Příklady publikací

Opdivo (Nivolumab), NSCLC

- Brahmer J, et al. Nivolumab versus Docetaxel in Advanced **Squamous**-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373:123-35
  (**CheckMate 017**)

Ultibro (Indacaterol + Glycopyrronium), COPD

- Wedzicha J A, et al. Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. N Engl J Med 2016; 374:2222-2234
  (**FLAME**)

Spiolto (Tiotropium + Olodaterol), COPD

- Buhl R, Benefits of tiotropium + olodaterol over tiotropium at delaying clinically significant events in patients with COPD classified as GOLD B. Poster presented at the American Thoracic Society International Conference, San Francisco, California, USA, May 13–18, 2016

MU
IBA

Opdivo (Nivolumab)

- Imunoterapie rakoviny
- “-mab” = monoclonal antibody
- Inhibitor kontrolního bodu (checkpoint) imunitní reakce PD-1
  - PD-1 = protein exprimovaný na aktivovaných T-buňkách
  - PD-L1 (PD-L2) = programmed cell death 1 ligand 1, naváže-li se na PD-1, deaktivuje T-buňky. Produkován mnoha nádorovými buňkami.
  - Nivolumab blokuje vazbu PD-L1 a PD-L2 na PD-1 → T-buňky zůstávají aktivovány
- Schválen poprvé 12/2014 (FDA), BMS
- Melanom, 2. linie nemalobuněčného karcinomu plic (NSCLC) a 2. linie karcinomu ledvin (RCC)

- Registrační studie (“pivotal trial”)
- Tato studie + CheckMate 067 (fáze II) → 03/2015 schválen FDA
  - “for the treatment of patients with metastatic squamous-cell NSCLC who had disease progression during or after platinum based chemotherapy”

Ultibro (Indacaterol + Glycopyrronium)

- Chronická obstrukční plicní nemoc (CHOPN, COPD)
- Schválen (poprvé) 10/2015 (FDA), Novartis
- Registrován jako udržovací bronchodilatační léčba *ke zmírnění symptomů* u dospělých pacientů s CHOPN
- Prokázáno významné zlepšení funkce plic (FEV_1)

- Prevence exacerbací:
  - long-acting beta-agonists (LABA) + glucocorticoid (e.g. salmeterol–fluticasone) nebo
  - long-acting muscarinic antagonist (LAMA), e.g. tiotropium
- Lze kombinaci LABA + corticoid nahradit kombinací LABA + LAMA?
- Tato studie součástí "Phase III IGNITE clinical trial program"
  - 11 studií: **ILLUMINATE, SHINE**, BRIGHT, ENLIGHTEN, *SPARK*, BLAZE, ARISE, BEACON, RADIATE, LANTERN, FLAME
  - >10 000 pacientů

MU IBA

Regulatorní kontext

- Studie fáze III: typicky $\alpha=0.05$ pro oboustranný test, $\alpha=0.025$ pro jednostranný test (srovnání s placebem)
- Jedna studie: 5% pravděpodobnost chybného závěru (schválení neúčinného léku)
- Dvě nezávislé studie: 0.05*0.05=0.0025, t.j. 0.25% pravděpodobnost chybného závěru

- FDA's interpretuje *U.S. Food Drug and Cosmetic Act 1962*, "*adequate and well-controlled investigations*“:
  At least two “adequate and well-controlled” trials, each convincing on its own, can establish effectiveness.

Spiolto (Tiotropium + Olodaterol)

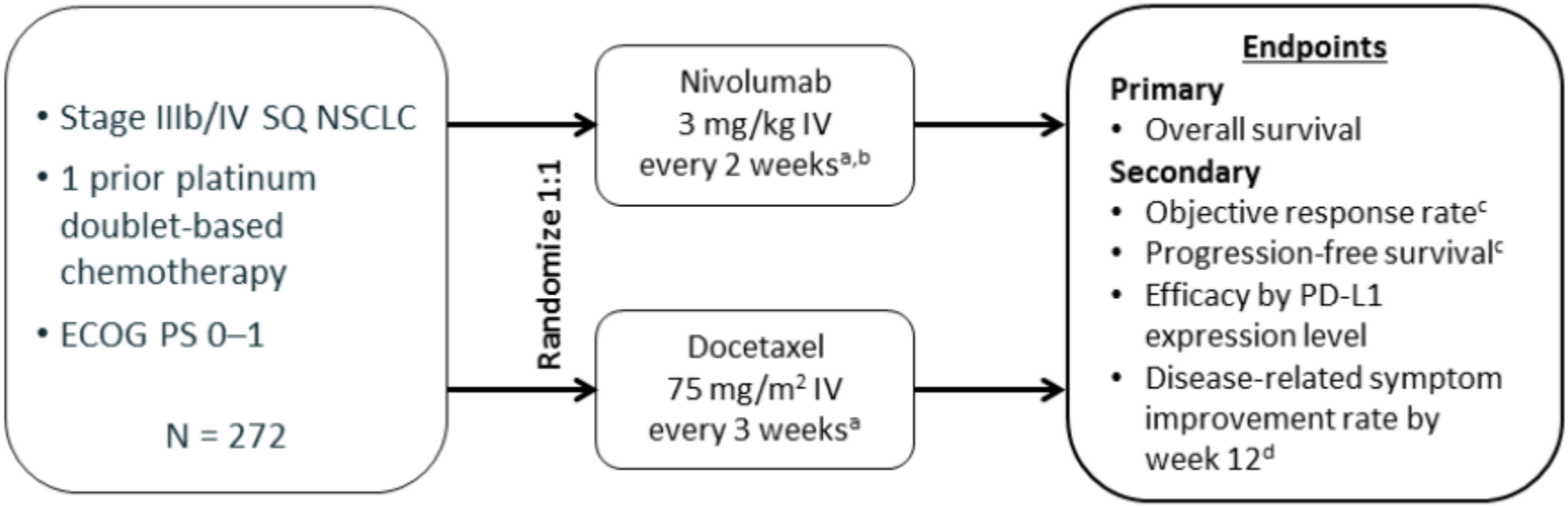
- Chronická obstrukční plicní nemoc (CHOPN, COPD)
- Boehringer Ingelheim
- LAMA + LABA
- Dvě registrační studie (TONADO 1 + 2), prokázáno významné zlepšení funkce plic (FEV1)
- Registrován jako udržovací bronchodilatační léčba k úlevě od příznaků u dospělých pacientů s CHOPN

- Prodloužení doby do zhoršení?
  - Doba do klinicky signifikantní události (zhoršení FEV_1, SGRQ skóre, exacerbace)
- Post-hoc analýza
- “Further studies are warranted to prospectively study this effect.”

NIVOLUMAB VS DOCETAXEL IN ADVANCED SQUAMOUS-CELL NSCLC (CHECKMATE 017)

Design

- Randomizovaná
- 1:1 nivolumab nebo docetaxel
- Pacienti léčeni do progrese nebo ukončení léčby kvůli toxicitě nebo jiným důvodům



Cíle/Endpointy

	Objective	Endpoint
Primary	To compare the OS of nivolumab vs docetaxel in subjects with squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy	OS (overall survival)
Secondary	To compare the ORR of nivolumab vs docetaxel	ORR (objective response rate)
	To compare the PFS of nivolumab vs docetaxel	PFS (progression-free survival)
	To evaluate whether PD-L1 expression is a predictive biomarker for OS, ORR or PFS	PD-L1 expression
	…	
Exploratory	…	

Endpointy se stanovují dle standardních přístupů v dané indikaci, pro onkologii je obecně akceptován OS, považován ze objektivní a robustní endpoint, v některých indikacích byl jako "surrogate" prokázán a akceptován PFS (výjimečně Time to progression, TTP) – jeden z bodů diskusí mezi sponzorem a FDA/EMA

MU IBA

Cíle/Endpointy

- OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive.
- ORR (**as determined by the investigator**) is defined as the number of subjects whose *best confirmed objective response (BOR)* is either a CR or PR divided by the number of randomized subjects.
  - BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first.
- PFS is defined as the time from randomization to the date of the first documented tumor **progression as determined by the investigator** (per RECIST 1.1), or death due to any cause.

Endpointy se odkazují na standardní definice a guideliny (solidní nádory RECIST 1.1)
Zde lokální vyhodnocení odpovědi (by the investigator), je-li PFS primární endpoint, častěji centrální čtení → standardizace

MU IBA

Vyhodnocování odpovědi

- Růst nádoru nelze sledovat kontinuálně, pro ORR a PFS: radiologická vyšetření v určitých intervalech
- Zde první vyšetření po 9ti týdnech, další potom vždy po 6
- Interval se určuje dle indikace (různá rychlost): 6, 8, 12 týdnů
- První interval 9 týdnů: zkušenosti s přípravkem/imunoterapií (počáteční růst nebo zánětlivá reakce)

Modifikace

ment. Initially, confirmed objective response rate was also a primary end point, but on the basis of mature data regarding the objective response rate in an expanded cohort of patients with NSCLC who had been treated in the phase 1b study MDX-1106-03 (ClinicalTrials.gov number, NCT00730639),[13] the current trial was amended before the planned interim analysis to make overall survival the sole primary end point. The rate of investigator-assessed confirmed objective response was modified to be the first secondary end point. Additional

Table 8.1: Schedule of Analyses

	Interim analysis for OS Final analysis for ORR	Final analysis for OS
Conditions	A minimum follow-up of 6 months and at least 123 deaths	At least 189 deaths
Expected timing	18 months (12 months accrual + 6 months follow-up)	24 months (12 months accrual + 12 months follow-up)
Alpha level	Final ORR at 0.01 level	
	Interim OS at 0.016 level[a]	Final OS at 0.035 level[a]

[a] Using Lan-DeMets α spending function with O'Brien and Fleming type of boundary when exactly 146 deaths are observed at the interim analysis for OS.

MU IBA

Co-primary endpoints

Problém mnohonásobného testování:

- Je-li každý endpoint testován na hladině α=0.05, celková pravděpodobnost chybného závěru (předpoklad nezávislosti):

  P(chybný závěr ohledně OS nebo chybný závěr ohledně ORR) = 0,05 + 0,05 - $0,05^2$ = **0,0975**

Co-primary edpoints

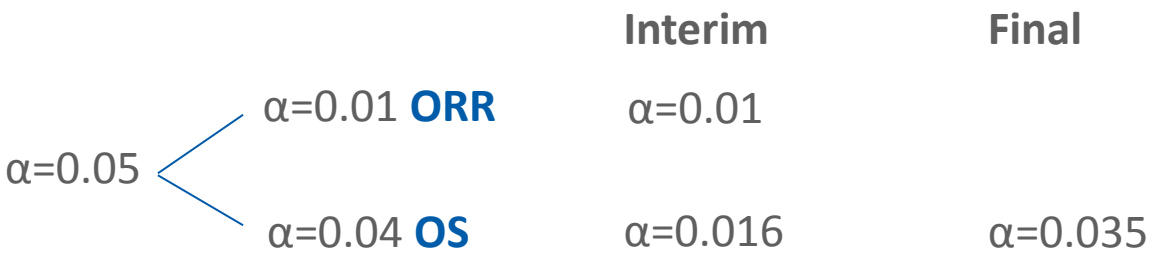


Table 8.1: Schedule of Analyses		
	Interim analysis for OS Final analysis for ORR	Final analysis for OS
Conditions	A minimum follow-up of 6 months and at least 123 deaths	At least 189 deaths
Expected timing	18 months (12 months accrual + 6 months follow-up)	24 months (12 months accrual + 12 months follow-up)
Alpha level	Final ORR at 0.01 level	
	Interim OS at 0.016 level[a]	Final OS at 0.035 level[a]

[a] Using Lan-DeMets α spending function with O'Brien and Fleming type of boundary when exactly 146 deaths are observed at the interim analysis for OS.

MU IBA

Co-primary edpoints

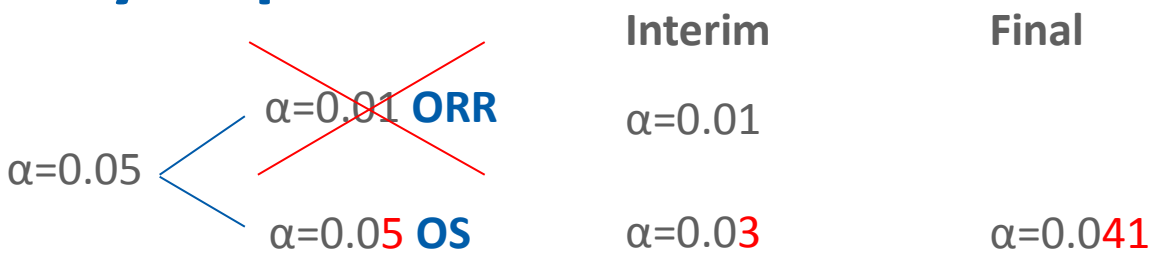


Table 8.1-1: Key Parameters of the Overall Survival Analysis				
	Analysis	Timing	Critical Value for significance	Probability for declaring superioritiy Under H1/H0
α= 0.05; Power=90% **Docetaxel arm: Exponential distribution with median OS= 7 months** **Nivolumab arm: Piecewise mixture distribution with median OS= 8.9 months**	Interim analysis for superiority	196 deaths	p < 0.030	55% / 3%
	Final analysis for superiority	231 deaths	p < 0.041	35%/ 2%
Total probability to declare superiority Under H1/H0				90% / 5%

Randomizace

- Stratifikovaná
  - prior use of paclitaxel therapy (yes vs. no)
  - geographic region (US/Canada vs. Europe vs. rest of the world)
  - 2x3 = 6 strat
- Zajistí rovnoměrné rozložení do skupin dle strat. faktorů
- Strata: malé množství významných prognostických faktorů

US/Canada Pacli YES	US/Canada Pacli NO	Europe Pacli YES	Europe Pacli NO	ROW Pacli YES	ROW Pacli NO
Nivo	Doce	Doce	Nivo	Nivo	Nivo
Doce	Nivo	Doce	Doce	Doce	Nivo
Doce	Doce	Nivo	Doce	Nivo	Doce
Nivo	Nivo	Nivo	Nivo	Doce	Doce
…	…	…	…	…	…
…	…	…	…	…	…

Zaslepení

- Open label
- Protokol zdůvodňuje tím, že zkoumané léky mají jiný “mechanisms of action”, tedy i podobné AE by se měly léčit jiným způsobem
- Podává se v jiných intervalech
- Chemoterapie vs imunoterapie

- Je vidět, že open-label studie jsou za určitých okolností přijatelné (randomizace je podstatnější než zaslepení)
- I v open-label studiích dnes sponzor zpravidla zůstává zaslepen, je-li to možné

MU IBA

Populace

- **Intention-to-treat (ITT)**: all the patients who underwent randomization,
  - analyzováno na základě léčby přiřazené při randomizaci, bez ohledu na skutečnost
- **Safety**: all the treated patients (who received at least one dose of study drug)
  - analyzováno na základě léčby skutečně obdržené, bez ohledu na randomizaci
- **Jindy: per-protocol population**, tj. všichni pacienti, kteří dodrželi protokol (žádné odchylky od protokolu), min. exposure

Statistická analýza

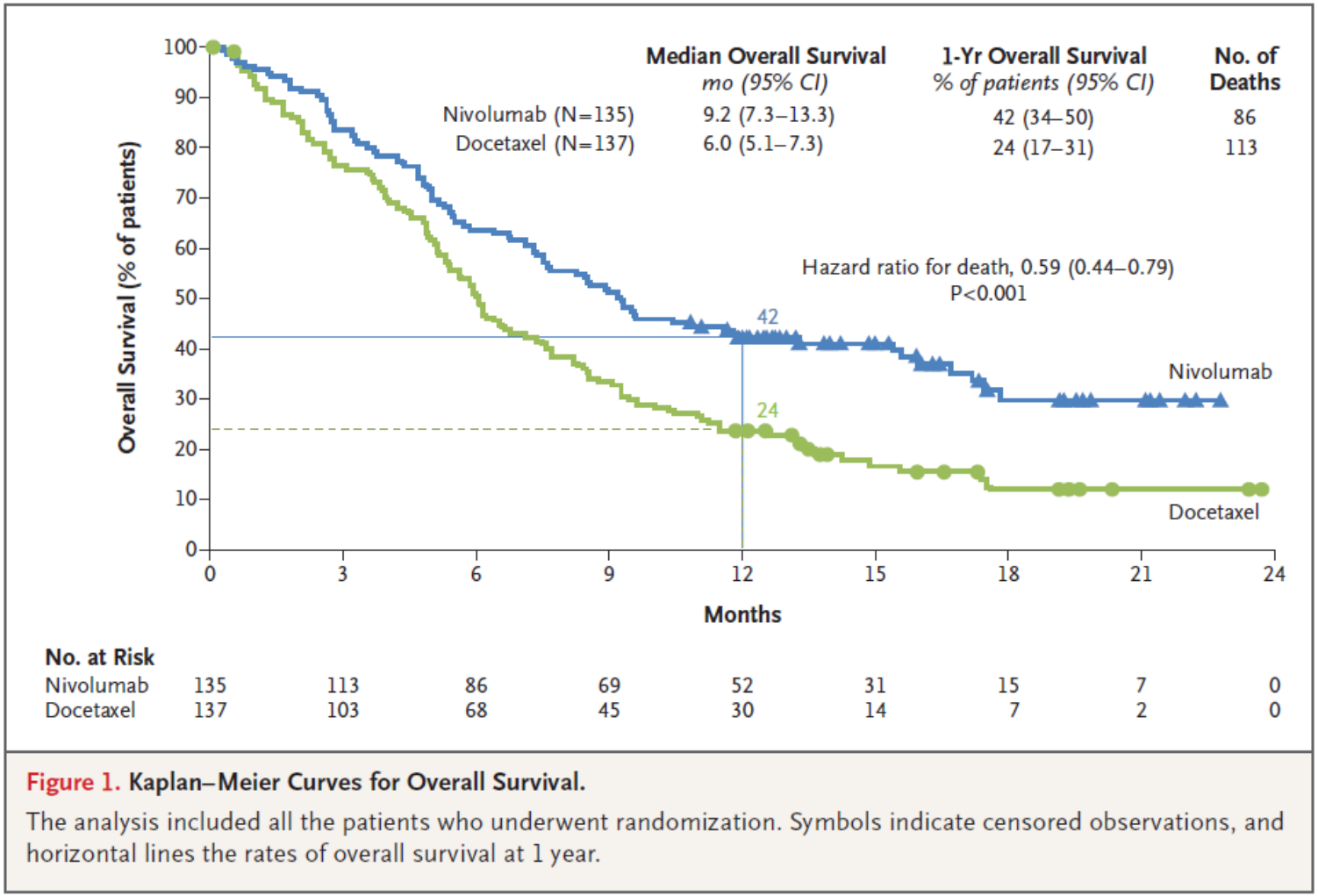
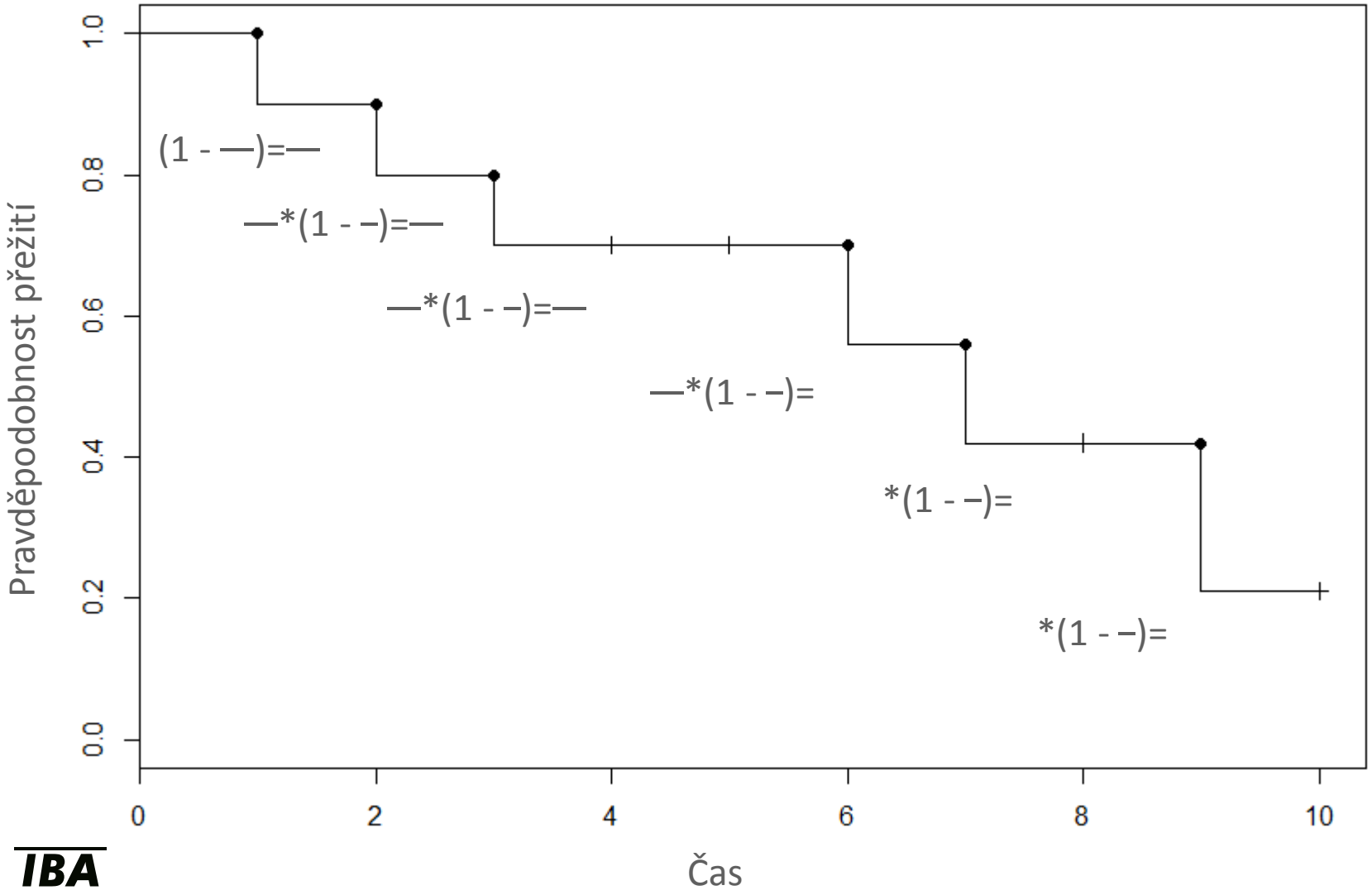


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

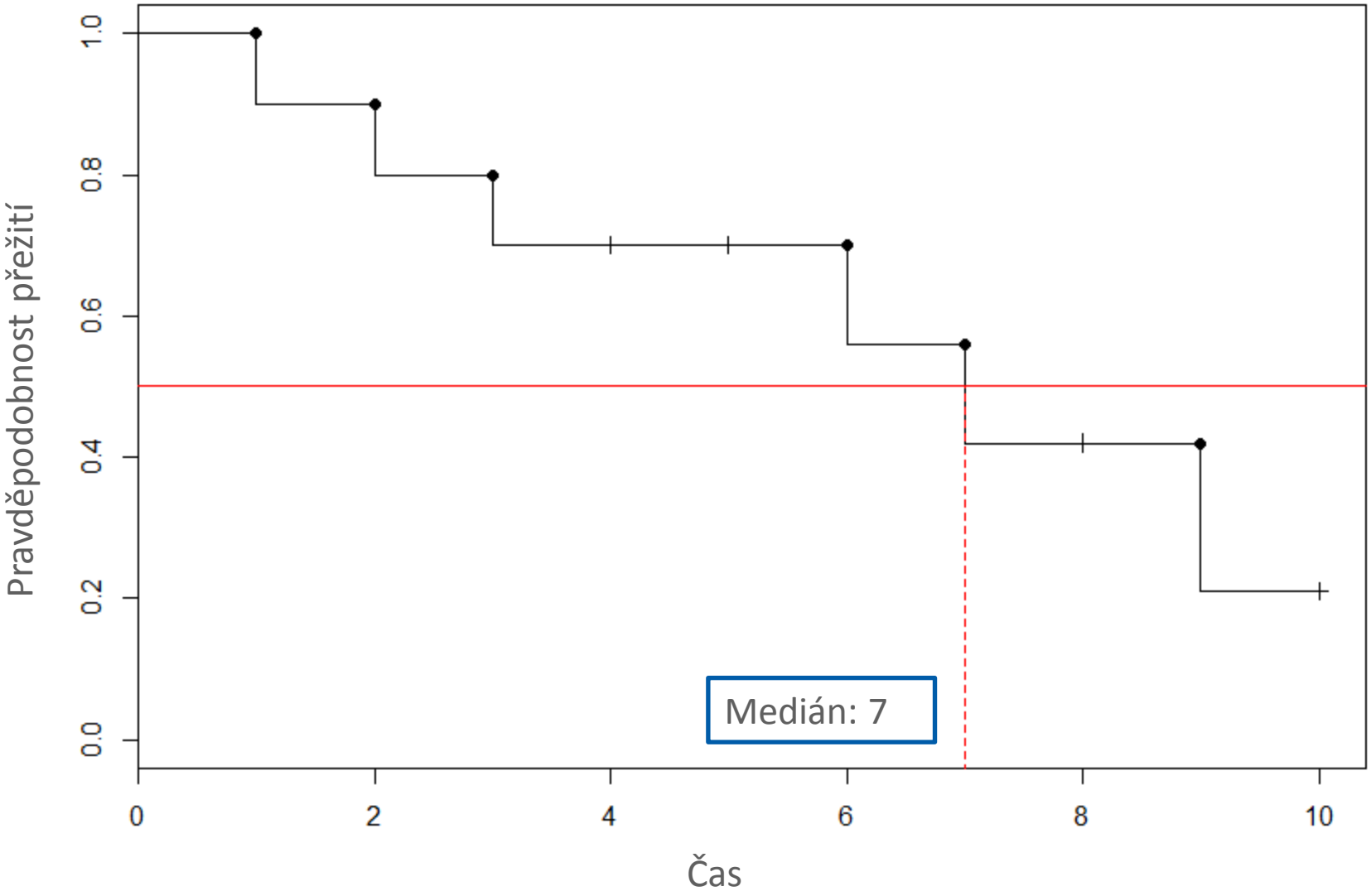
Kaplan-Meierova křivka přežití

Časy události: 1, 2, 3, 4*, 5*, 6, 7, 8*, 9, 10*



IBA

Kaplan-Meier



Kaplan-Meier, Log-Rank Test

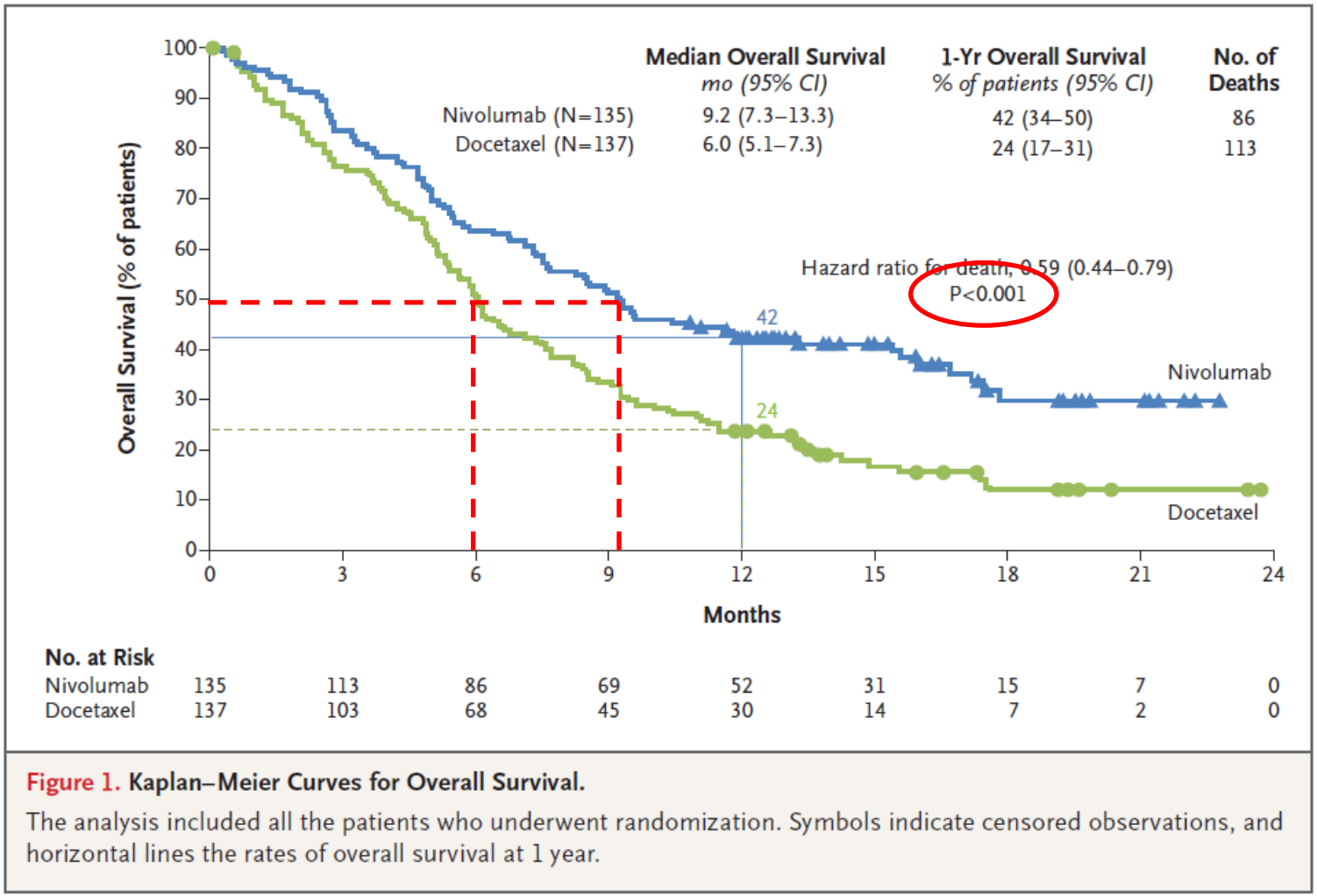


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Log-Rank Test

Testovaná statistická hypotéza

- H_0: $S_N(t) = S_D(t)$
- H_1: $S_N(t) \neq S_D(t)$

- Log-rank test porovnává vzdálenost mezi dvěma empirickými křivkami přežití a testuje, jestli mohou indikovat stejné teoretické rozdělení, nebo už jsou tak vzdálené, že nasvědčují dvou různým rozdělením

Hazard ratio

HAZARD

- Hazard=intenzita=riziko, resp. riziková funkce, může se měnit v čase
- Pravděpodobnost, že u pacienta v daném okamžiku nastane daná událost, za předpokladu, že do tohoto okamžiku událost u tohoto pacienta nenastala/přežil bez události
- *Intenzita, s jakou události nastávají*

HAZARD RATIO

- Pojem HR vychází z tzv. Coxova modelu: předpoklad proporcionality hazardů. Neznáme intenzitu, může se i měnit ve sledovaném intervalu, ale poměr intenzit mezi léčenou a kontrolní skupinou zůstává vždy stejný.
- Exponenciální model (konstantní hazard): HR podíl mediánů
- HR zpravidla uvádí podíl hazardů experimentální vs kontrolní, tj. očekává se HR<1

Hazard ratio

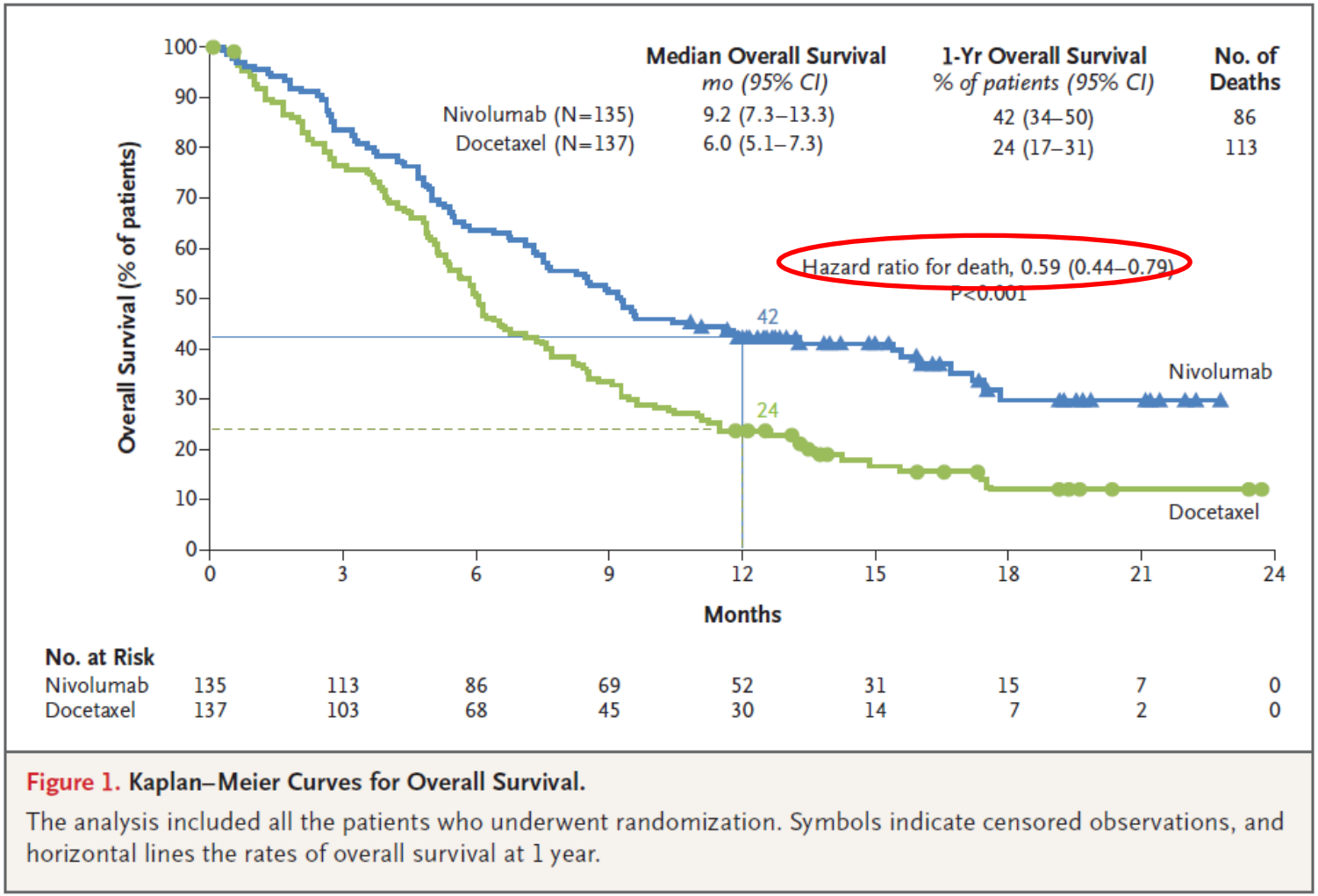


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Následná léčba

At the time of the database lock, 16% of the patients in the nivolumab group and 2% of those in the docetaxel group were continuing treatment (Table S2 in the Supplementary Appendix). After discontinuation of treatment, 36% of the patients in the nivolumab group and 30% of those in the docetaxel group received subsequent systemic cancer therapy. In the nivolumab group, 24% of the patients received subsequent docetaxel, reflecting the open-label nature of the study; 2% of the patients in the docetaxel group received subsequent immunotherapy (Table S3 in the Supplementary Appendix).

Následná léčba může ovlivnit OS.
Možnosti další léčby hrají roli především ve studiích, kde je primární endpoint PFS.

MU IBA

ORR

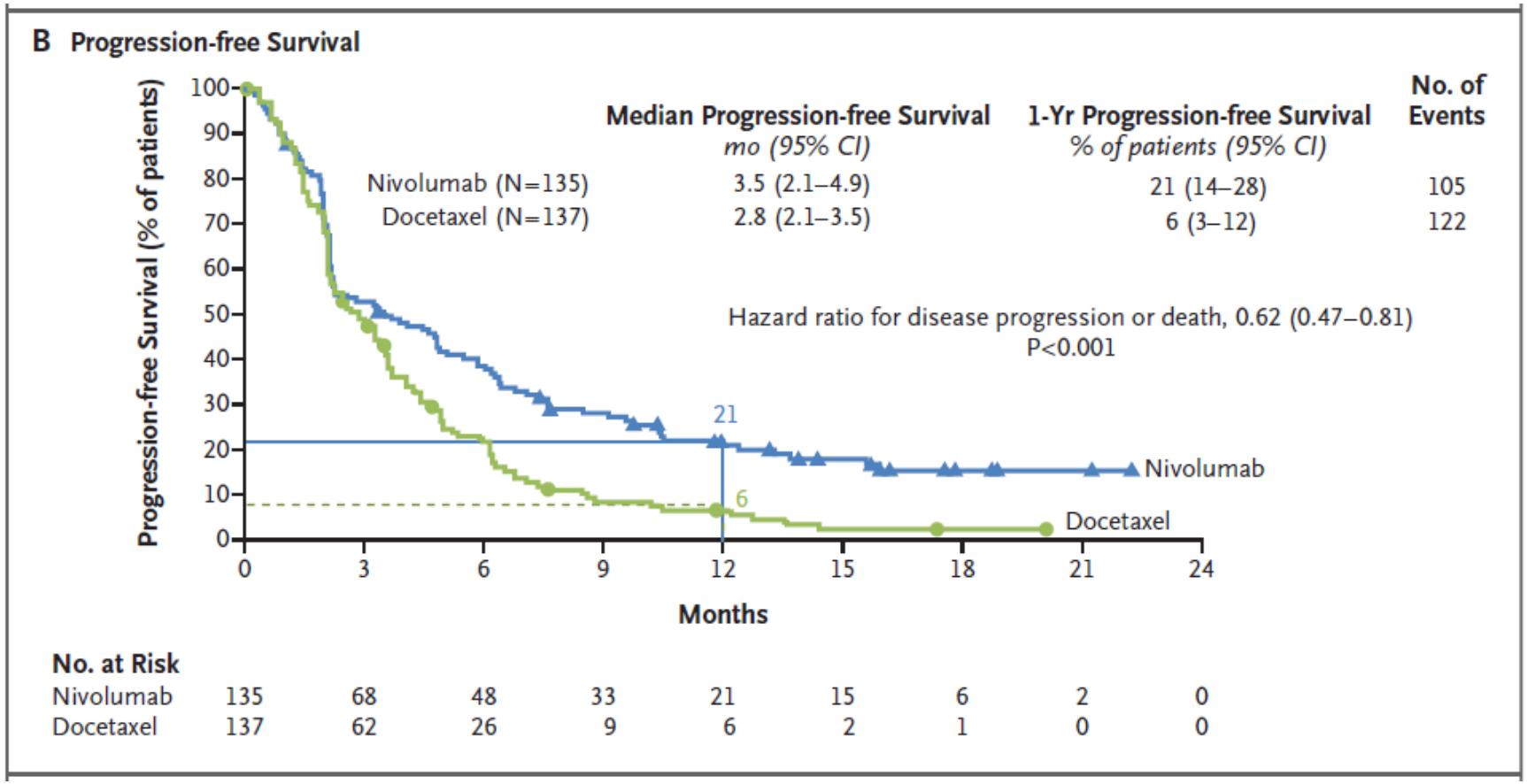
Table 2. Clinical Activity of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N = 135)	Docetaxel (N = 137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)

Jedná se o sekundární endpoint, výsledek se tedy interpretuje jenom v případě, že výsledek pro primární endpoint (OS) je stat. signifikantní.

MU IBA

PFS


B Progression-free Survival
Progression-free Survival (% of patients)
100
90
80
70
60
50
40
30
20
10
0
Median Progression-free Survival
mo (95% CI)
1-Yr Progression-free Survival
% of patients (95% CI)
No. of Events
Nivolumab (N=135)
3.5 (2.1–4.9)
21 (14–28)
105
Docetaxel (N=137)
2.8 (2.1–3.5)
6 (3–12)
122
Hazard ratio for disease progression or death, 0.62 (0.47–0.81)
P<0.001
21
6
Nivolumab
Docetaxel
0
3
6
9
12
15
18
21
24
Months
No. at Risk
Nivolumab 135 68 48 33 21 15 6 2 0
Docetaxel 137 62 26 9 6 2 1 0 0

Bezpečnost

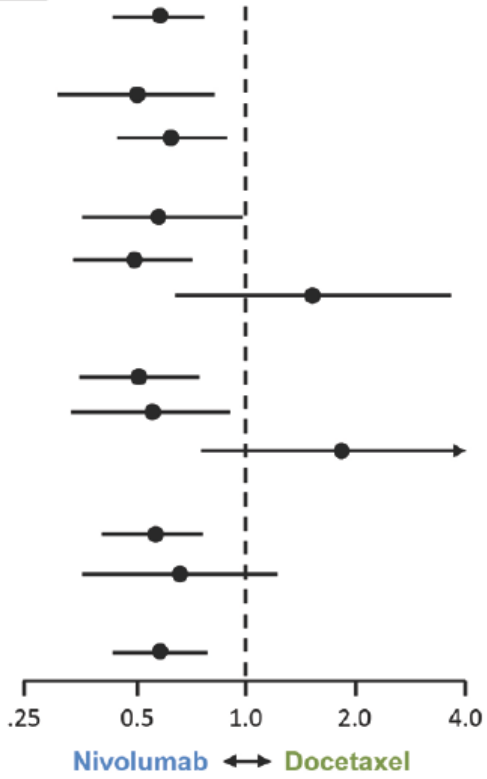
- Nežádoucí události = **adverse events (AE)**
- Intenzita dle **NCI CTCAE** (National Cancer Institute Common Terminology Criteria), v. 4.0
- Vybrané AE (imunologické příčiny) předdefinované kategorie – sledováno se zvýšenou pozorností
- Závažné (serious, SAE)
- Kódování pomocí **MedDRA**
- Žádné stat. testy – **ne**lze říci: nepodařilo se nám prokázat, že je zde bezpečnostní problém, tudíž jednáme, jako by nebyl)

Prezentace AE

- *Treatment-related* AEs– není zde jasné, co znamená
  - Treatment emergent (vyskytl se v době od zahájení léčby do 28 dní po vysazení)
  - Označena lékařem jako „treatment related“, často se ale nebere příliš v úvahu, neumožňovala by detekovat neočekávané AE
- Grading (NCI CTCAE)
- Serious adverse events
- Treatment-related select adverse events (AEs of special interest)
- AEs leading to treatment discontinuation

Analýza podskupin

	N	Unstratified HR (95% CI)
Overall	**272**	**0.59 (0.44, 0.78)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.51 (0.31, 0.83)
Another agent	180	0.63 (0.45, 0.90)
Region		
US/Canada	86	0.59 (0.36, 0.98)
Europe	155	0.50 (0.34, 0.72)
Rest of world	31	1.53 (0.65, 3.62)
Age		
<65 years	152	0.52 (0.35, 0.75)
≥65 and <75 years	91	0.56 (0.34, 0.91)
≥75 years	29	1.85 (0.76, 4.51)
Gender		
Male	208	0.57 (0.41, 0.78)
Female	64	0.67 (0.36, 1.25)
Race		
White	252	0.59 (0.44, 0.79)



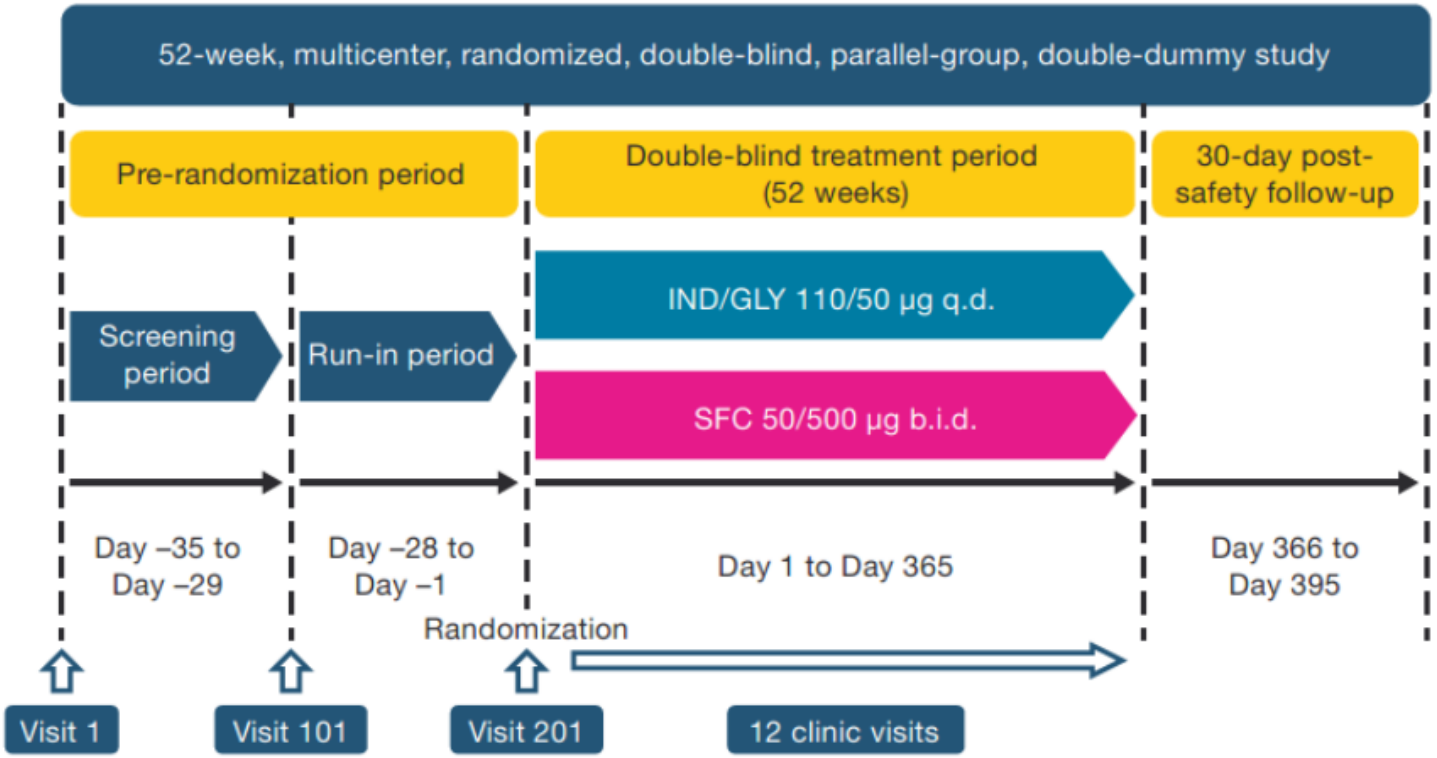
A consistent treatment effect was observed in prespecified subgroups, except in the group of patients 75 years of age or older and the group in the ROW. This result was probably attributable to small sample sizes, a lack of adjustment of type I error for multiple comparisons, and an imbalance in ECOG performance-status score that favored the docetaxel group in the subgroup of patients who were 75 years of age or older (in this subgroup, an ECOG performance-status score of 1 was assessed in 91% of the patients in the nivolumab group, vs. 61% of those in the docetaxel group). Further studies that are focused on a larger elderly population than was included in our trial may more fully characterize the degree of benefit with nivolumab in this subgroup.

MU IBA

INDACATEROL–GLYCOPYRRONIUM VS SALMETEROL–FLUTICASONE IN COPD (FLAME)

Design

- Randomizovaná
- Dvojitě zaslepená, “double-dummy”
- 1:1 IND + GLY nebo SAL + FLU
- Léčba 52 týdnů



Cíle/Endpointy

	Objective	Endpoint
Primary	To demonstrate that IND+GLY (110/50 µg o.d.) is to SAL+FLU (50/500 µg b.i.d.) in terms of rate of COPD exacerbations (mild/moderate/severe) during 52 weeks of treatment.	Rate of COPD exacerbations
Secondary	To demonstrate that IND+GLY (110/50 µg o.d.) is **superior** to SAL+FLU (50/500 µg b.i.d.) in terms of rate of all COPD exacerbations during 52 weeks of treatment.	Rate of COPD exacerbations
	To evaluate the effect of IND+GLY compared to SAL+FLU during 52 weeks of treatment in terms of: • Time to first COPD exacerbation (mild/moderate/severe) • Rate and time to first moderate/severe COPD exacerbations …	Time to first exacerbation Rate and time to first moderate/severe COPD exacerbation …
Exploratory	…	

Exacerbace definovány dle Anthonisen et al., pokus o standardizaci subjektivního vnímání zdravotního stavu pomocí elektronických diářů.

MU IBA

Populace

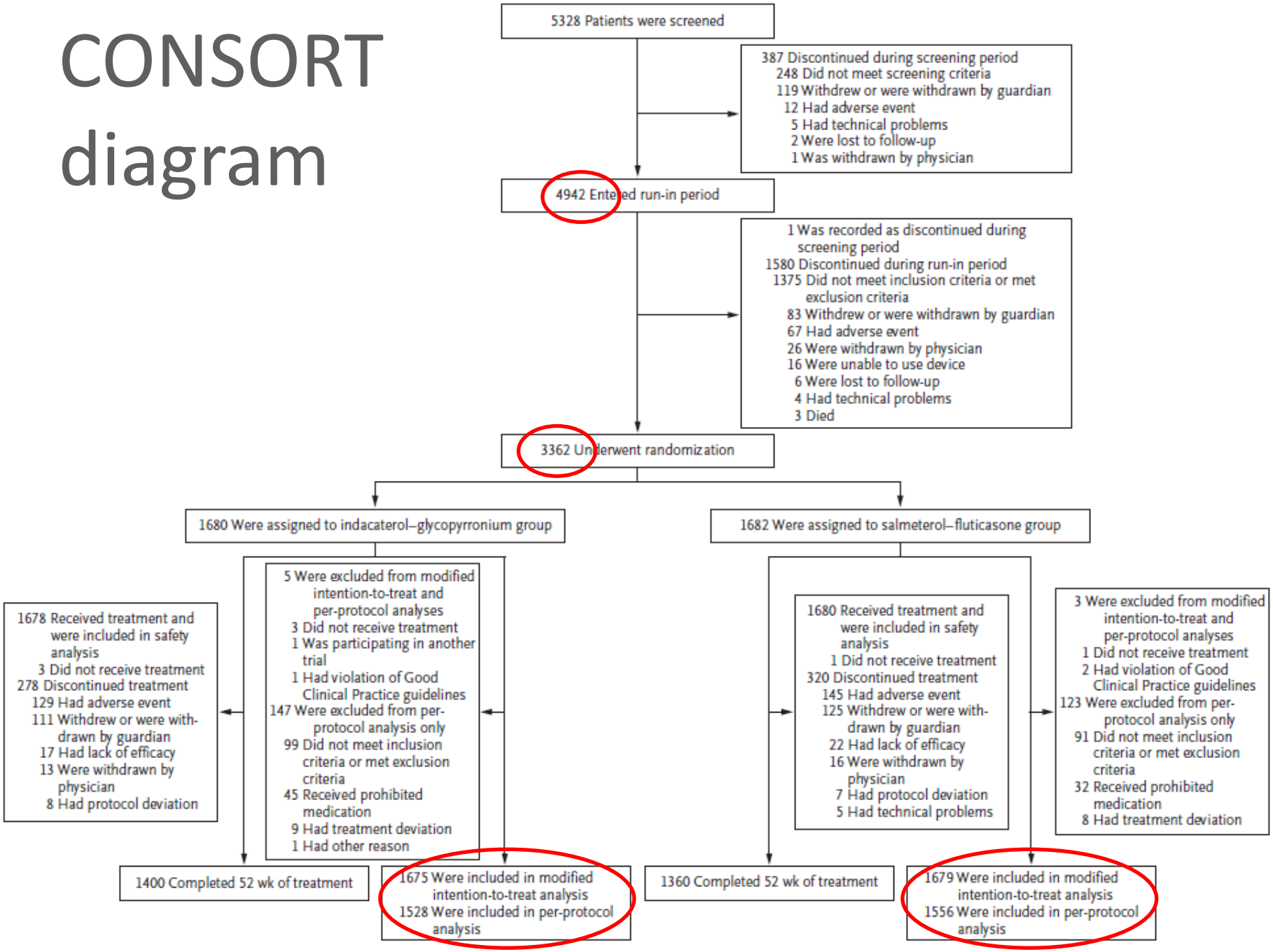
- **Per-protocol population:** Patients in mITT who did not have any major protocol deviations (definitions of major protocol deviations were specified before unblinding occurred).
  - Primary objective
- ***Modified* Intention-to-treat (mITT)**: all the patients who underwent randomization, received at least one dose of a drug during the treatment period, and did not have major GCP violations
  - Secondary objectives

- "Although the per-protocol analysis was prespecified as the main analysis of the primary outcome and the modified intention-to-treat analysis as the supportive analysis, it was important to achieve consistent results in the two analyses in order to draw convincing conclusions regarding noninferiority and superiority."

- All efficacy analyses on "on-treatment data"

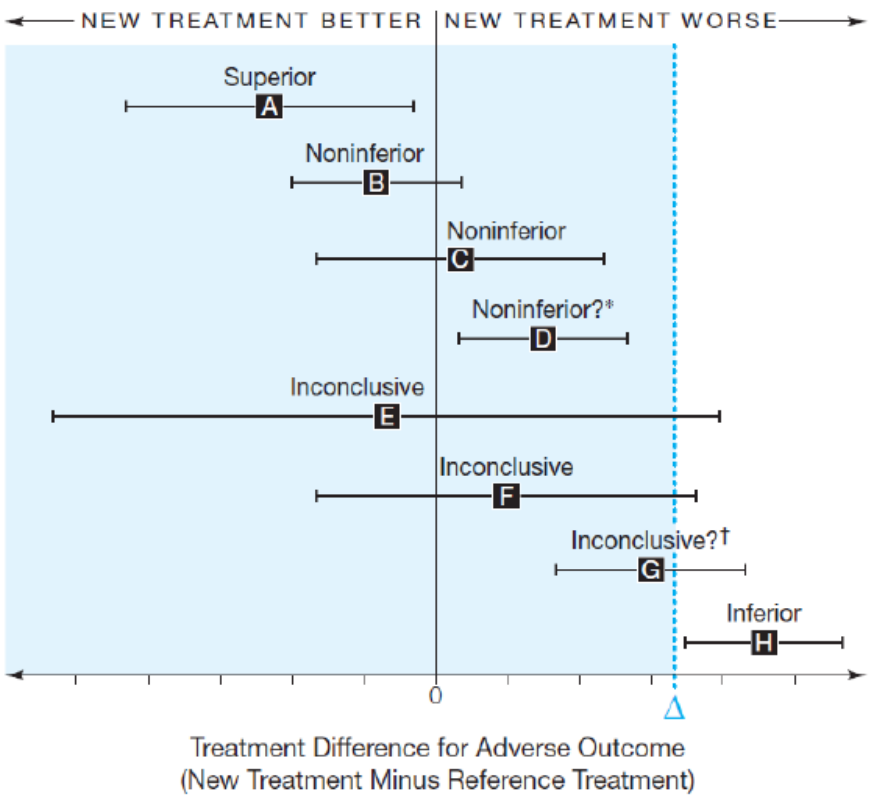
MU
IBA

CONSORT diagram



Statistická hypotéza

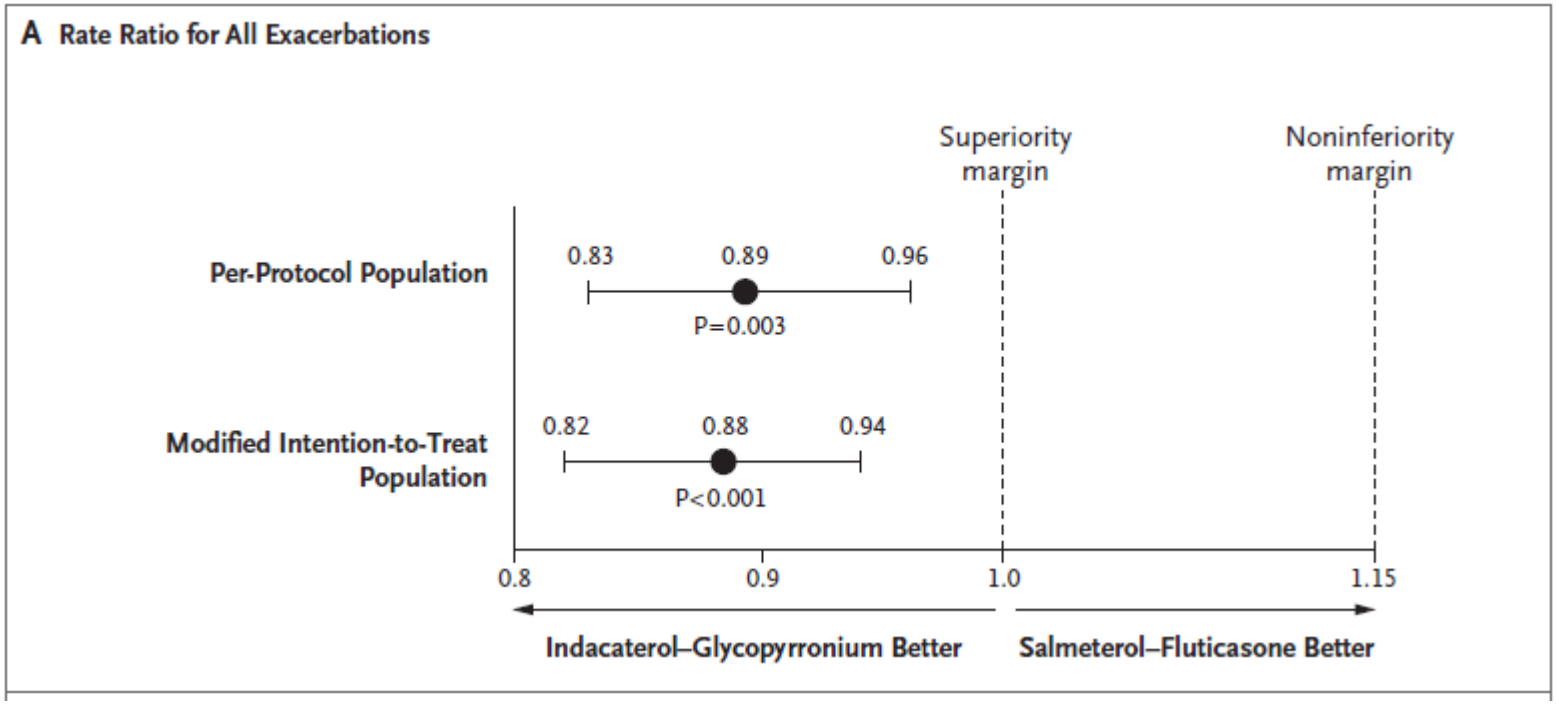
- H_0: There is at least 15% increase in rate of COPD exacerbations for patients treated with IND+GLY compared to SAL+FLU
  - RR (rate ratio) ≥ 1.15
- H1: Rate ratio of COPD exacerbations for patients treated with IND+GLY compared to SAL+FLU is less than 1.15
  - RR < 1.15



Statistická analýza

The annual rate of all COPD exacerbations

- 3.59 (95% CI, 3.28 to 3.94) in IND+GLY
- 4.03 (95% CI, 3.68 to 4.41) in SAL+FLU



Statistická signif. vs klinická signif.

Ultibro CHMP Assessment report

SPARK

Effect on reducing the rate of exacerbations (A2304)

According to the EMA Guideline on clinical investigation of medicinal products in the treatment of COPD, the rate of moderate and severe exacerbations is a clinically relevant endpoint that should be assessed during a study period of at least 1 year due to seasonal variation. Two comparators, NVA237 and open label tiotropium, were evaluated in this study in patients with severe to very severe COPD, with at least 1 exacerbation in the preceding year. Neither of the comparators have the licensed indication of reducing rate of exacerbations. A major issue concerned the primary endpoint, rate of moderate to severe exacerbations,

Key secondary endpoint was a comparison to tiotropium, giving very similar results as for NVA237, although not statistically significant. Time to first moderate to severe COPD exacerbation was comparable between the three treatments (QVA149, NVA237 and tiotropium) with time-to-event (25% percentile) of 83 days.

This included historical data with QAB149, NVA237, tiotropium and placebo. It has to be acknowledged that Study A2304 seen in the context of the historical data *may* suggest that QVA149 likely reduces exacerbations compared to placebo to a clinically significant extent. However, QVA149 has not convincingly shown incremental benefit in reducing exacerbations compared to NVA237 and tiotropium – none of which have been granted a specific exacerbation claim. Therefore, the exacerbation claim was removed from the indication.

Treatment group	QVA149	NVA237	OL tiotropium
Number of subject	729	739	737
Number of exacerbations pr patient in the treatment period	1.11	1.22	1.22
SD	1.35	1.48	1.66
Rate of exacerbations per year	0.94	1.07	1.06
Primary endpoint	QVA149 vs NVA237		
	Rate of ratios	0.88	
	95% CI	0.77-0.99	
	P-value	0.038	

SPC:
Ultibro is indicated as a maintenance bronchodilator treatment **to relieve symptoms** in adult patients with COPD

MU IBA