אוגוסט 2021

**רופא/ה, רוקח/ת נכבד/ה,**

הנדון: **Tasigna 150& 200 mg capsules**
**טסיגנה 150 ו-200 מ"ג, כמוסות**

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון בעלון לרופא של התכשיר.

**התכשיר בנדון מתווה להתוויות הבאות:**

Tasigna 150 mg and 200 mg are indicated for:
Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase.

Tasigna 200 mg **only** is indicated for:
Treatment of Philadelphia chromosome positive chronic myeloid leukaemia (Ph+ CML) in chronic or accelerated phase in patients resistant to or experiencing significant toxicity during treatment with imatinib.

**המרכיב הפעיל:**

NILOTINIB (AS HYDROCHLORIDE MONOHYDRATE)

בהודעה זו מפורטים העדכונים המהותיים בלבד. למידע מלא על התרופה יש לעיין בעלון לרופא העדכני של התכשיר.

(טקסט שנוסף מסומן בצבע אדום עם קו תחתי, טקסט שהוסר מסומן בצבע אדום ~~ובקו חצייה~~, שינויים אשר מהווים החמרה מסומנים ברקע צהוב).

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על-ידי פניה לבעל הרישום נוברטיס ישראל בע"מ.

בברכה,

מרינה רוזנפלד
רוקחת ממונה
נוברטיס ישראל בע"מ

**נוברטיס ישראל בע"מ**
רח' תוצרת הארץ 6
ת.ד. 7126 תל אביב
טלפון: 03-9201123 פקס: 03-9229331

**Novartis Israel Ltd.**
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

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**4.8 Undesirable effects**

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**Table 3 Adverse reactions in adult patients in Tasigna clinical studies (<5% of all patients)**

| | |
|---|---|
| **Infections and infestations** | |
| Common: | Folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis), pneumonia* |
| Uncommon: | Urinary tract infection, gastroenteritis, bronchitis, herpes virus infection, candidiasis (including oral candidiasis) |
| Not known: | Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Common: | Skin papilloma |
| Not known: | Oral papilloma, paraproteinaemia |
| **Blood and lymphatic system disorders** | |
| Common: | Leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia |
| Uncommon: | Thrombocythaemia, leukocytosis |
| **Immune system disorders** | |
| Not known: | Hypersensitivity |
| **Endocrine disorders** | |
| Uncommon: | Hyperthyroidism, hypothyroidism |
| Not known: | Hyperparathyroidism secondary, thyroiditis |
| **Metabolism and nutrition disorders** | |
| Very common: | Hypophosphataemia (including blood phosphorus decreased) |
| Common: | Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, decreased appetite, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia |
| Uncommon: | Dehydration, increased appetite, gout, dyslipidaemia |
| Not known: | Hyperuricaemia, hypoglycaemia, appetite disorder |
| **Psychiatric disorders** | |
| Common: | Depression, insomnia, anxiety |
| Not known: | Disorientation, confusional state, amnesia, dysphoria |
| **Nervous system disorders** | |
| Common: | Dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia |
| Uncommon: | Intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia |
| Not known: | Cerebrovascular accident, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome, basilar artery stenosis |

**Novartis Israel Ltd.**
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
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| | |
|---|---|
| **Eye disorders** | |
| Common: | Eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia) |
| Uncommon: | Visual impairment, vision blurred, conjunctival haemorrhage, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation |
| Not known: | Papilloedema, chorioretinopathy, diplopia, photophobia, eye swelling, blepharitis, eye pain, conjunctivitis allergic, ocular surface disease |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| Not known: | Hearing impaired, ear pain, tinnitus |
| **Cardiac disorders** | |
| Common: | Angina pectoris, arrhythmia (including atroventricular block, cardiac flutter, extrasystoles, tachycardia, atrial fibrillation, ventricular extrasystoles, bradycardia), palpitations, electrocardiogram QT prolonged, cardiac failure*, myocardial infarction |
| Uncommon: | Coronary artery disease, cardiac murmur, pericardial effusion, cyanosis |
| Not known: | Ventricular dysfunction, pericarditis, ejection fraction decreased, diastolic dysfunction, left bundle branch block |
| **Vascular disorders** | |
| Common: | Hypertension, flushing, peripheral artery stenosis |
| Uncommon: | Hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis |
| Not known: | Shock haemorrhagic, hypotension, thrombosis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia |
| Uncommon: | Pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation |
| Not known: | Pulmonary hypertension, wheezing, oropharyngeal pain |
| **Gastrointestinal disorders** | |
| Common: | Pancreatitis, abdominal discomfort, abdominal distension, dysgeusia, flatulence |
| Uncommon: | Gastrointestinal haemorrhage, melaena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth |
| Not known: | Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis |
| **Hepatobiliary disorders** | |
| Very common: | Hyperbilirubinaemia (including blood bilirubin increased) |
| Common: | Hepatic function abnormal |
| Uncommon: | Hepatotoxicity, toxic hepatitis, jaundice |
| Not known: | Cholestasis, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform) |
| Uncommon: | Exfoliative rash, drug eruption, skin pain, ecchymosis, swelling face |
| Not known: | Erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cysts, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis, psoriasis |

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6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

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| | |
|---|---|
| **Musculoskeletal and connective tissue disorders** | |
| Common: | Musculoskeletal chest pain, musculoskeletal pain, back pain, flank pain, neck pain, muscular weakness, bone pain |
| Uncommon: | Musculoskeletal stiffness, joint swelling |
| Not known: | Arthritis |
| **Renal and urinary disorders** | |
| Common: | Pollakiuria, renal failure* |
| Uncommon: | Dysuria, micturition urgency, nocturia |
| Not known: | Haematuria, urinary incontinence, chromaturia |
| **Reproductive system and breast disorders** | |
| Uncommon: | Breast pain, gynaecomastia, erectile dysfunction |
| Not known: | Breast induration, menorrhagia, nipple swelling |
| **General disorders and administration site conditions** | |
| Common: | Chest pain (including non-cardiac chest pain), pain, pyrexia, chest discomfort, malaise |
| Uncommon: | Face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold) |
| Not known: | Localised oedema |
| **Investigations** | |
| Very common: | Alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased |
| Common: | Haemoglobin decreased, blood amylase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, weight decreased, weight increased, blood insulin increased, globulins decreased |
| Uncommon: | Blood lactate dehydrogenase increased, blood glucose decreased, blood urea increased |
| Not known: | Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased |

* Frequency estimates based on data from a prospective non-interventional study in adult patients with imatinib-resistant or intolerant CML in chronic phase with a two-year observation period (n=507)

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## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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*Treatment discontinuation in adult Ph+ CML patients in chronic phase who have been treated with nilotinib as first-line therapy and who have achieved a sustained deep molecular response*

In an open-label, single-arm study, 215 adult patients with Ph+ CML in chronic phase treated with nilotinib in first-line for ≥2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL test were enrolled to continue nilotinib treatment for additional 52 weeks (nilotinib consolidation phase). 190 of 215 patients (88.4%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criteria:

- the 4 last quarterly assessments (taken every 12 weeks) were at least MR4.0 (BCR-ABL/ABL ≤0.01% IS), and maintained for one year

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6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

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- the last assessment being MR4.5 (BCR-ABL/ABL ≤0.0032% IS)
- no more than two assessments falling between MR4.0 and MR4.5 (0.0032% IS < BCR-ABL/ABL ≤0.01% IS).

The primary endpoint was the percentage of patients in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder). ~~Of the 190 patients who entered the TFR phase, 98 patients (51.6% [95% CI: 44.2, 58.9]) were in MMR at 48 weeks.~~

~~Eighty-eight patients (46.3%) discontinued the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision and subject decision, respectively. Among these 88 patients, 86 patients restarted nilotinib treatment and 2 patients permanently discontinued the study. Eighty-five of these 86 patients (98.8%) regained MMR, (one patient discontinued study permanently due to subject decision) and 76 patients (88.4%) regained MR4.5 by the time of the cut-off date.~~

~~The Kaplan-Meier (KM) estimated median time on nilotinib treatment to regain MMR and MR4.5 was 7.9 weeks (95% CI: 5.1, 8.0) and 13.1 weeks (95% CI: 12.3, 15.7), respectively. The KM estimated MMR and MR4.5 rates at 24 weeks of re-initiation were 98.8 % (95% CI: 94.2, 99.9) and 90.9 % (95% CI: 83.2, 96.0), respectively.~~

~~The KM~~

**Table 12 Treatment-free remission after nilotinib first-line treatment**

| Patients entered TFR phase | 190 | |
|---|---|---|
| weeks after starting TFR phase | 48 weeks | 264 weeks |
| patients remaining in MMR or better | 98 (51.6%, [95% CI: 44.2, 58.9]) | 79[2] (41.6%, 95% CI: 34.5, 48.9) |
| Patients discontinued TFR phase | 93 [1] | 109 |
| due to loss of MMR | 88 (46.3%) | 94 (49.5%) |
| due to other reasons | 5 | 15 |
| Patients restarted treatment after loss of MMR | 86 | 91 |
| regaining MMR | 85 (98.8%) | 90 (98.9%) |
| regaining MR4.5 | 76 (88.4%) | 84 (92,3%) |

[1] One patient did not lose MMR by week 48 but discontinued TFR phase.
[2] For 2 patients, PCR assessment was not available at week 264 therefore their response was not considered for the week 264 data cut-off analysis.

The time by which 50% of all retreated patients regained MMR and MR4.5 was 7 and 12.9 weeks, respectively. The cumulative rate of MMR regained at 24 weeks after treatment re-initiation was 97.8% (89/91 patients) and MR4.5 regained at 48 weeks was 91.2% (83/91 patients).

The Kaplan-Meier estimate of median treatment~~-~~-free survival (TFS) ~~has not yet been reached~~was 120.1 weeks (95% CI: 36.9, not estimable [NE]) (Figure 4); ~~99~~91 of 190 patients (~~52.1~~47.9%) did not have a TFS event.

**Novartis Israel Ltd.**
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

**נוברטיס ישראל בע"מ**
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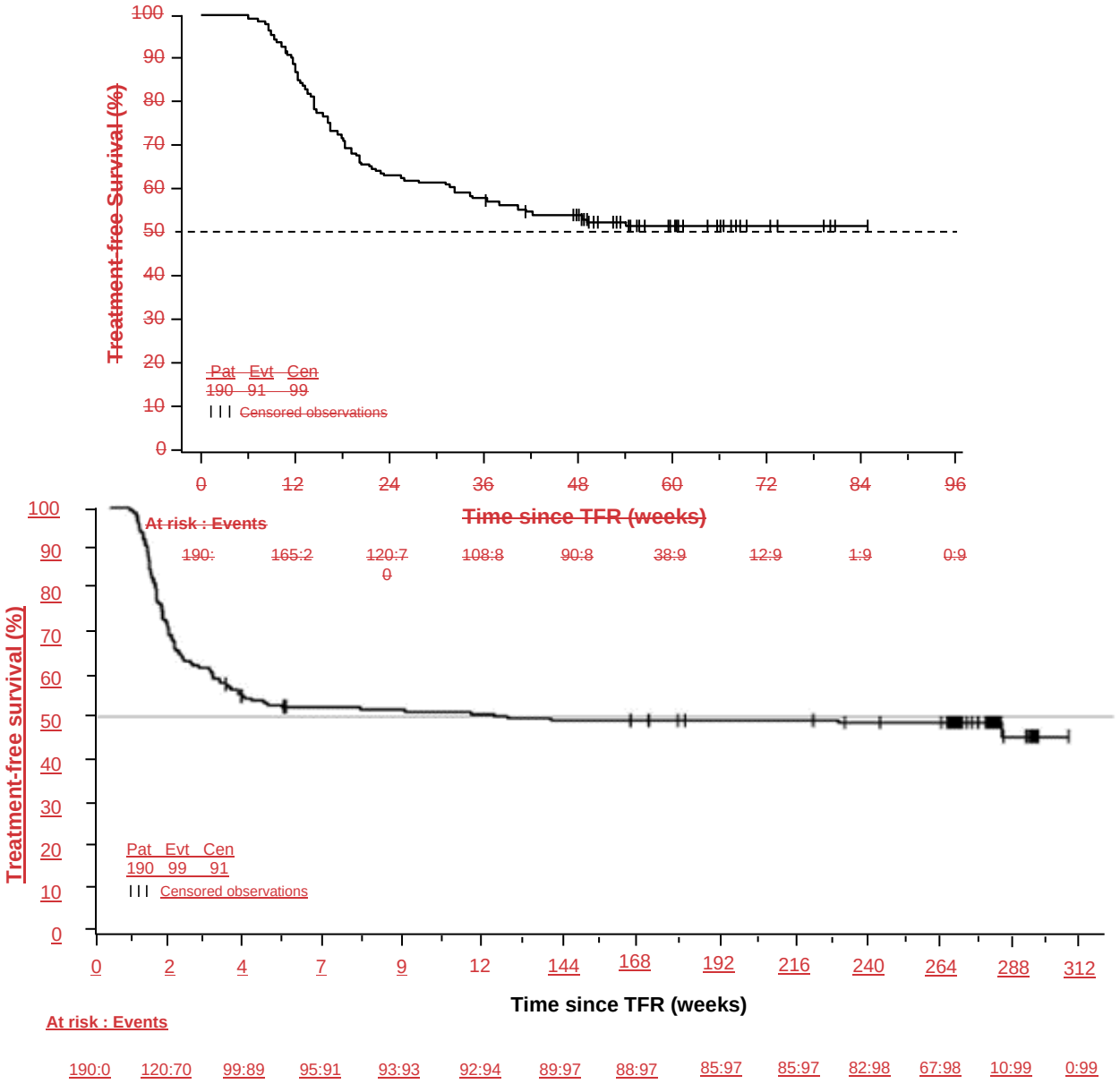
**Figure 4** **Kaplan-Meier estimate of treatment-free survival after start of TFR (full analysis set)**




*Treatment discontinuation in adult CML patients in chronic phase who have achieved a sustained deep molecular response on nilotinib treatment following prior imatinib therapy*

In an open-label, single-arm study, 163 adult patients with Ph+ CML in chronic phase taking tyrosine kinase inhibitors (TKIs) for ≥3 years (imatinib as initial TKI therapy for more than 4 weeks without

**Novartis Israel Ltd.**
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

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documented MR4.5 on imatinib at the time of switch to nilotinib, then switched to nilotinib for at least two years), and who achieved MR4.5 on nilotinib treatment as measured with the MolecularMD MRDx™ BCR-ABL test were enrolled to continue nilotinib treatment for additional 52 weeks (nilotinib consolidation phase). 126 of 163 patients (77.3%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criterion:

- The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL ≤0.0032% IS) during one year.

The primary endpoint was the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following treatment discontinuation. ~~Of the 126 patients who entered the TFR phase, 73 patients (57.9%, [95% CI: 48.8, 66.7]) had no loss of MMR, no confirmed loss of MR4.0, and no re-initiation of nilotinib within 48 weeks.~~

~~Among the 53 patients who discontinued the TFR phase due to confirmed loss of MR4.0 or loss of MMR, 51 patients restarted nilotinib and 2 patients discontinued the study. Forty-eight of these 51 patients (94.1%) regained MR4.0 and 47 patients (92.2%) regained MR4.5 by the time of the cut-off date.~~

**Table 13 Treatment-free remission after nilotinib treatment following prior imatinib therapy**

| Patients entered TFR phase | 126 | |
|---|---|---|
| weeks after starting TFR phase | 48 weeks | 264 weeks |
| patients remaining in MMR, no confirmed loss of MR4.0, and no re-initiation of nilotinib | 73 (57.9%, [95% CI: 48.8, 66.7]) | 54 (42.9% [54/126, 95% CI: 34.1, 52.0]) |
| Patients discontinued TFR Phase | 53 | 74 [1] |
| due to confirmed loss of MR4.0 or loss of MMR | 53 (42.1%) | 61 (82.4%) |
| due to other reasons | 0 | 13 |
| Patients restarted treatment after loss of MMR or confirmed loss of MR4.0 | 51 | 59 |
| regaining MR4.0 | 48 (94.1%) | 56 (94.9%) |
| regaining MR4.5 | 47 (92.2%) | 54 (91.5%) |

[1] two patients had MMR (PCR assessment) at 264 weeks but were discontinued later and had no further PCR assessment.

The Kaplan-~~-~~Meier ~~(KM)~~ estimated median time on nilotinib to regain MR4.0 and MR4.5 was ~~12.0~~11.1 weeks (95% CI:~~8.3~~1, 12.~~7~~1) and 13.1 weeks (95% CI:~~12.4, 16.1~~0, 15.9), respectively. The ~~KM estimated~~cumulative rate of MR4~~.0~~ and MR4.5 ~~rates at~~regained by 48 weeks ~~of~~after treatment re-initiation ~~were 100.0% (95% CI: not estimated~~was 94.9% (56/59 patients) and ~~94.8% (95% CI: 85.1, 99.0~~91.5% (54/59 patients), respectively.

The median TFS ~~has not yet been reached~~Kaplan-Meier estimate is 224 weeks (95% CI: 39.9, NE) (Figure 5); ~~74~~63 of 126 patients (~~58.7~~50.0%) did not have a TFS event.

**Novartis Israel Ltd.**
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

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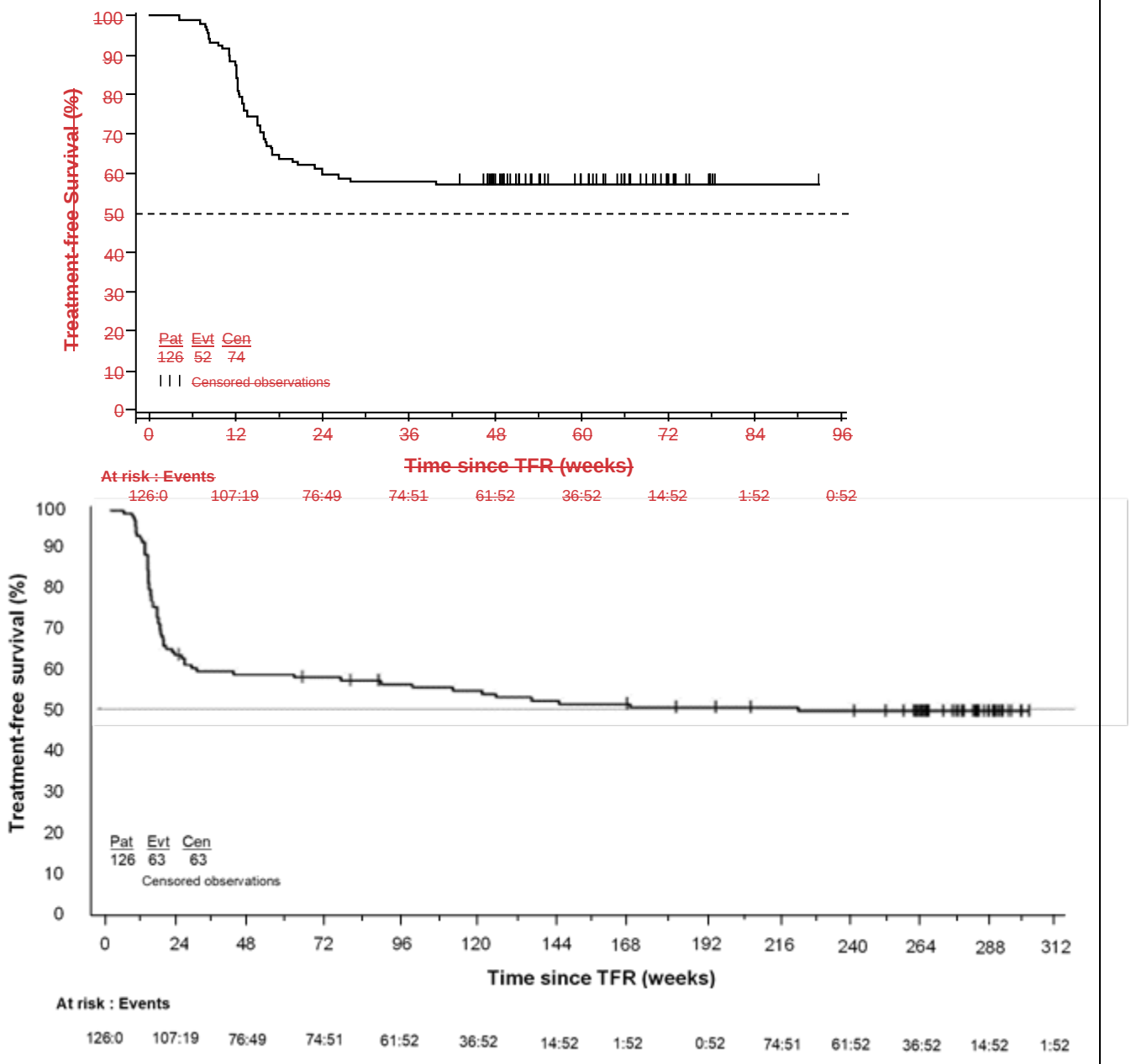
**Figure 5 Kaplan-Meier estimate of treatment-free survival after start of TFR (full analysis set)**

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Revised ~~on December 2020~~in August 2021 according to MOH guidelines.

**Novartis Israel Ltd.**
6 Totzeret Ha'arets St.
P.O.B 7126, Tel Aviv, Israel
Tel: 972-3-9201123 Fax: 972-3-9229331

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