Public Assessment Report
YERVOY

INFORMASI PRODUK

Nama obat	:	YERVOY
Bentuk sediaan	:	Larutan konsentrat untuk infus
Zat aktif	:	Ipilimumab 5 mg/mL
Kemasan	:	Dus, 1 vial @ 50 mg
Pendaftar	:	PT Mecosin Indonesia
Produsen	:	Diproduksi dan dikemas Oleh Samsung Biologics Co. Ltd., Incheon, Republic of Korea Dirilis oleh Sword Laboratories Unlimited Company, Dublin, Irlandia
Kategori Registrasi	:	Registrasi produk biologi baru
Indikasi yang diajukan	:	*Renal cell carcinoma (RCC)* *YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.* *Non-small cell lung cancer (NSCLC)* *YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.*
Posologi yang diajukan	:	***YERVOY in combination with nivolumab*** *Renal cell carcinoma* *The recommended dose is 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, as presented in Table 1. For the monotherapy phase, the first dose of nivolumab should be administered;* - *3 weeks after the last dose of the combination of ipilimumab and nivolumab if using 240 mg every 2 weeks; or* - *6 weeks after the last dose of the combination of ipilimumab and nivolumab if using 480 mg every 4 weeks.*

Table 1: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab for RCC

	Combination phase, every 3 weeks for 4 dosing cycles	Monotherapy phase
Nivolumab	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minute or 480 mg every 4 weeks over 60 minutes
Ipilimumab	1 mg/kg over 30 minutes	

YERVOY in combination with nivolumab and chemotherapy
Non-small cell lung cancer
The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 1 mg/kg ipilimumab every 6 weeks in combination with

360 mg nivolumab administered intravenously every 3 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Duration of treatment
Treatment with YERVOY in combination with nivolumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with YERVOY in combination with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Table 2 and section 4.4).

Children younger than 18 years of age
The safety and efficacy of ipilimumab in children younger than 18 years of age has not been established.

Permanent discontinuation of treatment or withholding of doses
Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see section 4.4).
Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
Guidelines for permanent discontinuation or withholding of doses are described in Table 2 for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment.

Table 2: Recommended treatment modifications for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment.

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete.
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete.
	Grade 3 or 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete.
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin.	Permanently discontinue treatment.
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete.
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment

Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment
	Grade 4 rash	Permanently discontinue treatment (see section 4.4)
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b] Permanently discontinue treatment
	Grade 3 or 4 myocarditis	
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

[a] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

[b] The safety of re-initiating ipilimumab in combination with nivolumab therapy in patients previously experiencing immune-related myocarditis is not known.

YERVOY in combination with nivolumab should be permanently discontinued for:

- *Grade 4 or recurrent Grade 3 adverse reactions.*
- *Persistent Grade 2 or 3 adverse reactions despite management.*

When YERVOY is administered in combination with nivolumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient.

Special populations

Paediatric population
The safety and efficacy of YERVOY in combination with nivolumab in children younger than 18 years of age have not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Elderly
No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from first-line RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). No specific dose adjustment is necessary in this population.

Renal impairment
The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction.

Hepatic impairment
The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild hepatic impairment (see section 5.2). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.

PENGANTAR

Yervoy adalah produk biologi baru dengan zat aktif Ipilimumab. Ipilimumab adalah *human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody* yang diindikasikan untuk pengobatan *unresectable* atau *metastatic melanoma.*

Yervoy merupakan larutan konsentrat untuk infus dimana tiap mL mengandung 5 mg Ipilimumab, dengan indikasi untuk non-small cell lung cancer (NSCLC) dan Renal cell carcinoma (RCC). Ipilimumab (Yervoy) adalah obat inovator di Indonesia dan saat ini satu-satunya produk yang disetujui beredar di Indonesia.

Renal cell carcinoma meliputi 2% dari semua malignancy pada dewasa. Di seluruh dunia, sekitar 270.000 kasus baru didiagnosis, dan sekitar 116.000 pasien meninggal tiap tahun. Pengobatan menggunakan sitokin, seperti IL-2 dan IFN, dapat memberikan respon pada 5% hingga 20% pasien, mencakup *complete response* yang panjang pada beberapa pasien, namun pengobatan ini dikaitkan dengan potensi *life-threatening toxicity*.

Kanker paru merupakan kanker yang paling umum di seluruh dunia, dengan 1,8 juta kasus baru didiagnosis tiap tahun, dan diperkirakan 1,6 juta kematian terjadi tiap tahun. NSCLC merepresentasikan sekitar 85% dari semua kanker paru.

Saat ini, *platinum-doublet chemotherapy* merupakan standar terapi yang direkomendasikan untuk *first-line treatment* pada *metastatic NSCLC*. Namun, *first-line platinum-based chemotherapy* tidak memberikan hasil yang cukup baik dengan median OS 10-14 bulan, median PFS 5-6 bulan, dan ORR 30% - 35%.

ASPEK MUTU

Pengantar

Produk jadi Yervoy tersedia dalam bentuk larutan konsentrat untuk infus, dikemas dalam vial (1 Vial @ 50 mg), dimana tiap mL mengandung ipilimumab 5 mg. Obat jadi Yervoy mengandung bahan tambahan yang terdiri dari Tris hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride), Sodium chloride, Mannitol (E421), Pentetic acid (diethylenetriaminepentaacetic acid), Polysorbate 80, Sodium hydroxide (for pH-adjustment), Hydrochloric acid (for pH-adjustment), Water for injections. Produk harus disimpan pada suhu 2-8ºC, tidak dibekukan, terlindung cahaya.

Zat Aktif

Zat aktif Ipilimumab diproduksi oleh Samsung Biologics Co. Ltd. 300, SongDo Bio-Daero, Yeongsu-gu, Incheon, Republic of Korea. Pengembangan produk termasuk cell bank dilakukan di Bristol-Myers Squibb Company (BMS)-Syracuse dan Lonza Biologics di Portsmouth, New Hampshire (Lonza).

Ipilimumab diproduksi melalui proses kultur sel menggunakan Chinese hamster ovary (CHO) *cell line*. Proses pembuatan zat aktif atau drug substance (DS) Ipilimumab terdiri dari proses thawing WCB (working cell bank), perbanyakan sel menggunakan shake flask, seed bioreactor dan production bioreactor. Setelah proses kultur, kemudian dilanjutkan pada proses downstream yaitu serangkaian proses pemurnian menggunakan kromatografi dan filtrasi. Pada proses downstream juga mencakup tahapan inaktivasi viral. Produk yang dihasilkan adalah unformulated bulk drug substance. Selanjutnya produk diformulasikan dengan Polisorbat 80 untuk menghasilkan bulk drug substance. Tiap lot formulated bulk drug substance difiltrasi menggunakan membrane filter ke dalam bioprocess container hingga dihasilkan drug substance. Tersedia sertifikat bebas BSE/TSE, dan dilakukan kontrol terhadap adventitious agent.

Parameter proses yang kritis, uji IPC dan release telah ditetapkan untuk mengendalikan proses. Kontrol terhadap tahapan kritis dalam proses produksi ditetapkan dan diserahkan.
Prosedur pengujian dan ringkasan validasi metode uji IPC diberikan dengan hasil yang memenuhi kriteria penerimaan yang ditetapkan. Validasi proses produksi zat aktif Ipilimumab diserahkan dengan hasil validasi menunjukkan proses produksi konsisten dan memenuhi kriteria penerimaan validasi yang ditetapkan. Karakterisasi terhadap zat aktif telah dilakukan secara memadai. Impurities telah diidentifikasi dan kadarnya terkontrol secara memadai.
Spesifikasi zat aktif telah ditetapkan mencakup parameter uji, informasi metode uji serta kriteria penerimaan. Informasi prosedur uji diserahkan serta telah divalidasi. *Shelf life* zat aktif didukung dengan data stabilitas pada 5 ± 3°C selama 36 bulan.

Obat jadi

Obat jadi Yervoy (Ipilimumab) merupakan sediaan steril, bebas pyrogen dan pengawet. Obat jadi Yervoy diproduksi oleh Samsung Biologics Co. Ltd. 300, SongDo Bio-Daero, Yeongsu-gu, Incheon, Republic of Korea, dan dirilis oleh Sword Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics, Ireland.
Rangkaian proses pembuatan produk jadi terdiri dari pooling drug substance ke dalam mixing tank dengan pengendalian bioburden, sterilisasi dengan membrane filter dan filling secara aseptis. Proses produksi diserahkan dengan rincian yang memadai. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan. Validasi terhadap proses produksi telah dilakukan, mencakup validasi proses pembuatan (proses formulasi, *filling)* dan validasi *media fill*. Hasil validasi menunjukkan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.
Spesifikasi obat jadi telah ditetapkan, mencakup parameter uji, referensi metode uji serta kriteria penerimaannya. Prosedur uji telah divalidasi. Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain kapabilitas proses, hasil uji bets yang digunakan dalam uji klinik dan hasil validasi proses skala komersial.
Data stabilitas obat jadi mendukung penyimpanan obat jadi selama 36 bulan pada suhu 2-8°C.

Kesimpulan

Dari aspek mutu, Produk Yervoy dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

Studi non klinik yang dilakukan yaitu studi farmakodinamik primer, studi farmakokinetik dan studi toksikologi. Berdasarkan studi non klinik yang diserahkan menunjukkan bahwa:

1. Studi farmakodinamik primer
   a. Blokade CTLA-4 oleh ipilimumab menyebabkan penghambatan atau supresi pertumbuhan tumor pada *human CTLA-4 transgenic mouse model*.
   b. Studi pada *cynomolgus monkeys* menunjukkan ipilimumab menyebabkan peningkatan respon antibodi terhadap *T cell-dependent antigens* dan meningkatkan proliferasi sel T.

2. Studi farmakokinetik
   Secara umum, ipilimumab tidak imunogenik pada monyet. Pembentukan antibodi anti ipilimumab diamati pada 9 dari 106 (8%) hewan uji.

   a. Toksisitas dosis berulang
      NOAEL untuk studi toksisitas berulang, dosis iplimumab melampaui maximum anticipated clinical dose 3-10 kali (10 mg/kg)

Studi Klinik

Studi Klinik yang diserahkan yaitu sebagai berikut:

1. Indikasi Non-Small Cell Lung Cancer (NSCLC)

Terdapat 3 studi klinik yang mendukung indikasi NSCLC yaitu 1 studi klinik fase I (studi MDX-1006-01, 1 studi klinik fase II (studi CA209568) dan 1 studi klinik fase III (studi CA2099LA)
Studi CA2099LA
Studi klinik fase III CA2099LA (n=1150) yang dilakukan pada pasien usia ≥18 tahun dengan *histologically confirmed stage IV NSCLC* yang belum pernah menerima terapi antikanker sistemik, termasuk *epidermal growth factor receptor* (EGFR) dan *anaplastic lymphoma kinase [ALK] inhibitors*, sebagai terapi primer untuk kondisi *advanced* atau *metastatic disease*.
Subjek dirandomisasi 1:1 ke dalam kelompok nivobluma+ipilimumab+kemoterapi atau kemoterapi. Faktor stratifikasi untuk randomisasi berdasarkan pada level PD-L1 (31% vs < 1%), histologi (*squamous [SQ]* vs *non-squamous [NSQ]*), dan jenis kelamin (pria vs wanita).

2. **Indikasi Renal cell carcinoma (RCC)**
Terdapat 2 studi klinik yang mendukung indikasi RCC yaitu studi klinik fase I (CA209016) dan fase III (CA209214)
Studi CA209214
Studi klinik fase III (CA209214) (N=1082) merupakan studi open label yang membandingkan kombinasi nivolumab + ipilimumab dengan monoterapi sunitinib pada pasien usia ≥18 tahun dengan *previously untreated advanced* atau *metastatic renal cell carcinoma* (mRCC).
Subjek dirandomisasi 1:1 dan distratifikasi berdasarkan *International Metastatic RCC Database Consortium (IMDC) prognostic score* (0 vs 1-2 vs 3-6) dan region (*US vs Canada/Western Europe/Northern Europe vs Rest of World*).

Selain studi klinik, juga diserahkan dokumen *Periodic Benefit-Risk Evaluation Report (PBRER)* dan *Risk Management Plan.*
PBER (Periode 4 Jul 2022 – 3 Jul-2023) menunjukkan :
- Sebanyak 42.657 subjek mendapatkan nivolumab monoterapi, kombinasi nivolumab+ipilimumab dan nivolumab+produk lain dari BMS. Tidak ada *safety-related actions* yang bermakna terkait ipilimumab selama periode pelaporan.
- Benefit-risk profile ipilimumab dan kombinasi ipilimumab + nivolumab tetap *favorable* untuk indikasi yang diajukan.

Dokumen RMP tahun 2023 menunjukkan :
- Resiko penting yang teridentifikasi yaitu : *GI irARs (eg. Diarrhea, colitis, GI perforation), Hepatic irARs (eg, hepatitis), Skin irARs (eg, rash, pruritus, TEN, and DRESS), Neurologic irARs (eg, neuropathy), Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency), Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis), Severe infusion reactions*
- Risiko potensial penting yang teridentifikasi yaitu : *Immunogenicity, Risk of GVHD in patients with history of previous allogeneic HSCT during treatment with ipilimumab*.

Hasil evaluasi terhadap studi klinik

1. **Indikasi Non-Small Cell Lung Cancer (NSCLC)**
   - Nilai *Overall Survival* (OS) subjek kelompok nivo+ipi+kemo menunjukkan perbaikan signifikan dibandingkan kelompok kemoterapi tunggal, dengan HR = 0,69 (96.71% CI: 0.55, 0.87) dan *p-value* = 0,0006. Nilai Median OS (95% CI) nivo+ipi+kemo vs kemoterapi tunggal yaitu sebesar 14,13 bulan vs 10,74 bulan.
   - Hasil analisis subgrup nilai HR OS subgrup nivo+ipi+kemo vs kemoterapi tunggal terlihat konsisten pada subgrup berdasarkan histologi dan status PD-L1, yaitu:
     - Histologi: HR = 0,65 (95% CI: 0,46, 0.93) pada histologi squamous dan HR = 0,72 (95% CI: 0,55, 0,93) pada non-squamous.
     - Status PD-L1: HR = 0,67 (95% CI: 0,51, 0,89) pada PD-L1 >=1% dan HR = 0,65 (95% CI: 0,46, 0,92) pada PD-L1 < 1%.
   - *Nilai Progression Free Survival* (PFS) skelompok nivo+ipi+kemo menunjukkan perbaikan signifikan dibandingkan kelompok kemoterapi tunggal, dengan HR = 0,70 (97.48% CI: 0,57, 0,86) dan *p-value* = 0,0001. Nilai Median PFS (95% CI) nivo+ipi+kemo vs kemoterapi tunggal yaitu sebesar 6,83 bulan vs 4,96 bulan.

- Hasil analisis subgrup nilai HR PFS subgrup nivo+ipi+kemo vs chemotherapy tunggal:
  - Histologi: HR = 0,57 [95% CI: 0,42, 0,79] pada histologi squamous dan HR = 0,78 [95% CI: 0,63, 0,97] pada non-squamous.
  - Status PD-L1 HR = 0,67 [95% CI: 0,53, 0,85] pada PD-L1 >=1% dan HR = 0,77 [95% CI: 0,57, 1,03] PD-L1 < 1%.
- Nilai *Objective Response Rate* (ORR) nivo+ipi+kemo vs kemoterapi tunggal = 37,7% (95% CI: 32,7, 42,9) vs 25,1% (95% CI:20,7, 30,0) p-value = 0,0003; dan nilai HR terlihat konsisten berdasarkan subgrup histologi dan status PD-L1.
- *Median duration of response* (DoR) lebih panjang untuk nivo+ipi+kemo dibandingkan kemoterapi: 10,02 bulan vs 5,09 bulan.
- Keamanan
  - Kematian karena *study drug toxicity* lebih tinggi pada kelompok nivo+ipi+kemo dibandingkan dengan kemoterapi: 7(2,0%) vs 6 (1,7%)
  - Kejadian SAE yang terkait obat grade 3-4 lebih tinggi pada kelompok nivo+ipi+kemo dibandingkan dengan kemoterapi: 90 (25,1%) vs 51 (14,6%).

2. Indikasi Renal cell carcinoma (RCC)

- Nilai ORR pada subjek nivolumab + ipilimumab menunjukkan perbaikan signifikan dibandingkan dengan sunitinib monoterapi adalah sebesar 38,7% vs 32,2%.
- Median DOR tidak tercapai pada waktu *database lock* sedangkan median DOR pada sunitinib monoterapi adalah 18,17 bulan.
- Nilai PFS Subjek kelompok nivo+ipi menunjukkan perbaikan signifikan dibandingkan kelompok sunitinib tunggal, dengan 0,82, [99.1% CI: 0,64 - 1,05 p-value = 0,0331.
- Nilai Median PFS (nivo+ ipi vs sunitinib tunggal yaitu sebesar 11,56 bulan vs 8,38 bulan.
- Nilai OS Subjek kelompok nivo+ipi menunjukkan superior dibandingkan kelompok sunitinib tunggal, dengan HR: 0,63 [99.8% CI: 0.44, 0.89] p-value = 0,0001.
- Keamanan : Ada 7 kematian yang berkaitan dengan nivo+ipi vs 4 kematian yang berkaitan obat uji sunitinib monoterapi. Frekuensi all-causality AE grade 3-4 lebih rendah (65,3%) vs sunitinib (76,1%), AE dan IMAE kebanyakan adalah *low-grade*, membaik, dan dapat diatasi dengan pengobatan yang direkomendasikan.

EVALUASI

Penilaian Manfaat – Risiko

Ipilimumab adalah *human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody* yang diindikasikan untuk pengobatan *unresectable atau metastatic melanoma*.

Yervoy terdaftar dengan bentuk sediaan larutan konsentrat untuk infus. Zat tambahan yang digunakan adalah *polysorbate 80, tris hydrochloride, sodium chloride, mannitol, sodium hydroxide, hydrochloric acid, pentetic acid,* dan *water for injection*. Yervoy dikemas dalam vial dengan besar kemasan Dus, 1 vial @ 50 mg. Obat ini harus disimpan dalam lemari pendingin (2-8ºC) dan stabil selama 36 bulan.

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi klinik, Etapidi memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut:

1. Aspek yang menguntungkan
   a. Indikasi NSCLC
      - Nivolumab+ipilimumab+kemoterapi menunjukkan *overall survival* lebih baik dibanding kemoterapi tunggal, dengan HR = 0,69 (96.71% CI: 0.55, 0.87); p-value = 0,0006 dan nilai median OS (95% CI) nivolumab+ipilimumab+kemoterapi vs kemoterapi tunggal sebesar 14,13 bulan vs 10,74 bulan.
      - Analisis subgrup nilai HR OS subgrup nivolumab+ipilimumab+kemoterapi vs kemoterapi tunggal menunjukkan hasil konsisten pada subgrup berdasarkan histologi dan status PD-L1, yaitu:
        - Histologi: HR = 0,65 (95% CI: 0,46, 0.93) pada histologi squamous dan HR = 0,72 (95% CI: 0,55; 0,93) pada non-squamous.
        - Status PD-L1: HR = 0,67 (95% CI: 0,51, 0,89) pada PD-L1 >=1% dan HR = 0,65 (95% CI: 0,46; 0,92) pada PD-L1 < 1%.

- Tidak isu terkait keamanan atau toksisitas baru yang diidentifikasi, baik pada kombinasi nivolumab+ipilimumab+kemoterapi maupun monoterapi.

b. Indikasi RCC
   - Nilai ORR pada subjek nivolumab + ipilimumab menunjukkan perbaikan signifikan dibandingkan dengan sunitinib monoterapi adalah sebesar 38,7% vs 32,2%.
   - Nilai PFS Subjek kelompok nivo+ipi menunjukkan perbaikan signifikan dibandingkan kelompok sunitinib tunggal, dengan 0,82, [99.1% CI: 0,64 - 1,05 p-value = 0,0331. Nilai Median PFS (nivo+ ipi vs sunitinib tunggal yaitu sebesar 11,56 bulan vs 8.38 bulan.
   - Nilai OS Subjek kelompok nivo+ipi menunjukkan superior dibandingkan kelompok sunitinib tunggal, dengan HR: 0,63 [99.8% CI: 0.44, 0.89] p-value = 0,0001.
   - Frekuensi *all-causality AE* grade 3-4 lebih rendah (65,3%) vs sunitinib (76,1%), AE dan IMAE kebanyakan adalah *low-grade*, membaik, dan dapat diatasi dengan pengobatan yang direkomendasikan.

2. Aspek yang tidak menguntungkan

   a. Indikasi NSCLC
      - Kematian karena study drug toxicity lebih tinggi pada kelompok nivo+ipi+kemo dibandingkan dengan kemoterapi, yaitu 7(2,0) vs 6 (1,7).
      - Kejadian SAE yang terkait obat grade 3-4 lebih tinggi pada kelompok nivo+ipi+kemo dibandingkan dengan kemoterapi, yaitu 90 (25,1) vs 51 (14,6).

   b. Indikasi RCC
      Kematian yang berkaitan dengan nivolumab+ipilimumab lebih tinggi dibandingkan kematian yang berkaitan dengan sunitinib (7 vs 4).

3. Ketidak pastian dan keterbatasan (NA)

Kesimpulan evaluasi manfaat – risiko:
Secara keseluruhan Yervoy menunjukkan kemanfaatan dalam pengobatan NSCLC dan RCC. Kejadian efek samping yang terjadi sesuai dengan profil keamanan yang sudah dikenal dari obat studi dan rejimen kemoterapi serta tidak ada isu keamanan baru. Dengan demikian, dipertimbangkan manfaat Yervoy lebih besar dari risikonya.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi Yevoy **diterima sesuai dengan indikasi dan posologi yang diajukan,** yaitu:

Indication

Renal cell carcinoma (RCC)

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

Non-small cell lung cancer (NSCLC)

YERVOY in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

Posology

YERVOY in combination with nivolumab

Renal cell carcinoma

The recommended dose is 1 mg/kg ipilimumab in combination with 3 mg/kg nivolumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, as presented in Table 1. For the monotherapy phase, the first dose of nivolumab should be administered;

- *3 weeks after the last dose of the combination of ipilimumab and nivolumab if using 240 mg every 2 weeks; or*
- *6 weeks after the last dose of the combination of ipilimumab and nivolumab if using 480 mg every 4 weeks.*

Table 1: Recommended doses and infusion times for intravenous administration of ipilimumab in combination with nivolumab for RCC

	Combination phase, every 3 weeks for 4 dosing cycles	Monotherapy phase
Nivolumab	3 mg/kg over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes
Ipilimumab	1 mg/kg over 30 minutes	

YERVOY in combination with nivolumab and chemotherapy

Non-small cell lung cancer

The recommended dose is 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks in combination with 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 1 mg/kg ipilimumab every 6 weeks in combination with 360 mg nivolumab administered intravenously every 3 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Duration of treatment

Treatment with YERVOY in combination with nivolumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication).

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with YERVOY in

combination with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Table 2 and section 4.4).

Children younger than 18 years of age
The safety and efficacy of ipilimumab in children younger than 18 years of age has not been established.

Permanent discontinuation of treatment or withholding of doses
Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see section 4.4).
Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
Guidelines for permanent discontinuation or withholding of doses are described in Table 2 for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment.

Table 2: Recommended treatment modifications for YERVOY in combination with nivolumab or administration of the second phase of treatment (nivolumab monotherapy) following combination treatment.

Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete. Permanently discontinue treatment
	Grade 3 or 4 pneumonitis	
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete. Permanently discontinue treatment
	Grade 3 or 4 diarrhoea or colitis	
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete. Permanently discontinue treatment.
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin.	
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete.

	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment
	Grade 4 rash Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

[a] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

[b] The safety of re-initiating ipilimumab in combination with nivolumab therapy in patients previously experiencing immune-related myocarditis is not known.

YERVOY in combination with nivolumab should be permanently discontinued for:

- *Grade 4 or recurrent Grade 3 adverse reactions;*
- *Persistent Grade 2 or 3 adverse reactions despite management.*

When YERVOY is administered in combination with nivolumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient.

Special populations

Paediatric population
The safety and efficacy of YERVOY in combination with nivolumab in children younger than 18 years of age have not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Elderly
No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from first-line RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). No specific dose adjustment is necessary in this population.

Renal impairment
The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction.

Hepatic impairment
The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild hepatic impairment (see section 5.2). YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline.