SUPPPLEMENTARY MATERIALS

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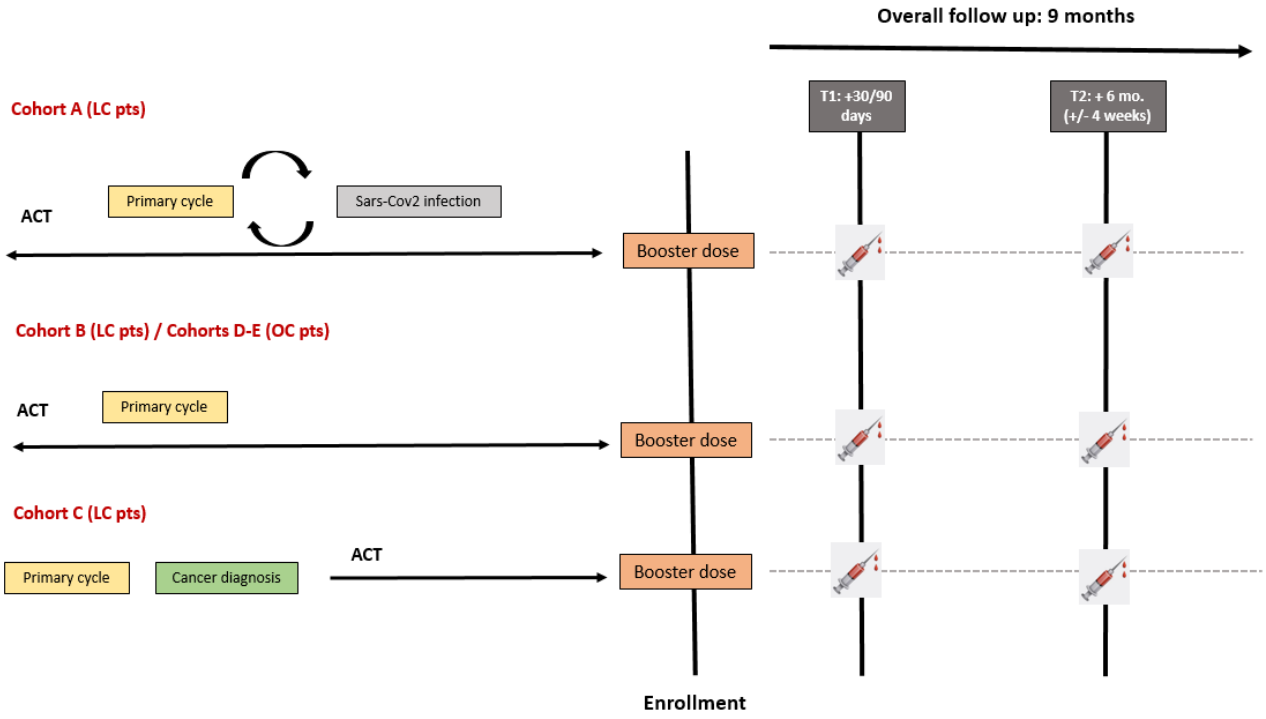


Figure S1 COVALENCE trial design

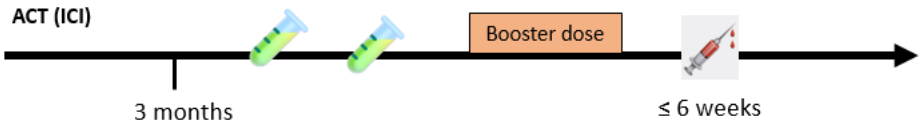


Figure S2 Study design and procedures for exploratory endpoint

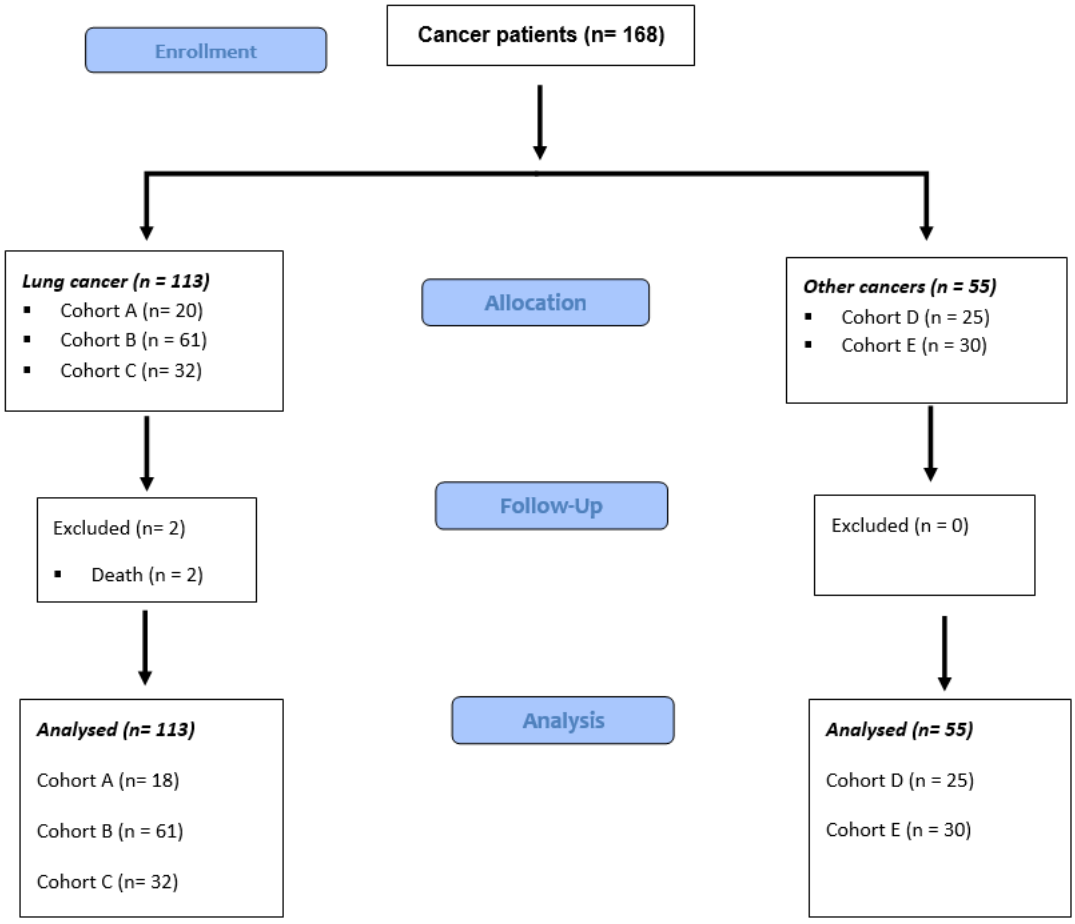


Figure S3 Consort diagram

Table S1. Primary vaccination details

	Cohort A n = 20	**Cohort B n = 61**	**Cohort C n = 32**	**Cohort D n = 25**	**Cohort E n = 30**
Vaccine used					
Comirnaty (BNT162b2)	15	53	23	25	28
Spikevax (mRNA-1273)	2	3	3	0	1
Vaxzevria (ChAdOx1-S)	2	5	5	0	1
Jcovden (Ad26.COV2.S)	1	0	1	0	0

Table S2. Baseline characteristics

Cohorts A-B-C-D-E	**Cohort D-E**
Age: p-value =0.83 (Kruskal Wallis test) Sex: p-value = 0.06 (Fisher test) ECOG: p-value = 0.58 (Fisher test) Line of therapy: p-value=0.02 (Fisher test)	Lung cancer histology: p value=0.22 (Fisher test)

Table S3. Outcomes and treatments of post-booster Sars-Cov-2 infection

	Cohort A n = 3	**Cohort B n = 8**	**Cohort C n = 14**	**Cohort D n = 7**	**Cohort E n = 8**
Outcomes					
Asymptomatic	1	2	9	0	6
Mild symptomatic	2	6	5	6	2
Hospitalization/UCI	0	0	0	1	0
Death	0	0	0	0	0
Treatment for Sars-Cov-2 infection					
None	3	7	9	0	6
Antibiotics	0	0	1	0	2
Antivirals	0	1	1	0	0
Monoclonal antibodies	0	0	3	1	0

Table S4. Kruskal-Wallis and Dunn's test results in COVALECE cohorts

Kruskal-Wallis test	***P-value: 0.0019***		
Dunn's test	*Mean rank diff.*	*Significance*	*Adjusted P value*
Cohort A vs. Cohort B	**39**	**Yes**	**0.01**
Cohort A vs. Cohort C	**42**	**Yes**	**0.02**
Cohort A vs. Cohort D	18	No	>0.99
Cohort A vs. Cohort E	16	No	>0.99
Cohort B vs. Cohort C	2.8	No	>0.99
Cohort B vs. Cohort D	-21	No	0.49
Cohort B vs. Cohort E	-23	No	0.23
Cohort C vs. Cohort D	-24	No	0.47
Cohort C vs. Cohort E	-26	No	0.25
Cohort D vs. Cohort E	-1.8	No	>0.99

Table S5. Rank correlation coefficient tests for age variable

Spearman's rank correlation coefficient		
Overall population	Rho -0.30 (95%CI = - 0.44 to - 0.16)*; p (two-tailed) <0.0001* Univariate regression analysis: beta=-0.038, p=0.0009; r2 = 0.07	
Uninfected patients	*Rho -0.21 (95%CI = - 0.38 to - 0.01); p (two-tailed) <0.0001* *Univariate regression analysis: beta=-0.030, p=0.06; r2 = 0.03*	
Kruskal-Wallis test P-value: 0.18		
Dunn's test	*Mean rank diff.*	*Significance*
<60 years vs. 60-69 years	5.9	No
<60 years vs. ≥70 years	14	No
Jonckheere-Terpstra test for trends: p=0.07		

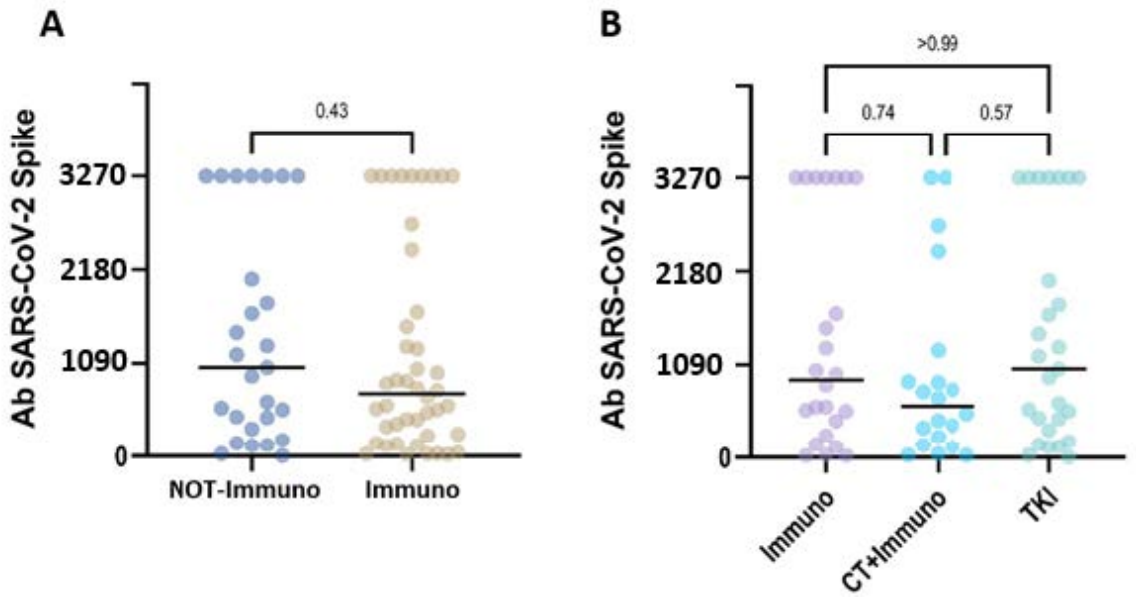


Figure S4 Comparison of anti-S IgG titres in LC patients

In the subgroup of LC patients, no statistically significant difference was observed in IO-treated patients compared to non-IO patients p=0.43) and no difference was also observed when comparing different treatments (IO vs CT+IO vs TKI; p=0.37).

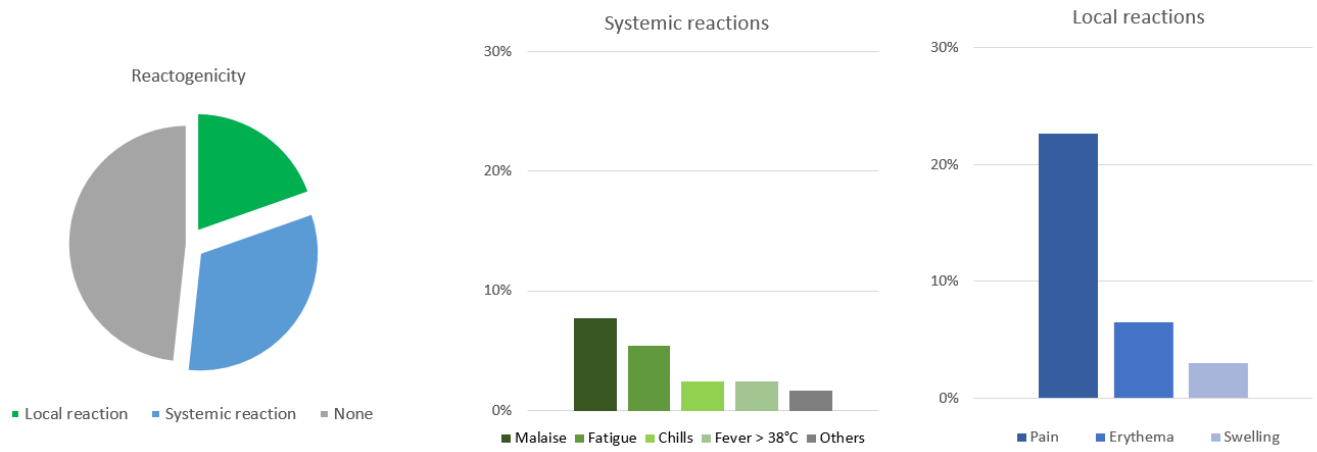


Figure S5. Reactogenicity of BNT-162b2 booster dose in uninfected patients

The majority of participants reported at least one local or systemic symptom after booster dose vaccination. Vaccine reactions have been graded according to CTCAE V.5. Any G3 AE were recorded.

Table S6. Characteristics of IO-treated included in exploratory cytokine analysis

	Lung cancer patients	**Other cancer patients**
	n = 47 (69.1%)	**n = 21 (30.9%)**
Age, years Median (range)	64 (44 -79)	65 (34 – 83)
Sex Male Female	30 (63.8%) 17 (36.2%)	14 (66.6%) 7 (33.4%)
Lung cancer histology Adenocarcinoma Squamous SCLC	38 (55.9%) 3 (4.4 %) 6 (8.8 %)	NA
Other cancers (primary) Melanoma Renal cell carcinoma HNSCC Merkel cell carcinoma Colorectal cancer	NA	9 (13.2%) 5 (7.3%) 3 (4.45%) 2 (3%) 2 (3%)
Treatment CHT + IO Single agent IO Combination IO	12 (25.5%) 33 (70.3%) 2 (4.2%)	- 17 (81%) 4 (19%)
Line of therapy 1st ≥ 2nd	37 (75.6%) 12 (24.4%)	14 (66.6%) 7 (33.4%)
Time from Treatment start to BD administration 3-6 months 6-12 months ≥12 months	10 (21%) 10 (21%) 27 (58%)	2 (9.5%) 6 (28.5%) 13 (62%)
List of abbreviations: CT = chemotherapy; IO = immunotherapy; BD: booster dose		

Table S7. Adverse events in patients with highest cytokine fold change

Patient ID	Alt CKs	Fold change	Diagnosis	IO start	Post-BD sample	AE	CTCA grade	Survival
Co-C6	IL-2R IL-6	1.8 4.3	Lung adc	3-6 mo.	+ 10 days	None	NA	Alive
Co-B13	IL-2R TNF-α	1.5 3.4	SCLC	> 12 mo.	+ 18 days	Fatigue	G1	Alive
Co-B2	IL-2R IL-6 TNF-α	1.5 2.2 2.0	Lung adc	> 12 mo.	+ 8 days	None	NA	Alive
Co-B61	IL-2R TNF-α	1.77 2.0	Lung adc	> 12 mo.	+21 days	Fatigue	G1	Alive
Co-E3	IL-2R IL-10	1.6 2.8	HNSCC	6-12 mo.	+26 days	None	NA	Alive
Co-E16	IL-2R IL-10	2.0 8.6	Melanoma	> 12 mo.	+ 34 days	Malaise	G1	Alive
Co-E27	IL-2R IL-6 TNF-α IL-10	3.0 6.9 1.9 2.14	Melanoma	> 12 mo.	+ 24 days	Malaise	G1	Alive

List of abbreviations: Alt CKs= altered cytokine(s); BD = booster dose; AE = adverse event

IO start = time from immunotherapy treatment start to BD