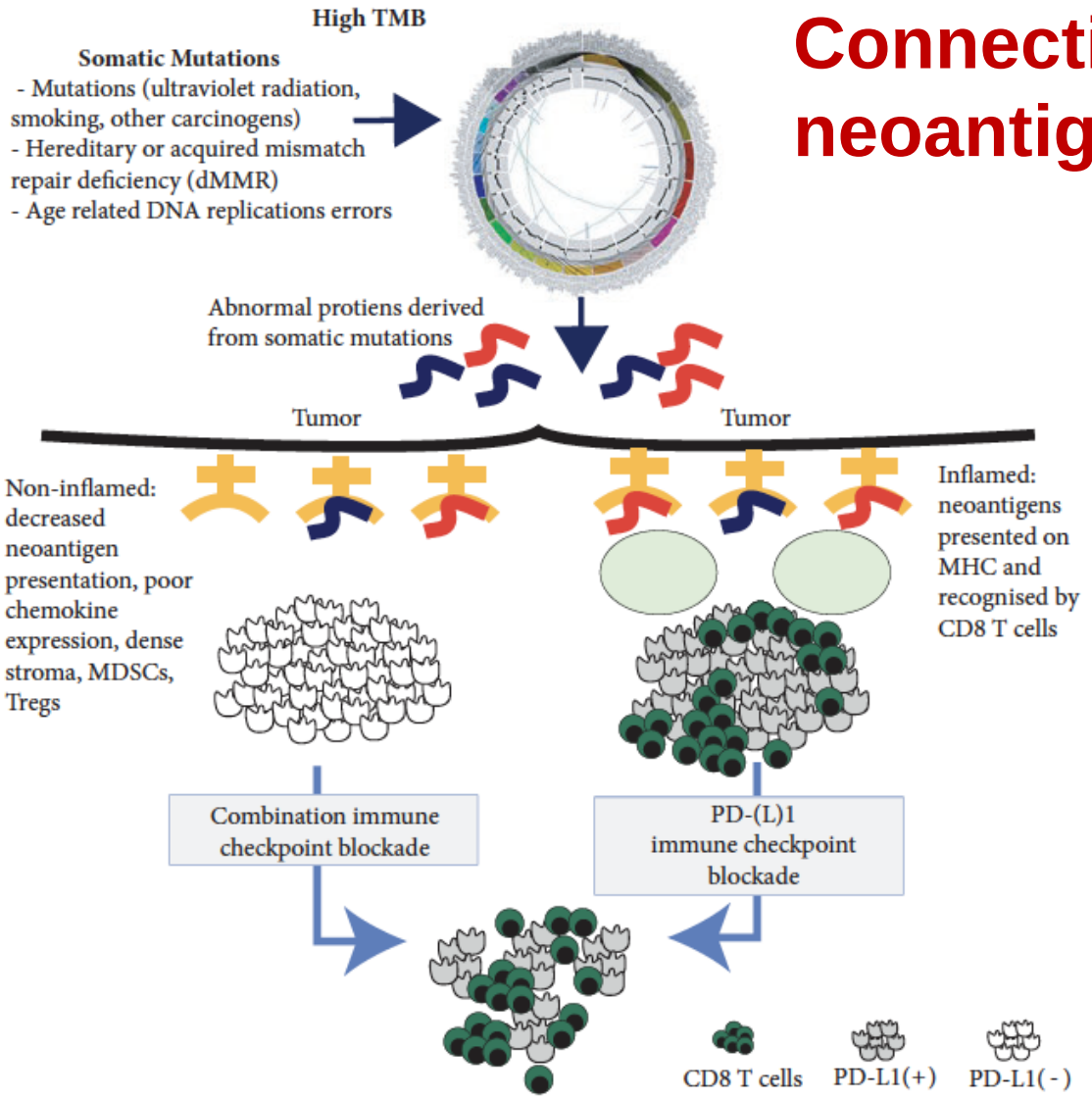
French study[3]

AstraZeneca study[4]



1. Hirsch FR, et al. J Thorac Oncol. 2017 ;12(2):208-222. 2. Rimm D et al. JAMA Oncol. 2017 ;3(8):1051-1058 3. Adam J et al. Oral presentation at IASLC WCLC 2016. PL04.04a. 4. Ratcliffe MJ et al. Clin Cancer Res. 2017;23(14):3585-3591.

Background of BUDDY



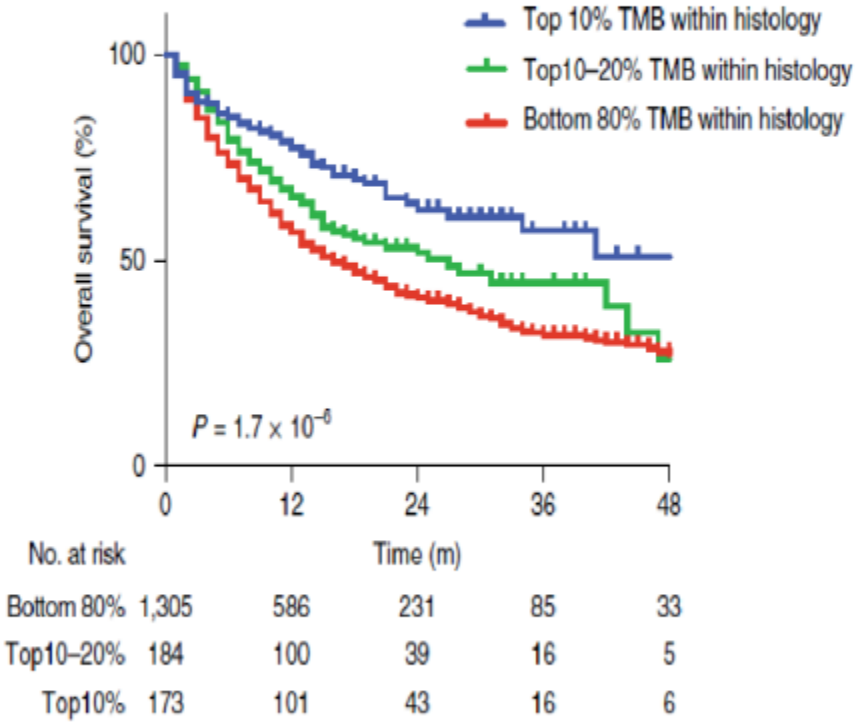
Connection between TMB, neoantigens and immunotherapy

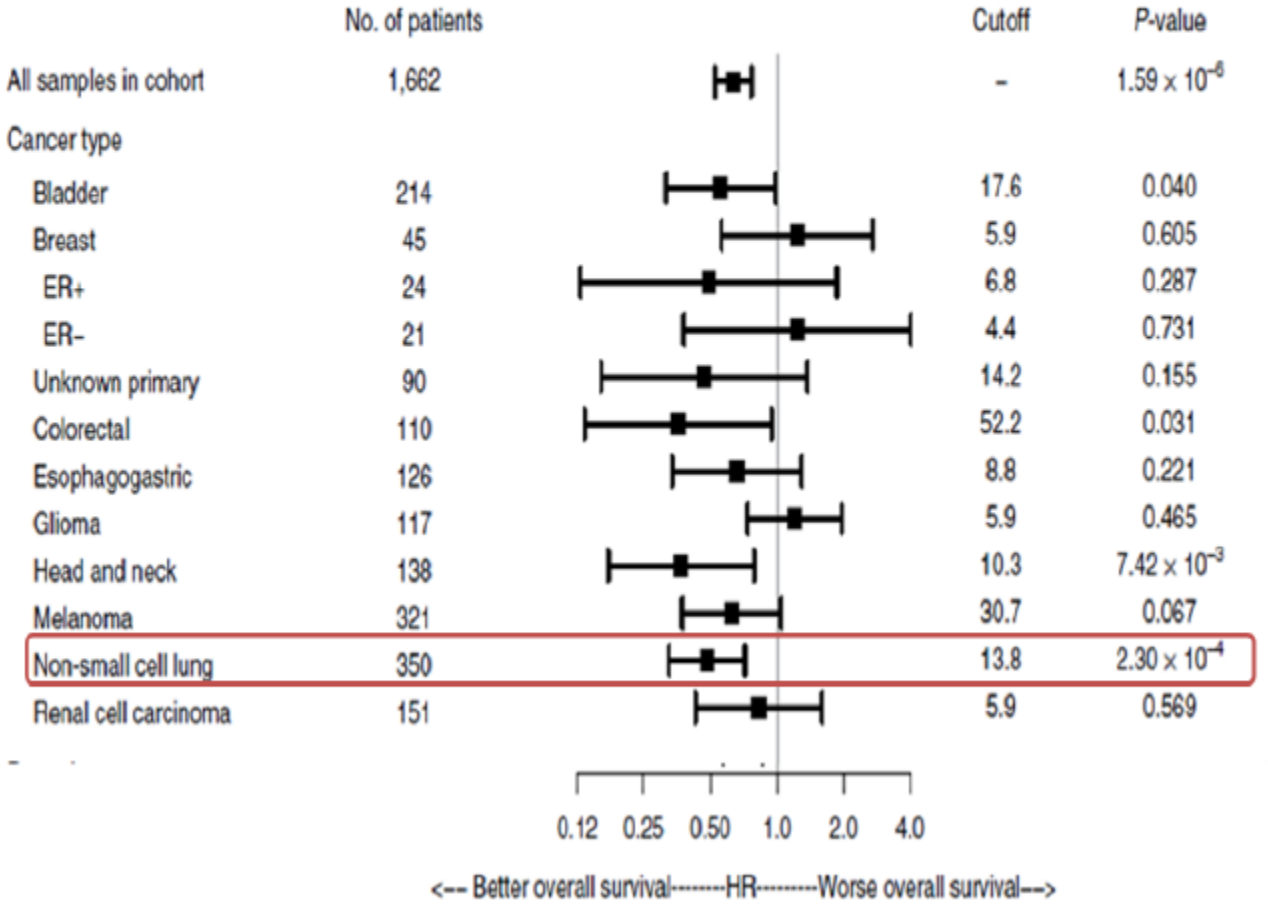
Chan et al. Ann Oncol 2019

Background of BUDDY

TMB is predictive of OS benefit across tumour types

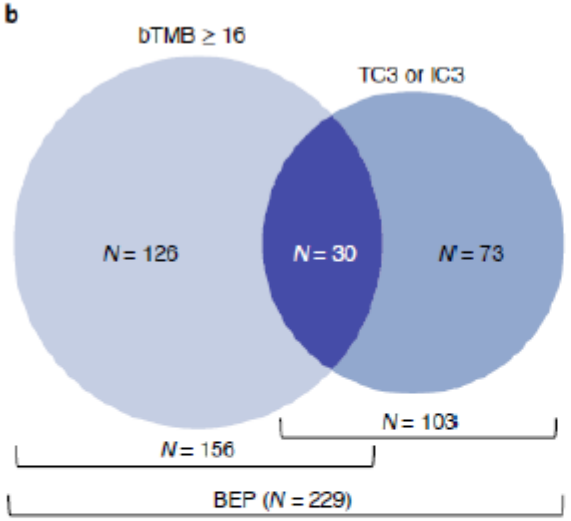
Clinical and genomic (MSK-IMPACT) data of 1,622 advances pts treated with ICI



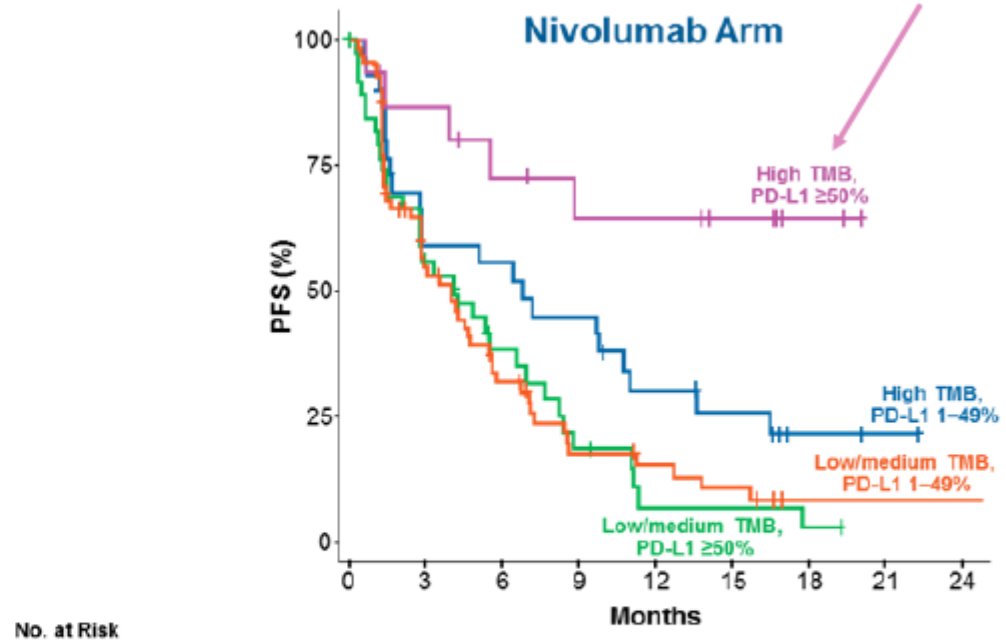


Chan et al. Ann Oncol 2019

Using TMB and PD-L1 as Two Independent Biomarkers



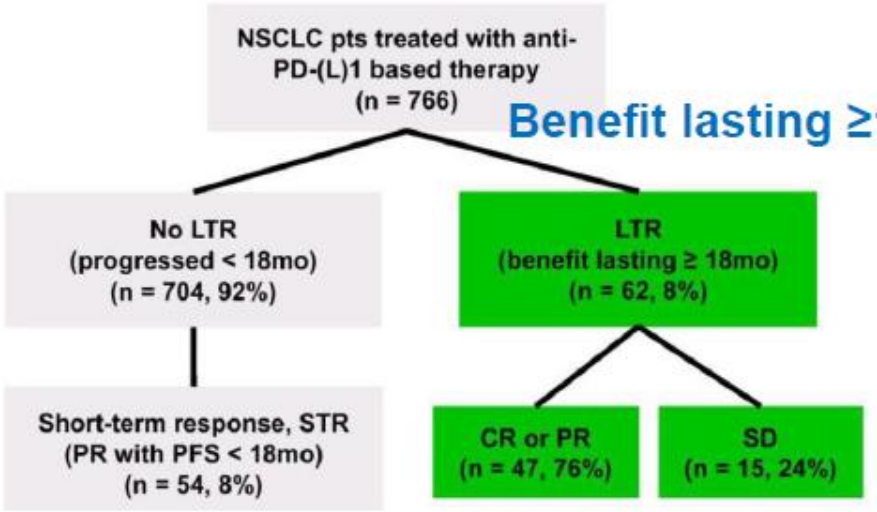
	N	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥ 16	156	0.64 (0.46-0.91)	0.64 (0.44-0.93)
TC3 or IC3	103	0.62 (0.41-0.93)	0.44 (0.27-0.71)
bTMB ≥ 16 and TC3 or IC3	30	0.38 (0.17-0.85)	0.23 (0.09-0.58)



Gandara, Nat Med 2018; Peters S et al., AACR 2017

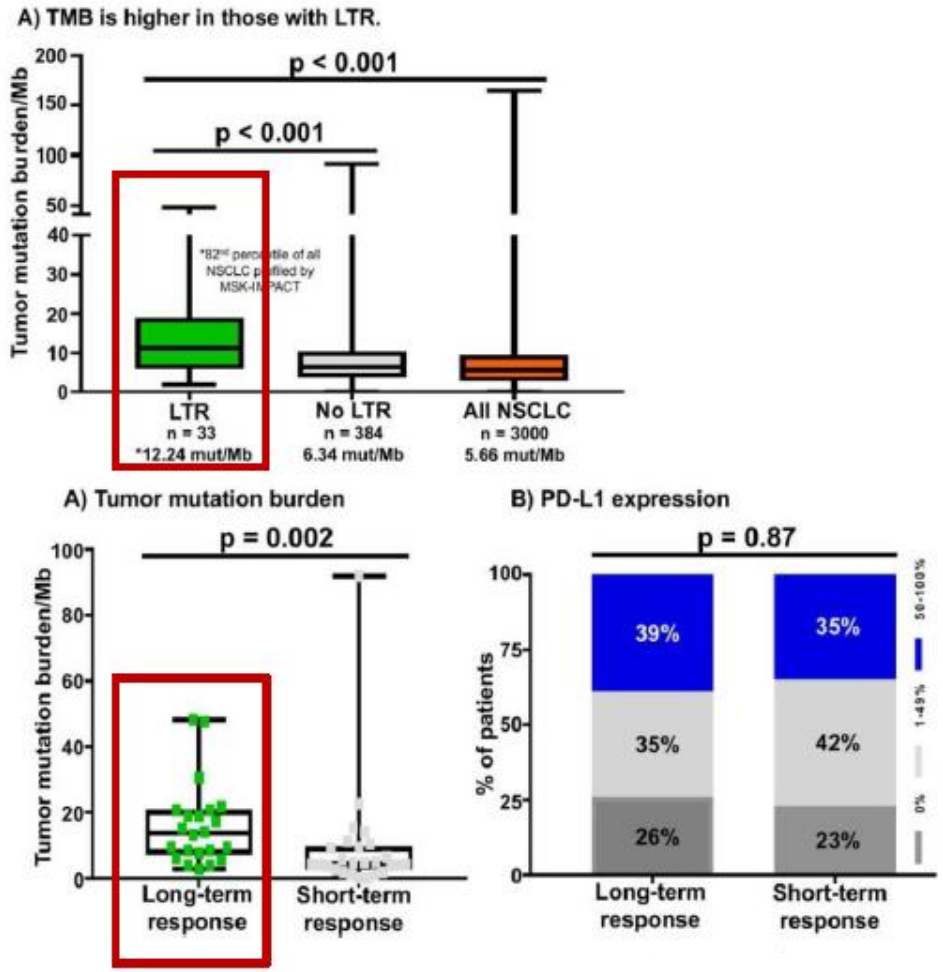
Background of BUDDY

TMB but not PD-L1 expression is predictive of response duration and of long term benefit from anti-PD(L)-1 therapy



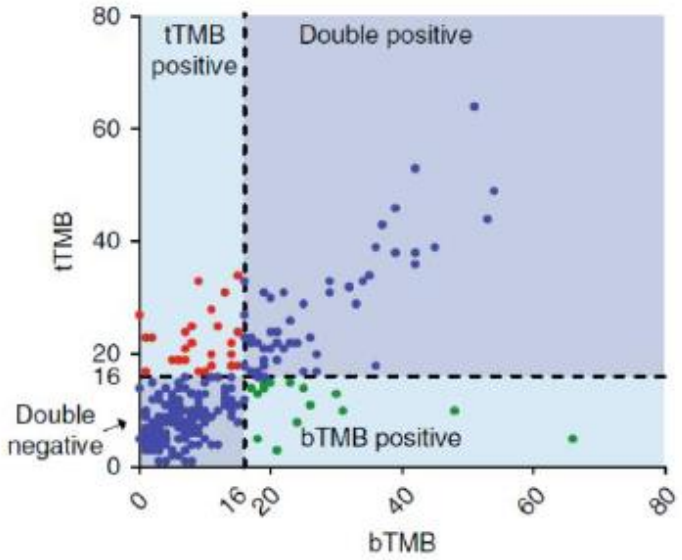
TMB assessed with MSK-IMPACT

76% (CR or PR) **24%(SD)**



Background of BUDDY

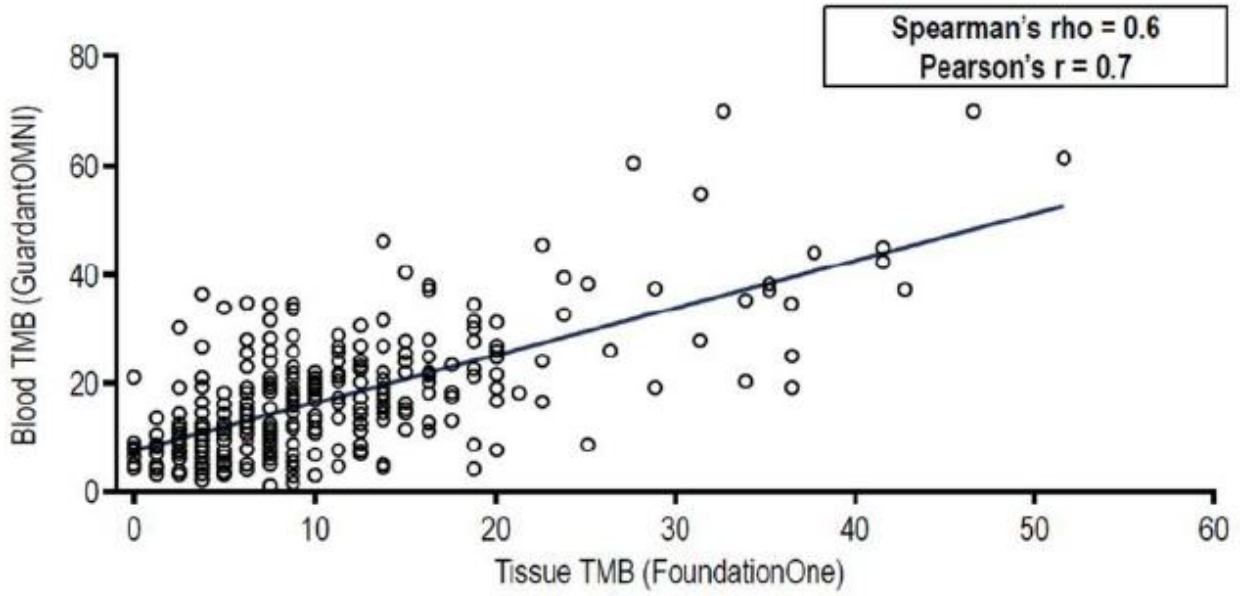
Correlation of Tissue and Blood Tumor Mutational Burden



Spearman rank correlation = 0.64 (95% CI: 0.56–071)

Metric	Performance
PPA	64% (95% CI: 54–74%)
NPA	88% (95% CI: 83–92%)

- In 352 (31.5% of ITT) matched patient specimens, tTMB values positively correlated with bTMB values



In 352 matched patient specimens, tTMB values positively correlated with bTMB values

NGS gene panels to assess TMB

Status	Test name	Number of genes	Coverage (Mb)*	Gene variants	Sample type
FDA-approved or authorised diagnostic assays†	MSK-IMPACT[15 56 68]	468	1.5	SNVs, indels, rearrangements/ fusions, CNAs, parallel analysis of genomic signatures (eg, TMB and dMMR/MSI)	FFPE
	Foundation Medicine FoundationOne CDx[14 49]	324	0.8	SNVs, indels, CNAs, select rearrangements, parallel analysis of genomic signatures (eg, TMB and dMMR/MSI)	FFPE
Commercial assays for research use only	Caris Molecular Intelligence[132]	592	1.4	Somatic missense mutations	FFPE
	Illumina TruSight 500 gene panel[133]	500	2.0	SNVs and indels	FFPE
	Thermo Fisher Scientific Oncomine Tumor Mutation Load Assay[77]	409	1.7	SNVs	FFPE
	NEO New Oncology NEOplus v2 RUO[134]	>340	1.1	SNVs, indels, fusions, CNAs, parallel analysis of TMB, MSI, and driver mutations	FFPE
	Foundation Medicine FoundationOne[50]	315	1.1	SNVs, indels, CNAs, select gene rearrangements, genomic signatures for MSI and TMB	FFPE
	Foundation Medicine bTMB assay[88 122]	394	1.1	SNVs	Blood
	TruSight Tumor 170[135]	170	0.5	Fusions, splice variants, SNVs, indels, amplifications	FFPE
	QIAGEN GeneRead DNAseq Comprehensive Cancer Panel[97]	160	0.7	SNVs, CNAs, indels, and fusions	FFPE
	NEO New Oncology NEOplus[105 136]	94		SNVs, indels, CNAs, rearrangements, and fusions	FFPE

요양급여의 적용기준 및 방법에 관한 세부사항 중 개정 (2019.7.23)

<table>
<tr><th>구분</th><th>개 정 전</th><th>개 정 후</th></tr>
<tr><td>2 비소세포폐암
[2군 항암제를
포함한 요법]</td><td>
3. 고식적요법(palliative)
나. 투여단계: 2차 이상
- stage IIIA 이상으로 각 연번(22, 23, 24번 제외)의 투여대상에 해당하는 경우 요양급여를 인정함
<table>
<tr><th>연번</th><th>항암요법</th><th>투여대상</th></tr>
<tr><td>24</td><td>atezolizumab주1</td><td>PD-L1 발현 양성(발현 비율 TC2/3 또는 IC2/3주4)이면서 이전 백금기반 화학요법에 실패한 stage IIIB 이상

※ EGFR 또는 ALK 변이가 확인된 환자는 이러한 변이에 대한 승인된 치료제를 투여한 후 질병 진행이 확인되고, 이전 백금기반 화학요법에도 실패한 경우
※ 이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함.</td></tr>
</table>
주1~3. (생략)
주4. VENTANA PD-L1(SP142) Assay 검사
<table>
<tr><td>TC2/3</td><td>종양세포의 PD-L1 발현 비율 ≥ 5%</td></tr>
<tr><td>IC2/3</td><td>종양침윤면역세포의 PD-L1 발현 비율 ≥ 5%</td></tr>
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※ EGFR 또는 ALK 변이가 확인된 환자는 이러한 변이에 대한 승인된 치료제를 투여한 후 질병 진행이 확인되고, 이전 백금기반 화학요법에도 실패한 경우
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2. Protocol Developement

Study Synopsis (1/3)

Roche

About Roche Solutions Innovation | Stories

Investigator initiated studies

CH

2018-03-25 (일) 오후 2:49

Cho, Hyunji <hyunji.cho@roche.com>

Re: <한국로슈의학부> 요청하신 Atezolizumab 관련 진행중인 임상 정보 전달 드립니다.

받는 사람 오인재

참조 Jinyoung Jang

그림을 다운로드하려면 여기를 클릭하세요. 개인 정보를 보호하기 위해 Outlook에서 이 메시지의 일부 그림은 자동으로 다운로드되지 않습니다.

ongoing atezolizumab studies in LC_rev.pptx
1 MB

오인재 교수님께

교수님, 안녕하세요?
한국 로슈 의학부 조현지 입니다.

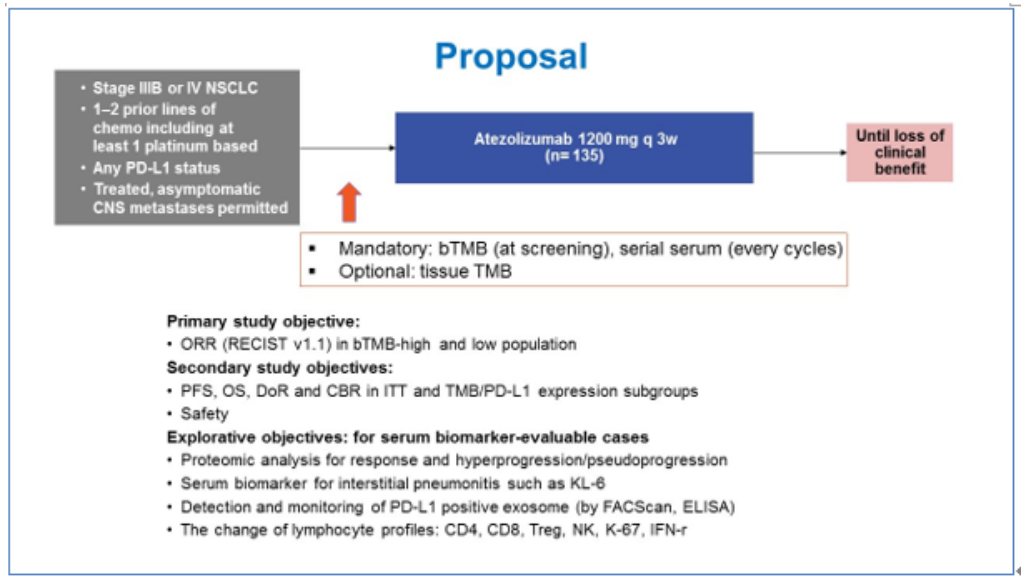
교수님, 요청하신 2L 에서의 스터디 디자인과, FMI+Atezolizumab 스터디 디자인 추가한 슬라이드 송부 드립니다.

FMI+Atezolizumab 으로 prospective 하게 진행 중인연구는 B-F1RST 와 B-FAST study 2 개 뿐이며, IMpower130, IMpower131, IMpower132, IMpower150 study 에서는 retrospective 하게 exploratory biomarker 로서 FMI 분석이 이 진행된다고 합니다.
첨부드리는 슬라이드 참고 부탁드립니다.

IIR-Concept

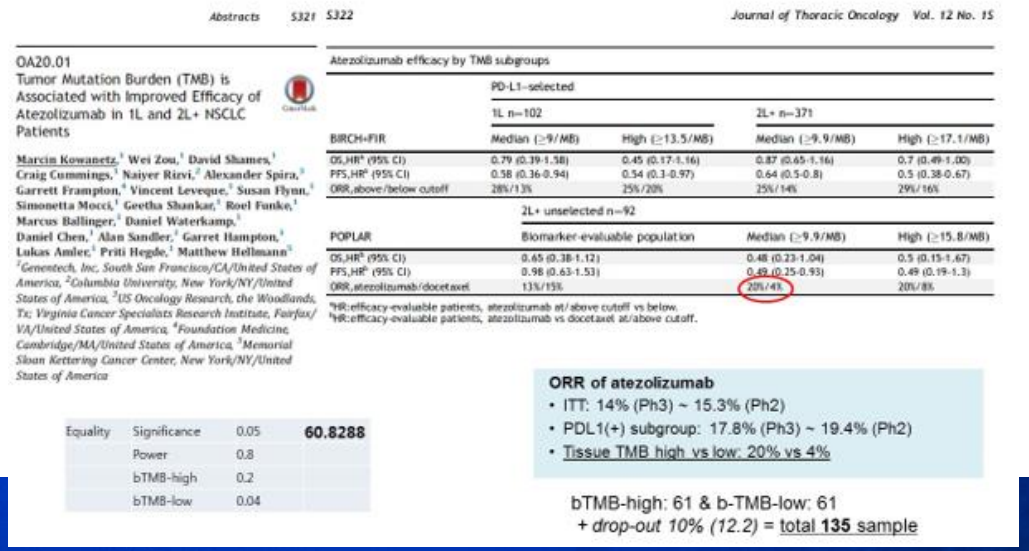
Name of requester	*In-Jae Oh, MD. PhD.*
contact details	*Chonnam National University Hwasun Hospital* *322 Seoyango-ro, Hwasun, Jeonnam, Republic of Korea* *+82 61 379 7617 / droij@chonnam.ac.kr*
Hypothesis	*The hypothesis is that the efficacy of atezolizumab by tumor mutation burden (TMB) of tissue can also be adapted to TMB of blood. Tissue TMB is associated with improved efficacy of atezolizumab in 1L and 2L+ NSCLC [JTO 2017;12(1):S321-S322]. Nevertheless, tissue TMB was only possible in about 30% of patients, but blood can be applied to all NSCLC patients. If blood TMB proves to be effective, we can get a powerful predictive biomarker besides PDL1.* *During immunotherapy, blood lymphocyte profile will also change, so serial liquid biopsy using serum can be useful for therapeutic monitoring.*
Primary endpoint	*Objective response rate (ORR) by RECIST version 1.1 in blood TMB-high and low population*
Study design	*Single arm, prospective multi-center open label study in 2L+ or 3L NSCLC who failed 1-2 prior lines of chemotherapy including at least 1 platinum-based.* *The mandatory tests are blood TMB in screening period and serial serum collections in every cycles of atezolizumab. Atezolizumab 1200 mg will be administrated every 3 weeks until loss of clinical benefit.*
Sample size	*Assuming 10% of drop-out, total sample size is calculated to 135 patients to prove ORR 20% vs 4% (cut-off was median TMB of tissue) [ref, JTO 2017;12(1):S321-S322].*
Support requested	*Blood TMB tests and atezolizumab 1200 mg q 3 weeks for 135 patients.* *Additional support for serial liquid biopsy which will mostly conduct our own research fund.*
When do you plan first patient first visit?	*Oct 2018*

Study Synopsis (2/3)



ORR, objective response rate; bTMB: blood tumor mutation burden; PFS, progression-free survival; OS, overall survival; DoR, duration of response; CBR, clinical benefit rate; ITT, intention to treat

Sample size calculation



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Support requested	*Blood TMB tests and atezolizumab 1200 mg q 3 weeks for 135 patients.* *Additional support for serial liquid biopsy which will mostly conduct our own research fund.*
When do you plan first patient first visit?	*Oct 2018*

Study Synopsis (3/3)

Study Title	Prospective validation of blood tumor mutation burden for improved efficacy of atezolizumab in 2L+ non-small cell lung cancer
Study Rational	The hypothesis is that the efficacy of atezolizumab by tumor mutation burden (TMB) of tissue can also be adapted to TMB of blood. Tissue TMB is associated with improved efficacy of atezolizumab in 1L and 2L+ NSCLC [JTO 2017;12(1):S321-S322]. Nevertheless, tissue TMB was only possible in about 30% of patients, but blood can be applied to all NSCLC patients. If blood TMB proves to be effective, we can get a powerful predictive biomarker besides PD-L1.
Study Objective	To prove the response of atezolizumab in patients with blood TMB-high is better than those with blood TMB-low in 2L+ NSCLC setting.
Study Design	Single arm, prospective multi-center open label study in 2L or 3L NSCLC who failed 1-2 prior lines of chemotherapy including at least 1 platinum-based.
In and Exclusion Criteria	***Inclusion criteria** ▪ Signed Informed Consent Form ▪ Ability to comply with protocol ▪ Aged ≥ 18 years ▪ Histologically or cytologically confirmed stage IV NSCLC ▪ Disease progression during or following treatment with a prior platinum-containing regimen ▪ Measurable disease, as defined by RECIST v1.1 ▪ ECOG performance status of 0 – 2 ▪ Adequate hematologic and end organ function ***Exclusion criteria** ▪ Active or untreated CNS metastases ▪ Malignancies other than NSCLC within 5 years prior to randomization ▪ Pregnant and lactating women ▪ Significant cardiovascular disease ▪ Severe infections within 4 weeks prior to randomization ▪ History of autoimmune disease ▪ History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia) ▪ Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to, prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization

Study Endpoints	***Primary endpoint** - Objective response rate (ORR) by RECIST version 1.1 in blood TMB-high and low population *** Secondary endpoints** 1) PFS, OS, DoR and CBR in ITT and subgroups [according to blood TMB, PD-L1 immunohistochemistry, peripheral blood NLR/PLR] 2) Safety profile *** Explorative objectives:** for serum biomarker-evaluable cases 1) Detection and monitoring of PD-L1 positive exosome 2) The change of lymphocyte profiles: CD4, CD8, Treg, NK, K-67, IFN-r (by FACScan) *3) If events occur, proteomic analysis for hyperprogression and pseudoprogression* *4) If events occur, serum biomarker for interstitial pneumonitis such as KL-6*
Randomization & Stratification	Not applicable because of single arm open label study
Statistical Methods	Intergroup comparisons of response will be performed using Pearson's χ^2 or Fisher's exact tests. Survival times will be estimated for each group using the Kaplan-Meier method.
Special Protocol Considerations (if applicable)	The mandatory tests are blood TMB using Guardant360 in screening period post-treatment 6 weeks. And serial serum collections in every cycles of atezolizumab. See the below figures for more details.
Sample Size	Assuming 10% of drop-out, total sample size is calculated to 135 patients to prove ORR 20% vs 4% (cut-off was median TMB of tissue) [ref, JTO 2017;12(1):S321-S322].
IMP, non-IMP, Comparators	IMP: atezolizumab 1200mg Non-IMP and Comparators: Not applicable because of single arm open label study
Dose and route of administration	Atezolizumab 1200 mg IV will be administrated every 3 weeks until loss of clinical benefit by investigator's decision.

Cardona, Andres {MDAF~Basel}
Change from baseline to any visit?

Cardona, Andres {MDAF~Basel}
These are not clear, specifically what is meant with "events"? Is it meant to show only descriptive tables?

Cardona, Andres {MDAF~Basel}
Which test will be used for the primary endpoint? (i.e. which one was used for the sample size calculation?)

Cardona, Andres {MDAF~Basel}
Consider using multivariate Cox models to adjust for any imbalance between group.

Cardona, Andres {MDAF~Basel}
Have you considered stratifying by TMB level (High vs Low)?

> **Yoo, Ashley {MDGS~Seoul}**
> 교수님, ORR 20% vs 4% 가 median TMB 를 기준으로 high/low group 간의 예상되는 ORR 이 맞는지요?

Cardona, Andres {MDAF~Basel}
See comment above

Cardona, Andres {MDAF~Basel}
Major: Will you use the same cutoff (median of 9.9)? Consider that this will be a different population and a different method so this cutoff might differ to your study.

Study Protocol (1/3)

PROTOCOL

TITLE: **EVALUATION OF BLOOD TUMOR MUTATION BURDEN FOR IMPROVED EFFICACY OF ATEZOLIZUMAB IN 2L+ NON-SMALL CELL LUNG CANCER [BUDDY]**

PROTOCOL NUMBER: ML40993

VERSION NUMBER: 1.0

VERSION DATE 2019.05.31

STUDY DRUG: Atezolizumab

COORDINATING INVESTIGATOR Chonnam National University Hwasun hospital

Pf. In-Jae Oh

계획서

연구명: **비소세포폐암 환자의 2 차 이상 치료에서 아테졸리주맙의 유효성 향상 지표로서 BLOOD TUMOR MUTATION BURDEN(BTMB)의 평가 [BUDDY]**

EVALUATION OF BLOOD TUMOR MUTATION BURDEN FOR IMPROVED EFFICACY OF ATEZOLIZUMAB IN 2L+ NON-SMALL CELL LUNG CANCER [BUDDY]

계획서 번호: ML40993

버전 번호: 1.1

버전 일 2019.07.13

연구 약물: 아테졸리주맙(Atezolizumab)

연구 조정자: 화순전남대학교병원 오인재 교수

TABLE OF CONTENTS

화순전남대학교병원 생명의학연구윤리심의위원회

우 58128 전라남도 화순군 화순읍 서양로 322 / ☎82-61-379-7598 / 전송 82-61-379-7593

심의결과 통보서

IRB No.	CNUHH-2019-138		
과제명	(국문) 비소세포폐암 환자의 2차 이상 치료에서 아테졸리주맙의 유효성 향상 지표로서 BLOOD TUMOR MUTATION BURDEN(BTMB)의 평가 [BUDDY]		
	(영문) EVALUATION OF BLOOD TUMOR MUTATION BURDEN FOR IMPROVED EFFICACY OF ATEZOLIZUMAB IN 2L+ NON-SMALL CELL LUNG CANCER [BUDDY]		
Protocol No.	ML40993		
연구 책임자	성명	소속(과)	직위
	오인재	호흡기내과	교수
생명윤리법에 따른 분류	■인간대상연구 □인체유래물연구		
연구 종류	□임상시험 외 연구	□ 보관된 검체연구 □ 조직 및 혈액연구 □ 의무기록을 이용한 환자군 연구 □ 의료시술 □ 설문조사 □ 관찰연구(단면조사연구, 환자대조군연구, 코호트연구 등) □ 시판후 사용성적 조사(PMS) □ 기타연구	
	■임상시험	연구 대상: □ 의약품 □ 생물학적제제 □ 세포치료제 □ 건강기능식품 □ 화장품 □ 의료기기(분류번호(등급) :) ■ 기타	
		일반명: 해당 없음 / 상품명: 해당 없음	
		의약품임상시험단계: □ 제1상 □ 제1/2상 □ 제2상 □ 제2/3상 □ 제3상 □ 제4상 □ 생물학적동등성 □ 학술연구 □ 기타	
		의료기기 임상시험 단계: □ 탐색 임상시험 □ 확증 임상시험	
		식약처 계획서 승인 대상 여부: □ 승인 대상 / 식약처 계획서 승인일 / ■ 승인 제외 대상	
		임상시험 목적: ■ 학술용 □ 국내허가용(MFDS) □ 해외 허가용 (국가명:)	
최초 계획서 승인일	2019년 08월 07일 (정기보고주기 : 12개월)		
승인유효만료일	2020년 08월 06일	심의대상	연구계획심의 의뢰서(신규)
심의 종류	정규심의(Panel A)	심의 일자	2019년 08월 07일
심의결과통보일	2019년 08월 12일		

Study Protocol (2/3)

Study Protocol (3/3)

"나"부터 실천하는 청렴韓세상

보 건 복 지 부

정부혁신 보다 나은 정부

수신 수신자 참조
(경유) 건강보험심사평가원장
제목 임상연구 요양급여 적용 결정 결과 통보

1. 귀 기관의 무궁한 발전을 기원합니다.

2. 「임상연구 요양급여 적용에 관한 기준」 제4조에 따라, 귀 기관의 임상연구 요양급여 적용 결정신청 결과를 통보하오니, 관련 규정을 준수하여 업무를 추진하여 주시기 바랍니다.

가. 접수번호 : 2019A00912(접수일 2019.11.13.)
나. 기관명 : 화순전남대학교병원(36100498)
다. 연구명 : 비소세포폐암 환자의 2차 이상 치료에서 아테졸리주맙의 유효성 향상 지표로서 BLOOD TUMOR MUTATIONBURDEN(BTMB) 의 평가 [BUDDY]
라. 연구기간 : 2018.8.7. ~ 2021.8.31.
마. 결정결과 : 승인

보험증권
No Fault Compensation For Clinic Trial

계약번호 : 81969217032000

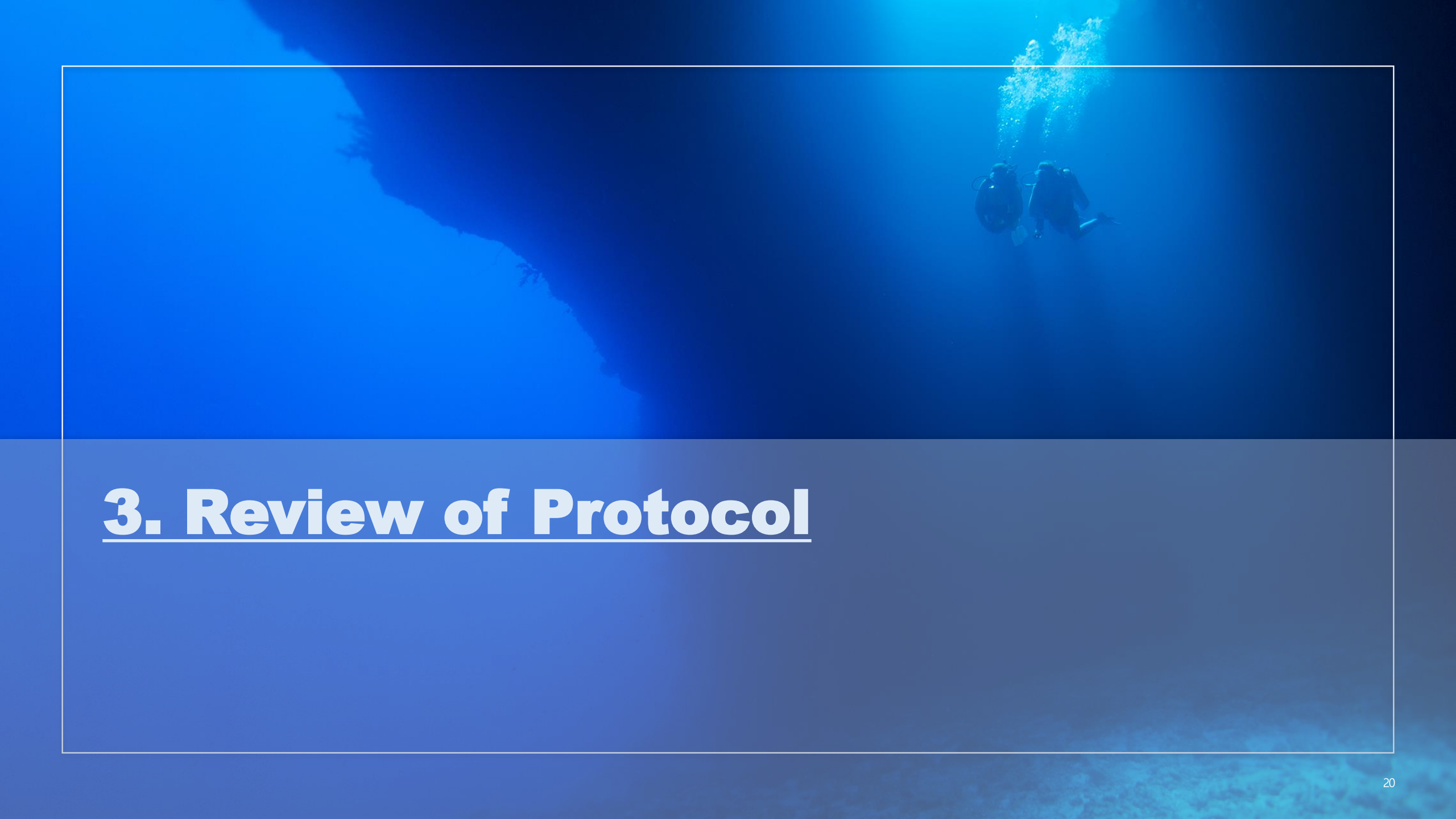
계약자	오인재	계약자번호	730119-1******
	(58128) 전남 화순군 화순읍 서양로 **********		
피보험자	오인재	피보험자번호	730119-1******
보험기간	2019.12.12 00:01 ~ 2021.08.12 00:01	청약일	2019.12.12
첫회보험료	1,914,000 원 (1회 /일시납)	총보험료	1,914,000 원

소재지

58128 전남 화순군 화순읍 서양로 322 외 (일심리,화순전남대학교병원)

가입내역 [총가입금액 : 100,000,000 원]

가입대상	보장조건	화폐	보장/공제금액	보험료	비고
임상시험	총보상한도	KRW	100,000,000	1,914,000	목적물명:임상시험 임상단계구분코드:4상 소급담보일자:2019-12-12 사업종류명:아테졸리주맙 보험기간개월수:20 피험자수:100 재판관할법원명:대한민국 임상담보지역구분코드:Korea 통지연장기간구분코드:없음 피험자건강상태코드:ill 피험자구성코드:그외 발견기간확장개월수:2 임상시험분류코드:주사/복용
	사고당 보상한도	KRW	1억		
	인당 보상한도	KRW	1억		
	자기부담금	KRW	100만		
보험료합계					1,914,000 원



3. Review of Protocol

Study Objective

◆ Primary Objective

- 이전의 백금제제가 포함된 항암치료에 실패한 등록시 국소 진행성 또는 전이성 비소세포폐암(NSCLC) 환자의 2차 이상 치료에서 bTMB-High 집단과 bTMB-Low 집단간에 아테졸리주맙의 반응을 비교하여 bTMB 검사 방법을 평가

*'TMB high'는 TMB가 50번째 백분위수보다 높은 경우로 정의되며, 'TMB low'는 TMB가 50 혹은 50보다 낮은 경우로 정의된다

◆ Secondary Objective

- ITT 모집단과 각 하위집단 (bTMB, PD-L1 면역조직화학, 말초 혈액에서의 NLR/PLR)에서 PFS, OS, DoR, CBR 평가
- 안전성 프로파일 평가

◆ Exploratory Objective

- 탐색적 바이오마커 평가

Inclusion Criteria(1/2)

- ✓ 18세 이상
- ✓ 조직학적으로 혹은 세포학적으로 확인된 **등록시(Enrollment) 국소 진행성 또는 전이성(즉, definitive CCRT에 적합하지 않은 IIIB ~ IV 병기, 재발성) 비소세포폐암**
- ✓ NSCLC에 대하여 **백금 기반 화학 요법제 치료 중 또는 치료 이후 질병의 진행**
  - **환자는 하나 혹은 그 이상의 추가 세포독성 항암화학요법 처방을 받았을 수 있다.**
  - **EGFR 또는 ALK 변이가 확인된 환자는 아테졸리주맙을 투여하기 전에 이러한 변이에 대한 승인된 치료제를 투여한 후에도 질병의 진행이 확인된 경우여야 한다.**
- ✓ 계측 가능한 질환은 RECIST version 1.1에 따라 **적어도 1개 이상의 측정 가능한 병변**
- ✓ ECOG performance status 가 **0 – 2**
- ✓ 예측되는 생존기간 ≥ 12 주

Inclusion Criteria(2/2)

✓ **적절한 혈액 및 말단 장기 기능:**

- ANC ≥ 1.0 x 10^9/L
- WBC counts > 2.5 x 10^9/L
- Hemoglobin ≥ 8.0 g/dL
- Total bilirubin ≥ 2.5 X UNL

  * 알려진 길버트 질환이 있는 환자 중 혈청 빌리루빈이 ≤ 3 x ULN인 환자는 등록될 수 있다.

- AST, ALT, and alkaline phosphatase(ALP) ≤ 2.5 × ULN, 다음의 경우 예외:

  * 간 전이가 있는 대상자: AST and ALT ≤ 5 × ULN.
  * 간 혹은 뼈 전이가 있는 대상자: alkaline phosphatase(ALP) ≤ 5 × ULN

Exclusion Criteria(1/2)

- ✓ **활동성 또는 치료받지 않은 중추신경계(CNS) 전이**
  - 치료된 증상이 없는 CNS 전이 기왕력이 있는 환자는 등록 가능하다.
- ✓ **자가면역질환이 있거나 만성적 혹은 재발성 자가면역질환의 기왕력이** 있는 환자
  - 안정적인 용량의 갑성선 대체 호르몬 투여시 자가면역 매개 갑상선기능저하증 기왕력이 있는 환자는 본 연구에 등록 가능 할 수 있다.
  - 안정적인 인슐린 처방 투여시 조절되는 Type 1 당뇨병 환자는 본 연구에 등록 가능 할 수 있다.
- ✓ **연구 등록(Enrollment) 전 2주 이내에 전신 코티코스테로이드 또는 기타 전신 면역억제 약물**
  (프레드니손, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, 및 항-종양 괴사인자[TNF] 포함) 투여
  - 흡입용 코티코스테로이드나 megesterol acetate 투여는 허용된다.

Exclusion Criteria(2/2)

- ✓ **조절되지 않는 특발성 폐 섬유화증(idiopathic pulmonary fibrosis) 혹은 약물-유발 폐렴(drug-induced pneumonitis)**
- ✓ **연구 등록(Enrollment) 전 5년 이내에 NSCLC 이외의 악성질환**(전이 또는 사망 위험이 무시할만하고 치유적인 결과를 예상하고 치료한 악성질환(적절히 치료된 자궁경부상피내암, 기저 또는 편평세포 피부암, 치유목적으로 치료된 국소적 전립선암 또는 치유목적으로 외과적으로 치료된 관상피내암과 같은)은 제외)
- ✓ 뉴욕 심장 협회 심장 질환 (Class II 이상), 연구 등록(Enrollment) 전 **3개월 이내의** 심근 경색과 같은 유의한 심혈관 질환
- ✓ 아테졸리주맙 및 그 구성 성분에 과민증인 환자

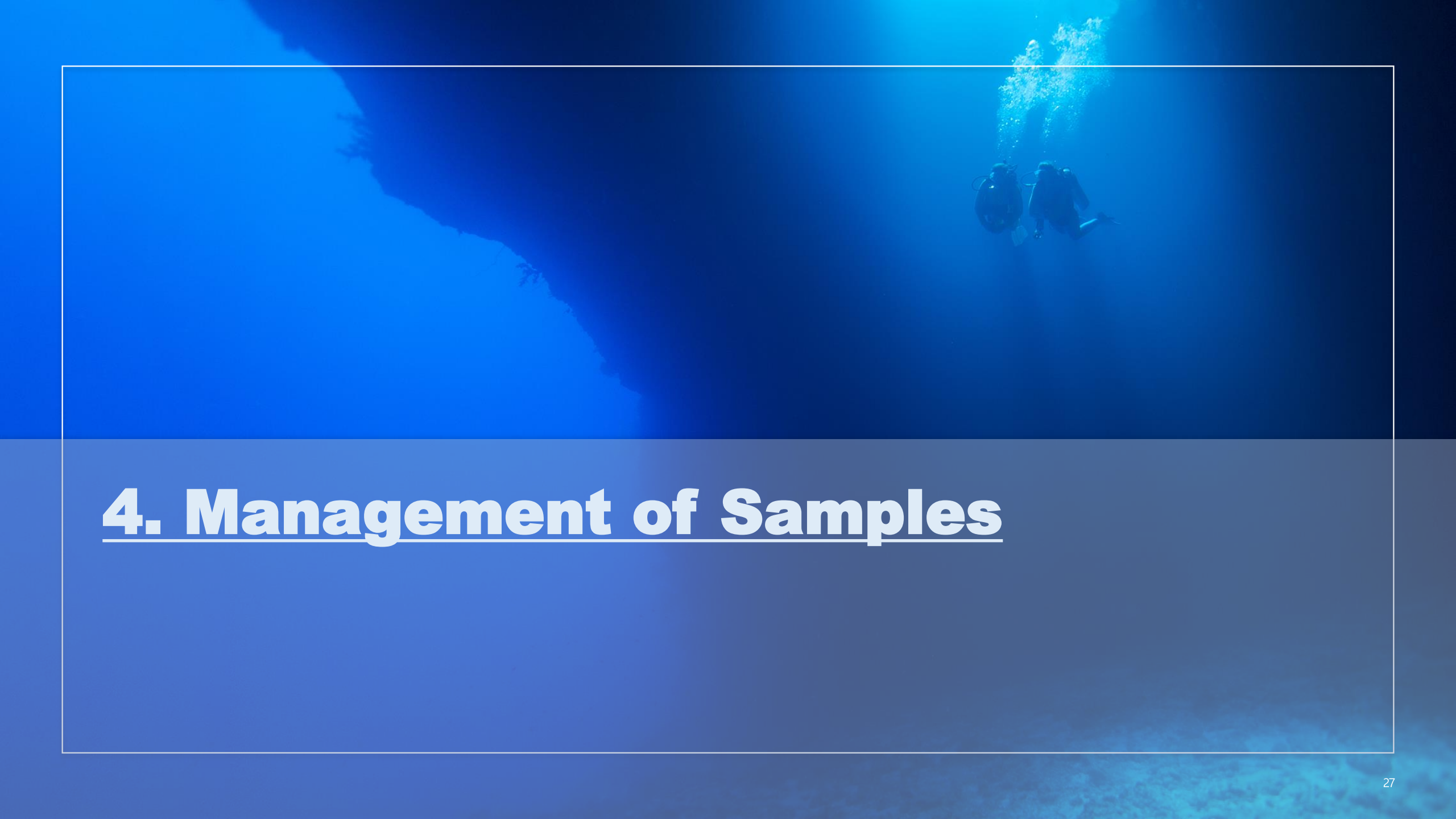
Subject Treatment

◆ **약물: Atezolizumab**

- 식약처의 승인 사항에 따라 아테졸리주맙 치료 계획이 있는 환자를 대상으로 진행
- 아테졸리주맙과 관련된 모든 절차는 통상적인 치료과정의 일환으로 수행

◆ **투여방법**

- 1200 mg을 3주 간격으로 정맥 점적주입
- 초회 용량은 60분에 걸쳐 주입 후, 첫 주입에 내약성을 보일 경우 이후 모든 주입은 30분 동안 투여
- 이 약을 급속 정맥주입(IV push 또는 IV bolus)으로 투여해서는 안 된다.
- 임상적 이점이 없거나 허용 불가능한 독성 발생 전까지 아테졸리주맙을 투여
- 계획된 투여를 놓친 경우에는 다음 계획된 일정까지 기다리지 않고 가능한 빨리 투여



4. Management of Samples

Meeting Minute

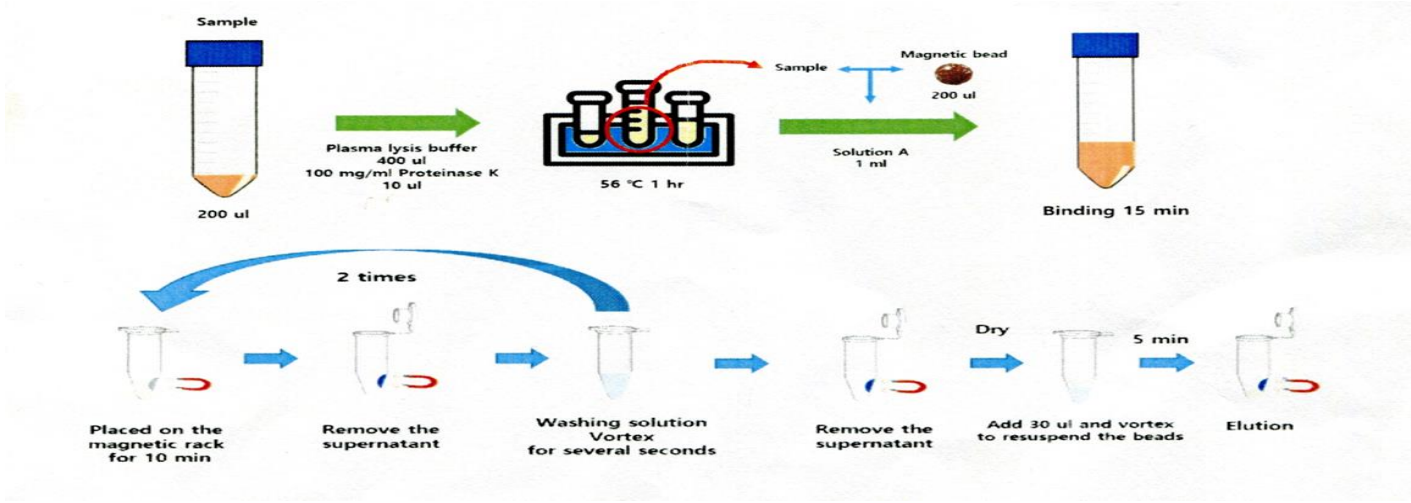
Project or Protocol No.	BUDDY/ ML40993	**Sponsor Name**	화순전남대학교병원
Date & Time	2019-07-27(토) 10:00~11:30	**Place**	서울아산병원 동관6층 6세미나실
Purpose	Investigator Meeting		
Written by	홍정숙		
Attendee (Omission of Honorific Title)	• 화순전남대병원(3명): 오인재, 조현주, 고은영 • 충남대병원(3명): 이정은, 강다현, 이정은 • 양산부산대병원(2명): 윤성훈, 이수현 • 서울아산병원(4명): 이재철, 최창민, 천성민, 윤성희 • 고려대구로병원(4명): 이승룡, 최주환, 정주애, 이현우 • 칠곡경북대병원(1명): 이신엽 • 로슈(3명): 조현지, 배소연, 김희정 • 프로큐라티오(2명): 홍정숙, 이나래		

Sample 준비 방법

1. **EDTA tube**에 혈액 10cc를 채혈한다.
2. EDTA tube를 3200rpm, 10min, 20℃로 원심분리 한다.
3. EDTA tube를 원심분리 후 가라앉은 적혈구와 백혈구 세포층 상단에 있는 맑은 혈장을 혈청 분리관을 이용하여 1.8ml의 cryogenic vial 2개에 최대 동량으로 옮겨 담는다.
4. 1 vial 당 최소 보관 기준은 500ul로 한다.
5. **Plasma에서 cfDNA prep를 가능한 빨리 시행**한다.
   (최대한 혈액 수집 후 2시간 이내 시행을 권고한다.)
6. cfDNA를 서울아산병원으로 전달한다.(배송 시점 논의)
7. NGS wet 및 SNV/indel data 생산한다.
8. Target exonic 영역내의 Non-synonymous variant number를 계산한 TMB 수치 확인

방법 1_NEXmag™ cell free DNA capturing kit

① 200ul의 plasma샘플을 2ml tube에 옮긴다.
② 400ul의 plasma lysis buffer(PLB)와 10ul의 proteinaseK를 넣는다.
③ Vortexing을 약 10초간 하여 잘 섞어준 뒤, 56℃에서 60분간 incubation한다.
④ 사용해야 할 bead를 잘 섞어준 뒤, 200ul의 bead와 1000ul의 solution A를 위 sample tube에 넣는다.
⑤ Vortexing을 약 10초간 하여 잘 섞어준 뒤, 상온에서 15분간 반응한다.
⑥ 위 sample을 magnetic stand에 10분간 부착 후, bead를 제외한 상층액을 버린다.
⑦ 2ml의 washing solution을 첨가 후 상온에서 30초간 반응한다.
⑧ 위 washing solution을 제거하기 위해 magnetic stand에 부착 후 bead를 제외한 상층액을 버린다.
⑨ 7~8 과정을 2번 반복한다.
⑩ bead가 완전히 마를 때까지 건조시킨다.
⑪ 30ul의 elution buffer를 넣고 bead가 잘 풀리도록 섞어준 뒤 magnetic stand에 부착한다.
⑫ 약 5분간 부착한 뒤 용리된 sample을 새로운 1.5ml의 tube에 옮긴다.



방법 2_QIAamp MiniElute ccfDNA Mini Kit

① 15ml tube에 plasma 1ml과 magnetic bead suspension 30ul와 proteinase K 55ul 그리고 Bead Bing Buffer (BBB) 150ul 를 섞은 후 상온에서 rotator 로 10분간 반응한다.(shaking (slow speed) end-over-end)400ul의 plasma lysis buffer(PLB)와 10ul의 proteinaseK를 넣는다.

② 반응이 끝난 후 200xg 30초간 원심분리를 진행한다.

③ Magnetic rack에 최소 1분이상 부착시킨 후 solution이 clear 해지면 supernatant 제거한다.

④ Magnetic rack에서 tube를 빼서 Bead Elution Buffer 200ul를 넣고 vortex 후 Bead Elution Tube로 옮겨 담아 상온에서 300rpm으로 5분간 microcentrifuge tube shaker에서 반응한다. (shaking-Thermomixer®사용)

⑤ Magnetic rack에 부착해 solution이 clear해질 때까지 최소 1분이상둔다.

⑥ Supernatant를 new Bead Elution Tube로 옮겨 300ul Buffer ACB를 첨가 후 vortex로 잘 섞는다.

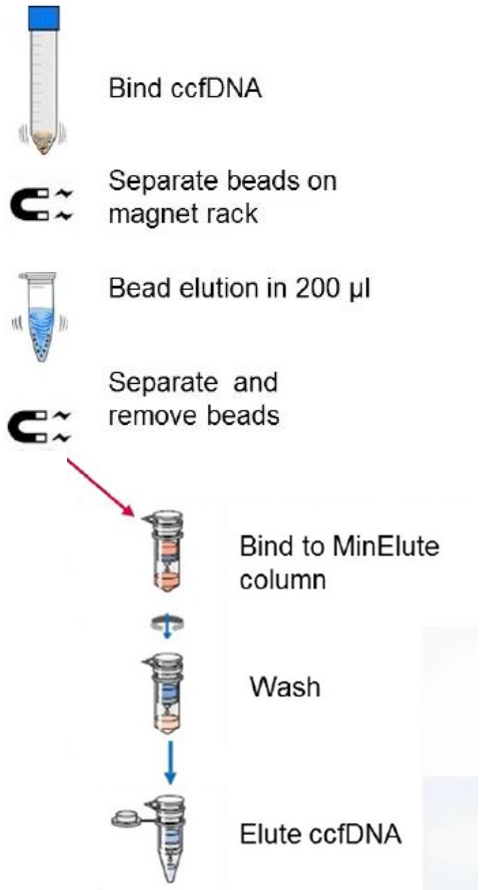
⑦ QIAamp UCP MiniElute column에 6000xg에서 1분간 원심분리를 진행한다.

⑧ Column에 Buffer ACW2 500ul를 넣고 다시 6000xg에서 1분간 원심분리를 진행한다.

⑨ Full speed (20000xg)에서 빈 column을 3분간 원심분리 진행한다.

⑩ column을 clean 1.5ml elution tube로 옮겨서 뚜껑을 열고 microcentrifuge tube shaker 에서 56℃에서 3분간 건조한다.

⑪ Ultra-clean water 20~80ul를 column에 넣고 3~5분정도 incubation 후 Full speed (20000xg) 에서 1분간 원심분리해서 elution진행한다.



Sample Handling Manual_v 1.1

목차

종류	혈액 수집 방법
bTMB (모든 기관)	1. K2 EDTA tube에 해당 환자의 정보를 기입한다. 2. 혈액 10mL을 수집 후 Tube를 흔들지 말고 위아래로 부드럽게 10~15회 정도 섞는다. 3. 채혈 후 Tube를 세운 상태로 유지하여 검체 담당자에게 전달한다. 4. 채혈 후 늦어도 2시간 이내에 원심분리가 완료되어야 한다.

I. 연구용 검체 수집 일정표

Type	Site	Baseline (Cycle 0)	Cycle 2	Cycle 4	EOT
bTMB	**All**	V (첫 투여전)		V (투여전)[a]	
Biomarker 1& 2 (PD-L1 Positive exosome, Immune profiles) [c]	**All**	V (첫 투여전)		V (투여전)[b]	V
Biomarker 3(NK cell activity)[d]	**해당기관**	V (첫 투여전)		V	V
Buffy coat[e]	**All**	2 주기 투여전 또는 어느 시점이든 상관 없음			
Biomarker CTC(선택적)	**CNUHH**	V (첫 투여전)	V (투여전)		
TMB & PD-L1 IHC 를 위한 조직 수집(선택적)[f]	**All**	V			

종류	해당 물품		
EDTA Tube		**Heparin Tube**	
Magnetic bead (1.5mL, 15mL)		**QIAamp MiniElute ccfDNA Mini Kit**	
채혈용 라벨	[bTMB 채혈 Tube용] **ML40993** Type: bTMB/EDTA ENR No: E__ __ __ Cycle No: __ Date: _ _ _ /_ /_ _ Time: __:__		[Biomarker 채혈 Tube용] **ML40993** Type: Biomarker/Heparin ENR No: E__ __ __ Cycle No: __ Date: _ _ _ /_ /_ _ Time: __:__

분석 기관 및 검체 보관

◆ 분석 기관

검사항목	검사기관
bTMB	서울아산병원 Lab
Exosome PDL1(ELISA, exosome purification kit)	프리즘씨디엑스
Plasma cytokine (ELISA)	프리즘씨디엑스
Immune cell profiling (CYTOP)	프리즘씨디엑스
NK cell activity(서울아산병원만 수집)	NKMax
CTC(화순전남대병원만 수집)	화순전남대병원 Lab

◆ 검체 보관

- 연구를 위해 수집된 검체는 연구 지정 번호로 라벨링 될 예정이다.
- 코드화된 검체는 개인 식별자를 포함하지 않는다.
- 검체는 안전한 장소에서 연구 종료 후 2년까지 보관되며, 이후 적용되는 관련 규정에 따라 폐기된다.
- **추후 Lab manual를 별도로 제공할 예정**이다.

Sampling Process

- Stage IIIB ~ IV, recurrent NSCLC
- 1–2 prior lines of chemo including at least 1 platinum based
- Any PD-L1 status
- Treated, asymptomatic CNS metastases permitted

→ **Atezolizumab 1200 mg q 3w (n= 100)** → **Until loss of clinical benefit**

- Mandatory: **bTMB** (at baseline & after cycle 3) +/- serial **plasma**

CT restaging

	baseline	cycle 1	cycle 2	cycle 3	cycle 4	…	EOT
AMC (total 20cc) **bTMB**	**X**				**X**		
AMC (total 20cc) **Plasma + PBMC**	X				X		X
Local lab for IO	X		X	X	X	X	X
CNUHH (total 10cc) Whole blood (10cc) - option	X		X				

*Sampling should be performed before atezolizumab administration in each cycle. The sample at cycle 4 can be taken at CT restaging day.

Sample Collection

차수	시점	cfDNA QC 결과			합계
		Pass	Check	Fail	
1	2020-07-15	13 (54.2%)	8 (33.3%)	3 (12.5%)	24
2	2020-12-09	35 (57.4%)	14 (23.0%)	12 (19.7%)	61
3	2021-06-15	6 (85.7%)	0 (0.0%)	1 (14.3%)	7
4	2021-07-21	30 (85.7%)	5 (14.3%)	0 (0.0%)	35
5	2021-08-03	47 (90.4%)	3 (5.8%)	2 (3.8%)	52
합계		**131(73.2%)**	**30 (16.8%)**	**18 (10.1%)**	**179**

*Amount(ng): Pass > 20, Check 10~20, Fail <10

*1 차: 화순전남대병원 & 서울아산병원에서 직접 추출함.

*2 차: 6 개 기관에서 직접 추출

*3 차~5 차: 화순전남대병원은 4 개 기관(충남대병원, 양산부산대병원, 고대구로병원, 칠곡경북대병원)의 검체까지 cfDNA 추출하고, 서울아산병원은 기관에서 직접 추출함. (Qiagen Kit 공급 및 2 차 cfDNA QC 결과 등으로 고려하여 변경함)

No.	Site name	Baseline			C4			EOT			합계
		Pass	Check	Fail	Pass	Check	Fail	Pass	Check	Fail	
1	화순전남대병원	25	3	2	11	3	0	12	1	0	57
2	충남대병원	6	1	3	3	2	0	2	1	1	19
3	양산부산대병원	6	2	1	1	0	1	3	0	1	15
4	서울아산병원	23	11	4	6	4	3	17	1	0	69
5	고대구로병원	9	0	0	2	0	0	3	0	0	14
6	칠곡경북대병원	2	1	1	0	0	1	0	0	0	5
합계		**71**	**18**	**11**	**23**	**9**	**5**	**37**	**3**	**2**	**179**

[ML40993] Newsletter

9^{th} Newsletter 2021-10-21

[BUDDY]

비소세포폐암 환자의 2차 이상 치료에서 아테졸리주맙의 유효성 향상 지표로서 BLOOD TUMOR MUTATION BURDEN(BTMB)의 평가 [BUDDY]

EVALUATION OF BLOOD TUMOR MUTATION BURDEN FOR IMPROVED EFFICACY OF ATEZOLIZUMAB IN 2L+ NON-SMALL CELL LUNG CANCER [BUDDY]

안녕하세요.

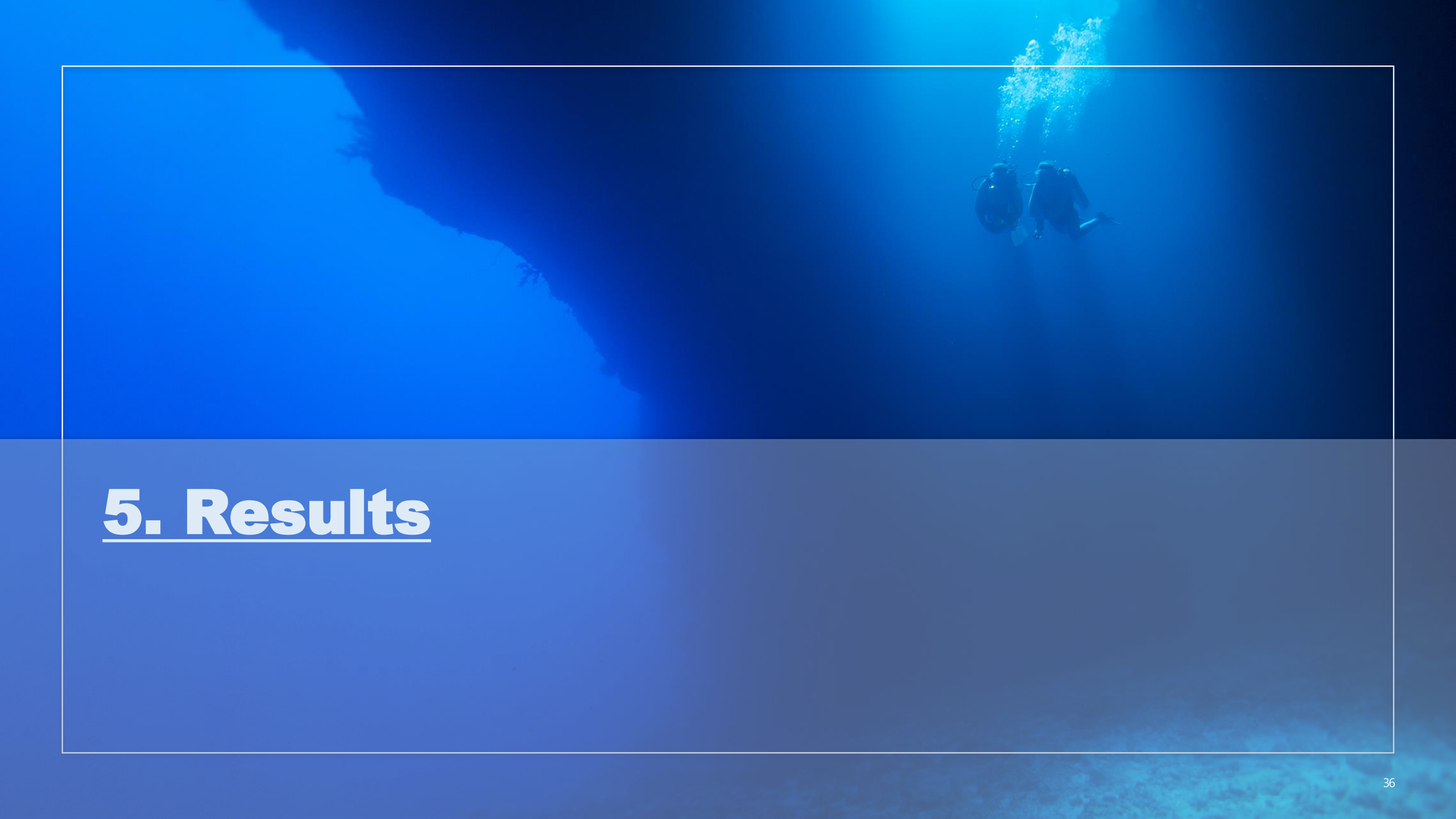
BUDDY 연구의 Project Manager를 담당하고 있는 프로큐라티오 홍정숙입니다.

1. Study Status

2019년 7월 27일 본 연구의 연구자 모임을 시작으로 2019년 12월부터 2021년 4월까지 목표대상자 수 100명을 등록 완료하였습니다. 각 기관별 최종 등록 현황은 아래와 같습니다.

Updated 2021-10-21

Site No.	Site Name	PI	Target	SCR	SF	ENR	Ongoing	EOT				완료	D/O*
								PD	AE	철회	기타		
1	화순전남대병원	오인재	20	30	0	30	4	18	2	2	4	26	4
2	충남대병원	이정은	15	10	0	10	3	6	0	0	1	10	0
3	양산부산대병원	윤성훈	15	9	0	9	2	3	1	0	3	5	4
4	서울아산병원	이재철	20	39	1	38	2	28	4	4	0	34	4
5	고려대구로병원	이승룡	15	9	0	9	1	5	1	0	2	8	1
6	칠곡경북대병원	이신엽	15	5	1	4	0	3	1	0	0	4	0
			100	102	2	100	12	63	9	6	10	87	13



5. Results

2022 ESMO ePoster #1085P

(contact : ckpark214@jnu.ac.kr)

Evaluation of Blood Tumor Mutation Burden for Efficacy of Second-Line Atezolizumab Treatment in Non-small Cell Lung Cancer

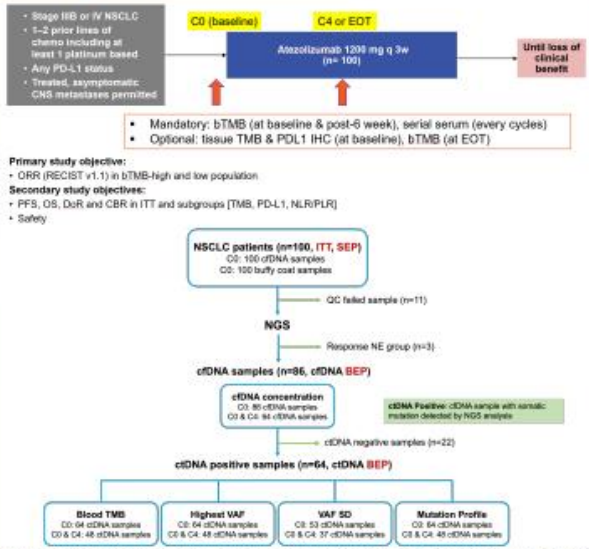
[1]Cheol-Kyu Park, [2]Ha Ra Jun, [1]Hyung-Joo Oh, [2]Ji-Young Lee, [1]Hyun-Ju Cho, [1]Young-Chul Kim, [3]Jeong Eun Lee, [4]Sung Hoon Yoon, [5]Chang Min Choi, [5]Jae Cheol Lee, [6]Sung Yong Lee, [7]Shin Yup Lee, [8,*]Sung-Min Chun, [1,*]In-Jae Oh

[1]Department of Internal Medicine, Chonnam National University Medical School and Hwasun Hospital, Jeonnam, Korea, [2]Department of Medical Science, Asan Medical Institute of Convergence Science and Technology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea, [3]Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Korea, [4]Department of Internal Medicine, Pusan National University Yangsan Hospital, Gyeongnam, Korea, [5]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, [6]Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea, [7]Department of Internal Medicine, Kyungpook National University Chilgok Hospital, Daegu, Korea, [8]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea. ***Co-corresponding authors.**

Background

- We aimed to investigate the feasibility of blood-based biomarkers, including blood tumor mutation burden (bTMB), to predict the atezolizumab efficacy in relapsed or advanced non- small cell lung cancer (NSCLC).

Study Subjects & Methods



EOT, end of treatment; ORR, objective response rate; CBR, clinical benefit response; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ITT, intention-to-treat; SEP, safety-evaluable population; cfDNA, circulating cell-free DNA; QC, quality control; NGS, next-generation sequencing; NE, non-evaluable; BEP, biomarker-evaluable population; ctDNA, circulating tumor DNA; VAF, variant allele frequency; SD, standard deviation.

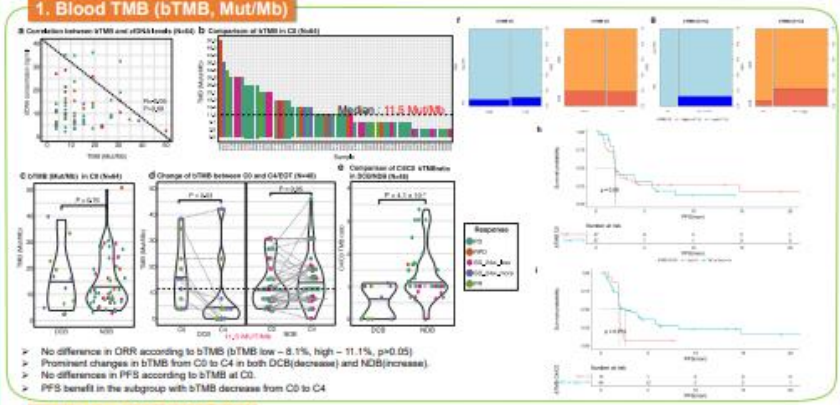
Patients' Characteristics		NDB (n=75)	DCB (n=25)	P-value
Age	< 65years	33 (44.0)	11 (44.0)	1.000
	≥ 65years	42 (56.0)	14 (56.0)	
Sex	Female	14 (18.7)	2 (8.0)	0.345
	Male	61 (81.3)	23 (92.0)	
Smoking	Never smoker	18 (24.0)	3 (12.0)	0.202
	Ever smoker	57 (76.0)	22 (88.0)	
Histology	Squamous cell ca	32 (47.1)	7 (30.4)	0.164
	Adenocarcinoma	36 (52.9)	16 (69.6)	
Liver metastasis		7 (9.3)	0 (0.0)	0.187
Brain metastasis		5 (6.7)	1 (4.0)	1.000
EGFR mutation : Yes		11 (18.0)	0 (0.0)	0.058
ALK rearrangement : Yes		1 (1.9)	0 (0.0)	1.000
PD-L1 (22C3)	TPS <50%	34 (66.7)	7 (43.8)	0.101
	TPS ≥50%	17 (33.3)	9 (56.3)	
PD-L1 (SP263)	TPS <50%	42 (66.7)	13 (61.9)	0.691
	TPS ≥50%	21 (33.3)	8 (38.1)	
PD-L1 (SP142, TC)	TPS <5%	10 (90.9)	3 (75.0)	0.476
	TPS ≥5%	1 (9.1)	1 (25.0)	
PD-L1, high*	No	49 (67.1)	11 (50.0)	0.144
	Yes	24 (32.9)	11 (50.0)	
NLR, median	<2.84	35 (46.7)	15 (60.0)	0.248
	≥2.84	40 (53.3)	10 (40.0)	
PLR, median	<158.15	35 (46.7)	15 (60.0)	0.248
	≥158.15	40 (53.3)	10 (40.0)	
Prior antibiotics	<90days	7 (50.0)	1 (25.0)	0.588
	≥90days	7 (50.0)	3 (75.0)	
Prior steroids	<90days	4 (66.7)	0 (0.0)	0.429
	≥90days	2 (33.3)	1 (100.0)	
Prior Chemo BR	PR	21 (28.0)	10 (40.0)	0.261
	Non-PR	54 (72.0)	15 (60.0)	

*22C3/SP263 ≥50% or SP142 TC ≥5%. †Patients who showed rapid progression and died before the first assessment of tumor responsiveness were included (n=9). NDB, non-durable clinical benefit; DCB, durable clinical benefit; TPS, tumor proportional score; TC, tumor cell; BR, best response.

Efficacy of 2L+ Atezolizumab	No. of Patients, n=100
Atezolizumab cycles (median, range)	3 (1-32)
Reason for cessation of treatment	
Progression	64
Adverse events	9
Withdrawal of consent	6
Others	21
Best response	
CR	0
PR	10
SD : ≥24weeks / < 24weeks	15 / 18
PD*	54
NE	3
Objective response rate, %	10
Durable clinical benefit, %	25
Progression	
Confirmed progression	76
No progression	20
Unknown	4
Follow-up duration, mo (median, 95% CI)	12.3 (10.0-14.6)
PFS, mo(median, 95% CI)	2.1 (1.6-3.0)
DoR, mo(median, 95% CI)	Not matured
OS, mo(median, 95% CI)	13.1 (10.1-16.2)
Alive	42
Death	39
Lost to follow-up	13
Withdrawal of consent	6

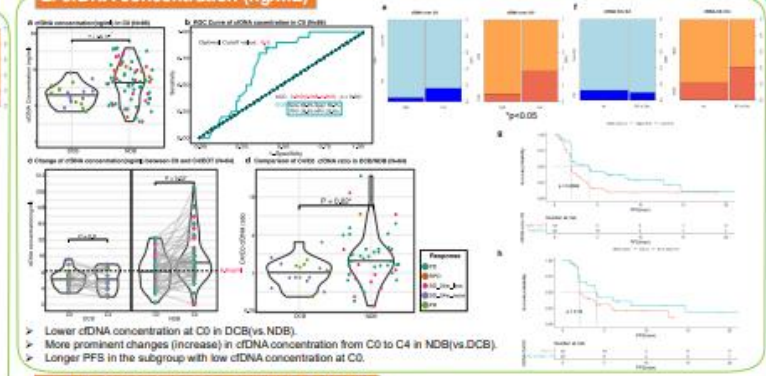
Results

1. Blood TMB (bTMB, Mut/Mb)



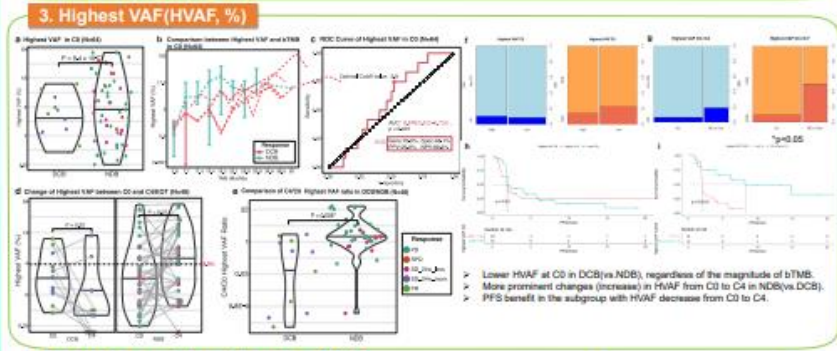
- No difference in ORR according to bTMB (bTMB low – 8.1%, high – 11.1%, p>0.05)
- Prominent changes in bTMB from C0 to C4 in both DCB(decrease) and NDB(increase).
- No differences in PFS according to bTMB at C0.
- PFS benefit in the subgroup with bTMB decrease from C0 to C4

2. cfDNA concentration (ng/mL)



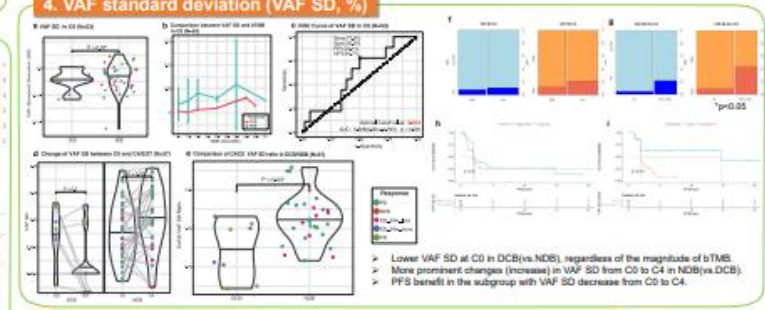
- Lower cfDNA concentration at C0 in DCB(vs.NDB).
- More prominent changes (increase) in cfDNA concentration from C0 to C4 in NDB(vs.DCB).
- Longer PFS in the subgroup with low cfDNA concentration at C0.

3. Highest VAF(HVAF, %)



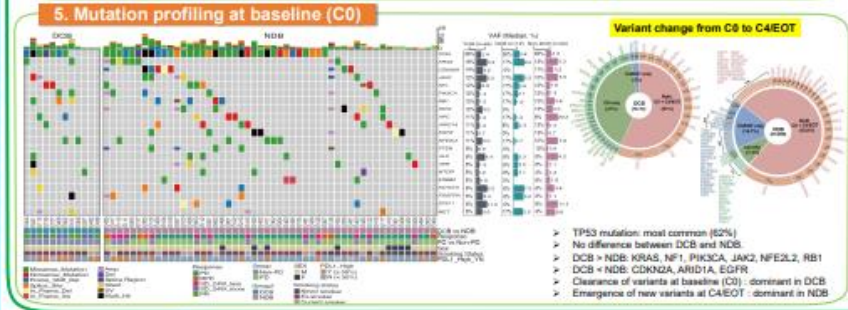
- Lower HVAF at C0 in DCB(vs.NDB), regardless of the magnitude of bTMB.
- More prominent changes (increase) in HVAF from C0 to C4 in NDB(vs.DCB).
- PFS benefit in the subgroup with HVAF decrease from C0 to C4.

4. VAF standard deviation (VAF SD, %)



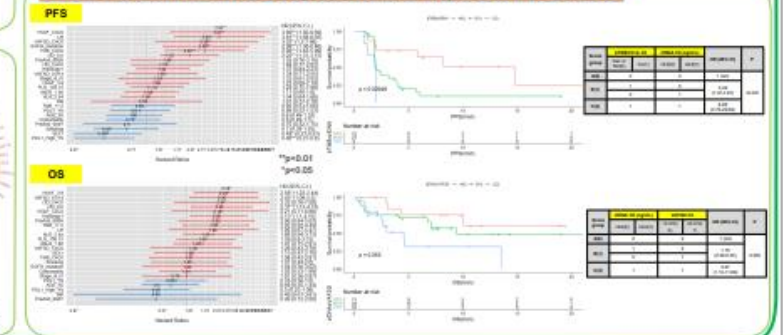
- Lower VAF SD at C0 in DCB(vs.NDB), regardless of the magnitude of bTMB.
- More prominent changes (increase) in VAF SD from C0 to C4 in NDB(vs.DCB).
- PFS benefit in the subgroup with VAF SD decrease from C0 to C4.

5. Mutation profiling at baseline (C0)



- TP53 mutation: most common (62%)
- No difference between DCB and NDB.
- DCB > NDB: KRAS, NF1, PIK3CA, JAK2, NFE2L2, RB1
- DCB < NDB: CDKN2A, ARID1A, EGFR
- Clearance of variants at baseline (C0) : dominant in DCB
- Emergence of new variants at C4/EOT : dominant in NDB

6. Univariate/Multivariate Cox proportional analysis for PFS and OS



Conclusion

- In previously treated advanced NSCLC patients, baseline levels and dynamic changes of blood-based biomarkers, including bTMB, cfDNA concentration, highest VAF, and VAF SD were predictive for clinical benefit rate and survival of atezolizumab treatment.
- Comprehensive analysis of those blood-based biomarkers and mutation profiling could assist the selection of the most profitable patients from immune checkpoint inhibitor treatment.

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

PARIS 2022 ESMO congress

APSR 2022

KALC 2022 Korean Association for Lung Cancer International Conference
November 10-11, 2022 | Lotte Hotel World, Seoul, Korea

Best Presentation Award
Oral Presentation

Evaluation of Blood Tumor Mutation Burden for the Efficacy of Second-Line Atezolizumab Treatment in Non-Small Cell Lung Cancer: BUDDY trial

Cheol-Kyu Park[a], Ha Ra Jun[b], Hyung-Joo Oh[a], Ji-Young Lee[b], Hyun-Ju Cho[a], Young-Chul Kim[a], Jeong Eun Lee[c], Sung Hoon Yoon[d], Chang Min Choi[e], Jae Cheol Lee[e], Sung Yong Lee[f], Shin Yup Lee[g], Sung-Min Chun[h]*, In-Jae Oh[a]*

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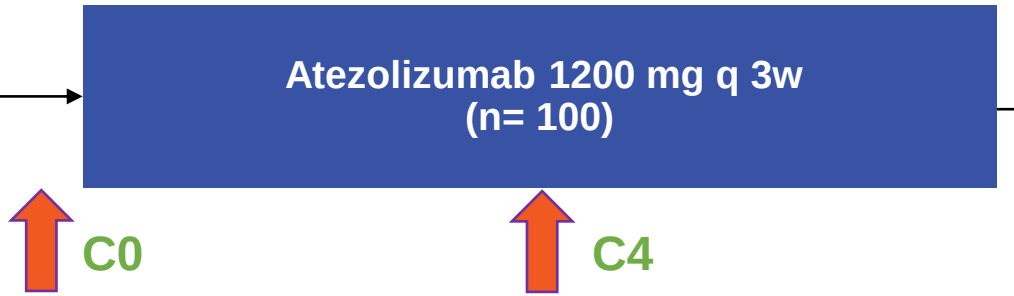
Cheol-Kyu Park
Chonnam National Univ.

Session VII [A]. Oral Presentation III

Objectives and Study Design

- Stage IIIB or IV NSCLC
- 1–2 prior lines of chemo including at least 1 platinum-based
- Any PD-L1 status
- Treated, asymptomatic CNS metastases permitted



Until loss of clinical benefit

- Mandatory: bTMB (at baseline & post-9 week), serial serum (every cycles)
- Optional: tissue TMB & PDL1 IHC (at baseline), bTMB (at EOT)

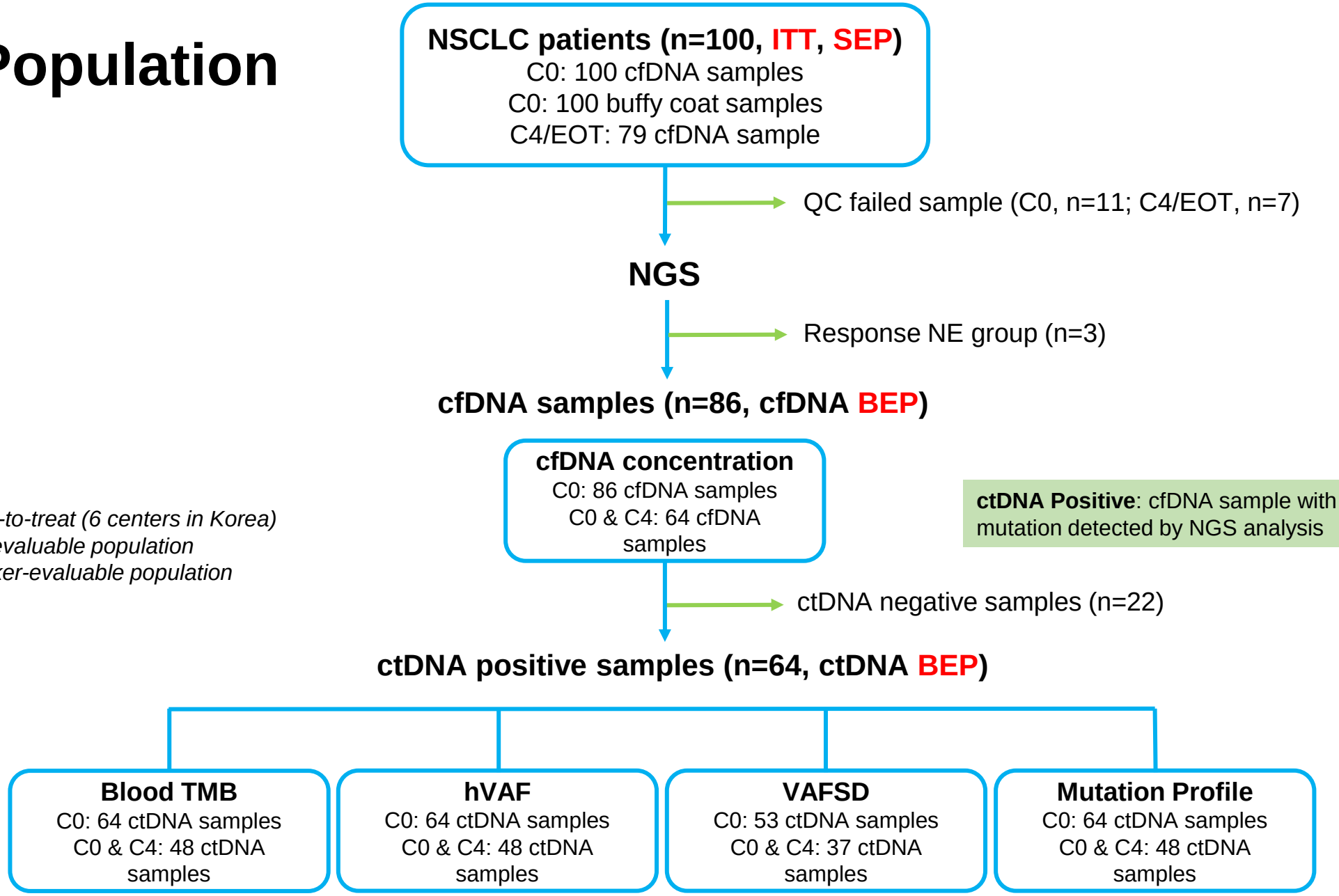
Primary study objective:

- ORR (RECIST v1.1) in bTMB-high and low population

Secondary study objectives:

- PFS, OS, DoR and CBR in ITT and subgroups [TMB, PD-L1, NLR/PLR]
- Safety

Study Population



ITT, intention-to-treat (6 centers in Korea)
SEP, safety-evaluable population
BEP, biomarker-evaluable population

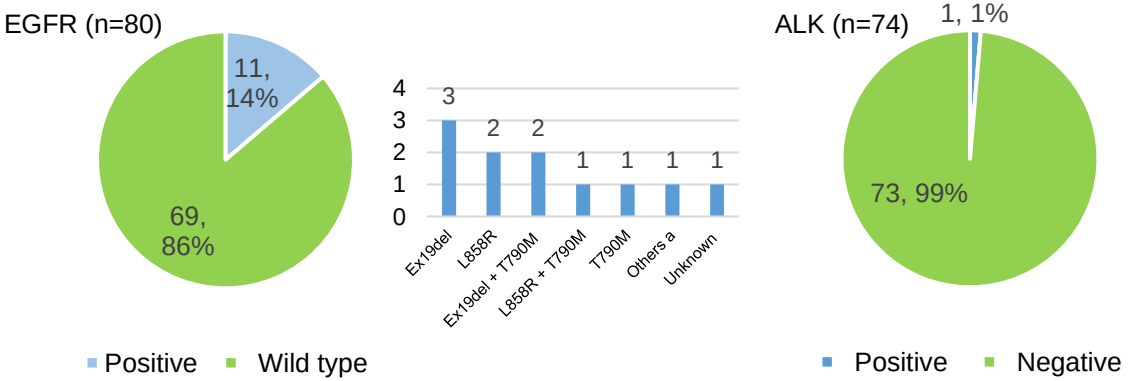
ctDNA Positive: cfDNA sample with somatic mutation detected by NGS analysis

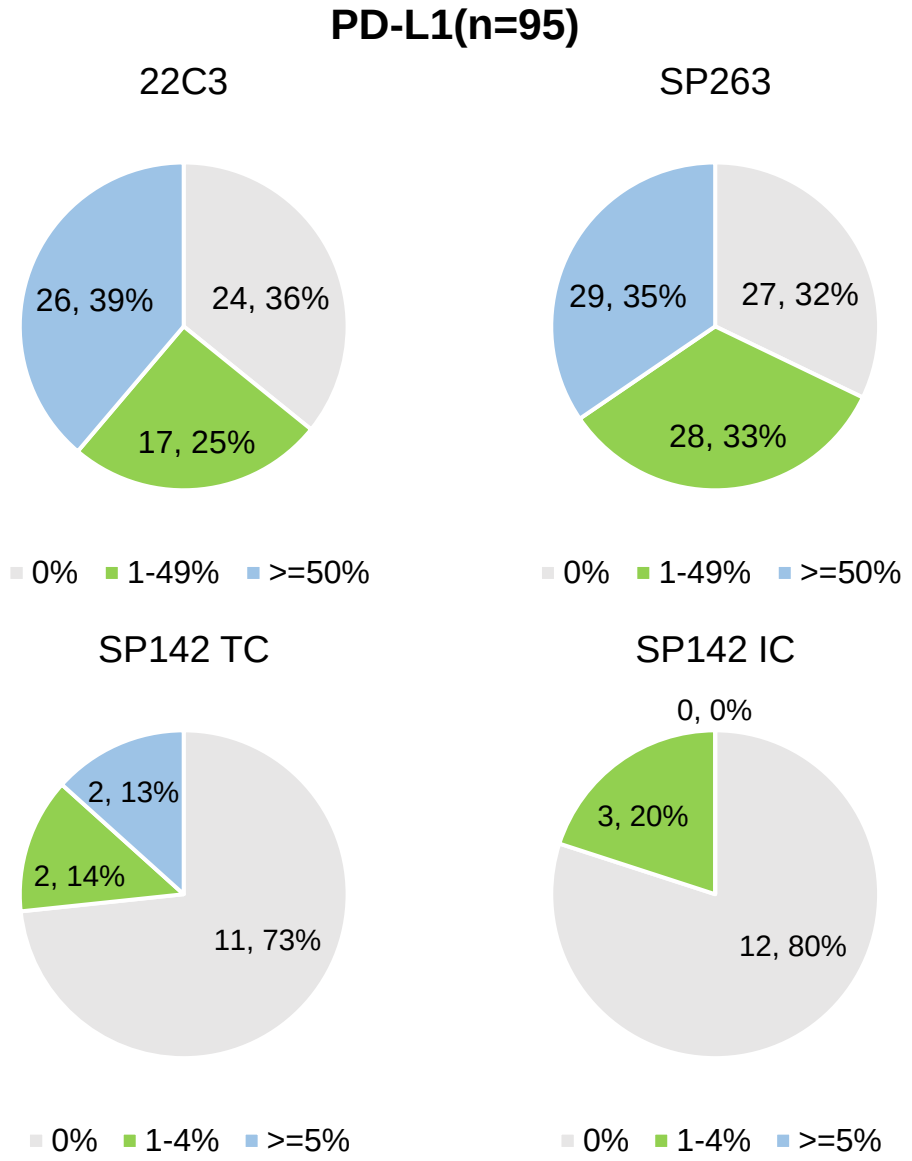
Highest VAF (variant allele frequency)

Standard deviation of VAF

Baseline Characteristics

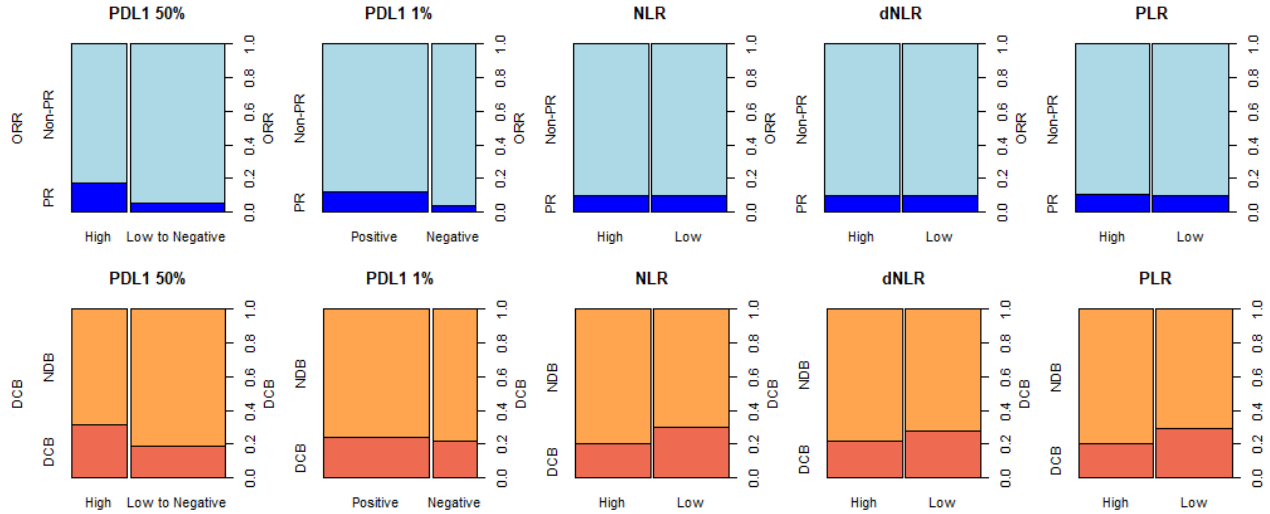
Characteristic	No. of Patients, n=100
Age (years, median, range)	65.0 (42-82)
Sex : Male / Female	84 / 16
ECOG PS : 0 /1 / 2	7 / 92 / 1
Smoking : Never / Ex / Current smoker	21 / 66 /13
Pack-years (median, range)	40.0 (1-100)
Histology	
Squamous cell carcinoma	39
Adenocarcinoma	52
NSCLC, NOS	7
Others [a]	2
Clinical stage (TNM 8th)	
IIIB/ IIIC	5 / 3
IVA/ IVB	51 / 39
Recurrence	2

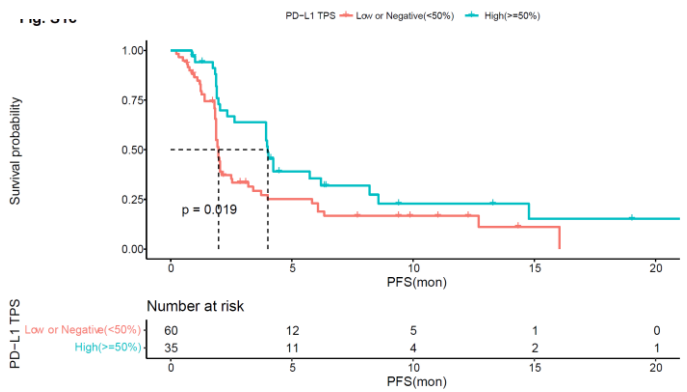


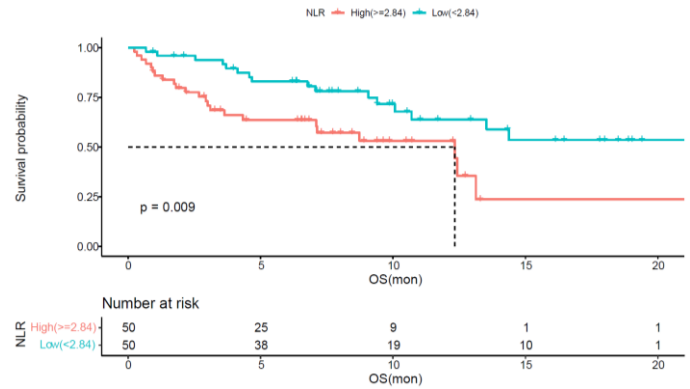


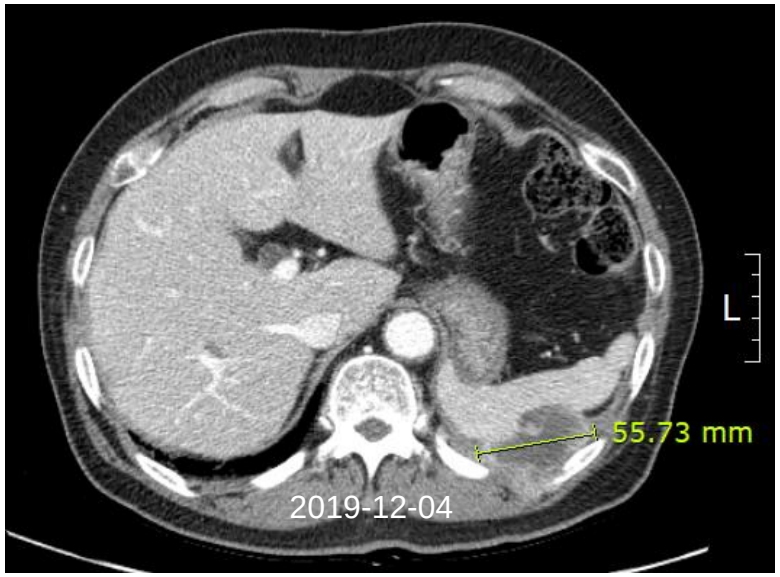
Efficacy of 2L+ Atezolizumab

Characteristic	No. of Patients, n=100
Atezolizumab cycles (median, range)	3 (1-32)
Reason for cessation of treatment	
Progression	64
Adverse events	9
Withdrawal of consent	6
Others	21
Best response	
CR / PR / SD(≥24wk) / SD(<24wk) / PD	0 / 10 / 15 / 18 / 54
NE	3
Objective response rate, %	10
Durable clinical benefit, %	25
Follow-up duration, mon (median, 95% CI)	12.3 (10.0-14.6)
PFS, mon (median, 95% CI)	2.1 (1.6-3.0)
DoR, mon (median, 95% CI)	Not reached
OS, mon (median, 95% CI)	13.1 (10.1-16.2)



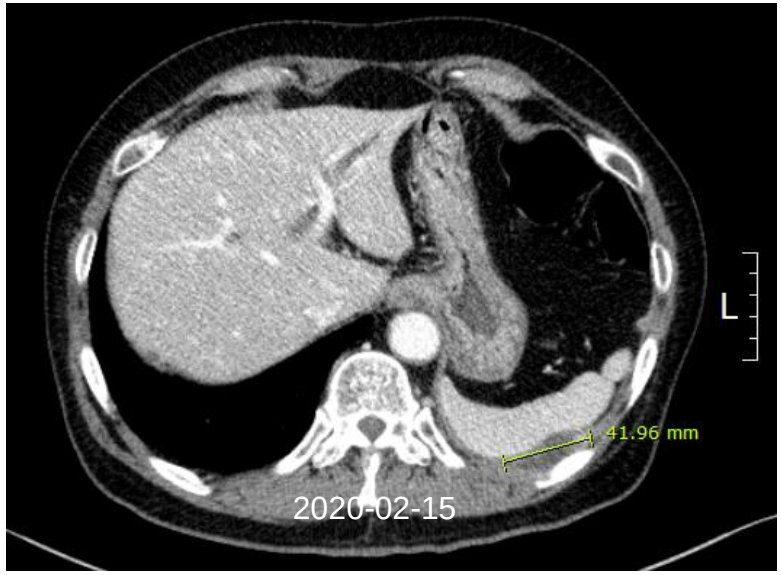






67 yo male
20 PYS, Ex-smoker
pADC, G2
EGFR/ALK(-/-)
PDL1[22C3]:100%,
[SP263](2+,70%),
[SP142]:TC0%, IC15%

Atezolizumab 3x



After C22 on 2021-03-09

ADC
EGFR/ALK/ROS1(-/-/-)
PDL1[22C3]:90%,
[SP263](3+,50%)

TREATMENT INDICATIONS	
Number of alterations with therapy indication	2 | 14 treatment(s) KRAS - p.G12C (Docetaxel, Selumetinib) PIK3CA - p.M1043V (Cetuximab)

TUMOR CHARACTERISTICS	
Tumor purity	Not Given
Microsatellite stability (MSI)	Probably stable
Tumor mutational burden (TMB)	34.6 Muts/Mb

GENE ALTERATIONS	
Genes with variant(s)	*CDH1, CTNNB1, FGFR1, KRAS, MET, PDGFRA, PIK3CA, RB1*
Number of reported variants	9
Genes with copy-gain	NONE
Genes with copy-loss	NONE
Gene fusion	NONE

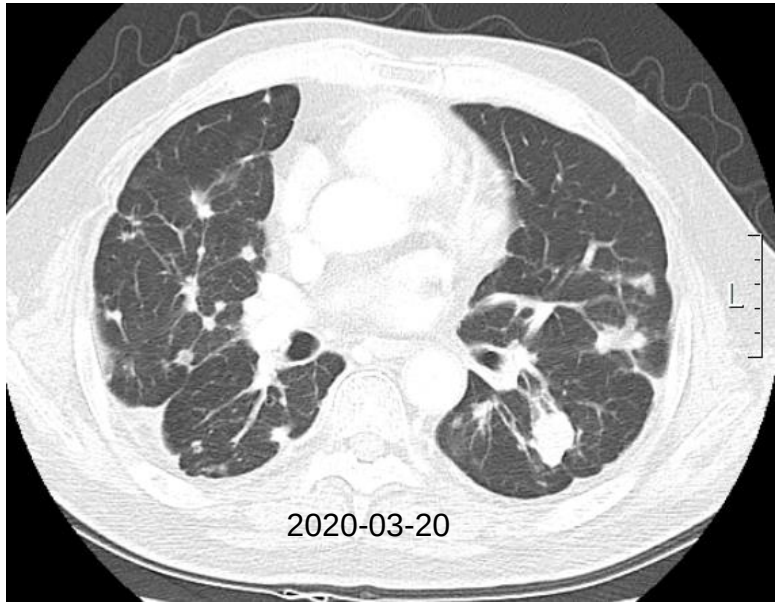
12 Disease-relevant genes with no reportable alterations: ***ALK, BRAF, BRCA1, BRCA2, EGFR, ERBB2, IDH1, IDH2, KIT, MYC, MYCN, NRAS***

TREATMENT INDICATIONS	
Number of alterations with therapy indication	0 | 0 treatment(s)

TUMOR CHARACTERISTICS	
Tumor purity	Not Given
Microsatellite stability (MSI)	Probably stable
Tumor mutational burden (TMB)	3.8 Muts/Mb

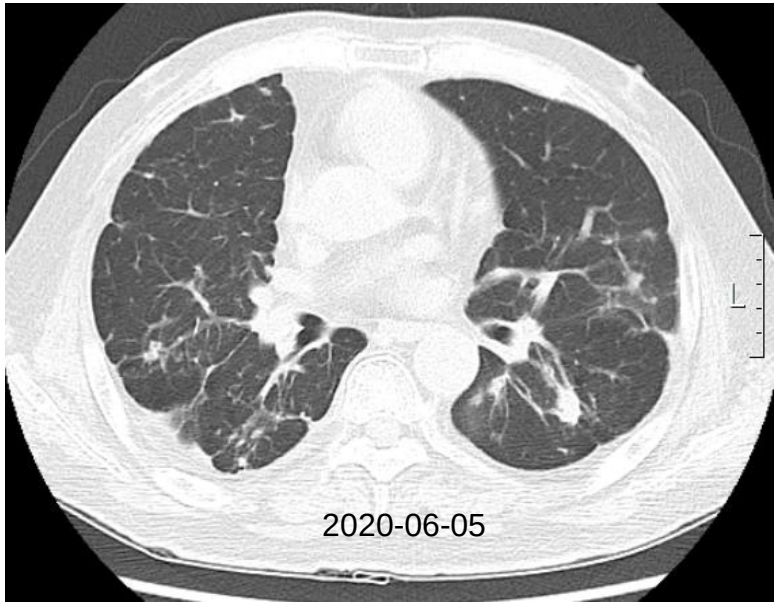
GENE ALTERATIONS	
Genes with variant(s)	NONE
Number of reported variants	1
Genes with copy-gain	NONE
Genes with copy-loss	NONE
Gene fusion	NONE

13 Disease-relevant genes with no reportable alterations: ***ALK, BRAF, BRCA1, BRCA2, EGFR, ERBB2, IDH1, IDH2, KIT, KRAS, MYC, MYCN, NRAS***



64 yo male
90 PYS, Ex-smoker
ADC, G1
EGFR/ALK/ROS1(-/-/-)
PDL1: NA

Atezolizumab 1x



TREATMENT INDICATIONS	
Number of alterations with therapy indication	0 | 0 treatment(s)

TUMOR CHARACTERISTICS	
Tumor purity	Not Given
Microsatellite stability (MSI)	Probably stable
Tumor mutational burden (TMB)	23.1 Muts/Mb

GENE ALTERATIONS	
Genes with variant(s)	*ERG, FGFR3, NF1, RAF1, TP53, VHL*
Number of reported variants	6
Genes with copy-gain	NONE
Genes with copy-loss	NONE
Gene fusion	NONE

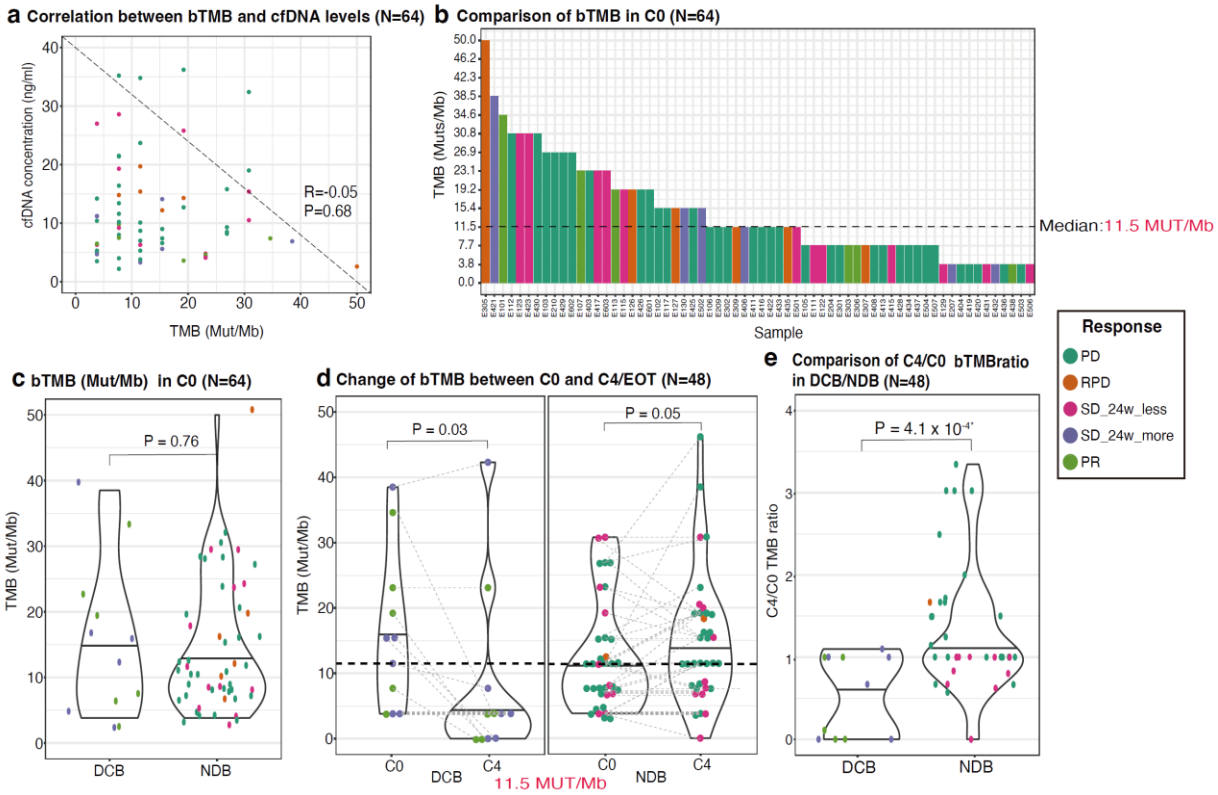
TREATMENT INDICATIONS	
Number of alterations with therapy indication	0 | 0 treatment(s)

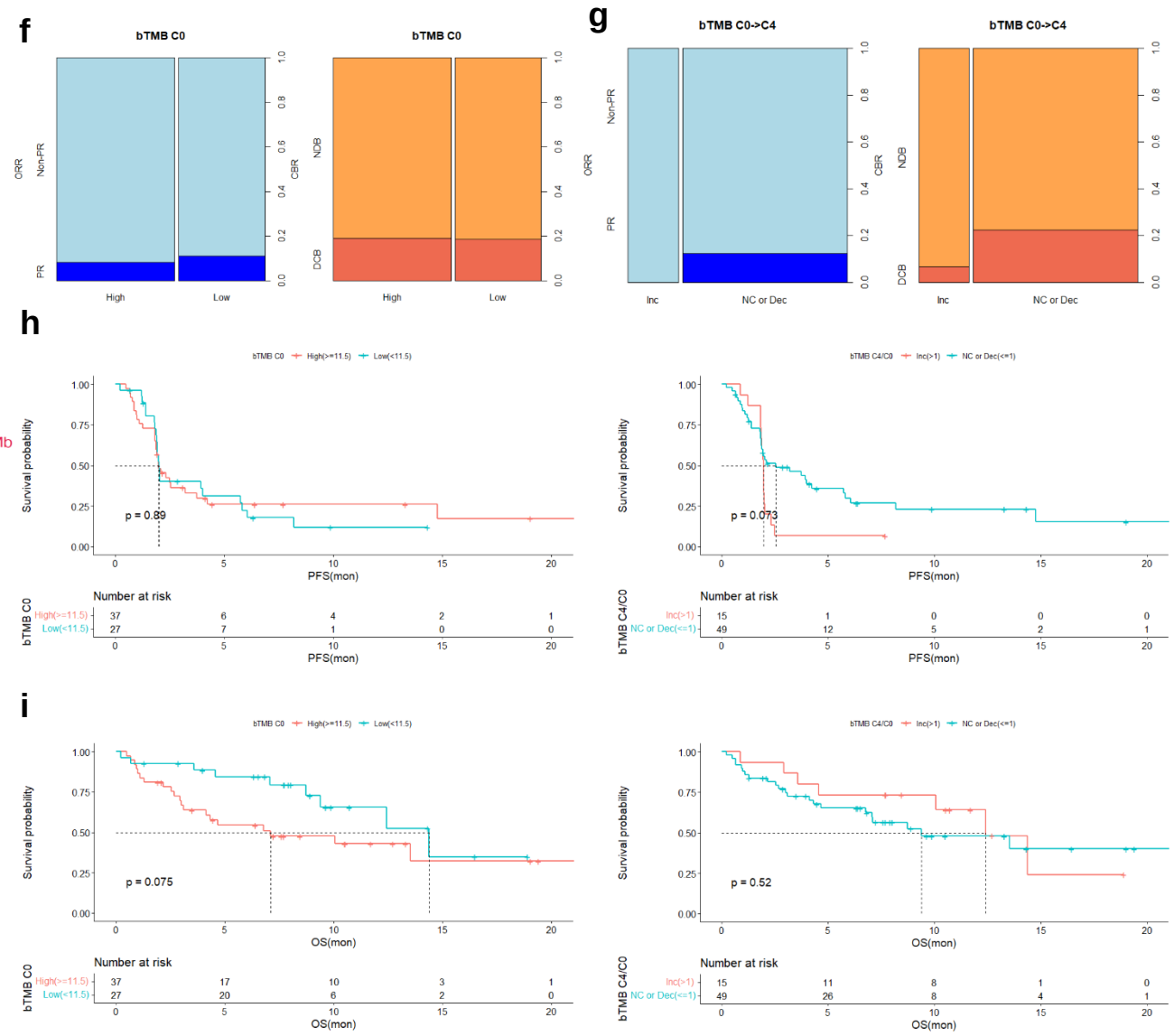
TUMOR CHARACTERISTICS	
Tumor purity	Not Given
Microsatellite stability (MSI)	Probably stable
Tumor mutational burden (TMB)	23.1 Muts/Mb

GENE ALTERATIONS	
Genes with variant(s)	*ERG, FGFR3, NF1, RAF1, TP53, VHL*
Number of reported variants	6
Genes with copy-gain	NONE
Genes with copy-loss	NONE
Gene fusion	NONE

2L+ Atezolizumab and blood TMB

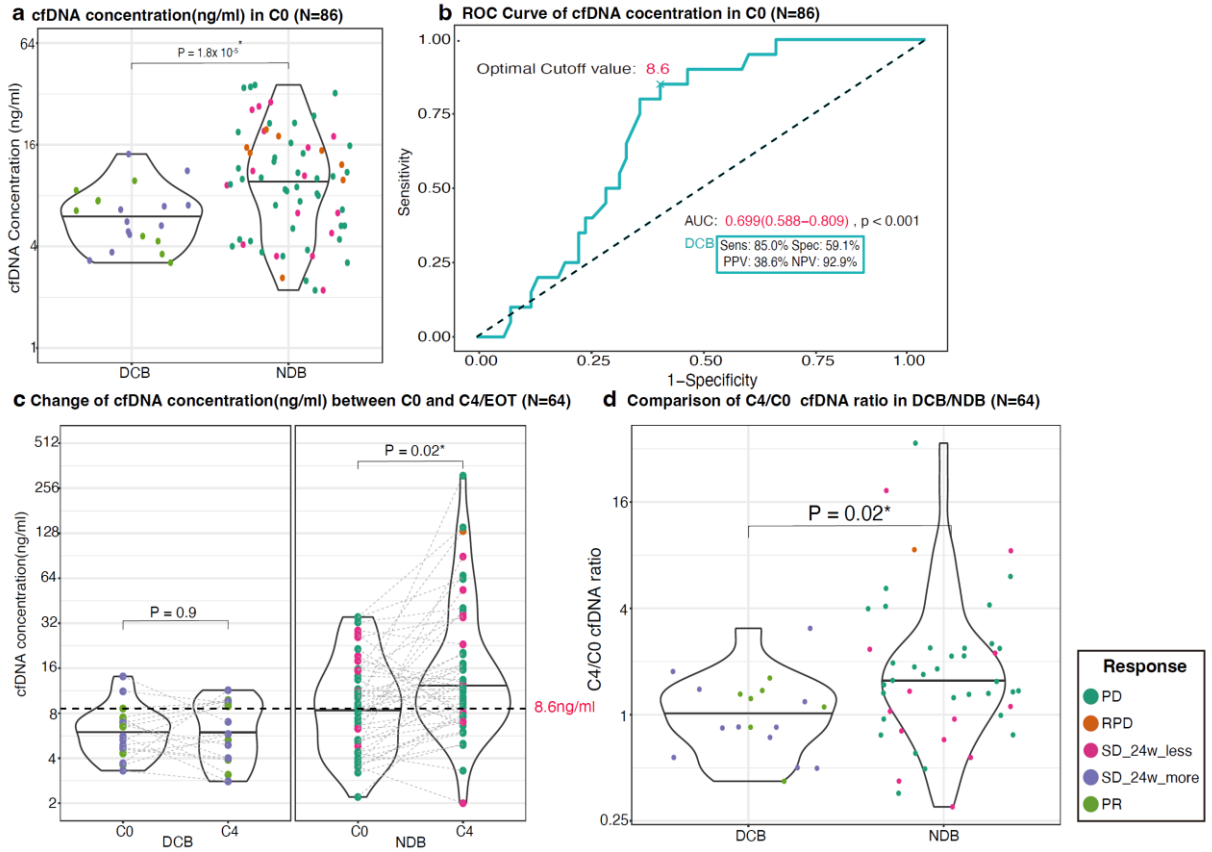
- NGS panel : CT-ULTRA (cfDNA > 10ng)
- **bTMB** = Whole exonic variations / Mb
- Whole exonic variations = synonymous + non-synonymous

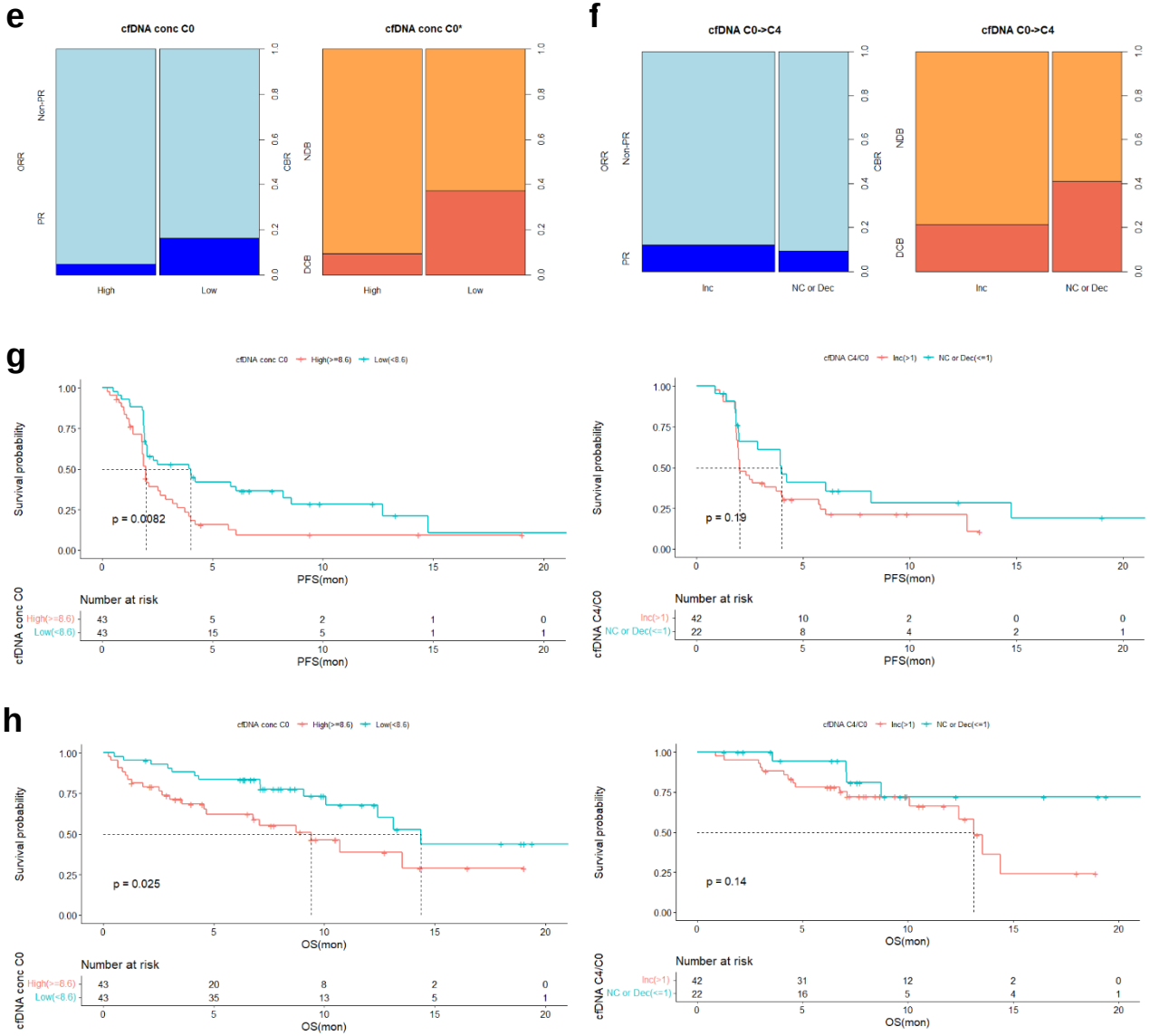




2L+ Atezolizumab and cfDNA concentration

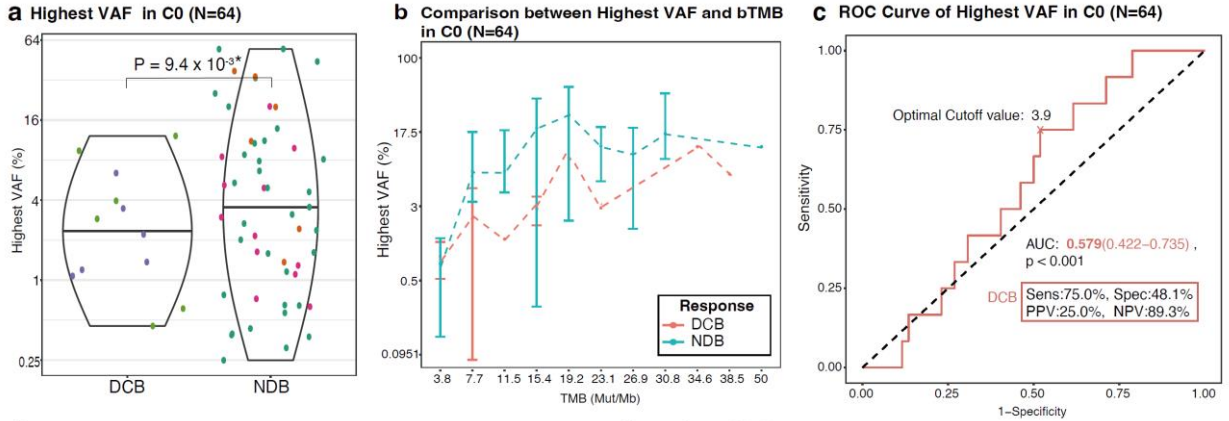
- Surrogate for tumor burden

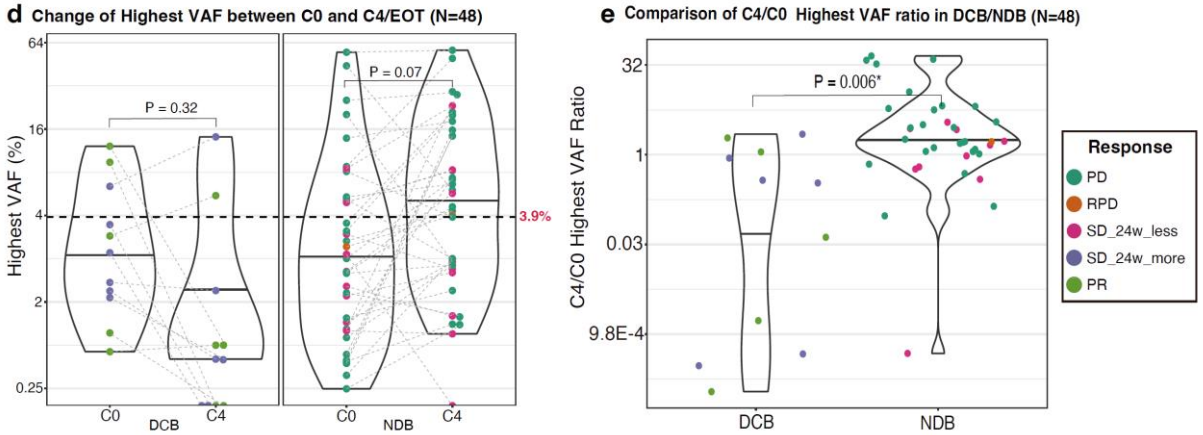


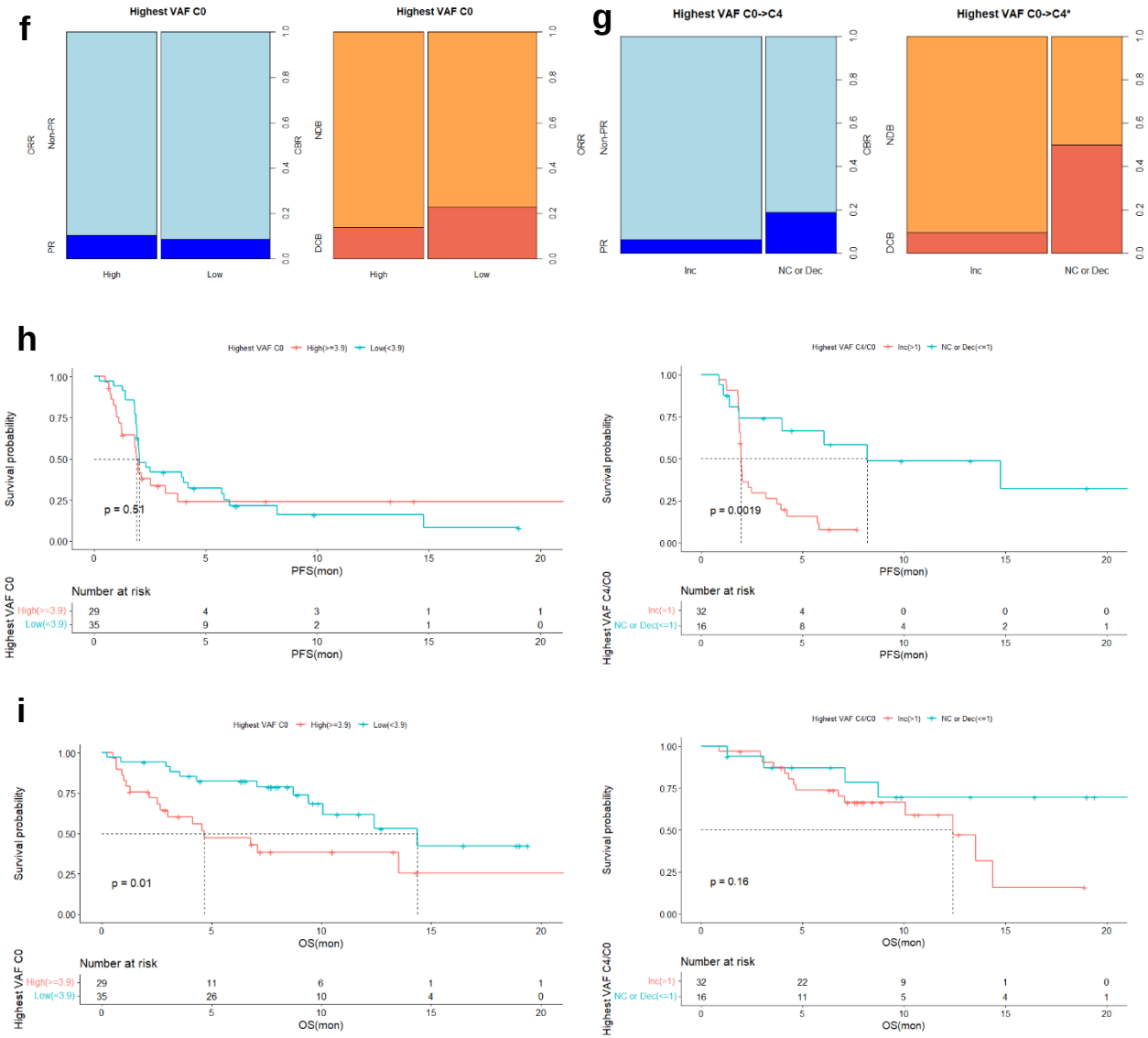


2L+ Atezolizumab and ctDNA hVAF

- **hVAF** (highest VAF) = VAF of the alteration with highest value
- Surrogate for tumor burden





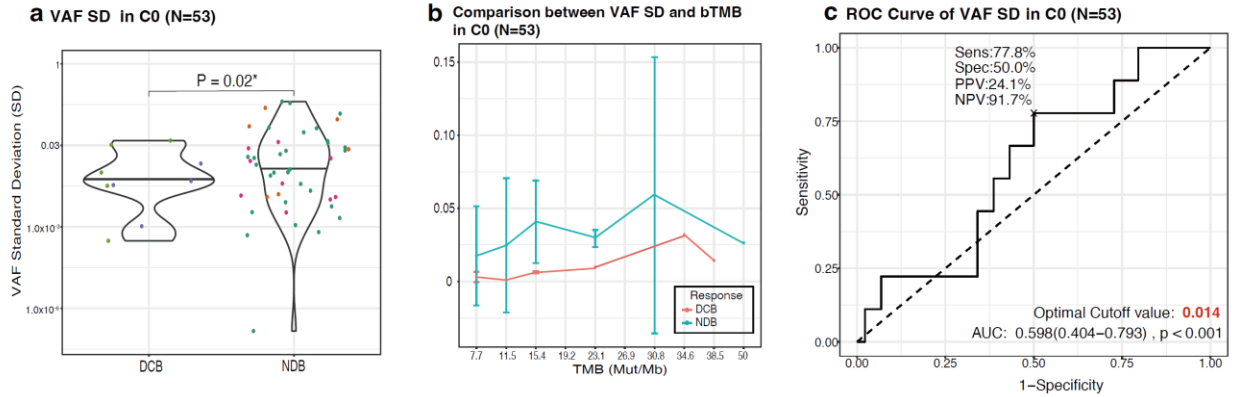


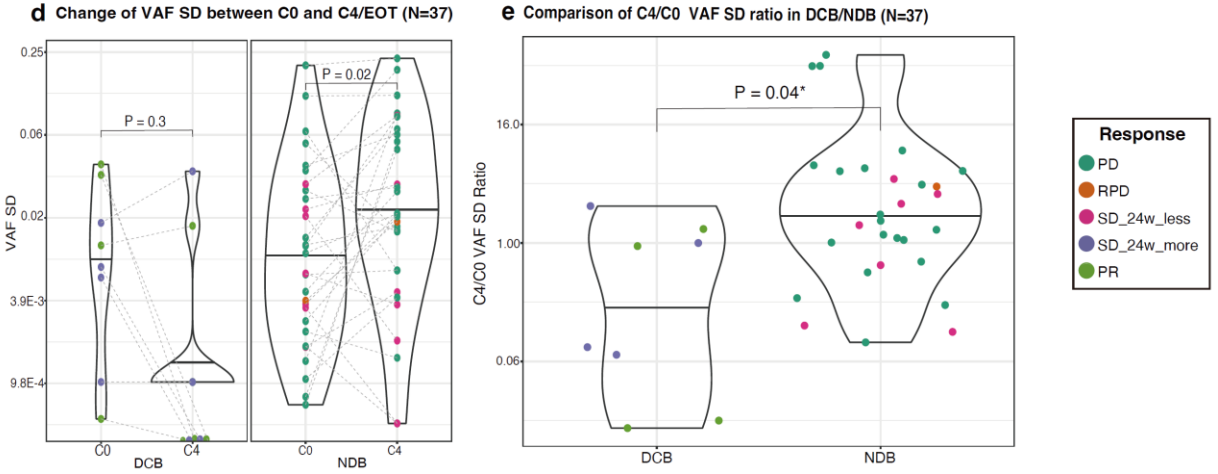
2L+ Atezolizumab and ctDNA VAFSD

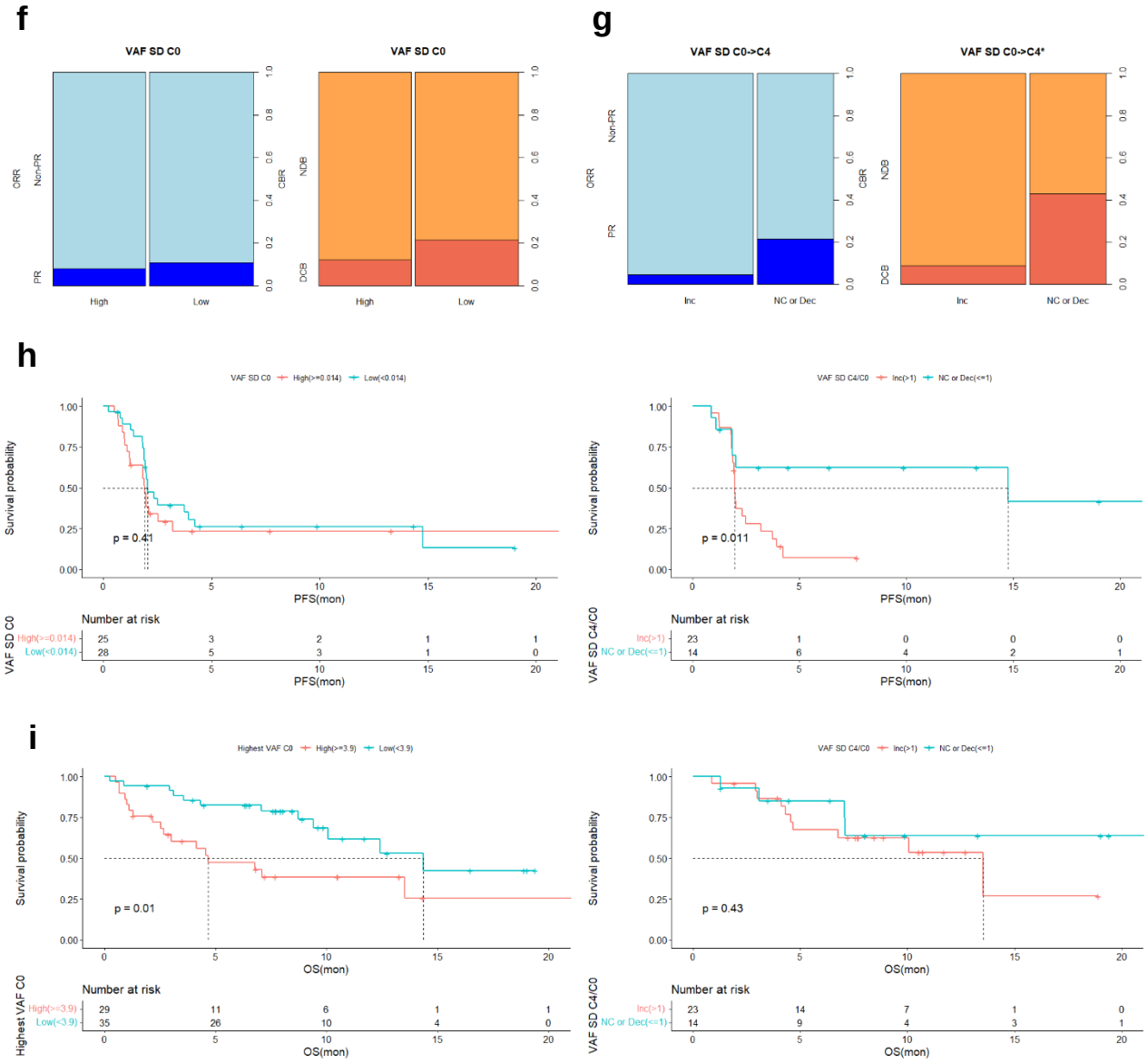
- **VAFSD** (standard deviation of VAF)

  = square root of variance of VAFs for alterations in each ctDNA

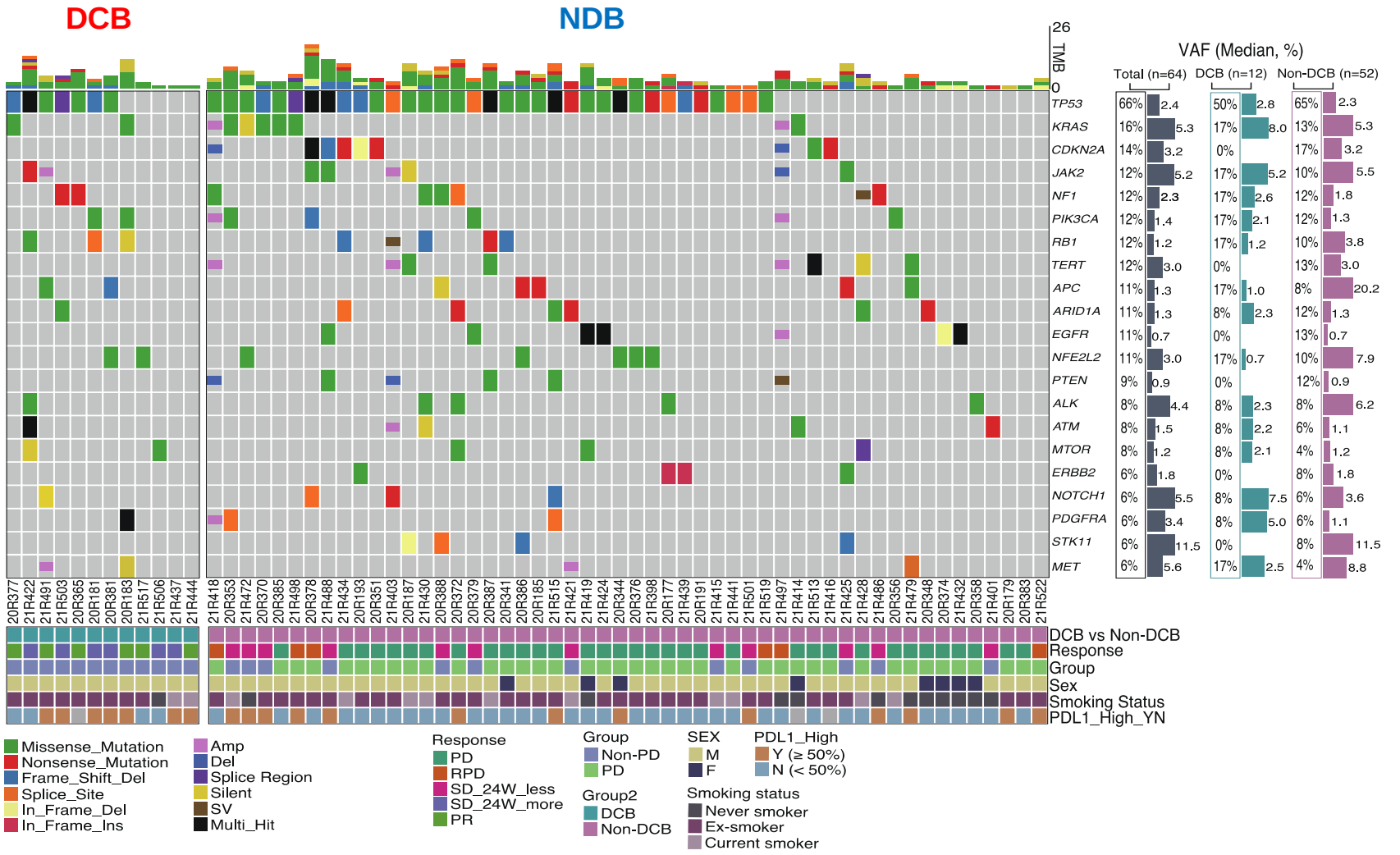
- Surrogate for intratumoral heterogeneity (ITH)

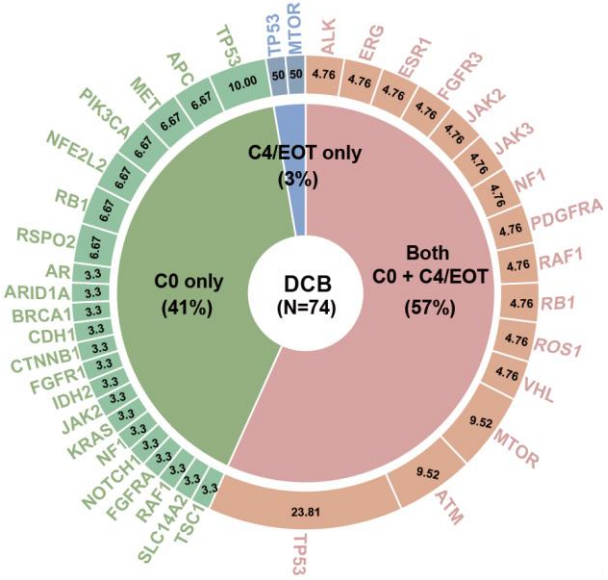


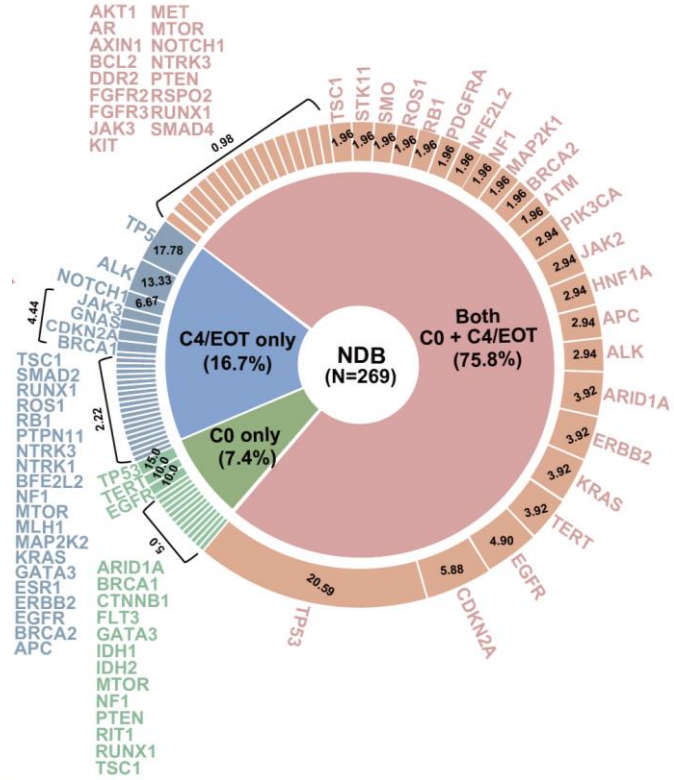




Mutation Profiling according to CBR

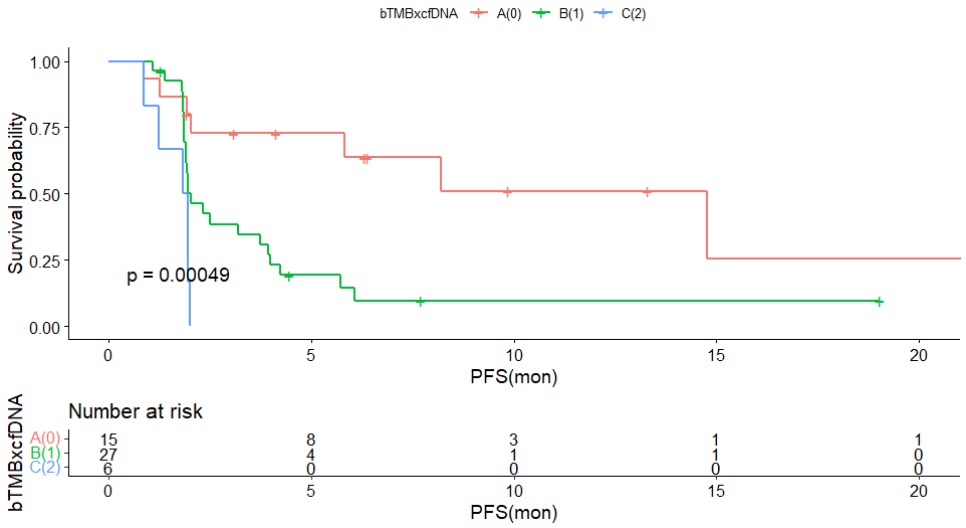






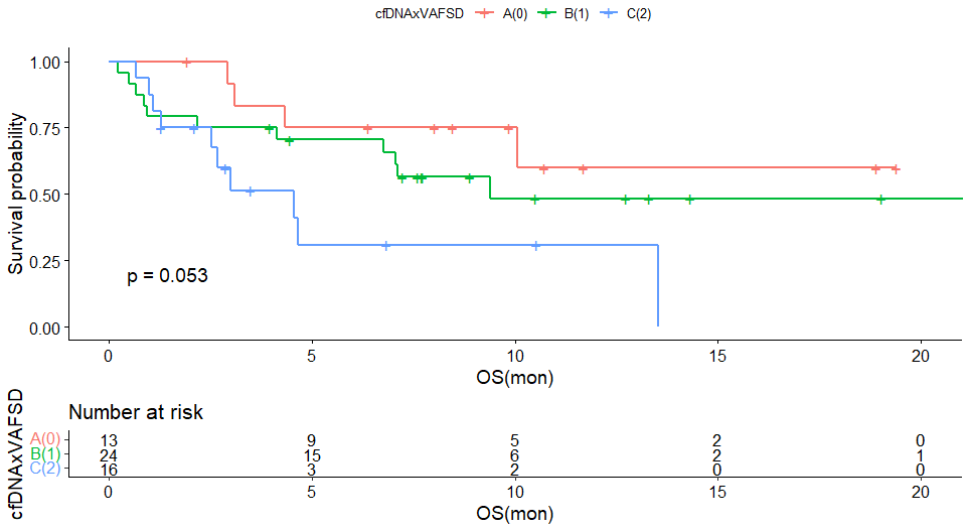
Multivariate Analysis for PFS and OS

PFS – multivariate



Score group	bTMB C0 to C4		cfDNA C0 (ng/mL)		HR (95% CI)	P
	Dec or NC(0)	Inc(1)	<8.6(0)	≥8.6(1)		
A(0)	0		0		1 (ref)	<0.001
B(1)	1		0		3.28 (1.37-7.87)	
	0		1			
C(2)	1		1		8.98 (2.73-29.56)	

OS – multivariate



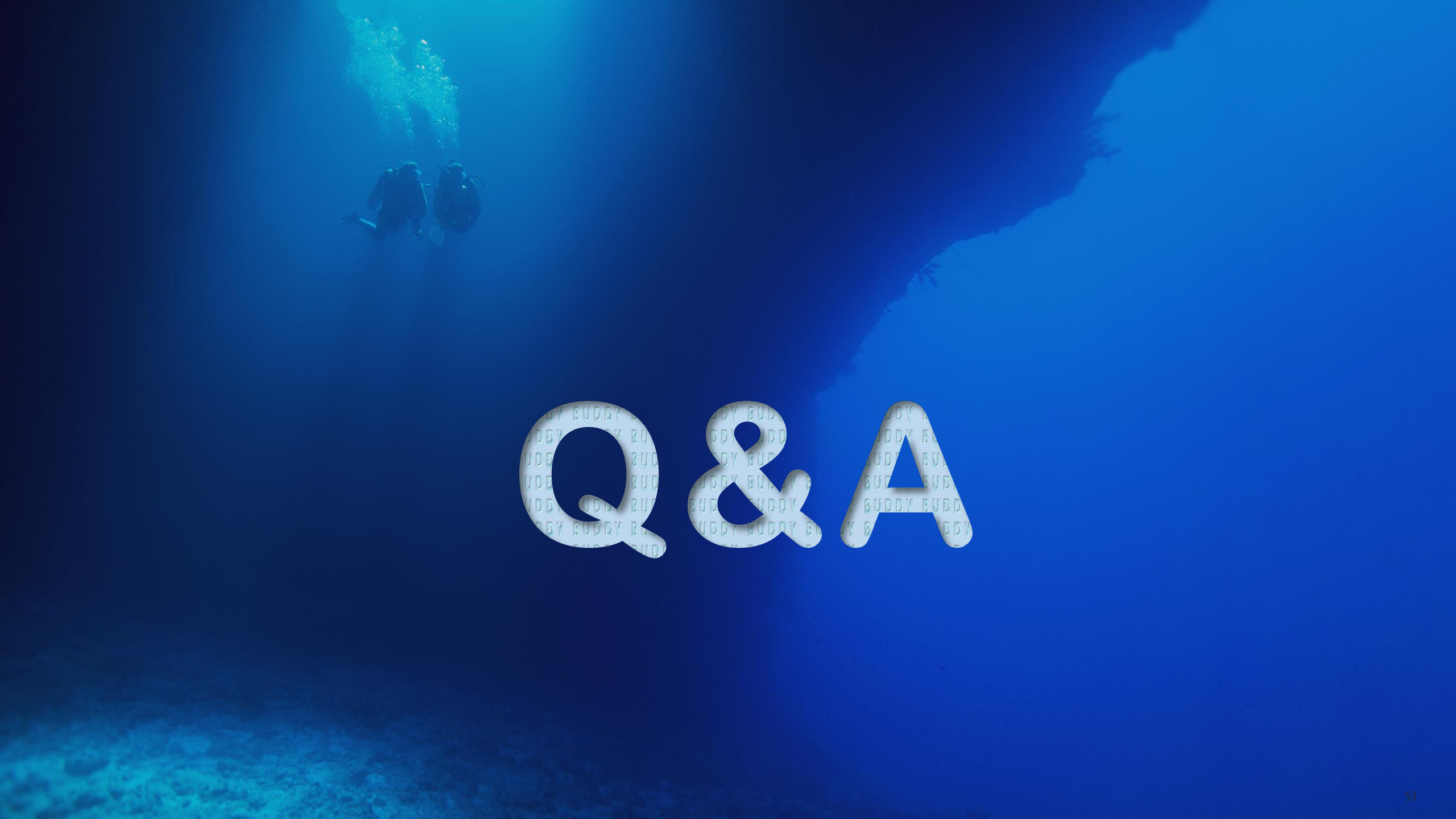
Score group	cfDNA C0 (ng/mL)		VAFSD C0		HR (95% CI)	P
	<8.6(0)	≥8.6(1)	<0.014(0)	≥0.014(1)		
A(0)	0		0		1 (ref)	0.053
B(1)	1		0		1.75 (0.56-5.50)	
	0		1			
C(2)	1		1		3.67 (1.13-11.88)	

Summary & Conclusion

- In previously treated advanced NSCLC, the baseline levels and dynamic change in blood-based biomarkers could predict the favorable treatment efficacy of atezolizumab
  - **Low C4/C0 bTMB ratio** (DCB, PFS)
  - **Low C0 cfDNA concentration** (DCB, PFS, OS), **Low C4/C0 cfDNA concentration ratio** (DCB)
  - **Low C0 hVAF** (DCB, OS), **Low C4/C0 hVAF ratio** (DCB, PFS)
  - **Low C0 VAFSD** (DCB, OS), **Low C4/C0 VAFSD ratio** (DCB, PFS)
- ctDNA-based biomarkers are easily-accessible by using validated NGS panel for NSCLC
- Comprehensive analysis of blood-based biomarkers could aid in identifying NSCLC patients who would benefit from ICI in the initial phase of treatment

Summary of BUDDY Trial

Milestone	Actual date	비고
계획서 개발 완료	2019-03-08 ~ 2019-05-31	약 3개월
연구자 미팅	2019-07-29	장소: 서울아산병원
화순전남대병원 신규과제 제출 및 승인	2019-07-26 ~	
서울아산병원 신규과제 제출 및 승인	2019-07-30	
그 외 4개 기관 신규과제 제출 및 승인	2019-08-21 ~ 2019-08-26	
Trial registration	2019-08-16 ~ 2019-10-22	CRIS No.: KCT0004363
임상연구 보험 가입	2019-12-12	중재연구로 인해 가입
전체 기관 요양급여 적용결정 승인	2019-12-09 ~ 2020-01-13	
전체 기관 개시미팅	2019-12-18 ~ 2020-03-23	
첫 대상자 등록(FPI)	2019-12-18	
마지막 대상자 등록(LPI)	2021-04-26	등록기간 약 16개월
추적기간	2021-10-29	LPI으로부터 약 6개월
Data cut off	2021-10-29	
Data review 및 query	2021-11-01 ~ 2021-11-30	
eCRF PI's signature	2021-12-01	
Data lock	2021-12-02	
연구자 미팅	2022-02-18	화상회의
Manuscript	2022-10-26	


Q&A