Psychological side-effects of immunotherapies in the treatment of malignant melanoma

Ph.D. Dissertation

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The body has its stock, the mind its treasures.[1]
(Beckett, 1957, pg. 67)

Quand vous avez la chance de ne pas comprendre quelque chose, il ne faut pas la laisser échapper.[2]
(Ajar, 1979, pg. 193)

[1] "A testnek állaga van, a szellemnek kincse." (Beckett, 2003, 123.o. - Tandori Dezső fordítása)

2 “Ha van szerencsénk valamit nem érteni, azt nem szabad kihagyni.” (Ajar, 2014, 173.o. - Bognár Róbert fordítása)

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Abbreviations

5-HT – 5-hidroxytriptamine (serotonin)

5-HTTLPR – serotonin-transporter-linked polymorphic region

AJCC – American Joint Committee on Cancer

ANOVA – Analysis of variance

ANCOVA – Analysis of covariance

anti-CTLA-4 – anticytotoxic T-lymphocyte-associated antigen 4

APC – antigen presenting cell

BC – Before Christ

BCG – Bacillus Calmette–Guérin

BDI – Beck Depression Inventory

CD8 – cluster of differentation 8

CTL – cytotoxic T lymphocytes

CRH – corticotropin releasing hormone

DNA - deoxyribonucleic acid

DTIC -Dimethyl triazeno imidazole carboxamide

FDA – U.S. Food and Drug Administration

HDI – high-dose interferon

HPA – hypothalamic–pituitary–adrenal(axis)

HLA – human leukocyte antigen

IFN – interferon

IL – interleukin

IL-1RA – interleukin-1 receptor antagonist

irAE – immune related adverse effects

LAK – lymphokine activated killer

LDH – lactate dehydrogenase

MHC – major histocompatibility complex

MIU – million international units

MM – malignant melanoma

NCCN -National Comprehensive Cancer Network

NK – natural killer (cell)

PD-1 – programmed death-1 (protein)

PD-L1 – programmed death ligand-1 (protein)

SD – standard deviation

SDS – Zung Self-Rating Depression Scale

SPSS – Statistical Package for the Social Sciences

SSRI – selective serotonin reuptake inhibitors

STAI – State-Trait Anxiety Inventory for Adults

TCR – T-cell receptor

Th1 – T-helper 1

TNF – tumour necrosis factor

TNM – Tumour-Node-Metastases classification system

UV – ultraviolet

XP - Xeroderma pigmentosum

1. Introduction

1.1. Malignant melanoma

Malignant melanoma is a type of cancer arising from melanocytes. Melanocytes in the epidermis of the skin produce the pigment melanin, which occurs in several forms that variably protect the skin from ultraviolet (UV) radiation. Environmental insults followed by proto-oncogene activation coupled with suppression of tumour suppressor genes, and defects in DNA repair mechanism further exacerbated by the inability of the immune system to contain these insults results in melanoma (Kraemer et al. 1994). Melanomas typically occur in the skin but may rarely occur in the mouth, intestines, or eye. Melanoma often affects a relatively younger population and it metastasizesat an early stage. Early detection leads to a cure rate of over 90% in low-risk melanomas but advanced melanomas respond poorly to current therapies (Ehret, 2014).Immunotherapies and their combinations are one of the new ways of treatments in advanced melanoma. Immunotherapy is a general term referring to artificial activation of the immune system to induce objective responses and/or disease stabilization (Drake et al. 2014). Immunotherapies can cause an early neurovegetative syndrome characterised by depression, anxiety, fatigue, anorexia, pain and psychomotor slowing which pathophysiological background are not fully understood yet (Lotrich, 2013; Lin, 2014; Kovács et al. 2015).

1.1.1. The "black cancer" – *the history of melanoma*

In Greek "melas" means dark and "oma" means tumour. The first description of melanoma dates back to Hippocrates in the 5th century BC. Melanoma can be diagnosed from skeletons with osteolytic bone metastases. The earliest physical evidence of the disease comes from the metastases of melanoma found in skeletons of Pre-Columbian mummies (Vito et al. 2012). Between 1650 and 1760 the medical literature referred the disease as "*fatal black tumours with metastases and black fluid in the body*" (Vito et al. 2012, pg 2.). The first surgical removal of a melanoma was performed by John Hunter in 1787 and he labelled it as "*cancerous fungous excrescence*" (Gorantla and Kirkwood,

2014). Rene Laennec (the inventor of stethoscope) was the first who realized that melanoma is a distinct disease – he used the term *melanose* to describe the tumour.In 1966 Clark developed a standard five-level scale to assess the prognosis of melanoma based on histological examination (Clark's levels): deeper invasion of tumour cells (epidermis, dermis, subcutaneous tissue) means worse prognosis (Clark, 1969). Alexander Breslow defined the tumour thickness as prognostic factor of malignant melanoma in 1970 (Breslow thickness) (Breslow, 1970). Clark's standard scale and the tumour thickness are currently still relevant prognostic factors (Balch et al. 2001).

1.1.2. The incidence of melanoma

The incidence of melanoma has been increasing in the past few decades (Petrella et al. 2012). Worldwide the incidence of melanoma continues to rise and despite advances in local and systemic therapy, mortality continues to rise with 80% of skin cancer-related deaths attributable to melanoma (WHO, 2013). Melanoma accounts for less than 5% of all skin cancers, but is the leading cause of skin cancer mortality.

In the United States from 1973 to 2004 the incidence of melanomas has risen from 8 to 34 per 100.000 in males and 7 to 25 per 100.000 in females and the worldwide incidence rates vary significantly: to 0.2-0.5 per 100.000 in India, to 12-15 per 100.000 in Germany and to 40-50 per 100.000 in Australia (Roesch and Volkenandt, 2009). Data of 10-years incidence in four countries were shown in Table 1.

Table 1. Lifetime risk, incidence and mortality trends in melanoma based on statistics of Australia, USA, The Netherlands and UK (adapted from Thompson et al. 2005)

	Lifetime risk (incidence)	**Incidence trend over 10 years**	**Mortality trend over 10 years**
Australia			
Male	1 in 25	22% increase	2% increase (1991-2001)
Female	1 in 35	12% increase	0% increase (1991-2001)
USA			
Male	1 in 53	31% increase	0% increase (1991-2001)
Female	1 in 78	25% increase	1% decrease (1991-2001)
The Netherlands			
Male	---	21% increase	24% increase (1989-98)
Female	---	11% increase	5% increase (1989-98
UK			
Male	1 in 147	59% increase	20% increase (1991-2001)
Female	1 in 117	41% increase	3% increase (1991-2001)

Also in Hungary the incidence of melanoma has been progressively rising in the past decade. According the data of Hungarian National Cancer Registry and Center of Biostatistics in the last 10 years the number of melanoma cases has doubled in Hungary (Figure 1., Table 2.).

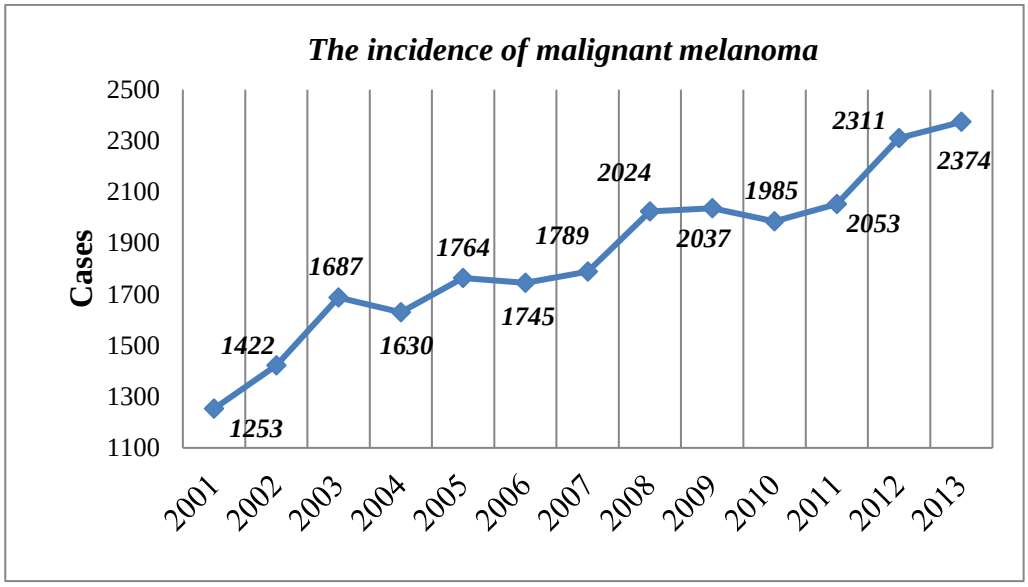


Figure 1. The incidence of malignant melanoma (without melanoma in situ) in Hungary (2001-2013) (National Cancer Registry and Center of Biostatistics, Hungary)

Table 2. Incidence data from Hungary (2001-2013). The incidence of in situ melanoma and melanoma malignum in females and males in Hungary (2001-2013). National Cancer Registry and Centre of Biostatistics, Hungary. *MM: malignant melanoma*; *in situ: in situ melanoma.*

Year	Male		Female	
	In situ	MM	In situ	MM
2001	91	569	100	684
2002	119	626	147	796
2003	123	742	209	945
2004	159	741	228	889
2005	187	807	261	957
2006	196	817	264	928
2007	134	847	204	942
2008	176	936	207	1088
2009	187	956	248	1081
2010	194	914	242	1071
2011	210	1014	265	1039
2012	234	1072	272	1239
2013	295	1116	324	1258

1.1.3. Risk factors

Major risk factors of melanoma are the following (NCCN Guidelines, 2015):

1. *Exposure to ultraviolet (UV) rays* is a major risk factor for most melanomas. This exposure can be characterised by the cumulative solar exposure and sunburn events (UV-B). UV rays originated from sunlight, tanning beds and sun lamps damage the DNA of skin cells and from the point when this damage affects the DNA of genes that control skin cell growth skin cancers develop. The nature of the UV exposure may be important in melanoma development. For example, the development of melanoma on the trunk (chest and back) and legs has been linked to frequent sunburns (especially in childhood).
2. *Benign pigmented naevus* are dense areas of melanin. Naevuses are not usually seen on babies they often begin to appear in children and young adults. Most naevuses will never cause any problems, but withincreasing number of naevuses the risk to develop melanoma is also increased. Thus many and/or large and/or atypical naevuses could mean higher risk for the disease.
3. *The white colour of the skin* carries a much higher risk for melanoma. Whites with red or blond hair, blue or green eyes, or fair skin that freckles or burns easily are at increased risk.
4. *If one or more first-degree relatives (parent, brother, sister, or child) has had melanoma* the risk of melanoma is greater. Around 10% of all people with melanoma have a family history of the disease (Thompson et al. 2005).
5. Already *having a melanoma* increase the risk to of getting it again. About 5% of people with melanoma will develop a second one at some point. People who have had basal or squamous cell skin cancers are also at increased risk of getting melanoma. Xeroderma pigmentosum (XP) is a rare, inherited condition that affects skin cells ability to repair damage to their DNA caused by ultraviolet lights which is also associated with increase occurrence of melanoma.

6. Melanoma is more likely to occur in *older people*, but it is also found in younger people. In fact, melanoma is one of the most common cancers in people younger than 30 (especially younger women).
7. People with *weakened immune systems* (from certain diseases or medical treatments) are more likely to develop many types of skin cancer, including melanoma.

In summary both increased exposure to risk factors and decreased defence system of the individual could lead to melanoma which further emphasize the role of the immune system in the pathogenesis of this disorder.

1.1.4. Stagingof the disease

Despite the fast development of molecular medical approaches,at present the most important information to determine the most appropriate evidence-based treatmentfor a given patient is thestage of the disease.According to the guideline of the American Society of Clinical Oncologythe staging is based on the TNM Classification System, which is explained below (NCCN Guidelines, 2016).

1.1.4.1.Overview of the TNM Classification System of melanoma

The TNM staging system is widely used in clinical practice to classify tumours. TNM staging of melanoma describes the thickness of the melanoma and whether there is any spread to lymph nodes or other parts of the body.

The letters (T-N-M) describes the different areas of cancer growth:

- T-Tumour: how far it has grown within the skin and other factors
- N-Node: bean-sized collections of immune system cells, to which cancers often spread first
- M-Metastases: spread to distant organs and which organs it has reached

This staging system describes the size of a primary tumour (T), whether any lymph nodes contain cancer cells (N) and whether the cancer has spread to another part

of the body (M). The T part of the TNM describes the thickness of the melanoma (primary tumour) according to the Breslow scale.

The T part of the TNM system is further divided into two groups a and b, depending on whether the melanoma is ulcerated or not. Ulcerated means that the covering layer of skin over the tumour is broken. Ulcerated melanomas have a higher risk of spreading than those which are not ulcerated.

The N part of the stage is further divided into groups a, b and c. If the cancer in the lymph node can only be seen with a microscope (micrometastasis) it is classed as a. But if there are obvious signs of cancer in the lymph node (macrometastasis) it is classed as b.

The letter c means that there are melanoma cells in small areas of skin very close to the primary melanoma or in the skin lymph channels. These groups of melanoma cells in the skin are called satellite metastases. Melanoma cells in the lymph channels are called in transit metastases.

M0 means the cancer has not spread to another part of the body. M1 means the cancer has spread to another part of the body.

This staging system is the only internationally accepted classification system, and it includes also sentinel node staging (*AJCC: Americal Joint Comittee on Cancer*).

1.1.4.2.Treatment-relevant stages of melanoma

The T, N, and M groups can be combined to create overall stages for melanoma, which are denoted with the combination of Roman numerals I to IV (1 to 4) and capital letters. Thisclinical staging system (Table 3.) is a standard way to describe how far the disease has spread and will determine the treatment.Patients with lower stage melanomahave a better outcome regarding the long-term survival.

Table 3. The clinical staging of melanoma (AJCC)

Clinical staging			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	≥N1	M0
Stage IV	Any T	Any N	M1

Stage 0 melanomas have not grown deeper than the top layer of the skin (the epidermis). They are usually treated by surgery (wide excision) to remove the melanoma. Stage I and Stage II melanomas are treated also by wide excision. If the melanoma is stage IB or has other characteristics that make it more likely to have spread to the lymph nodes, sentinel lymph node biopsy is recommended. Lymph node dissection is recommended if cancer cells were found on the biopsy (Stage II). Adjuvant therapy after surgery may advise in Stage II melanoma. Stage III cancers have already reached the lymph nodes when the melanoma is first diagnosed. Surgery and adjuvant treatment and/or radiation therapy are recommended. Stage IV melanomas are very hard to cure, as they have already spread to distant lymph nodes or other areas of the body. Metastases that cause symptoms but cannot be removed may be treated with radiation, immunotherapy, targeted therapy, or chemotherapy. The treatment of widespread melanomas has changed in recent years as newer forms of immunotherapy (known as

immune checkpoint inhibitors) and targeted drugs have been shown to be more effective than chemotherapy.

Same stage means the same or similar prognosis. Observed survival rates shown below for the different stages (Table 4.).

Table 4. Observed survival rates in melanoma (adapted from the AJCC Melanoma Staging Database, 2008.). Observed survival rates based on data of 60.000 patients *:*The outlook is better if the spread is only to distant parts of the skin or distant lymph nodes rather than to other organs, and if the blood level of lactate dehydrogenase (LDH) is normal.*

Observed survival rates		
	5-year survival	***10 year survival***
Stage IA	97%	95%
Stage IB	92%	86%
Stage IIA	81%	67%
Stage IIB	70%	57%
Stage IIC	53%	40%
Stage IIIA	78%	68%
Stage IIIB	59%	43%
Stage IIIC	40%	24%
Stage IV*	15-20%	10-15%

1.2. Treatment of melanoma

1.2.1. The history of melanoma therapy

The intent of treatment for advanced melanoma which was once considered incurable has changed in the last decades from palliative to potentially curative. Treatment and outcomes for advanced melanoma have improved over the past twenty years on the basis of rapid advances in the fields of tumour cell biology, immunology, and surgical techniques, radiosurgery (Garbe et al. 2012).

In the beginning of the use of medical treatments mostly palliative (and largely ineffective) treatments were used.

Since Ehrlich in 1909 first proposed the idea that nascent transformed cells arise continuously in the body and that the immune system scans for and eradicates these transformed cells before they are manifested clinically, immune surveillance has been a controversial topic in tumour immunology (Ehrlich, 1909).

Tumour transplantation models show the experimental evidence that tumours could be repressed by the immune system. These findings suggested the existence of tumour-associated antigens and formed the basis of "immune surveillance" (Burnet and Thomas, 1957). "Immune surveillance' implied surveillance of the host for malignant cells, which were presumed to be recognized and destroyed as they emerged. This idea was supported by the observation of spontaneous regression in human melanoma, the lymphocytic/dendritic infiltrates documented pathologically in and around primary melanoma tumours, and the increased incidence of melanoma among immunosuppressed patients (Gorantla and Kirkwood, 2014).

The idea of cancer immune surveillance resisted widespread acceptance until the 1990s. The central roles of immune effector cells, such as B, T, natural killer (NK) and natural killer T (NKT) cells, and interferon (IFN) have been clarified in cancer immune surveillance (Dunn, 2004; Kim et al. 2007).

Golub et al. demonstrated in vitro increased cytotoxic activity of melanoma patient-derived lymphocytes against melanoma cell lines (Golub, 1974). The discovery of interleukin 2 (IL-2) as a T cell growth factor helped in vivo studies of immune modulation and its role in advanced melanoma (Gorantla, 2014). Supporting this observationin metastatic melanoma the use of anticytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4 antibody) immunotherapy (ipilimumab) seems to be effective (2011 FDA approval) (Lee et al. 2013). Thus, a better understanding of the mechanisms of immunoediting during tumour progression may provide new insights for improving cancer immunotherapy.

The most important milestones in the history of melanoma immunetreatment are shown in Table 5.

Table 5. Major steps in the immunetreatment of melanoma (adapted from Lee et al. 2013). *FDA: Food and Drug Administration; HDI, high-dose interferon; IL, interleukin; LAK, lymphokine activated killer.*

years		*landmarks*
5th century B.C.	Hippocrates	first mention of melanoma
4th century B.C.	Pre-Columbian Mummies	discovered skeletons of mummies with the metastases of melanoma
1787	John Hunter	first describes melanoma and preserves a specimen
1812	René Laennec	first describes melanoma as a disease entity
1820	William Norris	first describes a case of melanoma in the English literature
1969	Ion Gresser	describes the role of interferons in antitumour immunity
1969	Wallace Clark	notes the pathologic heterogeneity of melanoma and levels of invasion that correlate with prognosis
1970	Alexander Breslow	describes the relationship between tumour thickness and prognosis
1970	Donald Morton	publishes first successful clinical application of immunotherapy directed against a metastatic human cancer
1974	Donald Morton	describes presence of melanoma antigens
1985	John Kirkwood	initiates high dose interferon studies in patients with high risk for relapse melanoma
1988	first AJCC staging	first version of AJCC staging for melanoma
1996	HDI	FDA approves HDI
1998	high dose IL-2	FDA approval of high dose bolus IL-2 for advanced, metastatic melanoma
2011	FDA approval	pegylated interferon for high-risk resected disease; ipilimumab for advanced, metastatic disease

90% of melanomas are diagnosed as primary tumours without metastasis and for patients with early-stage non-metastatic disease surgical management remains the mainstay of therapy (Garbe et al. 2012; Mocellin et al. 2013). Adjuvant immunotherapy is offered to those melanoma patients who have no evidence of metastases but at high

risk for further tumour spread, e.g. tumours thicker than 1.5 mm, or in stage II and III melanoma. Specifically, interferon alpha is the fundamental therapy as it was the first substance in the adjuvant treatment of melanoma to have shown a significant improvement of disease-free survival (Garbe et al. 2008; Friebe et al. 2010). However, adjuvant interferon treatment is frequently accompanied by psychological side effects including depression, fatigue, irritability, anxiety, or suicide.

The treatment of melanomas with distant metastases are still not satisfactory with the median survival of patients with melanoma is less than 1 year (Schaefer et al. 2002) and the expected 2-year survival rate is 10-20% (Rychetnick et al. 2012). Although the prognosis for melanoma is improving because lesions are diagnosed at a much earlier point, the therapy of disseminated melanoma has been unsolved for decades. Median survival with distant metastasis in the fourth stage based on former data is less than 1 year (Gray-Schopfer et al. 2007; Mocellin et al. 2010). Survival increased as a result of new therapies of recent years, but the mortality rate of the disease is still significant. In the event of localised diseases, surgical intervention plays a leading role. However, following excision further therapies may be needed due to the parameters of primer tumour (ulceration, tumour thickness, lymph node status) (Liszkay et al. 2003; Kasparian et al. 2009).

Systemic pharmacotherapies are widely used in the treatment of melanoma, especially if malignant cells spread beyond the skin to distant organs. Broad range of drugs are available including chemotherapies, targeted therapy and vaccine therapy. If distant metastases emerged, promising opportunities have been arising recently in the treatment of the disease with the progress of molecular pathology and immunology (Garbe et al. 2011). New products, primarily developed for other medical conditions, are retargeted for application in melanoma treatment by utilising their potentialto strengthen the immune response of the organism against foreign or altered antigens, such as tumour cells (Bhatia and Thompson, 2014).

1.2.2. Chemotherapy of melanoma

Surgery and radiation therapy remove, kill, or damage cancer cells in a certain area, but chemotherapy can work throughout the whole body. Chemotherapy is a medication-based, systemic therapy to treat many types of cancer, including melanoma, by destroying melanoma cells throughout the body. This means chemotherapy can kill cancer cells that have spread (metastasized) to parts of the body far away from the original (primary) tumour (Fuchs-Tarlovsky, 2013).Chemotherapy drugs kill the fast-growing cells, also cancer cells and also normal cells. Systemic chemotherapy uses anticancer drugs that are usually injected into a vein or given by mouth. These medications travel through the bloodstream to all parts of the body, where they attack cancer cells that have already spread beyond the skin to involve lymph nodes and other organs. Usually the combination of more than one drug is used. Many other chemotherapy agents are being evaluated for their use in the treatment of Stage IV melanoma as both single agents and in combination with other chemotherapy, targeted therapy and immunotherapy agents.

Although chemotherapy is usually not as effective in melanoma as in some other types of cancer, it may relieve symptoms or extend survival of some patients with stage IV melanoma (Middleton et al. 2000).

Chemotherapy drugs often used to treat melanoma include:

- Dacarbazine (DTIC) is the only FDA-approved chemotherapy agent for the treatment of Stage IV melanoma. It is administered as an intravenous infusion.
- Cisplatin, vinblastine, and DTIC is another chemotherapy combination for treating melanoma.
- Temozolomide is a drug that works like DTIC, but it can be given in the form of a pill.

Conventional chemotherapy with dacarbazine and temozolomide has yielded poor response rates of 7%–20% and a median survival of nine months, with mild toxicity profiles (Chapman et al. 1999).

These chemotherapy drugs may also be combined with immunotherapy drugs, such as interferon alpha and/or interleukin 2.

1.2.3. Vaccine therapy of melanoma

Melanoma vaccines are experimental therapies that are being tested in patients with stage III or stage IV melanoma. Anti-melanoma vaccines are similar to the vaccines used to prevent diseases caused by viruses. Antivirus vaccines usually contain weakened or killed viruses or parts of a virus that cannot cause the disease. The vaccine stimulates the body's immune system to destroy the more harmful type of virus.

In the same way, weakened melanoma cells or parts of melanoma cells called antigens can be injected into a patient in an attempt to stimulate the body's immune system to destroy melanoma cells. Usually, the melanoma cells are mixed with substances that help stimulate the body's immune system.

1.2.4. Targeted therapy of melanoma

Targeted therapy is a form of treatment in which drugs (or other substances) are developed with the goal of destroying cancer cells while leaving normal cells intact. These drugs are designed to interfere with the specific molecules that are driving the growth and spread of the tumour. Because they are “targeted” to the tumour, these therapies may be more effective and associated with fewer side effects compared to chemotherapy and radiation therapy (Davey et al. 2016).Targeted therapy drugs for melanoma see on Table 6.

Molecular targeted therapies have shown promise in the management of various malignancies, including melanoma, with lower toxicity profiles and better overall survival as compared with conventional therapy (Chakraborty et al. 2013).

Table 6. Targeted therapy drugs for melanoma(adapted from the NCCN Guidelines, 2016). *KIT- receptor tyrosine kinase - inhibition of KIT leads to defects in melanocyte migration, survival, proliferation, and differentiation; MEK - allostetic mitogen-activated protein/extracellular signal-regulated kinase - MEK inhibition blocks cell proliferation and induced apoptosis;BRAF - serine/threonine protein kinasewich is involved in sending signals inside cells which are involved in directing cell growth.*

	Generic name	***Brand name***	***Dose***
C-KIT-inhibitors	Nilotinib	Tasigna	2x200mg/day
	Imatinib	Glivec	1x400mg/day
MEK-inhibitors	Cobimetinib	Cotellic	1x3x20mg/day
	Trametinib	Mekinist	1x3x20mg/day
BRAF-inhibitors	Vemurafenib	Zelboraf	2x4x240mg/day
	Dabrafenib	Tafinlar	2x2x75mg/day

1.2.5. Immunotherapies of melanoma

Immunotherapy is a general term referring to artificial activation of the immune system to induce objective responses and/or disease stabilization (Drake et al. 2014).

Immunotherapy enhances and encourages a patient's immune system to recognize and destroy cancer cells more effectively. Several types of immunotherapy are used in treating patients with melanoma. Some are being studied as adjuvant treatment. Immunotherapy (also called biological therapy) is a treatment that increases the activity of immune system. These drugs improve the ability of the body to find and destroy cancer cells. Immunotherapeutic interventions offer the hope for effective treatment against melanoma as it is considered traditionally as immunogen tumour cancer because of its ability to undergo spontaneous regression (Thumar and Kluger, 2010). The most convincing evidence that melanoma can be immunogenic is derived from preclinical research on the fundamental aspects of T-cell biology and antigen recognition (Komenaka et al. 2004). Although the fundamentals of tumour immunology can be broadly applied to all types of tumours, many of these principles were first demonstrated in melanoma, and the clinical application of immunotherapy for cancer has been most widely studied in melanoma (Gogas et al. 2006).

1.2.4.1. The role of cytokines in the treatment of melanoma

Cytokines are proteins that activate the immune system in a general way. Two cytokines, interferon alpha and interleukin 2, can help boost immunity in patients with melanoma. Both drugs can help to shrink metastatic (stage III and IV) melanoma in about 10% to 20% of patients (Verma et al. 2006; Bhatia et al. 2009).

Interleukin 2, particularly in high doses, can cause fluid to accumulate in the body, so the person swells up and can feel quite sick. Some patients may need to be hospitalized because of this problem (Komenaka et al. 2004; Agarwala, 2009).

Patients with deeper melanomas often have cancer cells that break away from the primary melanoma and travel to other parts of the body. Interferons are immune substances produced by the body in response to infection. Interferon alpha 2b can be used as an adjuvant therapy (Garbe et al. 2008). Side effects include fever, chills, aches, and severe tiredness. Interferon alpha 2b can also affect the heart and liver, and patients should be followed by an oncologist who is experienced with this treatment (Schaefer et al. 2002). Interferon alpha 2b given to patients with stage III melanoma following surgery can delay the recurrence of melanoma but may not prolong patients' lives. Decisions about adjuvant therapy by patients and their doctors should take into account the potential benefits and side effects of this treatment.

Another cytokine is called tumour necrosis factor (TNF). This is a naturally occurring substance that seems to kill tumours. It is particularly effective when the TNF is given as an infusion directly into a tumour or a part of the body containing the tumour. This is called *regional perfusion* (Krementz et al. 1994).

Cytokines (interleukins and interferons) are part of the immune system and exist naturally in the body stimulating immune cells. Synthetically manufactured cytokines are also applied in treatment of melanoma. According to treatment protocols in Hungarypatients without distant metastases, with aprimarytumour parameter thicker than 1.5 mm adjuvant immunotherapyshould be given (Egészségügyi Közlöny, 2008). At present, interferon is the most widely used adjuvant therapy to increase asymptomatic survival after the removal of primer tumour. It is applied for almost 20

years usually at the early phase of the disease in various doses, as supported by clinical evidence (Garbe et al. 2008; Friebe et al. 2010).

1.2.4.2. The role of interferon in the treatment of melanoma

Interferons are pleiotropic molecules that share a number of biologic effects such as antiviral, antiproliferative and immunomodulatory actions. The alpha interferons are produced by leukocytes or lymphoblastoid cells.

Interferon-alpha has a general inflammatory action which skews the immune response towards a Thelper 1 (Th1) profile (Belardelli and Gresser, 1996). Type Th1 cells produce interferon-gamma, interleukin (IL)-2, and tumour necrosis factor (TNF)-beta, which activate cell-mediated immunity. When interferon-alpha are investigated in vitro they activate Th1 immune responses. In in vitro studies subtype alpha2 increased the expression of human leukocyte antigen (HLA) molecules wich correlate with interferon-alpha mediated activation of memory cluster of differentiation 8(CD8) cells and increased cytolytic action against tumour cells (Finter, 1991).

Interferon-alpha enhances the proliferation of human B cells as well as strongly activates natural killer (NK)-cells (Ortaldo and Herberman, 1984; Hibbert and Foster, 1999). The interferon-alpha2 also affect human T cell mobility and dendritic cell activation (Foster et al. 2004).

Effects of interferon linked to cell membrane include stimulation of the activity of macrophages and lymphocytes in addition to direct cytostatic effect.

Multi-subtype interferons such as human leukocyte interferon-alpha might be more appropriate for melanoma treatment than interferon-alpha2 given its wider spectrum of immunological activities. Another difference between human leukocyte interferon-alpha and recombinant interferons is the lack of glycosylation of specific subtypes in the recombinant formulations (Kontsek, 1994).

All interferon-alpha bind to the same receptor and are expected to have the same biological functions. Human leukocyte interferon-alpha consists ofsix major subtypes, and all subtypemay exert differentanti-viral or anti-tumour effects. For example,

recombinant interferon-alpha2b has been investigated in a recently published paper by Ruuth et al. (Ruuth et al. 2007). In this study three melanoma lines were treated with both types of interferon, and the effect on proliferation and survival was estimated both after short-term and prolonged treatment. The results indicated that the melanoma cell lines were sensitive to the antiproliferative effects of both interferon-alpha species during short-term treatment (Ruuth et al. 2007).

The induction of a characteristic Th1 response in melanoma patients appears to be an important indicative factor for best disease prognosis. The results of Gogas et al. (Gogas et al. 2006) indicate a clear correlation between the potential of strong interferon-alpha induced Th1 inflammatory response and longer disease free periods and overall survival in malignant melanoma patients (Go gas et al. 2006). Th1 inflammatory response has also been correlated with tumour regression. In studies with subcutaneous interleukin-2 and interferon-alpha circulating activated cytotoxic T lymphocytes (CTL) increased NK cells in the blood correlated with tumour growth retardation (Atzpodien et al. 1993; Schneeklothet al. 1993; Jorkov et al. 2003).

The therapeutic significance of multiple interferon-subtypes is still unclear. This multiplicity of activity may be a result of different specific biological activities, altering diffusability, tissue distribution and pharmacokinetics. Another possibility is that multiple interferon-subtypes may compete for receptor binding resulting in a natural selection process and possibly antagonistic effects. Some results suggest that particular subtypes, such as interferon alpha2 and alpha8 may be more effective than other subtypes at protecting cells from viral infection, and that combinations of these two subtypes or natural interferon alpha preparations containing such combinations appear to be optimal for treatment of melanoma (Hino et al. 1993).

Interferons affect many organs and cause multiple side effects in most of the treated patients (Schaefer et al. 2002). The most common, 1 out of 10-100 patients, includes anorexia, mild depression, headache and concentration disturbances, cough, dermatitis, fever and arthralgia. Inthe first period of treatmentanaemia, low white cell count and thrombocytopenia can occur, whichlevels usually are closelymonitored. These latter findings often result in dose reduction (Garbe et al. 2008). Among the rare side effects, 1 out of 1000-10000 patients can be mentioned: psychosis, suicide,

thyroiditis, erythema multiforme, retinal bleeding, endocarditis and liver failure (Kasparian et al. 2012). Their spectrum of toxicity is well documented with a 'flu-like syndrome' occurring universally in patients upon initiation of therapy but disappearing with repeated drug administration.

1.2.4.3.Ipilimumab – *new therapy in the treatment of melanoma*

The fast progress in understanding of immunobiology made significant break-throughs in immunotherapies that have radically changed and renewed the treatment of malignant melanoma (Anderton and Fillatreau, 2015; Atherton et al. 2016). The approval of anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody ipilimumab by US FDA in 2011, as well as the new drugs including antibodies to programmed cell death 1 (PD-1) such as pembrolizumab and nivolumab (both approved in 2014) have extended the potential of immunotherapy for advanced melanoma (Eggermont et al. 2008; Zhu et al. 2010). They have shown a significant increase in progression free and overall survival rate with long-term benefits in a proportion of patients compared with chemotherapy (Hodi et al. 2010; Wolchok et al. 2010; Zhu et al. 2010). Applied immunotherapies for stage III and IV melanoma exert different mechanisms of action that manifest in different adverse events (Ma and Armstrong, 2014). Each of the drugs used to treat metastatic melanoma exert particular mechanisms of action.

The anti-CTLA-4antibody ipilimumab was the first immunotherapy that showed a benefit for overall survival in two controlled trials in metastatic melanoma (Hodi et al. 2010). Ipilimumab is a human anticytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) monoclonal antibody which blocks the inhibitory signal of CTLA-4 molecule having an effect of "natural brake" to the immune system thereby stimulating T-cell activation and proliferation that leads to cancer cell death (Robert et al. 2015). Ipilimumab binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). This T-cell molecule suppresses the immune response. Ipilimumab in melanoma patients has an indirect effect through T-cell mediated anti-tumour immune response. Ipilimumab is a T-cell potentiator that blocks the inhibitory signal of CTLA-4 (Fong and Small 2008; Fecher et al. 2013). Suppression of CTLA-4 can augment the immune system's T-cell

response in fighting disease. T-cell-mediated antitumour therapies have played an important role in the treatment of advanced melanoma in last years. Tumour-associated antigens attached to the major histocompatibility complex (MHC) on specialized antigen-presenting cells (APC) bind with T-cell receptors (Chmielowski, 2013). CTLA-4 is a surface protein expressed on activated and regulatory T cells and is upregulated in malignancy. It functions as a negative regulator of T-cell function, binding to B7 antigen-presenting cells and inducing cell-cycle arrest. On the T cells, surface protein CD28, is a positive regulator of T-cell function and binds B7 with less affinity (Schatton et al. 2010). The goal of CTLA-4 blockade is to break immune tolerance to a cancer and trigger a prolonged tumour-specific immune attack (Fecher et al. 2013). Ipilimumab was registered in 2011 by the FDA.

During ipilimumab therapy, most often autoimmune side effects were reported (colitis, thyreoiditis, hepatitis) as well as depression, confusion, insomnia, change in mental condition, tiredness (fatigue) are mentioned in the literature (Pardoll, 2012).Its most common adverse events related to the study drugs were immune-related events. Severe autoimmune reactions commonly skin rash, colitis, thyreoiditis, hepatitis, hypophysitis may develop in some patients. Depression, confusion, insomnia, mental status changes are named as expected adverse events in ipilimumab treatment (Garbe et al. 2012), but there are only few data in the literature. Immune-related adverse events associated with the use of ipilimumab were already evident in randomized trials (Hodi et al. 2010;Quirk et al. 2015; Robert et al. 2015). Immune-mediated adverse effects are common, but not severe in most patients. Skin-related adverse events can occur 2–3 weeks after the first dose of ipilimumab, whereas liver and gastrointestinal events typically occur 6–7 weeks after treatment initiation, and endocrinopathies are usually observed 9 weeks after the initial drug administration (Di Giacomo et al. 2010). Less frequent, but well-documented and potentially serious or irreversible immune-related adverse events can involve the liver or endocrine or nervous systems, including sensory, motor or ocular manifestations (Quirk et al. 2015).

1.2.4.4. Other immunotherapies in the treatment of melanoma

Besides antibodies against CTLA-4, most experimental and clinical information was gathered on the inhibition of programmed death (PD)-1-route in connection with the treatment of advanced diseases. The aim is not to kill cancer cells directly but to block a pathway that shields tumour cells from immune system components able and to fight cancer.The pathway includes two proteins:

- programmed death-1 (PD-1), which is expressed on the surface of immune cells
- programmed death ligand-1 (PD-L1), which is expressed on cancer cells

When PD-1 and PD-L1 connect they form a biochemical barrier protecting tumour cells from being neutralised by the immune system.PD-1 is important mainly at the later phase of implementation of T-cell activation, in inhibiting inflammatory reactions and autoimmunity in peripheral tissues. The autoimmune side effects of the anti-PD-1 therapy are much lighter and develop later as compared to anti-CTLA-4. On the other hand, its interaction with the ligands of PD-1 receptor proved to be an important immune-resistant mechanism of tumours (Dong et al. 2002; Ladányi, 2002; Topalian et al. 2012), and therefore it is a promising objective of the therapy aimed at "accessibility" to antitumour immune response. Anti-PD-1 antibody is a fully human antibody presently in clinical use. At the moment, two medicinal products are registered: pembrolizumab and nivolumab. A test performed using higher number of cases confirmed that the ratio of objective response given to the treatment was 28% in the case of melanoma and the effect proved to be durable (Topalian et al. 2012). 6% of grave side effects were potentially immune associated. Most frequent side effects described in connection with the treatment were tiredness, apathy, loss of appetite, diarrhoea, nausea, cough, constipation, skin rash, fever and headache (Topalian et al. 2012; Robert et al. 2014).

A number of clinical trials aimed at blocking PD-1-route are pending in melanoma and other tumours especially as monotherapy with PD-1-antagonist antibodies and also in various combinations (Sznol and Chen, 2013). Therapy

combining anti-CTLA-4 and anti-PD-1 may further increase the effectiveness of treatments.

In PD-1 therapies generalized symptoms, including fatigue and asthenia, fever and chills, myalgias, and headaches, were reported frequently but were of low grade in more than 95% of the cases (Hamid et al. 2013). The most common adverse events, regardless of causality, were fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, vomiting, rash, pyrexia, and headache (Topalian el al. 2012). Fatigue is by far the most common symptom reported by patients and is often difficult to treat (Ribas, 2012; Hamid et al. 2013). Fatigue (56.3%), nausea (25%), diarrhea, xerostomia, and pruritus (18.8% each) were reported by anti-PD1 therapy (Freemann-Keller and Weber, 2015). In the comparative study of Robert et al. (Robert et al. 2014) the most common drug-related adverse events were fatigue (33%-37%), pruritus (19-26%) and rash (18%). Fatigue is among the most common side effects seen, with an estimated overall frequency of 16 to 24 percent for the anti-PD-1 and anti-PD-L1 agents and approximately 40 percent in those treated with ipilimumab (Horvat et al. 2015; Naidoo et al. 2015; Postow et al. 2015).

The two new immunotherapeutic agents, anti-CTLA-4 and anti-programmed cell death 1, show promise as potentially effective therapies with manageable side effect profiles in metastatic melanoma (Chakraborty et al. 2013).

1.3. Side effects of immune therapies in melanoma

As more-effective therapies become available based on modulation of the immune system in order to trigger or enhance anti-tumour immune responses, clinicians will need to become familiar with recognizing and controlling the adverse effects arising from immune therapy (Gangadhar and Vonderheide, 2014).

1.3.1. General symptoms

A new category of side effects, so called "immune-related adverse events" (irAE) could complicate cancer immunotherapy. It is mainly due to the inflammation of off-target organ system, such as well described immune-related dermatitis, hepatitis, colitis, and hypophysitis (Postow et al. 2015). The most common and earliest onset of irAE is dermatologic toxicity. Adverse effects are usually reversible, although early recognition and intervention are essential. In this context, patient awareness, close monitoring and good communication between the care provider and patient are imperative.

Side effects are unplanned physical or emotional conditions caused by treatment. Each treatment for melanoma has and can cause different side effects. The side effects of immunotherapies depend on:

- the drug
- how it is given
- the amount taken
- the length of treatment
- the person

1.3.2. Psychological side effects

In the long run, adjuvant interferon treatment has the most common and also clinically relevant psychological side effects. Fatigue, anhedonia, social isolation, psychomotor slowness is reported during treatment and is frequently accompanied by psychological side effects including depression, irritability, anxiety, or suicide(Gogas et al. 2006). These psychological problems may lead to a significant deterioration in quality of life and often result in premature suspension or discontinuation of treatments. Not only physical side effects presenting serious subjective symptoms, if any, may imply distress but the effects of immunotherapy in the central nervous system may also

cause grave anxiety and clinically significant depressive symptoms (Schaefer et al. 2002). Depression of clinically significant degree developing during interferon therapy varies between 20 and 40% (Schaefer et al. 2002) which at the same time is one of the most frequent reasons for premature discontinuation of the therapy (Reyes-Vazquez et al. 2012).

Besides early neurovegetative symptoms which manifest in the majority of patients during the first weeks of IFN-alpha treatment as fatigue, pain and anorexia, long-term IFN-alpha treatment often causes a wide variety of psychiatric side-effects, such as depression, fatigue, insomnia, anxiety, and cognitive disturbances (Capuron et al. 2002). 10%–40% of patients additionally develop a full depressive disorder syndrome that can include suicidal ideation, aboulia, lack of motivation, social withdrawal, guilt, anhedonia, irritability, anxiety, and crying (Lotrich, 2013). Mania, delirium, and psychosis are further but less common side effects of IFN-alpha treatment. Approximately 30–70% of hepatitis C virus-infected patients treated with IFN-alpha experience different degrees of depression. Most of them suffer from mild or moderate depressive symptoms, while severe major depression occurs in about 15% (Schaefer et al. 2012).

1.3.3. Differences in psychological side effects according to pharmacodynamics of drugs

In addition to these similarities, the symptom profile (Table 7.) of treatment-emergent depression and naturally occurring major depressive episode show some distinctions (Pala et al. 2016). Namely, during long-term IFN-alpha treatment patients reported more severe weight loss and decreased activity, while feeling of guilt was less prominent compared to medically healthy depressed subjects (Capuron et al. 2009). This observation was supported by a recent finding which suggested that risk genetic variant in the IL-6 gene more specifically increased depressive symptoms measured by the Zung Self-rating Depression Scale compared to the Brief Symptom Inventory, suggesting that inflammatory risk mechanisms are more responsible for

somatic/neurovegetative symptoms than cognitive-emotional signs of depression (Kovacs et al. 2015). Furthermore, newly developed immune checkpoint inhibitors, such as anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies or humanised immunoglobulins against programmed death 1/ligand 1 (PD-1/PD-L1) which also enhance tumour-specific immune activity are associated with a new category of side effects called "immune-related adverse events" (irAE), in which the most frequent symptom is fatigue (Postow et al. 2015).

Although both IFN-alpha and immune checkpoint inhibitors increase tumour-specific immune response their psychological side-effect profiles are strikingly different. It has been recently demonstrated that CTLA-4 antibodies (e.g. ipilimumab) decrease the number of regulatory T cells through non-classical monocytes (Romano et al. 2015). Nonclassical or patrolling monocytes are responsible for clearing up the consequences of inflammation at the vascular endothelium and maintaining the integrity of the BBB thus they might decrease expansion of the inflammation into the central nervous system (Ribas et al. 2015). PD-1/PD-L1 antibodies (e.g. nivolumab and pembrolizumab, both approved in 2014) increase effector T cell activity within tissues or tumours where cells express PD-1/PD-L1 which tends to be low in the brain (Postow et al. 2015; Ribas et al. 2015).

Table 7. Symptom profile of sickness behaviour, major depressive disorder, IFN-alpha induced depression, and psychological side effects of immune checkpoint inhibitors. *MDD: major depressive disorder, IFN-alpha: interferon alpha treatment, ICI: immune checkpoint inhibitor treatment, x: symptom is present, number of x: dominance of symptoms*

Symptom domain	**Symptom**	**Sickness behaviour**	**MDD**	**IFN-alpha**	**ICI**
Mood	depressed mood	x	xxx	xxx	
	anhedonia	x	xxx	(x)	
	guilt		x	(x)	
	suicidal thoughts		x	(x)	
Anxiety	tension/irritability	x	x	xx	
	fear	x	x	xx	
Cognitive	memory/concentration		x	x	
	decision making		x	x	
Somatic/neurovegetative	appetite	x⇩	x⇧⇩	xxx⇩	
	sleep	xx⇧	x⇧⇩	x⇩	
	psychomotor retardation	xx	x	xxx	
	fatigue	xx	x	xxx	xxx
	pain	x	x	xxx	

1.3.4. Psychological distress and cancer

Prevalence of clinically relevant psychological distress among patients with melanoma (all stages) is approximately 30% (Kasparian et al. 2012; Rychetnick et al. 2012). Several of the diagnostic criteria for major depressive disorder are related to symptoms resulting from malignant and chronic diseases or their treatment: among them the most prevalent are low energy, poor appetite and impaired concentration. Other cardinal psychological symptoms must be also present to diagnose major depressive disorder, such as low mood, loss of interest, rumination on negative emotions, grief, hopelessness, demoralization. Meyer et al. gave a thorough summary of cancer associated psychiatric problems (Meyer et al. 2009). Meyer et al. highlights that psychological problems depends on: premorbid psychiatric status, biological effect of cancer, biological effect of treatment, effect of coping style/psychological factors on cancer (quality of life, defense mechanisms, phases of illness). The most commonly

occurring psychiatric disease, according to the review of Meyer et al. are: depression (25%), anxiety disorders (panic disorder – 4.8%, generalized anxiety disorder – 3.2%, posttraumatic stress disorder – 4%), delirium (28-44%), fatigue (80%), bipolar disorders (0.4-1.6%), character disorders (2-3%), schizophrenia (0.5-1.5%), substance use disorders (~28%) (Meyer et al. 2009). The metaanalysis of Satin et al. showed that depression predicts mortality, but not progression, in cancer patients. Based on data from 25 studies, mortality rates were up to 25% higher in patients with depressive symptoms (Satin et al. 2009).

1.3.4.1. Depression

The incidence of clinically relevant depression during interferon therapy varies between 20% and 40% (Schaefer et al. 2002) making it the most common side effect and one of the main reasons for early discontinuation of treatment (Garbe et al. 2008). Depression has a broad list of symptoms. Typically, physical problems (like change in bodyweight, difficulty in sleeping, fatigue, motor agitation or inhibition, etc.) also often develop in somatic conditions requiring hospitalisation and so they provide for less solid points of reference in differential diagnosis of depression. Therefore, it is particularly important to identify and also to considerpsychosomatic symptoms according to the condition. Depressed mood, anhedonia, loss of interest, sense of guilt, self-accusation, thinking of death frequently, mentioning of thoughts of committing suicide may be the chief symptoms of depression (Schaefer et al. 2002).

1.3.4.2. Anxiety

Anxiety is often an expression of the sense of helplessness which may be generalised in all areas of life (Erim et al. 2013). Physical and emotional components also must be taken into consideration when making diagnosis. Somatic palpitation, muscle stiffness, dizziness, stomach pain, dry mouth that can be felt; otherwise, patients can be characterised by restlessness, sleep difficulty (nightmares), irritability and sensitivity (Stark and House, 2000). Nonverbal signals (look, pose, loudness, tone etc.) of patients may also convey important messages. It is particularly important to observe them in order for precise assessment of the condition (Traeger et al. 2012).

1.3.5. Vulnerability factors for psychological side effects

Depressive or anxiety disorders in the psychiatric history increase the risk of psychiatric side effects during treatment. In addition, female sex, younger age, lower education, and lack of social support were investigated as risk factors for evolving psychiatric side effects, but conclusive biological or psychological markers predicting psychological side effects of interferon treatment are lacking (Kasparian et al. 2009). Thus, routine monitoring of melanoma patients remains to identify clinically relevant psychological distress and possible protective factors (Friebe et al. 2010).

1.3.6. Screening and prevention of psychological side effects

Development of depression is a relatively slow process when immuntherapies are used (Friebe et al. 2010; Hanaizi et al. 2012). Prevention can be started early on by means of screening tests. It is necessary to evaluate the psychological state multi-dimensionally in order to establish individualised psychological care related to medical interventions. In addition to the knowledge based on the impressions of personal meetings and everyday practical experiences, psychological symptoms can be measured

by questionnaires developed internationally and validated for the given country or population.

1.4. Potential pathophysiology behind psychological side effect of immune therapies in melanoma

Below are listed some possible biological mechanisms that likely to mediate immunotherapy induced psychological adversities.

1.4.1. The inflammation theory of depression

Interferon alpha enhances production of proinflammatory cytokines which can create symptoms of psychiatric diseases through psychoneuroimmunological effects in the central nervous system (Sano et al. 1999; Chalise et al. 2013).

The inflammation theory of major depression hasbeen proposed several decades ago based on observations that unipolar major depression is paralleled by alterations in several immune parameters indicating chronic albeit low grade inflammation as well as cell-mediated immune activation (Maes et al. 1990; Maes et al. 1992a). These initial observations were later on followed by replication studies and new observations related to inflammation-associated alterations during major depression (Leonard and Maes, 2012) as well as metaanalyses also supporting the presence of inflammation and t-cell activation in depression (Dowlati et al. 2010; Liu et al. 2012).

The inflammatory response consists of several components including cellular, cytokine and complement reactions as well as an acute phase reaction. During the process, primary inflammatory mediators such as interleukin 1beta (IL1β) and TNFα lead to increased production of interleukins 6 and 8, as well as IFNγ. IL1β and TNFα also induce the production of such acute-phase proteinsas c-reactive protein,and decreased production of negative acute phase proteins including transferrin and albumin. These processes lead to the body reaction called anti-inflammatory response

syndrome including symptoms highly overlap with depression(Leonard and Maes, 2012).

The activation of cell-mediated immune response and other inflammatory pathways have been shown by several studies to be associated with the onset and pathophysiology of major depression (Leonard and Maes, 2012). Most studies focused on the role of such consequences of cell-mediated immune activation as increased IFNγ and IL2 levels, and the increased productions of pro-inflammatory citokins including IL1β, IL6 and TNFα and their association with several features and symptoms of depressive illness including melancholic symptoms and anhedonia, anxiety, somatic symptoms, neurocognitive symptoms and fatigue (Leonard and Maes, 2012). Most important observations supporting that depression is an inflammatory illness is

- a consistent elevation of brain or blood inflammatory cytokine levels including IL1β, IL6 and TNFα reported in depressed patients
- the presence of acute phase response in depression reflected in an increase in such positive acute phase protein serum levels as α1 antitrypsin, α1 acidglycoprotein, coeruloplasmin and haptoglobin paralleled by decreased negative acute phase protein levels such as transferrin and albumin
- higher concentrations of complement C3 and complement C4 in the plasma of depressed patients
- and increasedinterleukin-1 receptor antagonist (IL-1RA) synthesis (Maes et al. 1990; Maes et al. 1991; Maes et al. 1992a; Maes et al. 1992b; Maes et al. 1994; Leonard and Maes, 2012).

Besides the observations of the above parallel immunological and inflammatory parameter changes during depression, proinflammatory cytokines were directly found to be associated with induction of depressive symptoms. Administration or increase in IL6 levels is associated with anxiogenic and depressogenic behavioural effects as well as psychomotor retardation in various animal models (Sakic et al. 2001; Brydon et al. 2009). Increase in IL1β plasma levels also showed association with increased anxiety and depressive-like as well as melancholic behaviours, anhedonia, fatigue and neurocognitive deficits such as impaired memory (Anisman et al. 2008). TNFα increase

leads to somatic symptoms, anxiety, anorexia as well as autonomic symptoms also observable during depression (Anisman et al. 2005). Similarly, t-cell derived cytokines, such as IL2 and IL12 or IFNγ were also associated with depressive symptoms in various studies in humans and animal models including anorexia, anhedonia, cognitive dysfunction and reduced psychomotor activation (Capuron et al. 2001; Anisman et al. 2005; Little et al. 2006). Thus, the role of altered immune processes and responses in the development of depression and depressive symptoms is not questionable. In addition, increased cytokine levels observable during depression may contribute to the emergence of depressive symptoms in various ways.

1.4.2. Theory of HPA-axis hyperactivity in depression

The hypothalamic–pituitary–adrenal (HPA) axis is one of the main biological systems mediating the effects of stress in the body and in the central nervous system (CNS): the activity is significantly heightened in patients suffering from depression, compared with healthy controls (Murri et al. 2014). During experimental manipulation of HPA axis can lead to the occurrence of depressive-like behaviour. Also risk factors for depression (e.g. early life trauma, repeated psychosocial stress) are characterized by hyperactivity of the HPA axis (Pariante and Lightman, 2008).

The increase in HPA axis activity isfrequently observed in depressive mood changes (Nijm et al. 2007; Höhne et al. 2014). Proinflammatory cytokines may cause HPA axis hyperactivity by disturbing the negative feedback inhibition of circulating corticosteroids on the HPA axis (Raison et al. 2010).

As a further possible background mechanism, prolonged psychological stress and related HPA-axis hyperactivity may play an important role in the development of mood disorders (Müller and Schwarz, 2007). The inflammatory cytokines such as interferon (interleukin-1, interleukin-6) by increasing the activity of the HPA-axis generate sickness-behaviour in animals and depression in human beings. Interferon treatment also creates similar effects by decreasing monoamine activation (Capuron et al. 2001; Reiche et al. 2004). Hyperactivity of corticotrophin releasing hormone (CRH) signals

the development of mood disorders in somatic diseases (Raison et al. 2005). However, the exact mechanism of interferon action on the central nervous system is not well understood although several hypotheses have been investigated (Tsao et al. 2004, Garbe et al. 2008). It has been suggested that alterations in the diurnal pattern of HPA axis activity play a major role in the development of psychological symptoms. Namely, flattening of theslope of ACTH and cortisol secretion and elevated evening ACTH and cortisol concentrationswere associated with depression and fatigue in hepatitis C patients (Raison et al. 2010). Furthermore, modulation of the HPA axis activity seems to play an important role in the biological response to antidepressant drugs (Anacker et al. 2011).

1.4.3. Serotonin and depression

Cytokines directly induce changes in serotonin transporters with an upregulation associated with IL1β, IL6 and TNFα treatment (Zhu et al. 2006; Zhu et al. 2010) and inflammation also decreases cortical 5HT1A and increases midbrain 5HT2A receptor expression (Kulikov et al. 2010). Furthermore, during inflammation, TNFγ, TNFα, IL2 and IL1β, prostaglandin E2 and lipopolysaccharide induces indoleamine 2,3-dioxigenase, which is responsible for the catabolisation of serotonin precursor tryptophan into tryptophan catabolites such as kynurenine or quinolinic acid. These metabolites are able to induce depression and anxiety in various models and studies. Tryptophan catabolism also leads to decreased plasma and brain tryptophan concentration and consequentially decreased serotonin availability with known depressogenic effects (Leonard and Maes, 2012). Changes in serotonin neurotransmission are connected not only with depression but with the development of various neuropsychiatric symptoms. Selective serotonin reuptake inhibitors (SSRI) show significant effectiveness in decreasing depressive symptoms in patients suffering from immunotherapy-induced depression thus it can be speculated that the serotonin system plays a role in the development of depression induced by interferon (Kilpatrick et al. 2007).

1.5. Percevied social support and psycho-neuro-immunomechanism

The subjective perception of social support, the feeling of being supported by other people plays an important role in human well-being (Sato et al. 2016).Social support can be measured as perceived social support and received social support (Cohen and Janicki-Deverts, 2009). Perceived social support is a construct that is used to describe social support anticipated prospectively at a time of need in the future (Procidano and Heller, 1983). Received social support is based upon retrospective accounts of received social support (Barrera et al. 1981).Several previous psychological studies have shown that perceived social support is reliably linked to high life satisfaction, high positive affect, and low psychological distress (Diener and Fujita,1995; Lakeyand Lutz,1996). Persons with low levels of perceived social support have more negative mental and physical health outcomes than their more fortunate counterparts (Sato et al. 2016). Perceived social support is not a state resulting from support received by a social network, but rather a stable characteristic similar to traits and personalities (Uchino, 1996).

Despite accumulating psychological evidence for perceived social support, the neural substrate that implements perceived social support remains largely unknown.

According the review of Cohen and Wills, two models can be distinguished to describe the effect of social support. Models are applicable in different situations. According to the first model (main effects hypothesis) social relationships have a direct effect on health and may prevent the deleterious effect of stress (Cohen and Wills, 1985). People with strong support have greater well-being irrespective of exposure to stressful life events. The other model (buffering hypothesis) suppose that social support is protective in stressful situations. Social support buffer the ability to cope with distress. People have to appraise the stressful situations like cancer diagnosis, or the fact of a necessary long-term treatments. Greater supported patients have higher well-being than poorly supported peoples only if they are exposed to stressful life events. Social

support may result in reappraisal inhibition of maladaptive responses or facilitation of adjustive responses (Cohen and Wills, 1985; Wade and Kendler, 2000).

There are no clear confirmatory evidences for these models. It has been suggested that main effects tend to be found where structural support measures are used, and buffering effects are associated more with functional measures. Alternative hypothesis or processing the structure of social support are recommended (Wade and Kendler, 2000).

Söllner et al. found that active coping combined with high level of social support was associated with better adjustment, whereas depressive coping combined with lower level of social support was associated with poor adjustment. Adequate social support contributes to adaptive coping strategies, such as problem-focused coping. Lack of support is associated with less adaptive coping-strategies, such as avoidance behaviour (Schreurs and DeRidder, 1997; Söllner et al. 1999).

In the review of the literature of social support in melanoma patients Kasparian et al. identified low level of social support as risk factor for distress (Kasparian et al. 2009). There were also reported significant negative associations between social support and psychological distress, especially in major depression (Kendler et al. 2005; Allart et al. 2013).

The serotonergic system can play an important role in a possible connection between induced depression and social support. Perceived social support was positively correlated with brain serotonin transporter availability, which is also consistent with previous data showing that perceived support is more effective in helping individuals resist distress (Huang et al. 2013). Also the serotonergic system moderates the individual sensitivity of social experiences (Grabe et al. 2005). Kilpatrick et al. found relationship between major depression and social support in context of low-expression variant of 5-HTTLPR. The risk effect of polymorphism appear at low level of social support (Kilpatrick et al. 2007).

Furthermore, social support can influence the stress response of the HPA system (Murri et al. 2014).Namely, increased social support was associated with decreased basal cortisol level in a longitudinal human study (Rosal et al. 2004).

In addition several data emphasise that social support exert its effect on general health and mental health through the autonomic nervous system, by reducing the stress elicited sympathic activation, and through positively influencing the immune system (Ditzen and Heinrichs, 2014).

1.6. Synthesis of theories

The summarized context of connection between neurotransmitters, function of HPA axis, psychological distress and depressive mood, social support, and the effect of interferon is shown in Table 8.

Table 8. The biological effect of interferon alpha treatment, psychological stress and social support (based on the review of the literature according Murri et al. 2014 and Raison et al. 2010.). *HPA: Hypothalamic-pituitary-adrenal axis; CRF: Corticotropin-releasing factor; ACTH: Adrenocorticotrop hormone; NE: adrenaline; 5HT: serotonin; DA: dopamine*

	INF-alpha	Psychosocial Stress	Social Support
HPA	↑	↑	↓
CRF	↑	↑	↓
ACTH	↑	↑	↓
NE	↑	↑	↓
5HT	↓	↓	↑
DA	↓	↓	↑

It is important to note that the effect of interferon-alpha is similar to the stress response. Social support show the completely inverse effects on quantity of neurotransmitters, or function of HPA axis than INF-alpha and the stress response.

Neuropsychiatric symptoms, like depressive mood, sickness behaviour, are the most frequent long term effects of interferon-alpha and interferon-alpha induced cytokines on the central nervous system. The increased activityin hypothalamic–

pituitary–adrenal (HPA) axis is also frequently observed in depressive mood changes (Murri et al. 2014). Proinflammatory cytokines may cause HPA axis hyperactivity by disturbing the negative feedback inhibition of circulating corticosteroids on the HPA axis (Raison et al. 2010).

Cytokine synthesis and HPA activity are heavily influenced by acute and chronic environmental stressors (Murri et al. 2014). Thus, factors that can alleviate environmental stress may have a beneficial consequence on psychological side effects of low-dose interferon treatment by modulating overlapping biological mechanisms (Reyes-Vazquez et al. 2012).

1.7. Gap in the knowledge

At present promising drugs are available for the treatment of metastatic melanoma.However, long-term oncological treatments (e.g. immunotherapies) are frequently accompanied by psychological side effects, including anxiety, fatigue, irritability, depression, or suicide. Depression is one of the most common side effects and may lead to discontinuation of therapy (Friebe et al. 2010).

Thus it is important to further our knowledge whether the newer immunotherapies have better psychological side-effect profile than the traditional ones, like IFN-alpha. It is also an outstanding question how we can predict the risk of suffering from psychiatric side effects during immunotherapies and which preventive actions should be taken to help patients to complete their therapeutic course without major side-effects. Thus my research objective was to investigate these topics.

2. Hypothesis and aims

Based on the above the chief aim of the research was to measure and identify psychiatric adverse events, such as changes in depressed mood, and anxiety using psychological self-rating scales during immunotherapies used in the treatment of malignant melanoma. It was important to identify the factors which could influence the possible psychological (side-)effects of these therapies.

2.1. Interferon-induced depression- *first study*

In the first study the primary aim was to investigate the psychological side effects of low-dose interferon treatment in melanoma patients. Specifically, we tested the protective effect of social support on psychological side effects elicited by the increased activity of the pro-inflammatory cytokine pathway, such as depression and anxiety. We hypothesised that

- the level of depression significantly increases during long-term interferon treatment
- the level of anxiety significantly increases during long-term interferon treatment
- different socioeconomical aspects (sex, age, family status, education, financial status) have effect on emerging depression or anxiety during long-term interferon alpha therapy
- greater social support will be associated with better adjustment (namely less depressive and anxiety symptoms during treatment)

2.2. Ipilimumab vs. interferon - *second study*

The primary aim of this study was to measure psychiatric adverse events, such as changes in depressed mood during the ipilimumab treatment and compare the results to the psychiatric side effect profile of long-term low-dose interferon treatment. We hypothesised that

- both immuntherapies are in association with long-term psychiatric side effects including depression and anxiety
- ipilimumab-treated group has baseline increased level of depression and anxiety
- significant increase in level of depression and anxietywill occur during ipilimumab treatment
- significant increase in level of depression and anxiety will be observable during long-term interferon treatment

3. Methods

In this thesis two study paradigms were described.

Recruitment and design

Patients were recruited at the Department of Oncodermatology in the National Institute of Oncology (Budapest, Hungary) for the twoopen-label follow-up studies. All patients signed informed consent to participate in the studies,which was approved by the Ethics Committee of the National Institute of Oncology, and the studies were carried out in accordance with the Declaration of Helsinki. All subjects completed a psychological questionnaire booklet at least three times during the first year of therapy. Questionnaires were filled out at outpatient clinics during the regular visits.

Background questionnaire

Demographic data, such as sex, age, home, family and financial status, and level of education were measured by a standardised background questionnaire in both study, regularly used in our institute (Kovács et al. 2015). Age was calculated from birth year. Home was grouped withfour categories: *capital, town, village, other*. Family status was categorized with six selectable and possible answers*: single, in relationship, married, divorced, widow/widower, other*.Financial status was categorized with a single question "*How well do you feel you are managing financially these days*?" and was subjectively rated by the participant on a 5 item Likert scale ranging from very bad (0) to very good (4).

3.1. Interferon-induced depression – *first study*

3.1.1. Participants

127 patients were recruited for this open-label follow-up study.

Inclusion criteria were tumour thickness of 1.5 mm or thicker, no evidence of regional or distant metastases, except micrometastases in the sentinel lymph nodes. Exclusion criteria were mucosal or ocular melanoma, pregnancy, breast-feeding, autoimmune diseases and pre-existing Axis I or Axis II psychiatric disorders. All patients were recruited within 8 weeks after surgery for malignant melanoma. They received interferon alpha 2a treatment in a weekly dose of 3X3 MIU/week subcutaneously and regularly attended control examinations at month 0, 1, 3, 6, 9, 12.

3.1.2. Questionnaires

The Beck Depression Inventory (Beck et al. 1961) was used to detect symptoms of depression. The BDI is a 21-item self-report questionnaire that assesses the severity (0-3) of an individual's depressive symptoms. Sum of the item scores was used in the analysis. The BDI was validated in the Hungarian population and the cut-off score for minor depression was 14 (SD=4) and for clinically relevant depression 27 (Ágoston and Szili, 2009).

The State-Trait Anxiety Inventory(STAI) was used to measure anxiety symptoms. The STAI-State subscale presents 20 items describing anxiety states forwhich the patient selects one of four descriptors (not et al – somewhat – moderately so – very much so) that best represents his/her feelings (Sipos and Sipos, 1978). Sum of the item scores was used in the analysis. The STAI-State was validated in the Hungarian population and the cut-off score for clinical anxiety was 38.40 (SD=10.66) in men and 42.64 (SD=10.79) in women (Spielberger et al. 1983).

Social support was measured with the Social Dimension Scale developed by Caldwell et al. (Caldwell et al. 1987). This scale was validated for the Hungarian

population by Kopp and Skrabski (Kopp and Skrabski, 1995). Patients rated their subjective relationships with important others from 0 to 3. Sum of the item scores was used in the analysis.

3.1.3. Other measures

The data of thickness and invasion of primary tumour (Breslow's depth and Clark invasion) were determined by histopathological examinations following the national guideline (Garbe and Leiter, 2009). Breslow's depth is a measure of cell invasion into the skin in millimetres in case of malignant melanomas. Clark invasion describes the level of anatomical (e.g. epidermis, dermis or fat) invasion of skin melanomas. Besides ulceration (defined by interruption of the surface epithelium by tumour cells) and mitotic rate, Breslow's depth is the most important prognostic factor in the melanoma classification system recommended by the American Joint Commission on Cancer (AJCC) and Clark's level has far less importance (Edge et al. 2010).

3.1.4. Statistics

Data were analysed by SPSS 21 for Windows (IBM). The measured psychometric scores showed normal or F-distribution in our samples (Kolmogorov-Smirnov and Shapiro-Wilk tests). Baseline between-group comparisons were evaluated by t-tests (continuous variable) and by chi-square tests (nominal and ordinal variables; Pearson Chi-Square and Likelihood Ratio) for independent samples. Repeated measure of ANCOVA was used to analyse the effect of interferon treatment during the follow-up on psychometric measures. In all ANCOVAs Greenhouse-Geisser correction was applied and age, sex, financial status, social support, education were co-variants. As vertical tumour thickness (Breslow's depth) is the most important histological prognostic factor for primary melanoma (Garbe et al. 2008) this was also included in the model as covariate.The level of significance was p=0.05, two-tailed.

3.2. Ipilimumab vs. interferon – *second study*

3.2.1. Participants

Two groups were recruited for this study:

*Inclusion-exclusion criteria and treatment for **IPI-Group**.*

IPI-Group: included 10 participants treated with ipilimumab. Patients were eligible for inclusion in the study if they had a diagnosis of stage III or IV melanoma with a life expectancy of at least 4 months and had received previous chemotherapy. Exclusion criteria were pregnancy, breast-feeding, autoimmune diseases and pre-existing psychiatric disorders. Patients received 3 mg/kg YERVOY® four times in every 3rd week. Patients were controlled at week 0, 3, 6, 9.

*Inclusion-exclusion criteria and treatment for **INF-α Group***

The interferon group (**INF-α-Group)** included 18 participants. Inclusion criteria were tumour thickness of 1.5 mm or thicker, no evidence of regional or distant metastases, except micrometastases in the sentinel lymph nodes (Stage I or II). Exclusion criteria were mucosal or ocular melanoma, pregnancy, breast-feeding, autoimmune diseases and pre-existing psychiatric disorders. Patients received interferon-alpha 2a treatment in a weekly dose of 3X3 MIU/week subcutaneously and they were checked at month 0, 1, 3, 6.

3.2.2. Questionnaires

To detect symptoms of depression, we used the Zung Self-Rating Depression Scale (SDS) (Zung, 1965). SDS is a self-administered measure of depression severity with 20 items. Sum of the item scores was used in the analysis. SDS was validated in the Hungarian population and the cut-off score for clinical depression was 48 (Simon, 1994).

The level of anxiety was measured with the State-Trait Anxiety Inventory(STAI) self-administered questionnaire. The STAI presents 20 items describing anxiety states of which the patient records one of four descriptors (not et al – somewhat – moderately so – very much so) the degree of distress (Spielberger et al. 1983). Sum of the item scores was used in the analysis. STAI was validated in the Hungarian population and the cut-off score for clinical anxiety was 38.40 (SD=10.66) in men, and 42.64 (SD=10.79) in women (Sipos and Sipos, 1978).

Social support was measured with an adapted version of the Social Dimension Scale developed by Caldwell et al. (Caldwell et al. 1987). Patients had to rate their relationships with important others in the subjectively detected extent (0-no support, 1-few, 2-average, 3-very). Sum of the item scores was used in the analysis.

3.2.3. Statistics

Data were analysed by SPSS 21 for Windows. Baseline between group comparisons were evaluated by t-tests (continuous variable) and by chi-square test (nominal and ordinal variables; Pearson Chi-Square and Likelihood Ratio) for independent samples. The measured psychometric scores showed normal distribution in our samples (Kolmogorov-Smirnov and Shapiro-Wilk tests). Thus repeated measure of ANCOVA was used to analyse the time-effect of drugs on psychometric measures in the longitudinal data. The repeated measure of ANCOVA was run separately for the 2 study groups because of the differences in treatment schedules. In all ANCOVA Greenhouse-Geisser correction was applied and age, sex, and social support were co-variants. The level of significance was p=0.05, two-tailed.

4. Results

4.1. Interferon-induced depression - *first study*

Baseline characteristics of the study population can be seen in Table 9. None of the patients had depression or anxiety scores above the Hungarian cut-off score for clinical depression or anxiety at the beginning of the study.

Table 9. Description of the study populations and the properties of the primary tumours at baseline

Variable	Subgroups	Scores (percentages)
Sex	**female***no.(%)*	63 (49)
	male*no.(%)*	64 (51)
Age *years (range)*		54.67 (21; 90)
Home	**capital***no.(%)*	47 (37)
	town*no.(%)*	59 (47)
	village*no.(%)*	21 (16)
Social situation	**single***no.(%)*	10 (8)
	relationship *no.(%)*	25 (20)
	married*no.(%)*	70 (55)
	divorced*no.(%)*	12 (9)
	widow*no.(%)*	10 (8)
Education	**primary school** *no.(%)*	17 (13)
	high school *no.(%)*	61 (48)
	university*no.(%)*	41 (33)
	other*no.(%)*	8 (6)
Financial status	**very bad** *no.(%)*	7 (5)
	bad*no.(%)*	30 (24)
	average*no.(%)*	80 (63)
	good*no.(%)*	5 (4)
	very good *no.(%)*	5 (4)

Variable	Subgroups	Scores (percentages)
Social support *mean (SD)*		15.06 (6.022)
BDI depression score *mean (SD)*		5.68 (4.933)
STAI State anxiety score *mean (SD)*		40.33 (8.477)
Breslow's depth *mm (SD)*		3.5110 (2.089)
Clark level	**II** *no.(%)*	2 (2)
	III *no. (%)*	32 (25)
	IV *no. (%)*	79 (62)
	V *no. (%)*	9 (7)
	no data	5 (4)
Exulceration	**exulcerated***no. (%)*	49 (39)
	non exulcerated *no. (%)*	78 (61)
Localization	**Trunk** *no. (%)*	56 (44)
	Head & Neck *no. (%)*	17 (13)
	Upper limb *no. (%)*	26 (21)
	Lower limb *no. (%)*	28 (22)

4.1.2. Baseline differences in psychometric scores according to background variables

At baseline, there were significant differences in BDI depression scores according to education, financial status, and sex (Table 10.). Higher educated patients, patients with better financial conditions and male patients scored lower on BDI compared to the other group. There were no significant differences in BDI depression scores at baseline according to social support, family status or tumour parameters (Breslow's depth, exulceration of primary tumour, or Clark's level of invasion groups).

Table 10. Baseline differences in BDI depression scores according to demographic and clinical descriptors

Variables	**Subgroups**	**Scores**	**Statistics**		
			t	**df**	**p**
Sex	male	N=64	t=2.090	df=125	**p=0.039**
	female	N=63			
Family status	relationship or married	N=95 mean(SD)=5.40 (4.867)	t=-1.225	df= 125	p=0.184
	single, divorced, widow	N=32 mean(SD)=6.95 (5.150)			
Education	high school and/or university degree	N=102 mean(SD)=8.40 (5.759)	t=3.190	df=125	**p=0.002**
	not graduated	N=25 mean(SD)=5.01 (4.493)			
Financial status	average, good, very good	N=90 mean(SD)=4.90 (4.535)	t=2.846	df=125	**p=0.005**
	very bad or bad	N=37 mean(SD)=7.57 (5.398)			

Variables	Subgroups	Scores	Statistics		
			t	df	p
Social support*	high-supported patients	N=62 mean(SD)=5.71 (4.765)	t=-0.072	df=125	p=0.943
	low-supported patients	N=62 mean(SD)=5.65 (5.125)			
Breslow's depth*	less deeper tumour thickness	N=80 mean(SD)=5.81 (5.001)	t=0.974	df=120	p=0.332
	deeper tumour thickness	N=42 mean(SD)=4.64 (4.256)			
Clark's level of invasion	Clark's level II and III	N=34 mean(SD)=6.26 (4.488)	t=1.078	df=120	p=0.283
	Clark's level IV and V	N=88 mean(SD)=5.22 (4.940)			
Exulceration of primary tumour	non exulcerated	N=78 mean(SD)=5.38 (4.721)	t=-0.842	df=125	p=0.401
	exulcerated	N=49 mean(SD)=6.14 (5.268)			

**mean values (see Table 9.) were used as a cut-off to create 2 groups*

At baseline, there were significant differences in STAI-State anxiety scores according to sex and financial status (Table 11.). Women and subjects with very bad or bad financial situations scored higher on the STAI-State anxiety subscale at baseline compared to the other groups. There were no significant differences according to other investigated factors.

Table 11. Baseline differences in STAI state anxiety scores according to demographic and clinical descriptors

Variables	**Subgroups**	**Scores**	**Statistics**		
			t	**df**	**p**
Sex	male	N=64	t=-2.347	df=125	**p=0.020**
	female	N=63			
Family status	relationship or married	N=95 mean(SD)=40.07 (8.253)	t=-1.382	df=115	p=0.169
	single, divorced, widow	N=22 mean(SD)=42.82 (8.980)			
Education	high school and/or university degree	N=102 mean(SD)= 39.81 (8.087)	t=1.393	df=125	p=0.166
	not graduated	N=25 mean(SD)=42.44 (9.811)			
Financial status	average, good, very good	N=90 mean(SD)=38.90 (7.736)	t=3.064	df=125	**p=0.003**
	very bad or bad	N=37 mean(SD)=43.81 (9.273)			

Variables	Subgroups	Scores	Statistics		
			t	df	p
Social support*	high-supported patients	N=62 mean(SD)=5.71 (4.765)	t=-0.700	df=125	p=0.485
	low-supported patients	N=62 mean(SD)=5.65 (5.125)			
Breslow's depth*	less deeper tumour thickness	N=80 mean(SD)=40.72 (8.303)	t=0.784	df=120	p=0.434
	deeper tumour thickness	N=42 mean(SD)=37.97 (7.908)			
Clark's level of invasion	Clark's level II and III	N=34 mean(SD)=41.85 (7.820)	t=1.571	df=120	p=0.119
	Clark's level IV and V	N=88 mean(SD)=39.25 (8.349)			
Exulceration of primary tumour	non exulcerated	N=78 mean(SD)=39.87 (8.591)	t=-0.768	df=125	p=0.444
	exulcerated	N=49 mean(SD)=41.06 (8.328)			

**mean values (see Table 9.) were used as a cut-off to create 2 groups*

4.1.3. Longitudinal effect of interferon treatment on depression

In the study group, BDI depression scores steadily and significantly increased during the treatment (Figure 2.).

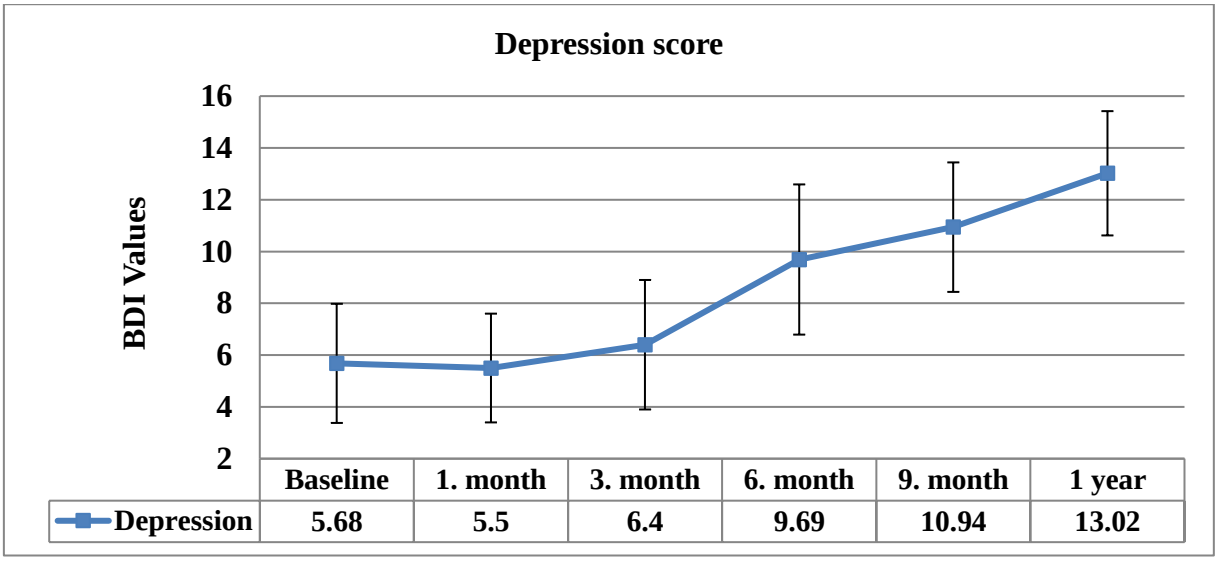


Figure 2. Changes in the mean (+/- SD) BDI depression scores during the interferon treatment. Covariates appearing in the model include sex, age, education, financial status, tumour thickness and social support.

Among the investigated co-variants only social support showed a significant effect on the increase of BDI depression scores. Main effects of the investigated variables are summarized in Table 12/A.

Table 12/A. Results of main effects on depression of repeated measures ANCOVA. *Results of main effects of repeated measures ANCOVA (F) with the degree of freedom (df) and level of significance (p). Covariates appearing in the model are:sex, age, financial status, education, tumour thickness (Breslow) and social support.*

Variables	**F** (df, error df)	**Sig. (p)**
interferon effect in time	6.386 (2.765, 298.673)	**0.000**
sex	0.842 (2.765)	0.464
age	1.427 (2.765)	0.237
financial status	1.318 (2.765)	0.269
family status	0.360 (2.765)	0.876
education	1.632 (2.765)	0.186
tumour thickness (Breslow)	0.703 (2.765)	0.540
social support	8.733 (2.765)	**0.000**

Post-hoc pair-wise comparisons showed significantly higher depression scores at month 9, which reached its maxima by month 12 compared to baseline(Table 12/B.). In our study 55 patients (43%) reached the mild depression cut-off point of the depression scale during the therapy, and 6 participants (4%) reached the clinically relevant level of depressive syndrome for the last check-up. According to post-hoc pair-wise comparisons social support effect became significant at month 9 and with increasing effect at month 12 (Table 12/B.).

Table 12/B. Post hoc comparisons for significant time effect and for significant social supporteffect with degree of freedom (df) and level of significance (p).

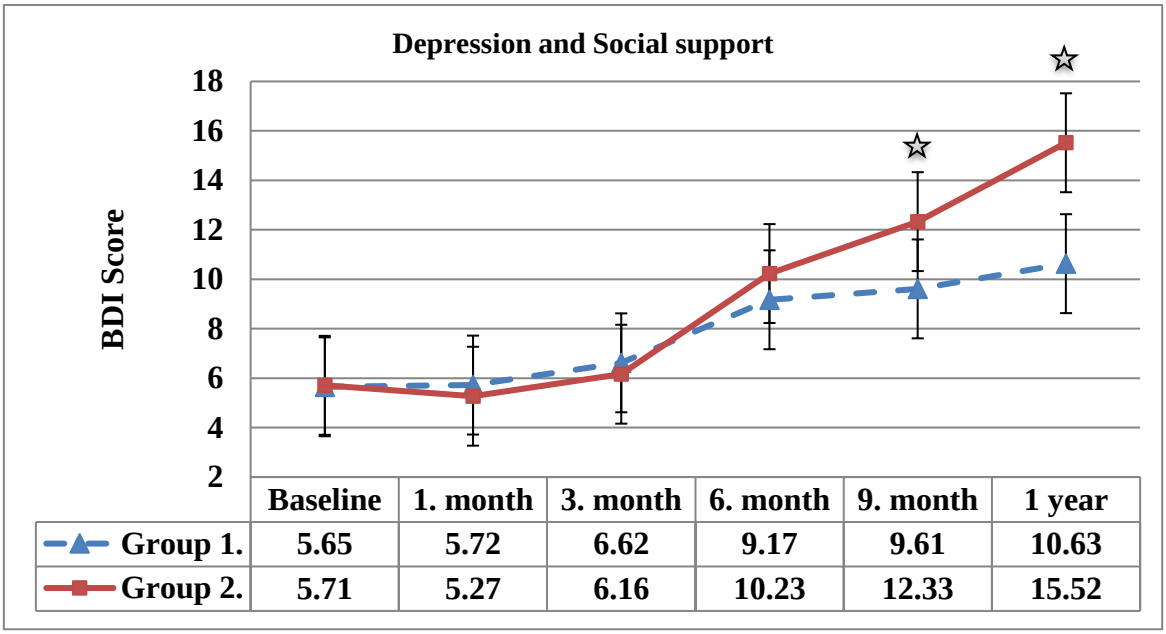
	Post-hoc comparisons	**F** (df, error df)	**Sig. (p)**
time effect	baseline vs month 1.	1.073 (1, 108)	0.303
	baseline vs month 3.	1.973 (1, 108)	0.163
	baseline vs month 6.	0.964 (1, 108)	0.328
	baseline vs month 9.	6.011 (1, 108)	**0.015**
	baseline vs month 12.	7.368 (1, 108)	**0.019**
effect of Social support	baseline vs month 1.	1.008 (1, 108)	0.282
	baseline vs month 3.	0.411 (1, 108)	0.408
	baseline vs month 6.	2.239 (1, 108)	0.144
	baseline vs month 9.	7.393 (1, 108)	**0.011**
	baseline vs month 12.	14.661 (1, 108)	**0.000**

In addition, the effect of social support remains significant after adding family status to the model (F=6.437, df=1, p=0.023) possibly because the majority (75%) of the subjects in our study lived in relationship or were married.

4.1.4. Effect of high versus low social support on depressogenic side effects of interferon treatment

Next, to further investigate how social support modulates the depressogenic side effect of interferon treatment two social support groups were classified according to the mean value of Social Dimension Scale scores (similarly to the analysis of the baseline parameters): patients in **Group 1** (N=65) had scores above 15, so this was the better-supported group, and in **Group 2** (N=62) subjects scored equal or below 15, so this group contained the lower-supported patients. The BDI depression score difference steadily increased between the two groups from the visit at month 6. The better-

supported group scored lower from this point compared to the other group and the difference reached significance at month 9 (Figure 3.).



	Baseline	1. month	3. month	6. month	9. month	1 year
Group 1.	5.65	5.72	6.62	9.17	9.61	10.63
Group 2.	5.71	5.27	6.16	10.23	12.33	15.52

Figure 3. Changes in the BDI depression scores during interferon treatment. *BDI depression scores (mean +/- SD) significantly increased in those who have lower social support (Group 2) compared to those who have better social support (Group 1) during interferon treatment.*

4.1.5. Longitudinal effect of interferon treatment on anxiety

There were no significant changes in STAI state anxiety scores during interferon treatment (Table 13/A.) in spite of a temporary increase at the first control visit (month 1, Figure 4.).

Table 13/A. Results of main effects on anxiety of repeated measures ANCOVA. *Non-significant main effect of time during interferon treatment on STAI state anxiety scores in the total population but significant main effect of sex. Results of repeated measures ANCOVA (F) with degree of freedom (df) and level of significance (p). Covariates appearing in the model are: sex, age, financial status, education, tumour thickness and social support.*

Variables	F (df, error df)	Sig. (p)
interferon effect in time	1.435 (3.251, 357.604)	0.230
sex	3.210 (3.251)	**0.002**
age	0.904 (3.251)	0.445
financial status	1.128 (3.251)	0.340
education	0.793 (3.251)	0.507
tumour thickness (Breslow)	1.797 (3.251)	0.142
social support	0.433 (3.251)	0.745

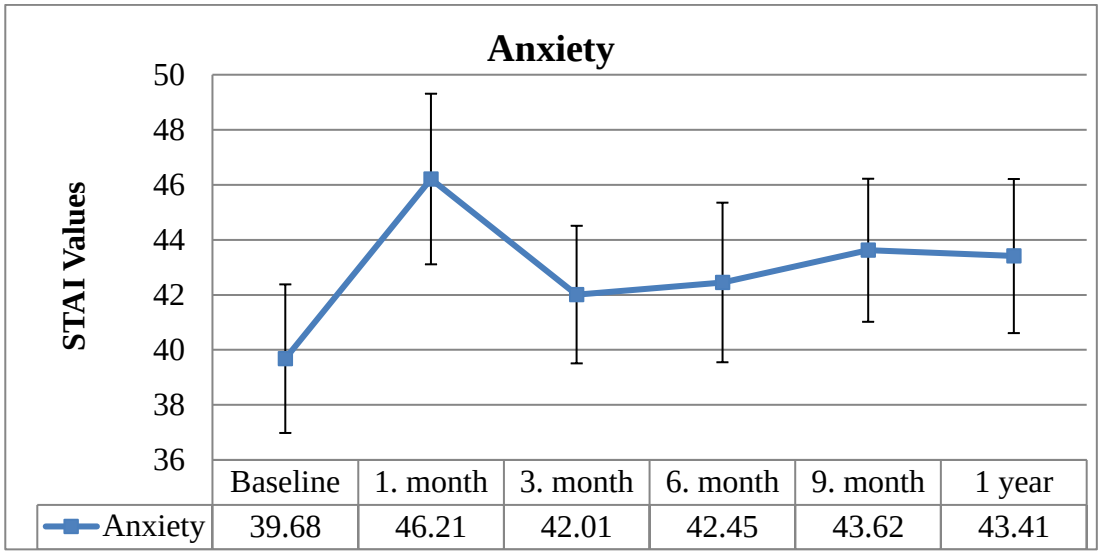


Figure 4. Changes in STAI-State anxiety scores (mean +/- SD) during interferon treatment. *No significant changes in STAI-State anxiety scores (mean +/- SD) occurred during interferon treatment. Covariates appearing in the model are: sex, age, education, financial status, tumour thickness and social support.*

However, sex had a significant main effect on interferon treatment-induced anxiety symptoms (Table 13/A). No other co-variants in the model had a significant effect on STAI state anxiety scores during the treatment.

Post hoc analysis demonstrated that female patients had increased anxiety scores from month 6 compared to males (Table 13/B, Figure 5.).

Table 13/B. Post hoc comparisons for nonsignificant time effect and for significant effect of sex

	Post-hoc comparisons	**F (df, error df)**	**Sig. (p)**
time effect	baseline vs month 1.	0.220 (1, 110)	0.640
	baseline vs month 3.	0.063 (1, 110)	0.803
	baseline vs month 6.	0.039 (1, 110)	0.843
	baseline vs month 9.	0.983 (1, 110)	0.324
	baseline vs month 12.	1.203 (1, 110)	0.275
effect of sex	baseline vs month 1.	2.095 (1, 110)	0.151
	baseline vs month 3.	1.881 (1, 110)	0.173
	baseline vs month 6.	**5.980** (1, 110)	**0.016**
	baseline vs month 9.	**6.257** (1, 110)	**0.014**
	baselinevs month 12.	**8.218** (1, 110)	**0.005**

Degree of freedom: df; level of significance: p.

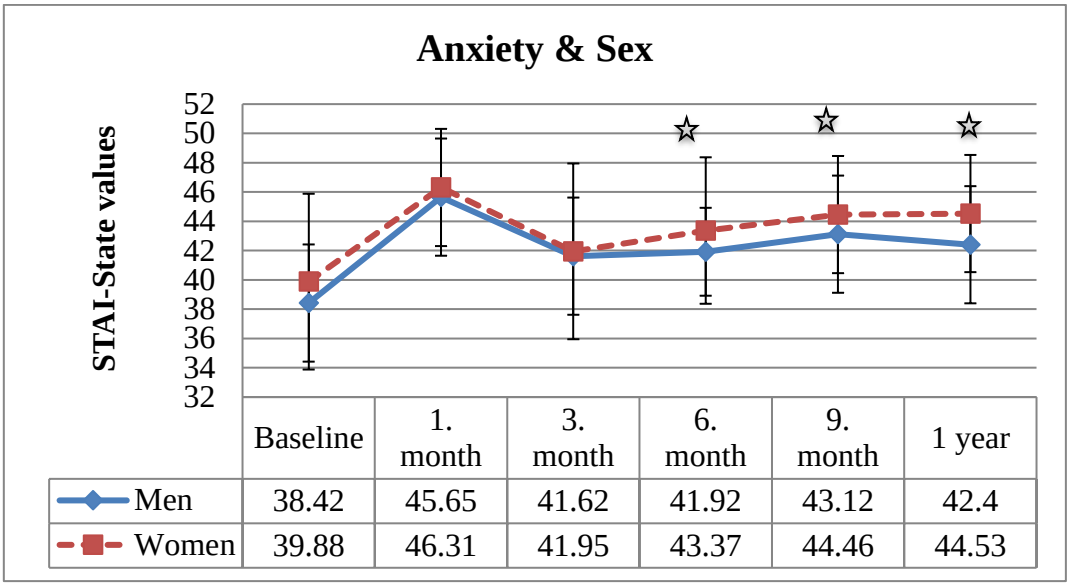


Figure 5. Changes in STAI-State anxiety scores during interferon treatment in men and women. *STAI-State anxiety scores (mean +/- SD) significantly increased in women but not in men during interferon treatment. Covariates appearing in the model are: sex, age, education, financial status, tumour thickness and social support.*

4.2.Ipilimumab vs. interferon – *second study*

4.2.1. Baseline

Descriptive statistics regarding the background information for the two groups can be seen in Table 14.

Table 14. Description of the study populations inthe second study

Factors		**IPI-Group**(N=10)	**INF-α Group**(N=18)
Gender			
	female *no.(%)*	8 (80)	13 (72.2)
	male *no.(%)*	2 (20)	5 (27.8)
Age *years (range)*		60.4 (37; 76)	50.11 (32; 78)
Home			
	capital *no.(%)*	5 (50)	4 (22)
	town *no.(%)*	4 (40)	10 (56)
	village *no.(%)*	1 (10)	4 (22)
Social situation			
	single *no.(%)*	2 (20)	1 (5.5)
	relationship *no.(%)*	1(10)	5 (28)
	married *no.(%)*	6(60)	9 (50)
	divorced *no.(%)*	---	3 (16.5)
	widow *no.(%)*	1 (10)	---
School			
	primary school *no.(%)*	2 (20)	2 (11.1)
	high school *no.(%)*	5 (50)	8 (44.4)
	university *no.(%)*	3 (30)	5 (28)
	other *no.(%)*	---	3 (16.5)

Factors		IPI-Group (N=10)	INF-α Group(N=18)
Financial status			
	very bad *no.(%)*	---	1 (5.5)
	bad *no.(%)*	3 (30)	6 (33.4)
	average *no.(%)*	4 (40)	9 (50)
	good *no.(%)*	2 (20)	2 (11.1)
	very good *no.(%)*	1 (10)	---
Social support *mean (SD)*		13.00 (7.902)	10.94 (6.024)

No significant differences were measurable in demographic factors between the two groups. At baseline, IPI-Group(ipilimumab) had higher level of depression scores compared to INF-α-Group(interferon-alpha 2a; $t=2.176$, $df=26$, $p<0.039$).Despite this difference the mean depression score in Group 1. did not reach clinically relevant level as defined by the Hungarian cut-off value of SDS (sum score<48).

Regarding anxiety, no significant differences were found at baseline ($t=-0.044$, $df=26$, $p=0.965$) comparing the two study groups and the anxiety level was below the Hungarian cut-off in both groups.

Table 15.shows the means and standard deviations of depression (SDS) and anxiety (STAI).

Table 15. Means and standard deviations of depression and anxiety. *SDS: Zung Self-Rating Depression Scale; STAI: State-Trait Anxiety Scale*

		SDS		STAI	
IPI-Group	**Time**	**Mean**	**SD**	**Mean**	**SD**
	1. week	37.7	4.3	38	10.64
	4. week	38.5	4.95	42.5	9.28
	8. week	39.2	7.48	38.7	11.64
	12. week	38.5	7.5	39.3	12.81
INF-α Group	1. week	33.5	5.18	38.17	9
	1. month	35.83	5.1	47.28	10.55
	3. month	37.56	6.1	39.5	8.424
	6. month	41.78	4.28	40.33	7.39

4.2.2. Drug effect in time on depression

In IPI-Group there were no significant changes in the depression scores using repeated measure of ANCOVA (Table 16. and Figure 6.). In INF-α-Group depression scores steadily and significantly increased during the treatment (Table 16. and Figure 6.). Pair-wise comparisons showed significantly higher depression scores at time point 3 and reached its maxima by the 4th time point compared to baseline.

Figure 6.shows the changes in the mean depression scores during the treatment in both groups.

Table 16. Changes in the level of depression during the treatment. *Results of ANCOVA (F) with the degree of freedom (df) and the level of significance (p). Covariates in the model are: gender, age and social support. SDS:Zung Self-Rating Depression Scale.*

Depression (SDS)	**Variables**	**F** (df)	**Sig.** (p)
IPI-Group	in time *overall*	3.023 (2.085, 12.507)	0.083
	week 0. vs week 4.	4.871 (1)	0.069
	week 0. vs week 8.	0.030 (1)	0.869
	week 0. vs. week 12.	2.078 (1)	0.200
INF-α-Group	**in time *overall***	**3.176 (2.317; 33.190)**	**0.047**
	week 0. vs month 1.	0.303 (1)	0.591
	week 0. vs month 3.	**6.253 (1)**	**0.025**
	week 0. vs month 6.	**9.401 (1)**	**0.008**

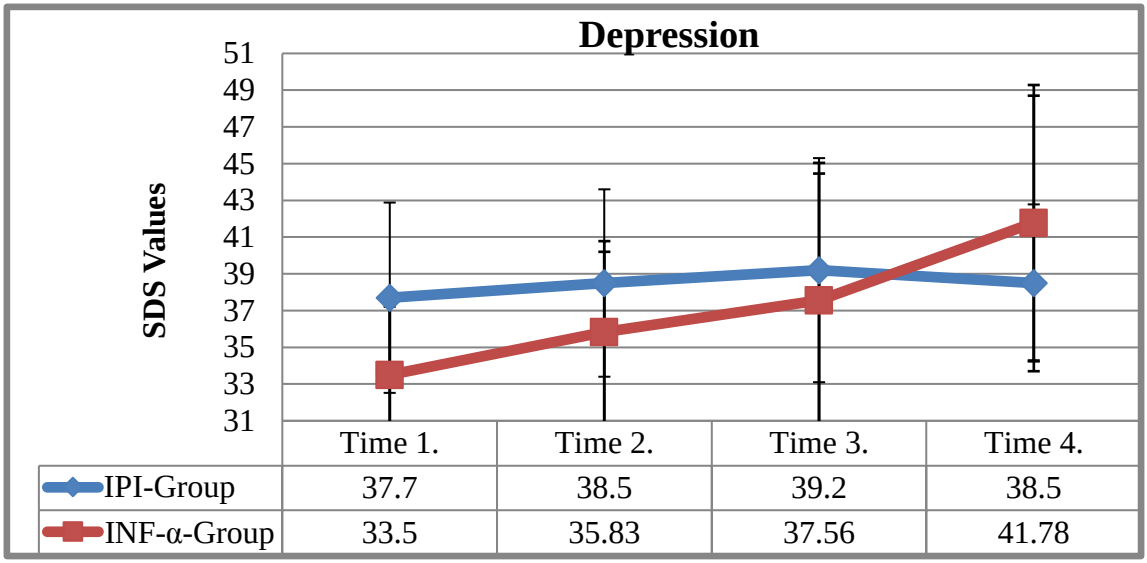


Figure 6. The change of mean depression scores during the treatments. *During ipilimumab treatment (mean +/- SD values) depression scores have not changed significantly, while interferon-alpha 2a treatment significantly increased depression scores. SDS:Zung Self-Rating Depression Scale*

4.2.3. Drug effect in time on anxiety

No significant drug effect in time was demonstrated in IPI-Group on anxiety scores (Table 17. and Figure 7.). Again, there were no significant changes in the anxiety scores in INF-α-Group. However, in both groups the anxiety scores increased for the 2nd time point but only in INF-α-Groupreached the Hungarian cut-off (Table 17. and Figure 7.).

Table 17. Changes in the level of anxiety during ipilimumab and interferon treatment. *Results of ANCOVA (F) with the degree of freedom (df) and the level of significance (p). Covariates appearing in the model are: gender, age and social support. STAI: State-Trait Anxiety Scale.*

Anxiety (STAI)	**Variables**	**F** (df)	**Sig.** (p)
IPI-Group	in time overall	1.852 (1.928; 11.570)	0.174
	week 0. vs week 4.	4.809 (1)	0.071
	week 0. vs week 8.	5.136 (1)	0.064
	week 0. vs. week 12.	1.048 (1)	0.346
INF-α-Group	in time overall	0.261 (2.277; 31.879)	0.853
	week 0. vs month 1.	0.074 (1)	0.790
	week 0. vs month 3.	0.330 (1)	0.575
	week 0. vs month 6.	0.663 (1)	0.429

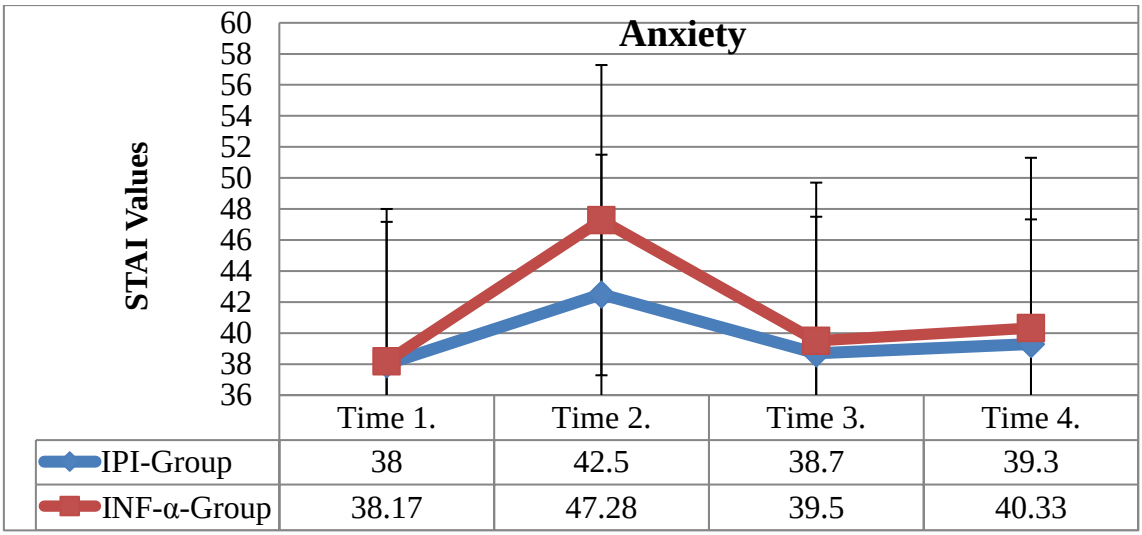


Figure 7. - The change of mean anxiety scores during the treatments. *No significant changes of mean anxiety scores (measured by STAI) can be seen during the treatments (mean+/- SD values of STAI).STAI: State-Trait Anxiety Scale*

5. Discussion

Our first study provided evidence for the protective effect of social support in the development of low-dose interferon alpha treatment-induced depression in melanoma patients. Our result suggests that environmental effects such as social support are able to moderate the depressogenic effect of activation in the pro-inflammatory cytokine pathway, possibly by acting through overlapping biological processes. In addition, we could not demonstrate a significant effect of interferon alpha treatment on anxiety, measured by the STAI-State questionnaire, although female patients had significantly more anxiety symptoms from the 6th month of the therapy compared to male patients. This finding of the first study emphasises that depressive symptoms and anxiety symptoms are not equally influenced by the pro-inflammatory cytokine pathway.

The second study was the first to demonstrate that ipilimumab elicited fewer psychological side-effects compared to interferon-alpha immunotherapy which suggests a better psychological side effects profile for ipilimumab treatment that could be especially important in advanced stage melanoma and in patients at risk for depression and anxiety (Kovács et al. 2014). In the ipilimumab treated group there were no significant overall changes in the level of depression during the treatment. No significant differences were measurable comparing the baseline level to the extent of depression at each time-points. Despite ipilimumab treated patients were in more severe stage of malignant melanoma, interferon treated patients showed greater increase of depression during the treatment period. In addition, we found similar level of increase in anxiety at the second time-point in both treatment groups. This increase was not significant longitudinally and the slightly/moderately increased anxiety returned to the baseline by the time-point 3 and 4 in both treatment groups. These results suggest that increased level of anxiety is not driven by the biological effects of drugs, and activated immune response, but rather associated with life events, such as introduction of a new treatment.

5.1. Depression in melanoma patients

Several of the diagnostic criteria for major depressive disorder endorsed by melanoma patients including low energy, poor appetite and impaired concentration are related to symptoms resulting from malignant and chronic disease or its treatment. Other psychological symptoms such as low mood or lack of pleasure must also be present to fulfil diagnostic criteria for major depression and several other psychological symptoms including rumination, grief or hopelessness may also add to the clinical picture. Depression and its cognitive, psychological symptoms are especially important for melanoma patients as a metaanalysis of Satin et al. showed that depression predicts increased mortality. Based on data from 25 studies, mortality rates were up to 25% higher in patients with depressive symptoms (Satin et al. 2009). Interestingly depression does not predict disease progression in cancer patients suggesting that it is an independent risk factor for negative outcome in this patient population.

Our study supported previous observations that adjuvant treatment of melanoma patients with low-dose interferon induces a rise in depressive symptoms, which became significant in the second half of the treatment period (9^{th} and 12^{th} month). Our results are in line with the findings of Heinze et al. who reported a delayed increase of depression scores during low-dose interferon alpha treatment (Heinze et al. 2010).

Although low level of social support was identified as a risk factor for the development of psychiatric side effects(e.g. anxiety and depression) in melanoma patients (Kasparian et al. 2012) and significant negative association between social support and psychological distress, especially major depression was reported (Heinze et al. 2010), not all studies demonstrated an association between social support and psychological distress in this patient group (Holland et al. 1999). Our results suggest that the effect of social support on depression may be dependent on the applied treatmentand especially important in interferon alpha treated patients (Kovács et al. 2015).

5.1.1. Potential pathophysiological effects of interferon of mood

One possible mechanism in the development of depression during interferon alpha therapy involves central nervous system serotonergic neurotransmission which has been associated with the pathogenesis of several neuropsychiatric disorders (Müller and Schwarz, 2007; Almeida et al. 2010). It has been observed that selective serotonin reuptake inhibitors (SSRI) are able to prevent or reverse depressive symptoms in interferon alpha-treated patients (Musselmann et al. 2001). The particular effectiveness of SSRIs in interferon alpha induced depression compared to depression in general populations where response rates are lower suggests a key role of the serotonergic pathway in the development of interferon-induced depression (Musselman et al. 2001).

Nevertheless, the exact mechanism of interferon-induced depression is not well understood and interferon may contribute to the emergence of mood changes or psychiatric disorders in several other ways (Schaefer et al. 2002 and see Introduction). Interferon alpha is a potent inducer of proinflammatory cytokine production. Cytokines are mediators for psychiatric disorders by acting through central neuropsychoimmunological mechanisms. As such, interferon alpha induces the production of proinflammatory cytokines (e.g. interleukin-1, interleukin-6) which are potent inducers of sickness behaviour and have neurotoxic effects in humans (Mocellin et al. 2013).

Furthermore, it is especially likely that interferon induces depression-related physical and emotional symptoms in patients already experiencing illness-related physiological alterations. For example, patients who responded to a first dose of interferon alpha with increased activity of the hypothalamic–pituitary–adrenal (HPA) axis stress pathways were significantly more likely to develop major depression during treatment than patients with modest stress system responses to the initial injection (Bagdy et al. 2012; Mostafavi et al. 2013).Another study suggests that HPA hyperactivity and psychological stress predisposes to the development of mood disorders in the context of medical illness (Satin et al. 2009).

5.1.2. Possible interaction between interferon treatment and social support

As we mentioned above, serotonergic mechanisms may play an important role in interferon treatment-induced depression. However, recent genetic association studies suggested that the serotonergic system has an impact on individual sensitivity to social experiences. Way and Taylor demonstrated that in a positive social environment, individuals with the short (low-expressing) allele of the serotonin transporter gene promoter polymorphism (5-HTTLPR) showed better psychological functioning than individuals with the long/long genotype (Way and Taylor, 2010). In case of adverse environments (Paykel, 2001) or in the absence of social support (Caspi et al. 2003) 5-HTTLPRshort allele carriers are more likely to develop depression.

The interferon alpha-induced proinflammatory cytokine pathway and its effect on the central nervous system could also be responsible for depressive symptoms and also modulated by social support. For example, Costanzo et al. (Costanzo et al. 2005) demonstrated that cancer patients who reported higher levels of social support had lower levels of interleukin-6 in peripheral blood after statistically adjusting for age and disease severity. Poorer physical and functional well-being and greater fatigue were associated with higher peripheral interleukin-6 concentration (Costanzo et al. 2005).

Finally, the function of the HPA axis can be influenced by interferon treatment, serotonin (Bagdy, 1995) and social support. Proinflammatory cytokines may cause HPA axis hyperactivity by disturbing negative feedback inhibition of circulating corticosteroids on the HPA axis, although the exact mechanism is not well understood (Raison et al. 2005). In addition, Capuron et al. showed that patients with sensitized stress response pathways are more vulnerable to interferon alpha-induced depression (Capuron et al. 2002). However, social support has been associated with decreased HPA activity and glucocorticoid concentration in previous studies (Giesbrecht et al. 2013; Muscatell et al. 2016).

5.2. Differences betweenipilimumab and interferon treatment

Ipilimumab treated patients in our study had a diagnosis of stage III or IV melanoma with a life expectancy of at least 4 months. Because these melanoma cases were more severe than the interferon treated patients (see exclusion and inclusion criteria) it is not surprising that they suffered from more depressive symptoms at baseline. Other advanced malignancies are often associated with increased level of depression and distress (Fawzy et al. 1993).Thus it was an expected result in our study that significantly higher baseline level of depression was present in the ipilimumab treated group, compared to the interferon treated group.

Not only the stage of the disease correlates with psychological side effects. It is well-known that oncological treatments, like adjuvant interferon-alpha therapy, have an impact on psychological well-being (Trask et al. 2004; Eggermont et al. 2008). Different forms of psychiatric symptoms may be observed in up to 80% of patients during the treatment. The incidence of clinically relevant depression varies between 20% and 40% (Schaefer et al. 2002). The increased level of depression and other psychiatric effects deteriorates quality of life which may lead to termination of the therapy. Some of the trials (Grob et al. 1998; Eggermont et al. 2005) pointed out that interferon loose its effectiveness on recurrence-free survival during treatment discontinuation.

Interferon-alpha is an important cytokine in the early immune response. Interferon-alpha may contribute to emergence of mood changes or psychiatric disorders in several ways (Schaefer et al. 2002). Cytokines are, as central effects, mediators for psychiatric disorders by neuropsychoimmunological mechanisms. Interferon-alpha can modulate the activity central neurotransmitters such as serotonin and glutamate, which are involved in the pathogenesis of several neuropsychiatric disorders (Licinio et al. 1998; Reiche et al. 2004; Müller and Schwarz, 2007). Serotonin reuptake inhibitors (SSRI) like paroxetine are able to prevent or reverse depressive symptoms in interferon-alpha-treated patients (Musselmann et al. 2001; Raison et al. 2006; Almeida et al. 2010). Our result confirmed the previous findings regarding depression and interferon treatment. We found that depression increased significantly during the interferon

treatment, as expected. For the first control point no significant changes were detectable. The increase of depression can be observed from the second medical control (3rd month) in the interferon treated group. The extent of increase wassignificant in this time, and also for the last control when measurable strong significant association between interferon treatment and the increased level of depression appeared. Our results coincide with the findings of Heinze et al. (Heinze et al. 2010). They found similar pattern in the increase of depression during low-dose interferon-alpha treatment. They also found that only a low number of participants (5%) reached the cut-off scores for clinically relevant depressive syndrome during the treatment time. In our study no participant reached the clinically relevant level of depression.

Interestingly, ipilimumab treated patents have not experienced significant increase in their depressive symptoms despite having higher depression scores at baseline compared to the interferon alpha treated group. Probably the different mechanism of drug action is the reason of the different psychological impact. Ipilimumab binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4, details can be seen in the Introduction), which T-cell molecule suppresses the immune response.Ipilimumab is a T-cell potentiator that blocks the inhibitory signal of CTLA-4 and thus it has an indirect effect through T-cell mediated anti-tumour immune response in melanoma patients. Suppression of CTLA-4 can augment the immune system's T-cell response in fighting against diseases. However, in this group there were no further increase in depression during the ipilimumab treatment which suggests that this drug,and the activated T-cell response, might have less psychological side effects compared to other immune therapies (Hodi et al. 2010; Kovács et al. 2014).

5.3. Implication of the results for the clinical practice

The application of routinely used complex psychosocial screening packages can provide the easiest method to identify worsening psychological condition during immunotherapy and give rapid feedback to the oncologist and the patient (Bidstrup et al. 2011; Mitchell et al. 2011). With the help of psychosocial screenings initial risk to develop psychological problems during the illness and treatment can be predicted, and the decline and pattern of distress or undesired side effects can be captured in time in order to enable the necessary intervention (Recklitis et al. 2003). In addition, in patients with high psychiatric risk guidelines should be modified to suggest alternative oncological immunotherapies with less psychological side effects. Through this method the patients' adherence to oncomedical therapies can be enhanced and better quality of life could be achieved which contribute significantly to the recovery of the patients (Brocken et al. 2012). Furthermore, psychological education of patients and their relatives aimed at prevention increases the likelihood of cooperation during oncological treatments. Adequately informed patients are more likely to achieve control over the situation and feel self-efficacy and self-confidence (McLoone et al. 2013; Pistrang et al. 2013). Thus proper communication and social support are fundamental to adherence and acceptance of treatments even in a situation when side effects frequently disturb the beneficial effects of a drug (Hamama-Raz et al. 2007; Jacobsen and Wagner, 2012; Rychetnik et al. 2013).

When providing somatic (oncology) care for melanoma patients, at least three aspects must be taken into consideration in respect of psychopathological problems. Psychical problems may arise in connection with oncomedical treatments in 1. acute and/or 2. chronic ways, as well as 3. co-morbid psychiatric diseases that already exist must also be taken into account.

In relation of immunotherapies, acute psychological side effects (acute stress) emerging during treatments develop in a way that can mostly be linked to environmental factors, e.g. notification of diagnosis, hospitalisation, progression, deterioration in quality of life, imminent dates of control. During complex and acute care, the involvement of an expert psychologist is recommended, as early as in the

screening period, in order to enhance early diagnosis and adequate intervention. Crisis is a temporary and threatening condition that endangers psychological balance. In such conditions, enhanced psychological vulnerability must be taken into account and physicians play a key role in the rapid recognition of the condition. Acute difficulty can be treated by specialists that are apt for the treatment of crisis who in collaboration with the oncologistcan and able to intervene in a timely fashion and proper manner.

Chronic psychological problems, which may arise from the depressogenic effect of the applied treatment or originated from a pre-melanoma psychiatric condition, may exceed the diagnostic and psychotherapeutic competences of a clinical specialist psychologist. Thus it may also become necessary to involve a psychiatrist. In such cases in addition to acute crisis intervention, the side effects of medical treatments (e.g., depression due to interferon therapy) will be treated. Fortunately, these side effects can be treated successfully using both psychotherapeutic methods and psychiatric medicines; in fact, knowing the severity of psychiatric side effects of immunotherapies (in serious cases e.g. psychotic depression, or perhaps thoughts of committing suicide) is important to prevent discontinuation of the therapy. In the case of chronic psychopathologies, experience shows that a combination of two-type of treatments, namely pharmaco- and psychotherapy, produces the greatest effectiveness (Hegerl et al. 2004).

5.4. Limitations

In the interferon-study there are some limitations that we should address. Our study had an open label design with the lack of an untreated control group. The usual double-blind, placebo-controlled design was not applied due to ethical reasons: according to the protocol of Hungarian Health Ministry for melanoma treatment, interferon alpha therapy has to be offered to every melanoma patient with an increased risk for metastatic disease. In addition, our study included only a 12-month follow-up period. However, longer follow-up would be required to see the long-term psychological and therapeutic effects of interferon treatment. And finally, it should be noted that all subjects included in this study were regularly explored by psychologists and patients with a high level of distress were psychologically supported. Thus, it is possible that the regular visits and psychological support partially explain the low rate of clinical depression and the non-significant increase in anxiety during the treatment.

Regarding the second study, because of the low number of participants, and the open label design no final conclusions can be drawn in the ipilimumab study. Further research including more participants and double-blind design is needed to increase the power of such studies. In addition, longer follow up is required to see the long term effect of the ipilimumab treatment.

6. Conclusion

In conclusion, our studies further supported that immunotherapy of melanoma patients increase the risk of psychological distress. However, we demonstrated that anxiety and depression are differentially influenced by interferon alpha treatment. Namely, only depression but not anxiety increased significantly during the 12-month follow-up. In addition, the depressogenic side effect of interferon alpha treatment can be diminished by increased social support. Finally, we demonstrated that ipilimumab has fewer psychological side effects than interferon alpha, probably because of the different biological pathways they act through.

The main findings and conclusions of the studies:

- the studies provided evidence for the protective effect of social support in the development of low-dose interferon alpha treatment-induced depression in melanoma patients
- the result suggests that environmental effects such as social support are able to moderate the depressogenic effect of activation in the pro-inflammatory cytokine pathway, possibly by acting through overlapping biological processes
- significant effect of interferon alpha treatment on anxiety could not be demonstrated
- female patients had significantly more anxiety symptoms from the 6th month of the therapy compared to male patients
- depressive symptoms and anxiety symptoms are not equally influenced by the pro-inflammatory cytokine pathway
- no significant drug effect in time was demonstrated in ipilimumab treated patients on anxiety scores
- no significant drug effect in time was demonstrated in ipilimumab treated patients on depression scores
- ipilimumab elicited fewer psychological side-effects compared to interferon-alpha immunotherapy which suggests a better psychological side effects profile for ipilimumab treatment that could be especially

important in advanced stage melanoma and in patients at risk for depression and anxiety

- our studies further support the importance of taking positive and negative environmental factors into consideration to be able to identify risk biomarkers or genes for depression.

To summarise our results it is important to note that team work is of particular importance in the clinical care of melanoma patients as this disorder and its treatment requires complex and high-level professional collaboration. Multidisciplinarity is the basic framework for modern tumour therapy where, under the guidance of oncologists, the work of specialist nurses, social workers, physiotherapists, dieticians and last but not least psychiatrists/psychologists are indispensable and play a significant role.

7.a. Summary

Immunotherapies play an important role in the modern treatment of melanoma malignum in various stages of the disease.Interferon has been applied for almost 20 years in early phase after the removal of primer tumour whileanti-CTLA-4 antibody (ipilimumab) immunotherapy represents one of the most modern opportunities for adequate treatment in patients having distant metastasis or irresectible tumour. However, immunotherapies frequently elicit clinically relevant psychological side effects:depression, fatigue, anhedonia, social isolation, psychomotor slowness is reported during treatment.

In this thesis two study paradigms were described where long-term oncological immunotherapies were examined with regard to psychological side effects. The main aim was to measure psychiatric adverse events, such as changes in depressed mood, and anxiety using psychological self-rating scales during interferon alpha and ipilimumab treatments. In addition, the effect of risk and preventive factors were analysed, such as financial situation, education or social support.

During low-dose interferon treatment in early melanoma patients,depressive symptoms significantly increased during the 12-month follow-up period. Furthermore, social support significantly moderated the depressogenic effect of the treatment. Patients with better social support showed attenuated increase of depression. Anxiety showed no significant changes during the therapy.In the second study we demonstrated differences in the psychosocial side-effect profile between the ipilimumab treatment and the interferon alpha therapy. Namely, ipilimumab has not increased significantly the depressive and anxiety symptoms in advanced melanoma patients.

Thus our results emphasise that enhancement of social support can reduce depressogenic side effects of interferon treatment. In addition we demonstrated that ipilimumab elicited fewer psychological side-effects compared to interferon-alpha immunotherapy which suggests a better psychological side effects profile for ipilimumab treatment.

7.b. Összefoglaló

A melanoma malignum kezelésében az immunterápiák egyre jelentősebb szerepet töltenek be a betegség különböző stádiumaiban. Az interferon terápiát már több mint 20 éve alkalmazzák adjuváns kezelésként a primer tumour sebészeti eltávolítását követően. Az anti-CTLA-4 antitest (ipilimumab) az első és az egyik legmodernebb olyan gyógyszer, amely statisztikailag igazolhatóan megnövelte a túlélést metasztatikus, vagy inoperábilis melanomában. Hosszú távon az immunterápiák gyakran okoznak klinikailag is releváns pszichológiai mellékhatásokat. Fáradékonyságról, anhedóniáról, szociális izolációról, pszichomotoros meglassultságról számolnak be a kezelés során a betegek.

Az értekezésben bemutatott két longitudinális kutatás a hosszú távon alkalmazott immunterápiák pszichológiai mellékhatásait vizsgálja. Az immunterápiák során önkitöltős kérdőívekkel, nyomonkövetéses módszerrel felmérésre került a depresszió értéke, a hangulat változása, a szorongás mértéke, valamint rizikótényezők és lehetséges protektív faktorok (anyagi helyzet, iskolázottság, társas támogatottság) egyaránt.

Az első vizsgálatban az alacsony dózisú adjuváns interferon kezelés során a depresszió mértéke szignifikáns emelkedést mutatott. A társas támogatottság szignifikáns hatással volt a 12 hónap alatt növekvő depresszió mértékére. Azoknál a személyeknél, akiknél magasabb észlelt társas támogatottságról számoltak be, kisebb mértékben és alacsonyabb valószínűséggel alakult ki depresszió. A szorongás nem változott szignifikáns mértékben az utánkövetéses időszakban. A második, összehasonlító vizsgálat az interferon és az ipilimumab terápiák pszichés mellékhatásprofiljának összehasonlítását célozta. Az ipilimumab-csoportban sem a depresszió, sem a szorongás tekintetében nem találtunk szignifikáns változást a terápia teljes időtartamát tekintve.

A társas támogatottság mértékének szintje preventív erejű az adjuváns interferon kezelés során kialakuló depresszió tekintetében. A kedvezőbb pszichológiai mellékhatásprofil az ipilimumab kezelés alkalmazásának szélesebb körét vetítheti előre.

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