Targets of Immunotherapy of Chronical Viral Infections and Cancer
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CANCER IMMUNOTHERAPY:

ONCOLYTIC VIROTHERAPY IN LATVIA

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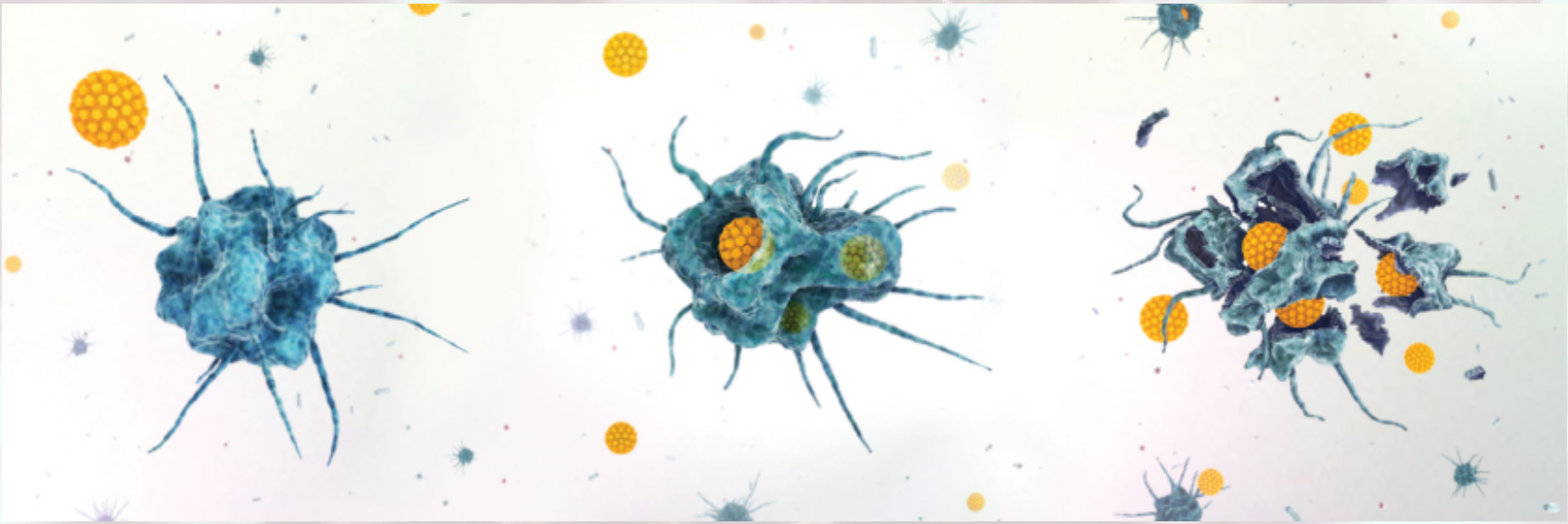
GLOBAL VIROTHERAPY CANCER CLINIC

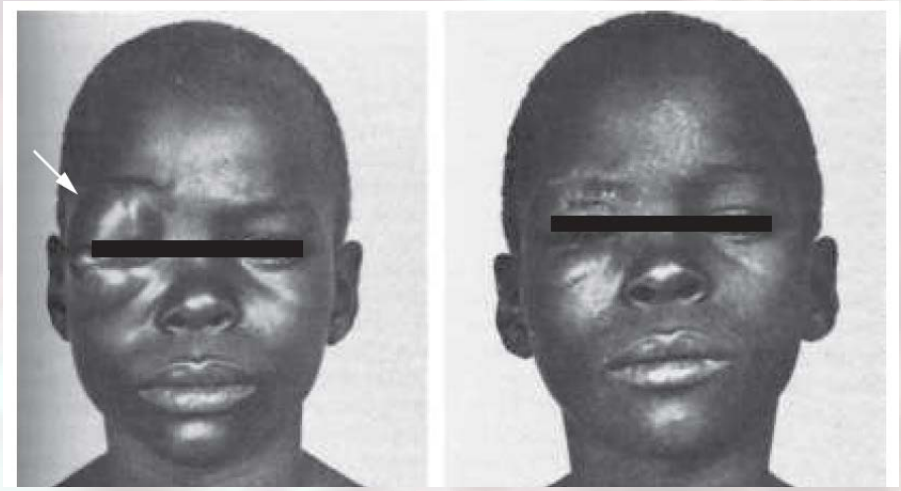
INTERNATIONAL VIROTHERAPY CENTER

Oncolytic virotherapy

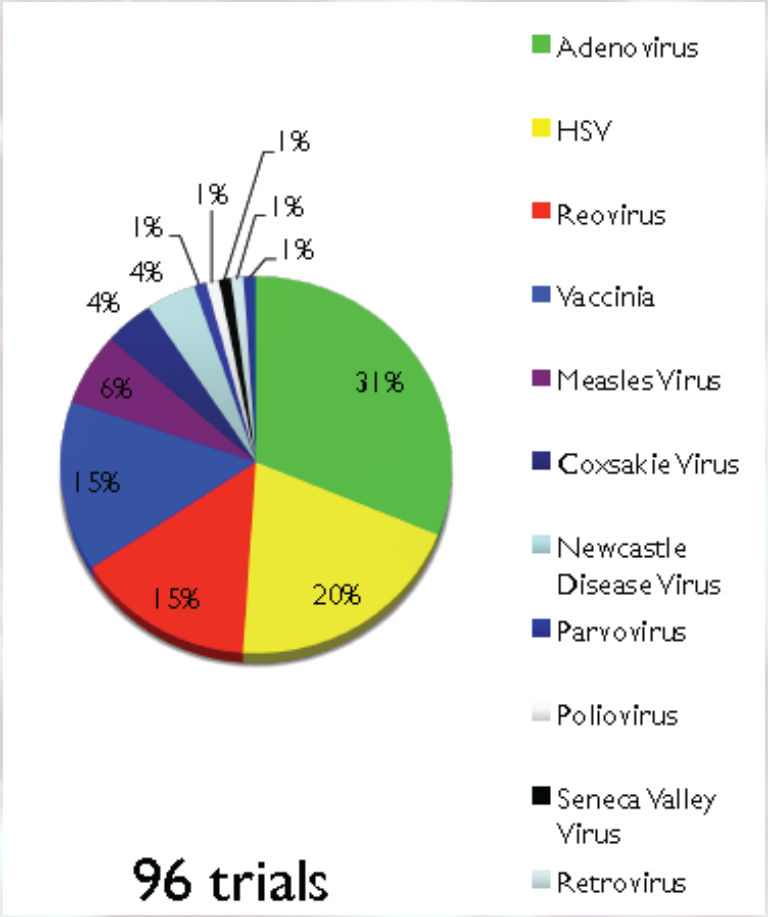


Early observations

In 1904 patient experienced remission of leukaemia after falling ill from a flu-like virus



Complete regression of Burkitt's lymphoma over 2 weeks in a patient experiencing acute measles infection (Bluming & Ziegler, 1971).



Russell et al. 2012

Only 3 Approved Oncolytic Viruses

1. Non-modified ECHO-7 virus, **Rigvir®**
   - **Latvia, 2004**
   - Georgia, 2015
   - Armenia, 2016
2. Genetically modified adenovirus, Oncorine
   - PR China, 2006
3. Genetically Altered Herpes Simplex Virus -1, T-Vec
   - FDA (USA), EMA (Europe) 2015

Breakthrough in Latvia

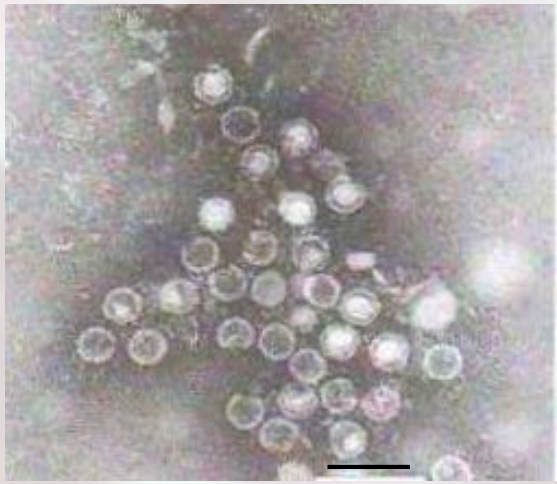
Year	Facts
1960	Rigvir® reduces the size of tumours hetero-transplanted in hamsters
1968	1st clinical trials in Latvia
1990ies	Clinical studies completed; efficacy and safety of Rigvir® established
2004	Rigvir® approved and registered by the State Agency of Medicines of Latvia
2012	Retrospective study on disease progression
2015	Retrospective study on overall survival
	Rigvir® included in National guidelines on melanoma treatment

Aina Muceniece

MD, Dr.habil.med. Discoverer of Rigvir®, author of several books and ca. 190 scientific papers

Content of the vial

- **Non-pathogenic wild type virus**
  - *Picornaviridae* family, Enterovirus genus, ECHO group, type 7
  - Positive single-stranded RNA
  - Small virus with stable icosahedrial structure
  - 4 structural proteins



TEM. Scale bar: 50 nm

- **No antibiotics, stimulants, potentially toxic substances**

Doniņa *et al.* Latvijas Ārsts 2012, 5, 39-42

Ādas melanomas medikamentozās terapijas iespējas Latvijā

ĪSUMĀ

Saslimstība ar ādas melanomu Latvijā pieaug strauji, īpaši pēdējo desmit gadu laikā. Melanomas norise ir grūti prognozējama, arī ārstēšana ir grūta, jo medikamentu izvēle nav liela un nav pārliecinošu paredzes marķieru, kas ļautu veiksmīgi izvēlēties katram pacientam atbilstošāko terapiju. Visbiežāk dažādu valstu vadlīnijās minētais preparāts melanomas ārstēšanai ir α interferons, taču tā lietošana ir ierobežota lielā medikamenta toksiskuma un zemās efektivitātes dēļ. Latvijā pacientiem ir vēl viena terapijas iespēja – vīrusu preparāts *Rigvir*. Metastātiskas melanomas gadījumā terapijas mērķis ir pagarināt bezprogresijas periodu un tiekties uz dzīvildzes pagarinājumu, saglabājot pienācīgu dzīves kvalitāti. Pagājušajā gadā pasaulē pieteikti divi jauni medikamenti metastātiskas melanomas ārstēšanai, no kuriem viens pašreiz Latvijā saņemams tikai klīniskā pētījumā iekļautiem pacientiem.

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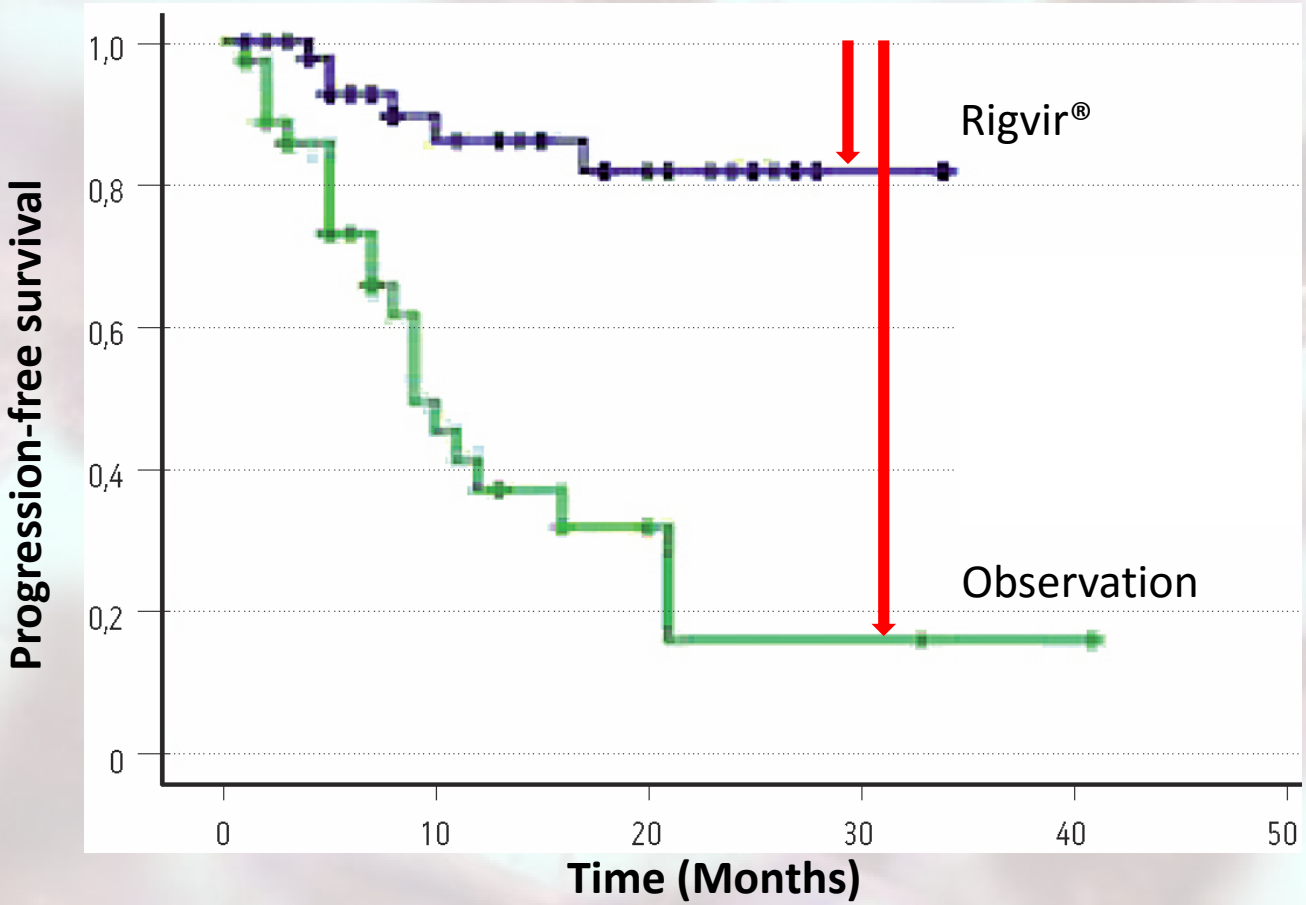
onkoloģe, imunoloģe, RAKUS klīnika Latvijas Onkoloģijas centrs

Evaluation of time to progression of disease



HR = 1:6.67

P < 0.001

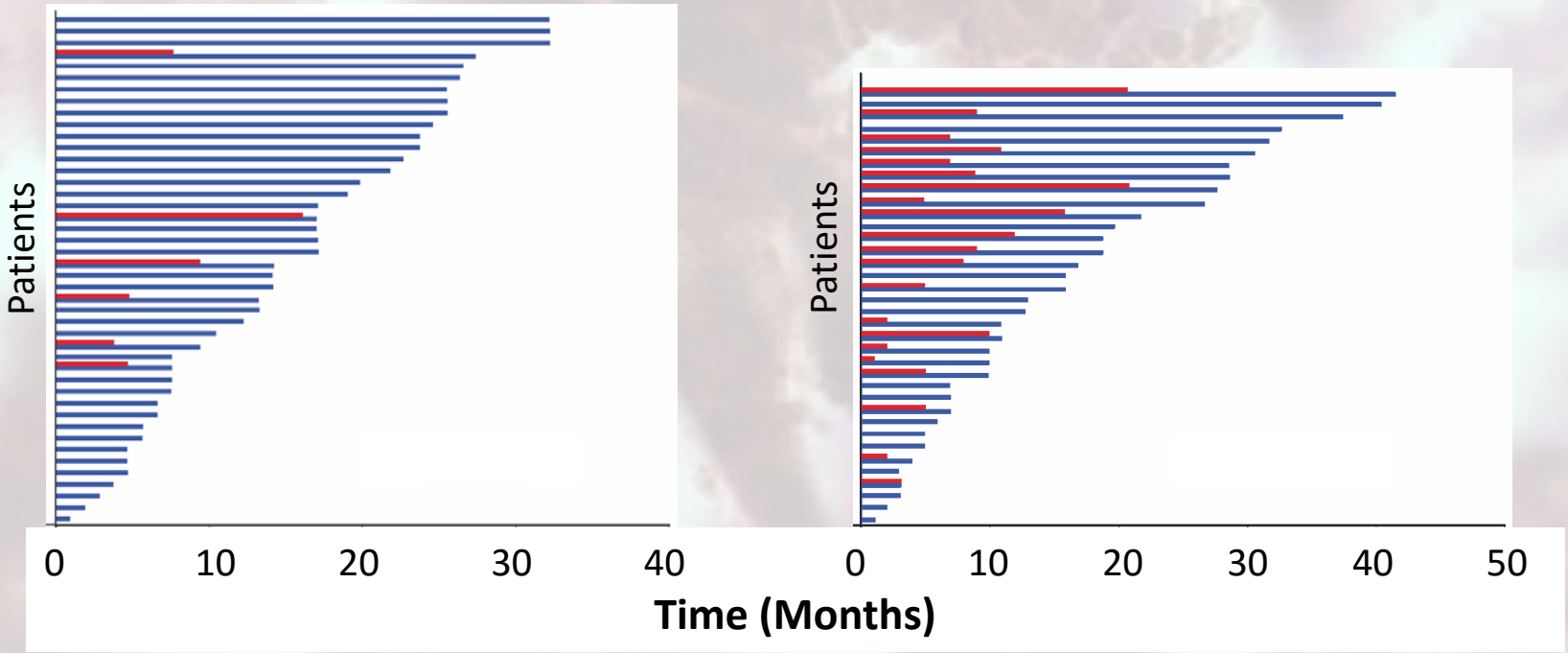
Doniņa et al. *Latvijas Ārsts*, 2012, 5, 39-42
Kaplan-Meier analysis of melanoma stage II patients

Evaluation of time to progression of disease

Progression of disease (red) in individual melanoma stage II patients

Rigvir® N=6/44

Observation N=21/36



Doniņa et al. *Latvijas Ārsts*, 2012, 5, 39-42

Doniņa *et al.* Melanoma Research 2015, 25, 421

OPEN

Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study

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An oncolytic, nonpathogenic ECHO-7 virus adapted for melanoma that has not been genetically modified (Rigvir) is approved and registered for virotherapy, an active and specific immunotherapy, in Latvia since 2004. The present retrospective study was carried out to determine the effectiveness of Rigvir in substage IB, IIA, IIB and IIC melanoma patients on time to progression and overall survival. White patients ($N = 79$) who had undergone surgical excision of the primary melanoma tumour were included in this study. All patients were free from disease after surgery and classified into substages IB, IIA, IIB and IIC. Circulating levels of clinical chemistry parameters were recorded. Survival was analysed by Cox regression. Rigvir significantly ($P < 0.05$) prolonged survival in substage IB–IIC melanoma patients following surgery compared with patients who were under observation (according to current guidelines). The hazard ratio for patients under observation versus treated with Rigvir was statistically significantly different: hazard ratio 6.27 for all, 4.39 for substage IIA–IIB–IIC and 6.57 for substage IIB–IIC patients. The follow-up period was not statistically different between both treatment groups. These results indicate that the patients treated with Rigvir had a 4.39–6.57-fold lower mortality than those under observation. In this study, there was no untoward side effect or discontinuation of Rigvir treatment. Safety assessment of adverse events graded according to NCI CTCAE did not show any value above grade 2 in Rigvir-treated patients. In conclusion, Rigvir significantly prolongs survival in early-stage melanoma patients without any side effect. *Melanoma Res* 25:421–426

Melanoma Research 2015, **25**:421–426

Keywords: ECHO-7 virus, immunomodulator, immunotherapy, melanoma, oncolytic, virotherapy

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✠Deceased.

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Evaluation of overall survival

Early stage (IB, IIA-C) melanoma patients following surgery

	Rigvir®	Observation	P value
Patients, N	52	27	
• Males • Females	17 35	11 16	NS
Age, years	56.5 ± 16.6	65.6 ± 13.9	< 0.020

HR was calculated using multivariate Cox regression analysis adjusting for patient age, sex and sub-stage of disease.

Doniņa et al. *Latvijas Ārsts*, 2012, 5, 39-42

Evaluation of overall survival

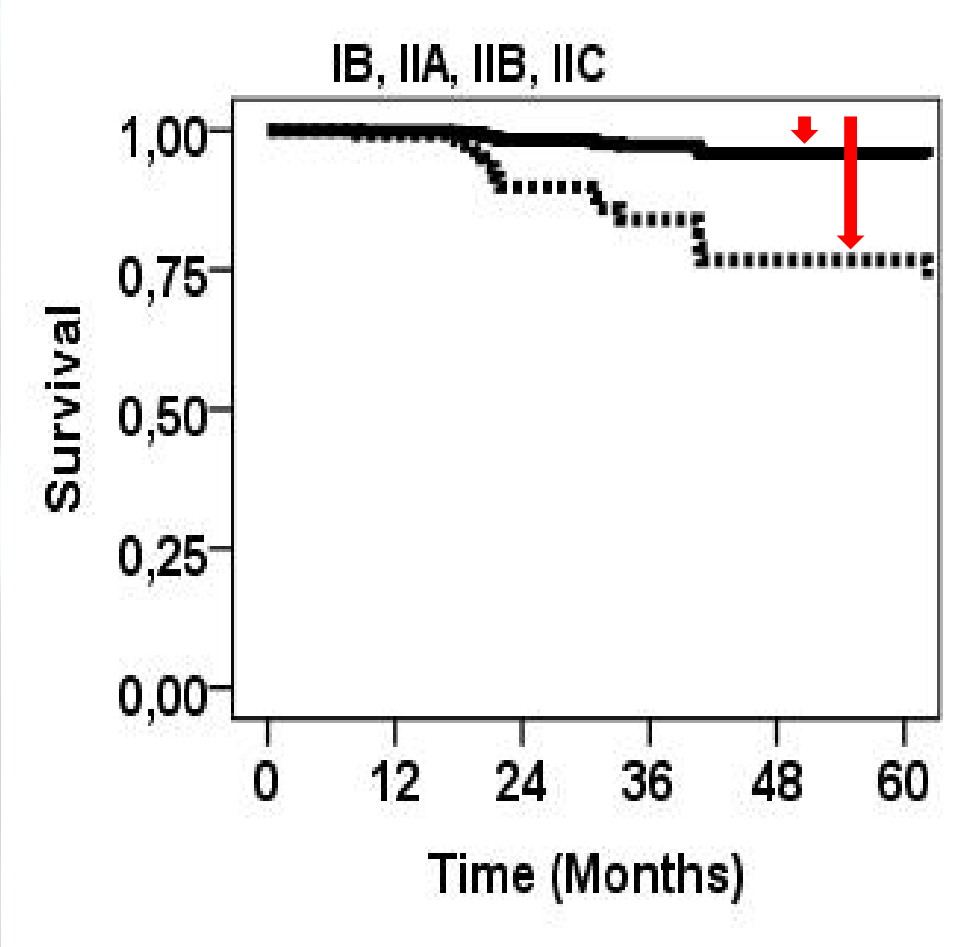
Serum clinical chemistry parameters graded according to NCI CTCAE

Parameter	Rigvir® Grade (N)	Observation Grade (N)
ASAT	-	I (9), III (1)
ALAT	I (1)	I (10), III (1)
ALP	I (1)	I (2), III (2)
Bilirubin	I (2), II (1)	I (2), III (1)
Creatinine	I (1)	I (4), II (1)
Neutrophils	I (8), II (2)	I (7), II (1)
Lymphocytes	I (1)	-

No adverse events, intolerability or discontinuation of treatment due to toxicity!

Doniņa et al. *Melanoma Research* 2015

Evaluation of overall survival



Rigvir®

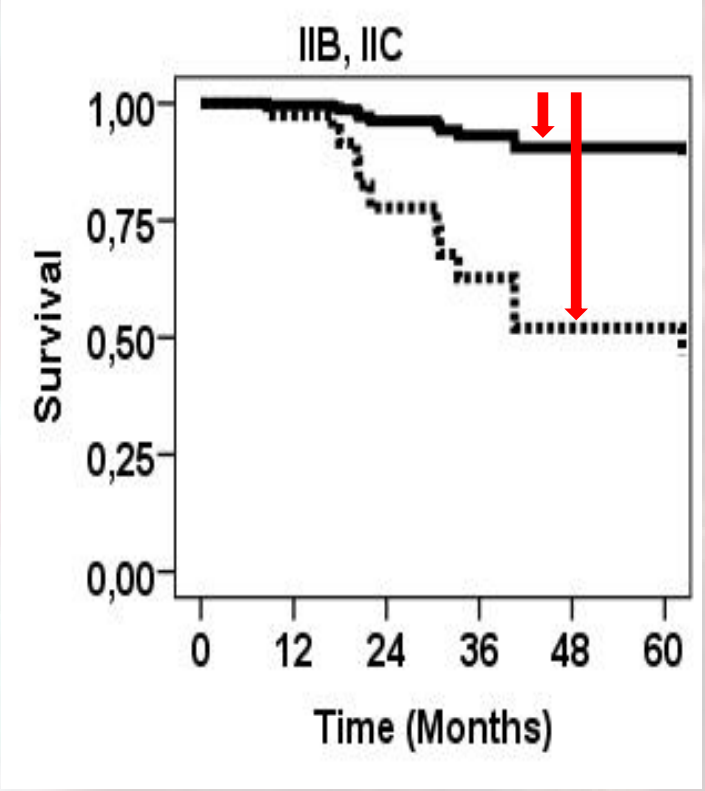
Observation

HR = 1:6.27

P < 0.005

Doniņa et al. *Melanoma Research* 2015
Cox analysis of early stage (IB; IIA-C) melanoma patients

Evaluation of overall survival

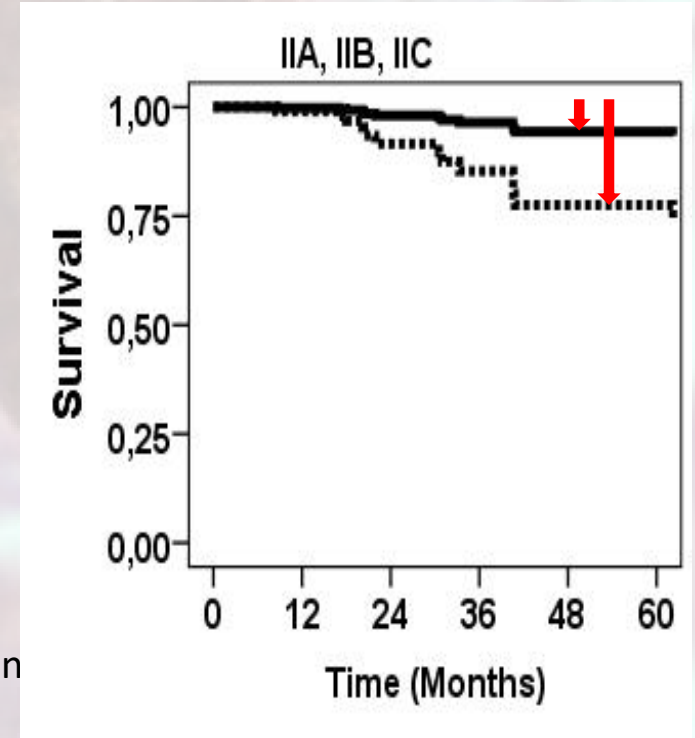


Rigvir®

HR = 1:6.57

Observation

P < 0.014



Rigvir®

Observation

HR = 1:4.39

P < 0.032

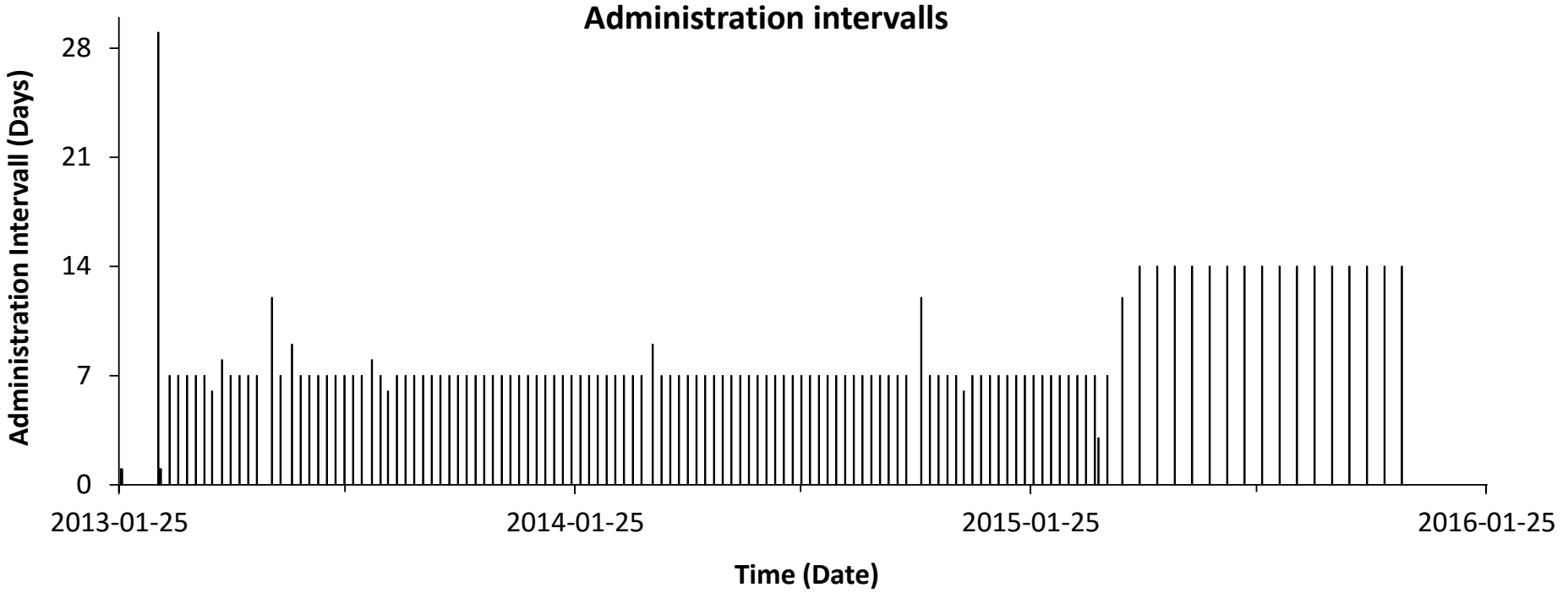
Doniņa et al. *Melanoma Research* 2015

Cox analysis of early stage (IB; IIA-C) melanoma patien

Case study

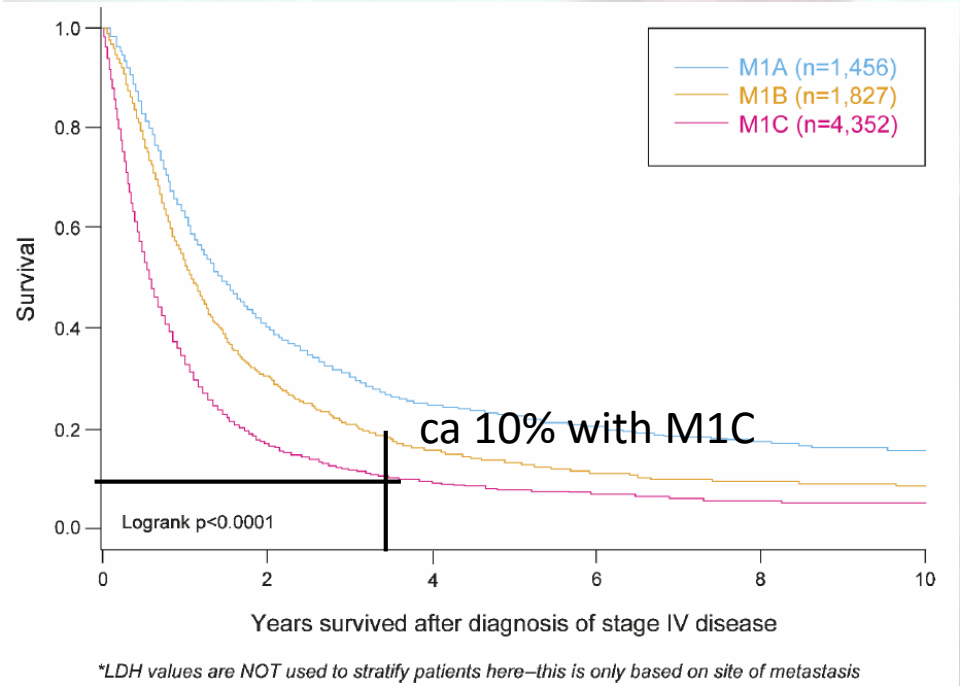
- **Female, born 9 June 1972, non-smoker, mother**
- **Stage IV melanoma cutis dorsi, Clark V, $pT_{4b}N_xM_{1c}$ (AJCC), liver and inguinal lymph node metastasis**
- 2010: a nevus, birthmark, on the lumbar part of the back starts to increase in size after a vacation on the sea
- 2012: the nevus twice injured; no bleeding, but the nevus increased in size and its boundaries started to get blurred
- 21 Dec. 2012: Tumour surgically removed (extirpatio tumoris dorsi)
- 9-11 Jan, 2013: One course of chemotherapy (Lomustine 200 mg); further chemotherapy cancelled due to intolerance
- **Feb. 2013 – Started Rigvir® therapy** according to Protocol No. 4
- **No other concomitant treatment**
- CT
  - 22 Aug. 2013 - abdominis: Liver metastasis do not show any change since 16 Jan. 2013
  - 1 Dec 2014
  - 25 May 2015

Intensive Rigvir® Administration



- The first three days: 3 administrations
- After 4 weeks: another 3 administrations during three days
- Subsequently: administration every week for 24 months
- Then: administration once every 14 days

Melanoma IV M1C 3.5-Year Survival: 10-30%



*LDH values are NOT used to stratify patients here–this is only based on site of metastasis

FIGURE 31.4. Survival curves of 7,635 patients with metastatic melanomas at distant sites (stage IV) subgrouped by M category site of disease (LDH levels not included in stratification). The number of patients is shown in *parentheses*.

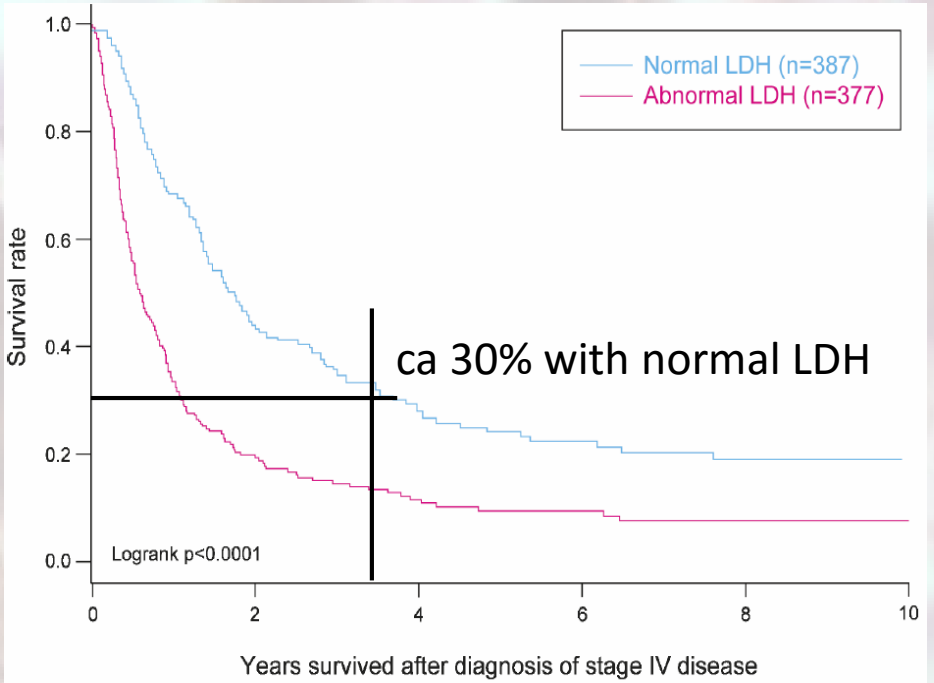


FIGURE 31.5. Survival curves of 764 patients with metastatic melanomas at distant sites (stage IV) subgrouped by normal and abnormal serum LDH levels. The number of patients is shown in *parentheses*.

Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC cancer staging manual, 7th ed. New York, NY: Springer; 2010. p. 333-334.

Conclusions

- **Melanoma IV**
  - Discontinued chemotherapy due to intolerance
  - > 3.5 years with diagnosis
- **Rigvir® treated**
  - Since Feb 2013
- **Liver lesions stabilized**
  - Since Aug 2013
- **An inguinal lymph node decreased in size by half, and stabilized**
  - Since Aug 2013

Thank you very much for your attention!