Electronic Supplementary Material

Article title: Interstitial Lung Disease as an Adverse Drug Reaction in Japan: Exploration of Regulatory Actions as a Basis for High Reporting

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Below are the results:

A table with detailed information about regulatory records for the top 6 drugs with highest reporting of ILD, plus nivolumab

A figure of reporting patterns

	Methotrexate	Gefitinib	Gemcitabine	Docetaxel	Everolimus	Erlotinib	Nivolumab
Indication	1. Acute leukaemia Chronic lymphocyte leukaemia, chronic myeloid leukaemia Trophoblastic diseases (choriocarcinoma, invasive mole, hydatidiform mole) Sarcoma Malignant myeloma Breast cancer Urothelial cancer Stomach cancer with concomitant use of other agents 2. Rheumatoid arthritis Plaque psoriasis with inadequate response to local therapy Psoriatic arthropathy Pustular psoriasis Erythrodermic psoriasis Juvenile idiopathic arthritis with joint symptoms	EGFR mutation positive inoperable or recurrent non-small cell lung cancer	1. Non-small cell lung cancer 2. Pancreatic cancer 3. Biliary tract cancer, urothelial cancer, inoperable/recurrent breast cancer, ovarian cancer exacerbated after cancer chemotherapy and recurrent/refractory malignant lymphoma	Breast cancer, non-small cell lung cancer, stomach cancer, head and neck cancer, ovarian cancer, esophagus cancer, uterine corpus cancer, prostate cancer	< Afinitor tablets > 1. Unresectable and/or metastatic renal cell carcinoma 2. Neuroendocrine tumor 3. Unresectable and/or recurrent breast cancer 4. Tuberous sclerosis complex < Afinitor dispersible tablets > 5. Tuberous sclerosis complex < Certican > Inhibition of the rejection response to transplanted 6. heart 7. kidney 8. liver	1. Unresectable, recurrent and progressive non-small cell lung cancer exacerbated after cancer chemotherapy 2. Pancreatic cancer not amenable to curative resection 3. EGFR mutation positive chemotherapy-naive non-small cell lung cancer which is unresectable, recurrent and progressive	1. Malignant melanoma 2. Unresectable advanced and/or recurrent non-small cell lung cancer 3. Unresectable or metastatic renal cell carcinoma 4. Relapsed or refractory classical Hodgkin's lymphoma 5. Recurrent or metastatic head and neck cancer 6. Unresectable advanced or recurrent stomach cancer progressing after cancer chemotherapy 7. Unresectable advanced and/or recurrent malignant pleural mesothelioma progressing after cancer chemotherapy
Re-examination period	1. Not published 2. From 12 Mar 1999 to 11 Mar 2003	From 05 Jul 2002 to 04 Jul 2010	1. From 12 Mar 1999 to 11 Mar 2005* 2. From 04 Apr 2001 to 03 Apr 2011 3. -	From 09 Oct 1996 to 08 Oct 2002*	< Afinitor tablets > 1. From 20 Jan 2010 to 19 Jan 2018 2. (Pancreatic neuroendocrine tumor) From 22 Dec 2011 to 19 Jan 2018 (Neuroendocrine tumor except pancreatic neuroendocrine tumor) From 26 Aug 2016 to 19 Jan 2018 3. From 17 Mar 2014 to 19 Jan 2018 4. From 21 Nov 2012 to 20 Nov 2022 < Afinitor dispersible tablets > 5. From 25 Dec 2012 to 24 Dec 2022 < Certican > 6. From 26 Jan 2007 to 25 Jan 2017 7. From 22Dec2011 to 25 Jan 2017 8. From 23 Feb 2018 to 22 Feb 2022	1. From 19 Oct 2007 to 18 Oct 2015 2. From 01 Jul 2011 to 18 Oct 2015 3. From 14 Jun 2013 to 18 Oct 2015	1. From 04 July 2014 to 03 Jul 2024 2. From 17 Dec 2015 to 16 Oct 2021 3. From 26 Aug 2016 to 16 Oct 2021 4. From 02 Dec 2016 to 01 Dec 2026 5. From 24 Mar 2017 to 16 Oct 2021 6. From 22 Sep 2017 to 16 Oct 2021 7. From 21 Aug 2018 to 20 Aug 2028
Duration for use-results survey	1,2. Not published	From Jun 2003 to Mar 2004	1. Not published 2. From 01 May 2001 to 31 Mar 2004 3. -	From Oct 1996 to Oct 2002*	< Afinitor > 1. Mar 2010 to Jan 2018 2. 22 Dec 2011 to 18 Jan 2018 3. Not published 4. From 21 Nov 2012 to Dec 2018 5. From 25 Dec 2012 to Dec 2018 < Certican > 6,7. Not published 8. From Apr 2018 (ongoing)	1. Dec 2007 to Mar 2011 2. (For specific institutions) From Jul 2011 to Dec 2014 (For other institutions) From May 2014 to Mar 2016 3. -	1. From 04 Jul 2014 to May2020 2. From 17 Dec 2015 to Jun 2020 3. From 26 Aug 2016 to Apr2020 4. From 02 Dec 2016 to Nov 2022 5. From 24 Mar 2017 to Mar2020 6. From Nov 2017 to Apr 2021 7. From Nov 2018 to Apr 2022
Type of use-results survey and ILD position	1,2. Not published	The survey set lung injury including ILD as a safety priority item and was intended to identify risk factors of lung injury and ILD.	1. Not published 2. Use-results surveys were set. 3. -	Not published	< Afinitor > 1,2. Use-results surveys were set. Those surveys set ILD as safety priority item. 4,5. Use-results surveys were set. Those surveys set ILD as safety specifications in RMP. 3. Not published < Certican > 6. All-case surveillance was set. This survey set pneumonitis as a safety priority item.+ 7. Use-results survey was set. This survey set ILD as a safety priority item.+ 8. Special use-results survey is set. This survey set ILD as a safety specification in RMP.	1,2. All-case surveillances were set. Those surveys set ILD as safety priority items. 1. Post-marketing clinical trial to explore biomarkers of ILD was performed. 3. -	1-5. All-case surveillances are set (only unresectable malignant melanoma for 1). Those surveys set ILD as safety specifications. 6. Use-results survey is set. 7. Use-results survey is set.

As of November 2019
* Confirmed from Interview form
+ Confirmed from review reports

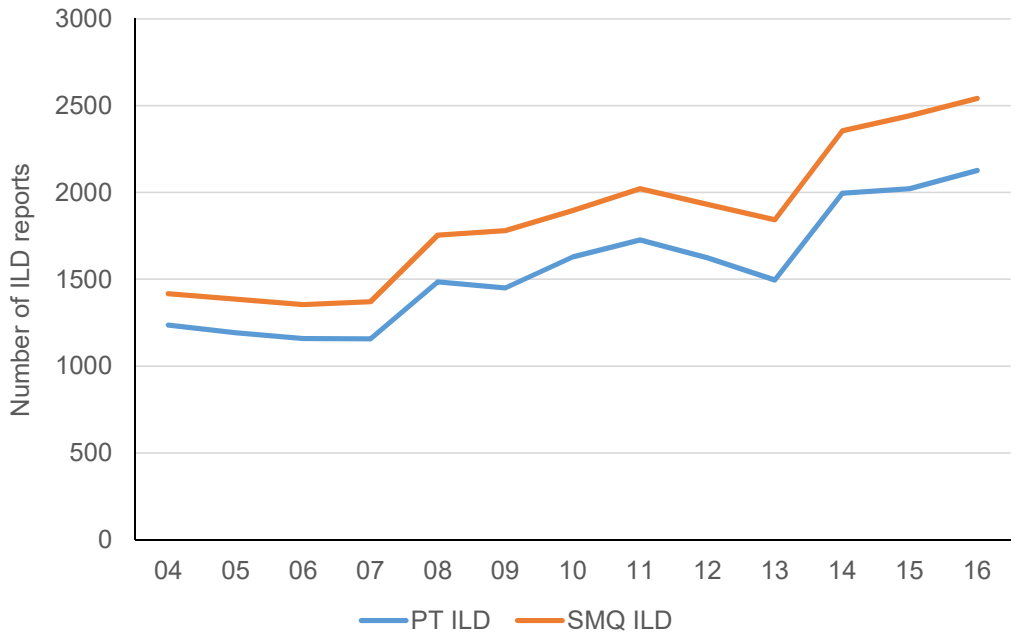

Fig.1 Comparison of reporting patterns of all drugs between PT ILD and SMQ ILD

The horizontal axis shows fiscal years as explained in the method section in the main article.