- Ultimovacs -

Winning odds hidden in plain sight

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Who we are: A small, private investor-group, including professional clinicians with oncology expertise at PhD-level and beyond. Our extended network comprises of academics familiar with Ultimovac's clinical studies and who have first-hand experience with the company's lead asset Universal Vaccine 1 (UV1). We do not possess insider information.

Why we care: First, because we are shareholders who want the company to have a fair market capitalisation. Second, we believe that we possess unique insight into the randomised phase-2 program and the individual study designs in the context of known patient recruitment and historical control studies.

Why we make contact: Recently, it has become public that Janus Henderson UK has an active short interest in the company (per the Norwegian Short Sale Register). Based on objective, historically available information, we maintain that this position has a very poor risk-reward outlook.

What we provide: In the following, we will focus on the company's main study (INITIUM) and provide you with a brief explanation as to why available information on patient recruitment, relevant historical controls, and the study design itself makes a short position ill-advised. Finally, we will comment on the topline results from NIPU.

INITIUM: trial design, recruitment rate and historical controls I

INITIUM (N = 156) is an event driven trial wholly designed and controlled by the company. As such, it is the most important Proof of Concept (PoC) for UV1.

Both INITIUM (and NIPU) are designed with one-sided alpha = 0.1, power = 0.80 and HR=0.60. The primary endpoint is progression free survival (PFS). It is reached if the calculated one-sided p-value is below 0.10. A one-sided p-value of 0.10 would in average yield an empirical HR = 0.736. This is confirmed by independent statisticians who contributed to the design of the trials.

Breaking with industry standard, Ultimovacs have provided the market with regular updates on patient recruitment. We consequently know how recruitment progressed until Last Patient First Visit (LPLV).

Inclusion and exclusion criteria in the INITIUM trial are deliberately made similar to comparator trials (CheckMate-067 and CheckMate-511). If we assume that INITIUM provides no additional benefit with UV1 intervention, trial duration can be calculated based on efficacy of Ipilimumab and Nivolumab combination therapy.

INITIUM: trial design, recruitment rate and historical controls II

INITIUM is still ongoing and topline results were originally guided 1H 2023. Late April of this year, however, guidance changed to 2H 2023 as patients take longer time to progress than anticipated. This development is aligned with the primary trial hypothesis: UV1 increases the efficacy of checkpoint inhibition.

We will demonstrate why we have high confidence that UV1 intervention is responsible for the slower than anticipated patient progression.

While unknown unknowns cannot be ruled out, recent topline results from the Moderna/Merck KEYNOTE-942 trial provides further grounds to be optimistic for the cancer vaccine approach itself: a personalised cancer vaccine significantly reduced the risk of recurrence or death in combination with checkpoint inhibition in unresectable metastatic melanoma.

UV1 targets telomerase reverse transcriptase (hTERT) which is expressed in 80 – 90 per cent of all cancer types. INITIUM and four additional randomised trials may provide the world's first randomised PoC for a universal cancer vaccine. One might argue that this is likely to already have been achieved with the recent topline results from the NIPU trial (see final slide).

Winning odds: statistics and probabilities I

As Ultimovacs have been wholly transparent on patient recruitment, let us first visualise this for INITIUM:

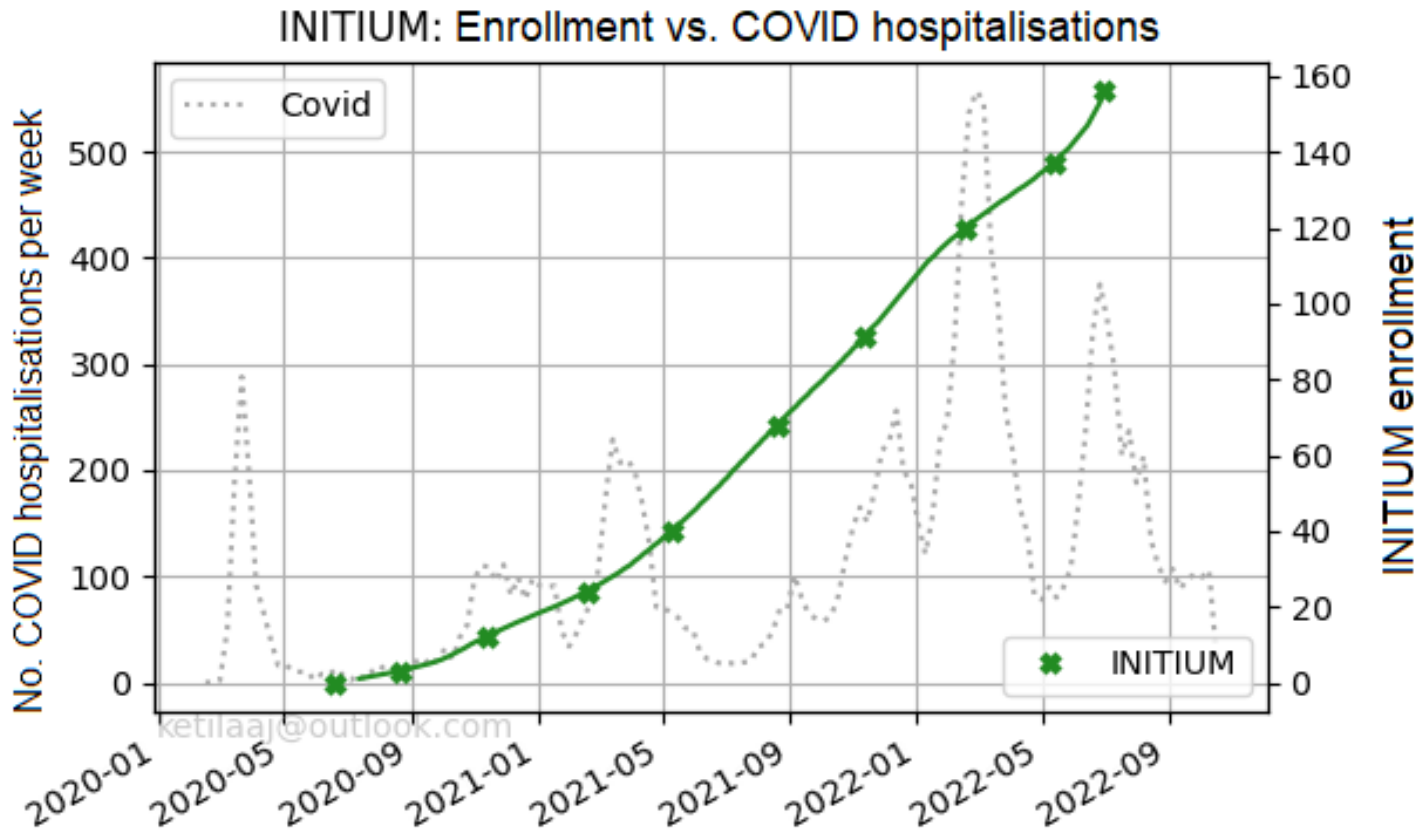
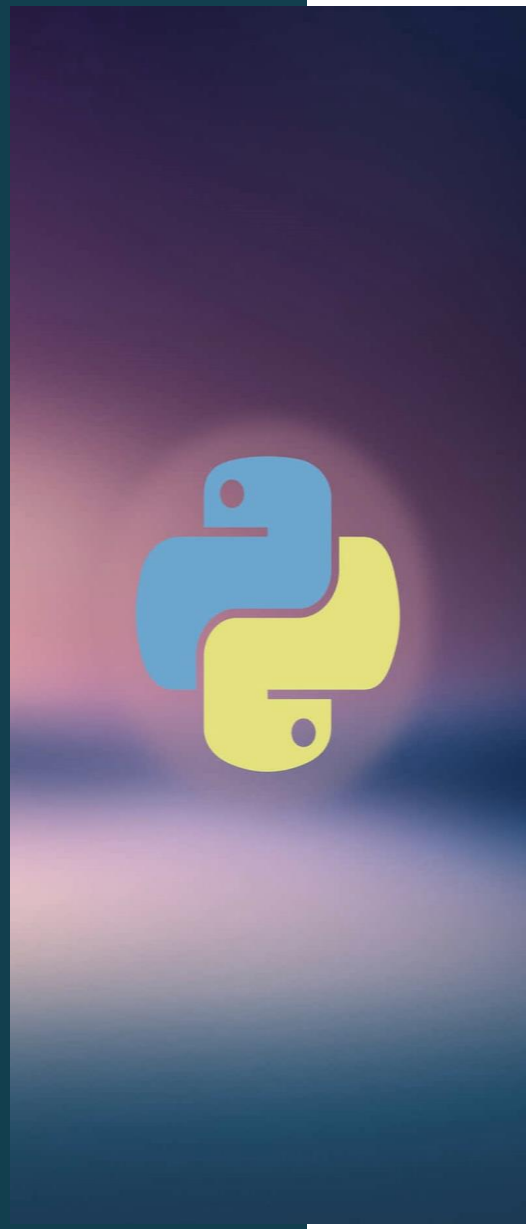


Fig.01: Patient recruitment INITIUM incl. COVID hospitalisations (Norway)



Winning odds: statistics and probabilities II

Moving on: when Ultimovacs designed INITIUM, CheckMate-067 (11,7 months mPFS) was the most recent and relevant historical control. A later relevant study is CheckMate-511 (9,8 months mPFS). Choosing CheckMate-067 as comparator is conservative. No other relevant studies demonstrate longer mPFS in malignant melanoma. Let us look at the Kaplan-Meier for CM067:

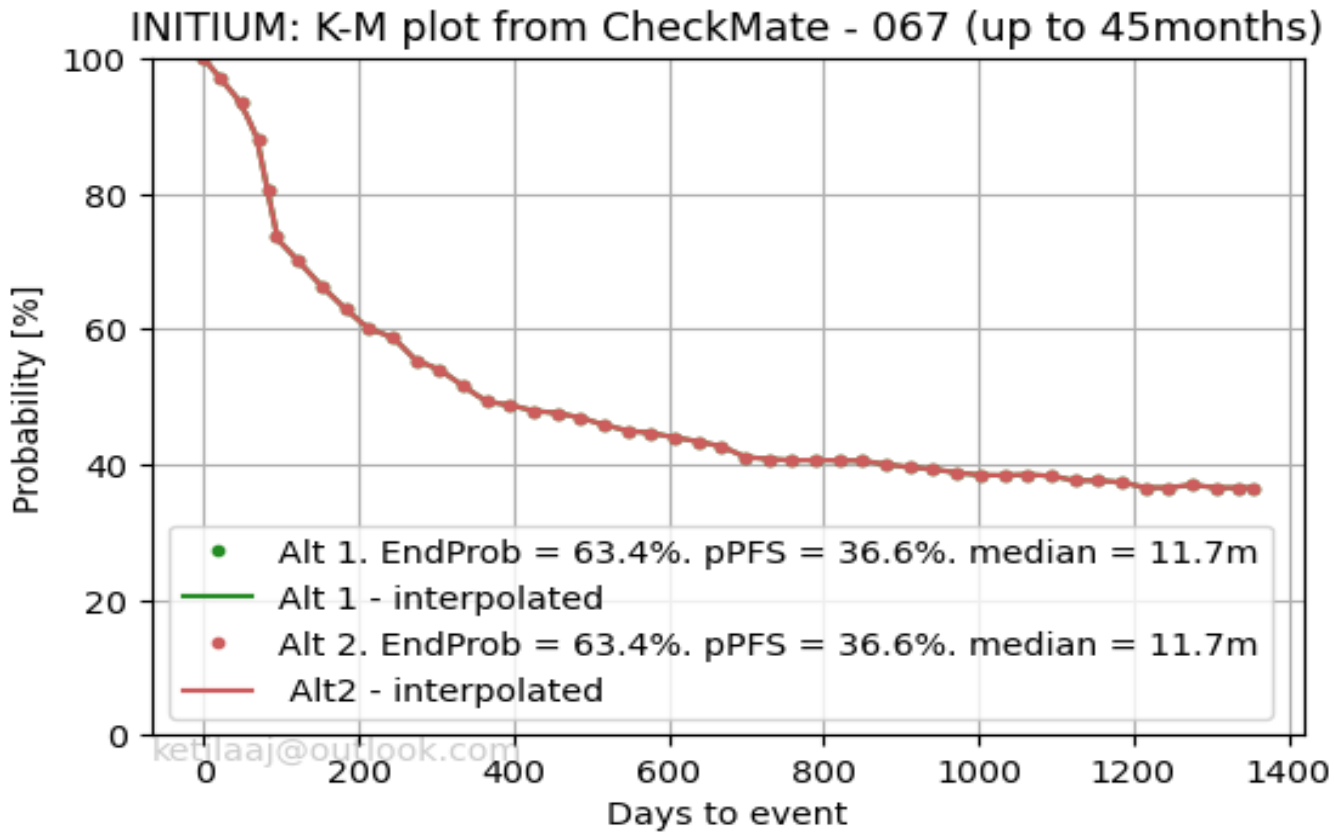
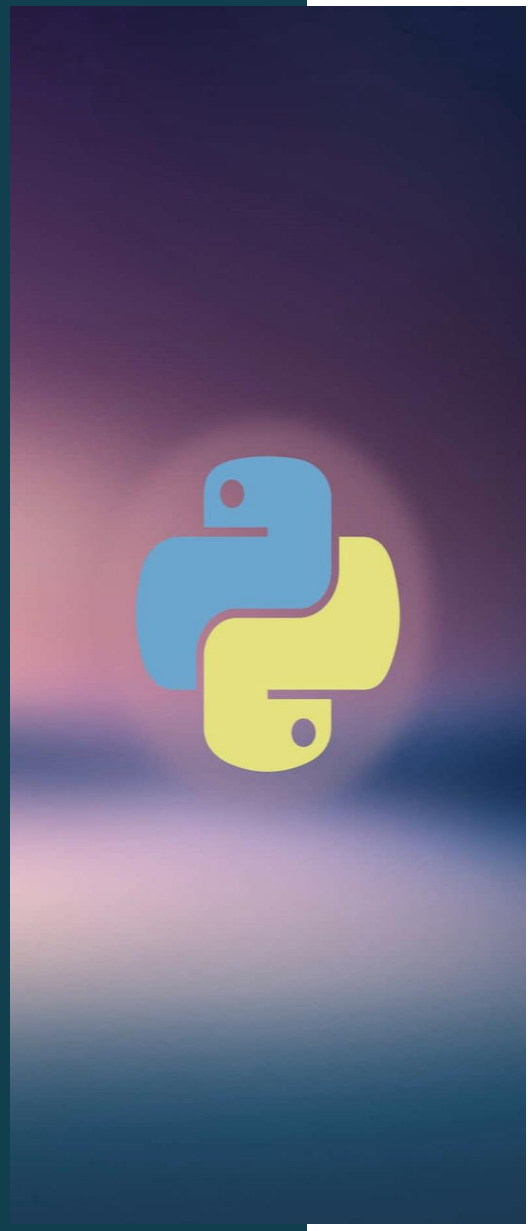


Fig.02: CM67 Kaplan-Meier



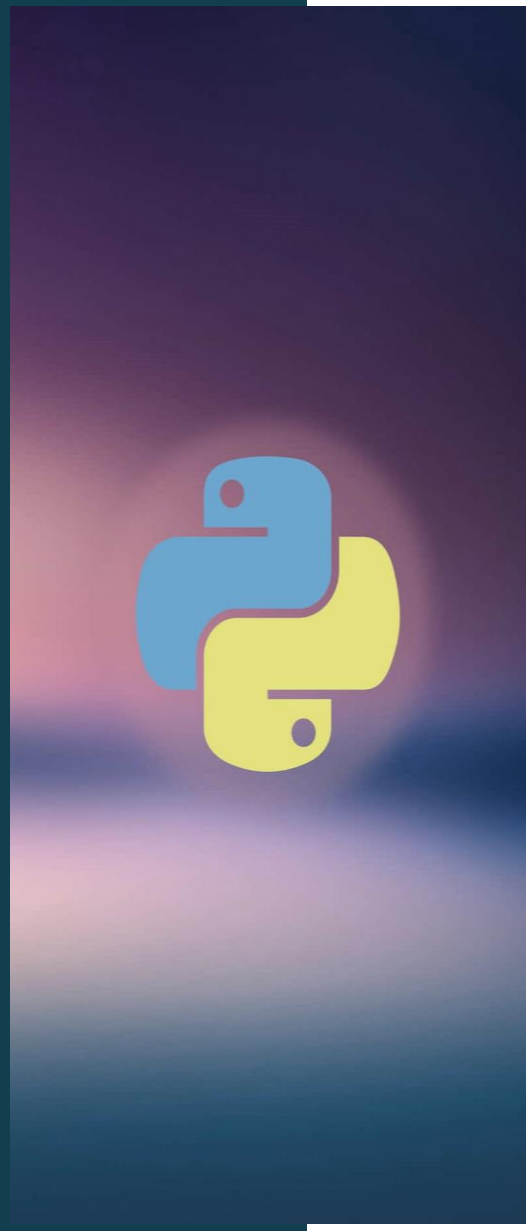
Winning odds: statistics and probabilities III

To reiterate, the fundamental assumption of this analysis is that patients in the control arm behaves in line with relevant historical studies (within the same indication and with the same treatment). We find no substantial reasons as to why INITIUM should diverge significantly. If anything, we believe that the trial might have been impacted by the pandemic in the sense that patients have suffered delayed screenings and diagnosis. If true, this would suggest a lower mPFS than historical controls.

Be that as it may, it is time to make things interesting: based on known patient recruitment in time, and the Kaplan Meier plot for CM067, let us make a Python script that runs 10.000 simulations of INITIUM. For every simulation, 156 synthetic patients are enrolled, and the distribution of the control- and experimental arm is done with block-randomisation.

For every individual in the control arm, the number of days to PFS is decided by randomly choosing a number on the vertical axis (figure 02), and then recording the number of days on the horizontal axis (figure 02). This means that both the date for enrolment and the number of days until PFS are random variables governed by the known enrolment rate for INITIUM and CM67's Kaplan-Meier plot.

When this is established for all 10.000 simulations, we calculate histograms on the distributions of when the number of events in the control arm are reached.



Winning odds: statistics and probabilities IV

The figure below shows results from 20, 35 (i.e. no effect of UV1 and no difference between arms) and 39 events (PFS-endpoint in INITIUM with HR 0.73, P-value <0.1):

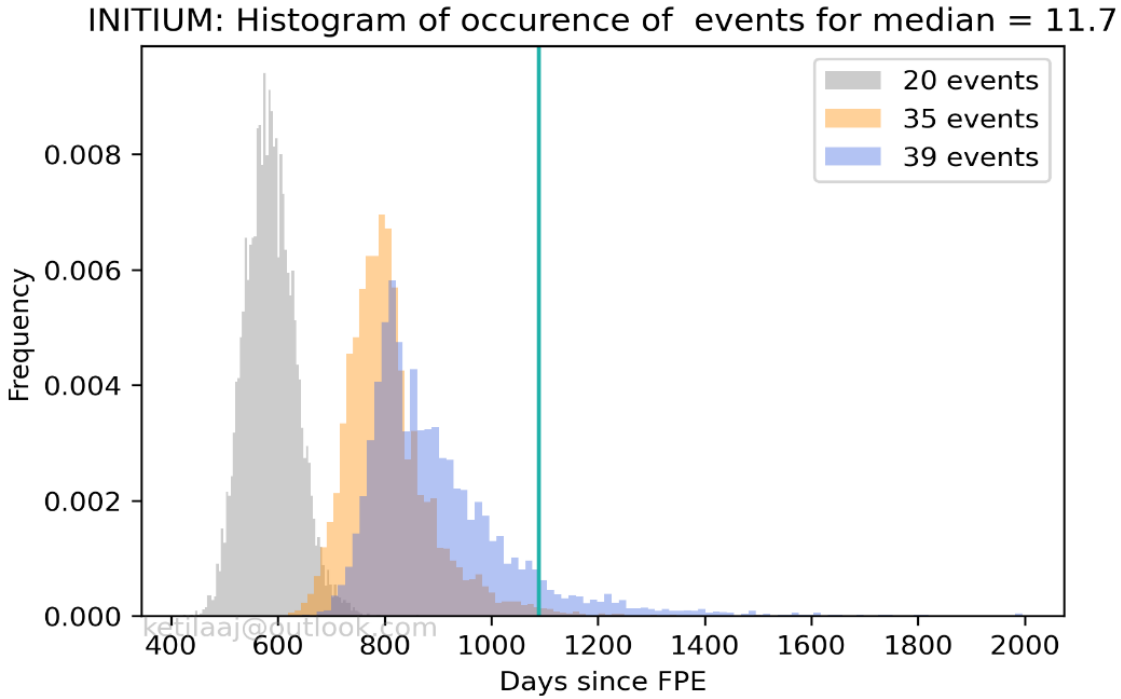
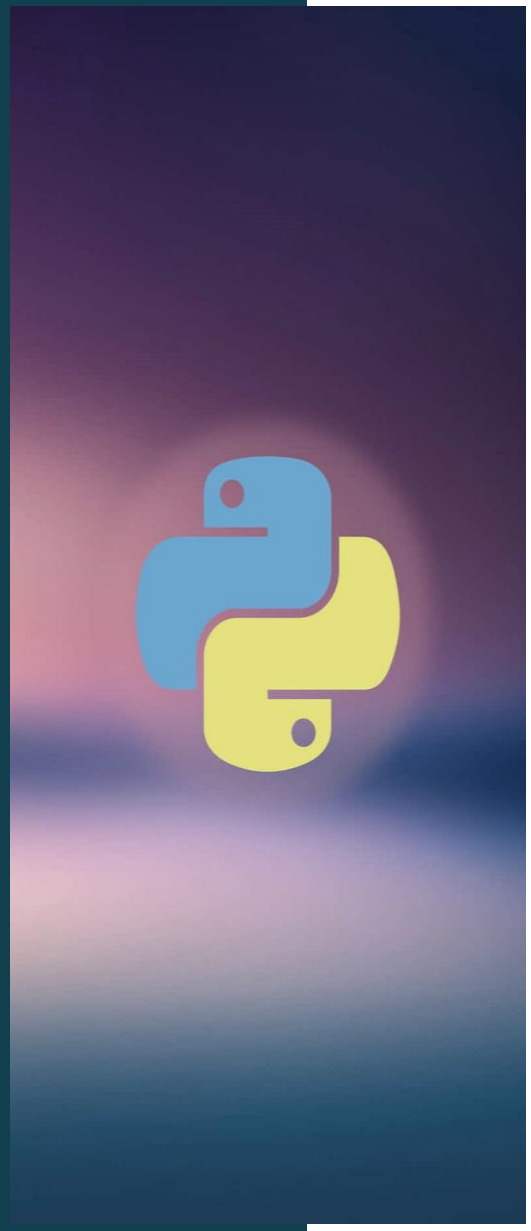


Fig. 03: Histogram on events and days since FPE

The histograms are plotted with reference to First Patient Enrolled (FPE). The green vertical line indicates the date the plot was generated (here: 2023-06-14). The blue histogram shows the distribution of 39 events in the simulations. It peaks at about 800 days after FPE. Clearly, we have progressed far into the narrow end of the event tail. This strongly suggest that that the majority of possible 39-events have occurred and that the endpoint of the trial is reached.



Winning odds: statistics and probabilities V

Let us look at the cumulative probability for number of events in the control arm:

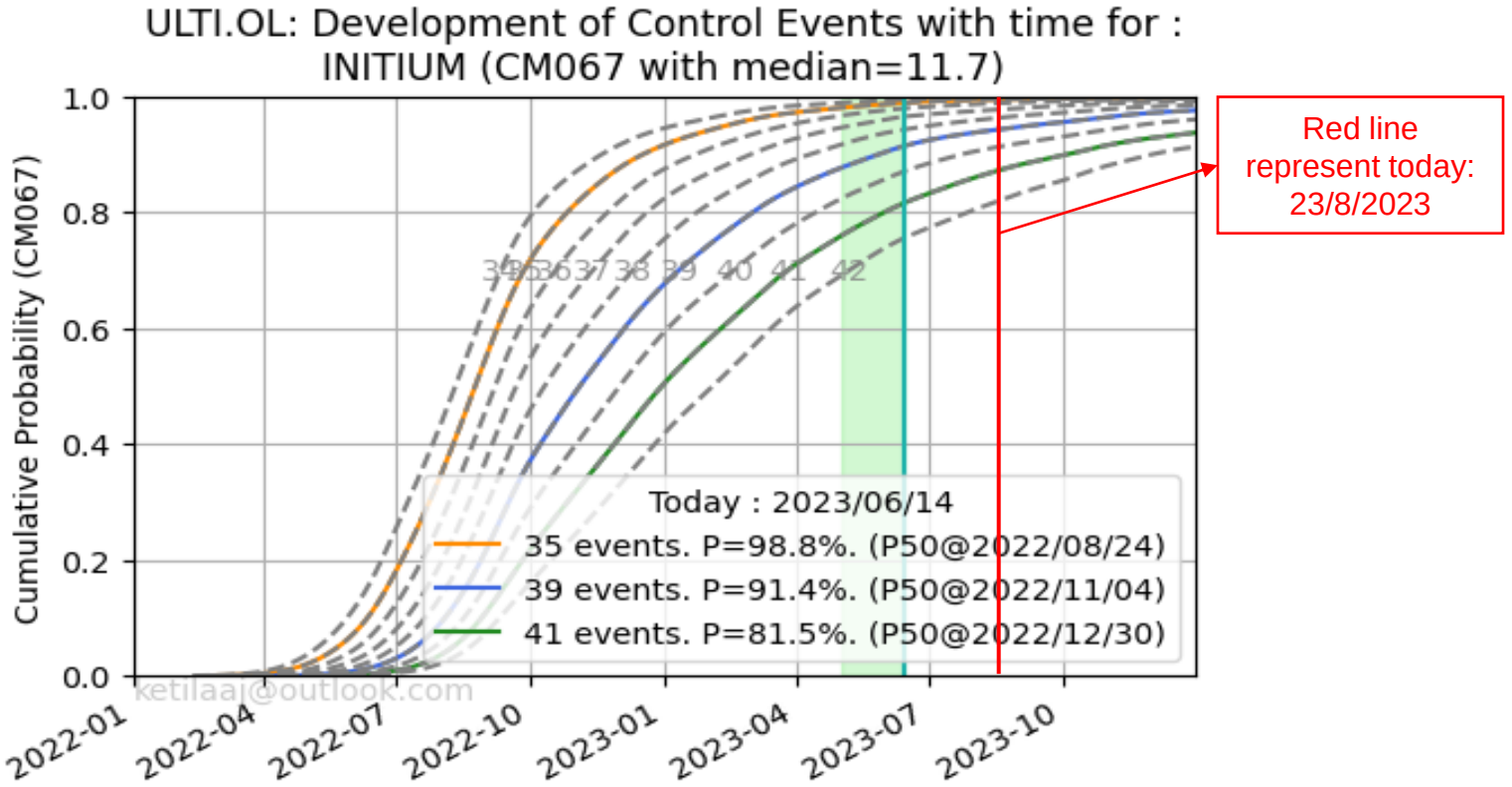


Fig. 04: Cumulative probabilities for events in INITIUM control arm

The PFS-endpoint (HR 0.73, P-value <0.1) in INITIUM is most likely reached with 39 events in the control arm (and 31 events in the experimental arm) ref. the blue line. The orange line represents no difference between arms. The green line for 41 events (or better) represents a very positive result which might provide a rationale for Accelerated Approval for UV1. The green shaded area represents a period of six weeks reserved for time utilised by the CRO on Database Lock.

"Don't be stupid.
It's not smart."

- Ty Pennington

Concluding remarks

We maintain that the market has not in any meaningful way understood the odds in favour of positive INITITIUM data. These data are likely to establish the world's first PoC for a universal cancer vaccine.

The conclusion on risk-reward ought to be evident:

Cover shorts, go long.

Thank you for reading – we hope you find this information interesting. If you have any questions, feel free to reach out at ultimoinvestgr@gmail.com

A brief comment on NIPU is also included.

"*You will see it, when you believe it.*"

- Wayne W. Dyer

NIPU: an academic-initiated trial in highly challenging 2L mesothelioma

We applied the same approach on NIPU as INITIUM. Our estimates were close on target. Blinded Independent Central Review (BIRC) found that the primary endpoint on progression free survival (PFS) was not met (i.e. Hazard Ratio higher than 0.73). However, the jury is still out.

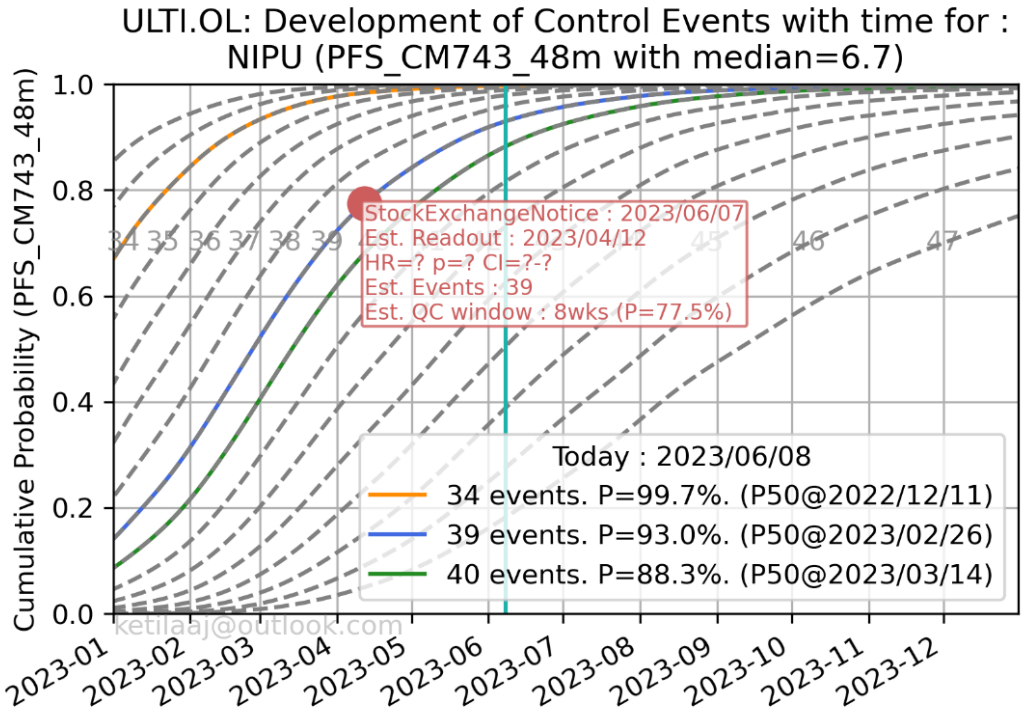


Fig. 05: NIPU-estimates and topline readout

The predefined analysis by the independent academic Principal Investigator (PI) and local specialists found PFS to be highly significant (HR <0.73). More importantly, PI and her team also reported improved overall survival (OS) in the UV1-arm. Data is under embargo as per the request of the PI, and complete, more mature data will be presented on ESMO in October. The PI in question has an H-index of 50 (499 publications and 9265 citations).

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