9.2.3 Analysis of Adverse Events

Most of the adverse events were mild or moderate (maximum NCI grade per patient of 1 or 2). In Table 12 severity of adverse events by the maximum grade per patient are shown. Adverse events with a maximum NCI grade per patient ≥ 3 are highlighted in grey.

Table 12 Adverse events - Maximum NCI grade per patient -

(Data source: Table 24 of the final statistical report. Adverse events with a maximum NCI grade per patients are highlighted in grey.)

AE- Maximum NCI grade	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Abdominal pain	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Alopecia	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Anemia	.	.	2	13.33	.	.	.	.	.	.	2	13.33
Anorexia	3	20.00	1	6.67	.	.	.	.	.	.	4	26.67
Bloating	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Breast pain	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Burn	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Chills	3	20.00	2	13.33	.	.	.	.	.	.	5	33.33
Colitis	.	.	.	.	1	6.67	.	.	.	.	1	6.67
Constipation	2	13.33	1	6.67	.	.	.	.	.	.	3	20.00
Cough	.	.	2	13.33	.	.	.	.	.	.	2	13.33
Creatinine increased	.	.	.	.	1	6.67	.	.	.	.	1	6.67
Depression	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Diarrhea	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Dry mouth	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Dysphagia	.	.	1	6.67	.	.	.	.	.	.	1	6.67
Dyspnea	.	.	2	13.33	.	.	.	.	.	.	2	13.33
Endocrine disorders - Other, specify	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Fatigue	3	20.00	3	20.00	2	13.33	.	.	.	.	8	53.33
Fever	5	33.33	.	.	.	.	.	.	.	.	5	33.33
Flank pain	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Flatulence	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Flu like symptoms	2	13.33	1	6.67	.	.	.	.	.	.	3	20.00
Flushing	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Fracture	.	.	.	.	1	6.67	.	.	.	.	1	6.67
GGT increased	.	.	1	6.67	.	.	1	6.67	.	.	2	13.33
Generalized muscle weakness	.	.	1	6.67	.	.	.	.	.	.	1	6.67
Hyperhidrosis	1	6.67	1	6.67	.	.	.	.	.	.	2	13.33
Hyperthyroidism	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Injection site reaction	1	6.67	.	.	.	.	.	.	.	.	1	6.67

AE- Maximum NCI grade	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Insomnia	1	6.67	1	6.67	.	.	.	.	.	.	2	13.33
Malaise	.	.	2	13.33	.	.	.	.	.	.	2	13.33
Myalgia	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Nausea	5	33.33	.	.	.	.	.	.	.	.	5	33.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	.	.	.	.	.	.	.	.	2	13.33	2	13.33
Neutrophil count decreased	.	.	.	.	1	6.67	.	.	.	.	1	6.67
Pain	2	13.33	1	6.67	1	6.67	.	.	.	.	4	26.67
Pain in extremity	.	.	1	6.67	.	.	.	.	.	.	1	6.67
Pain of skin	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Paresthesia	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Pleural effusion	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Pruritus	3	20.00	.	.	.	.	.	.	.	.	3	20.00
Rash acneiform	5	33.33	.	.	.	.	.	.	.	.	5	33.33
Rash maculo-papular	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Renal and urinary disorders - Other, specify	.	.	.	.	1	6.67	.	.	.	.	1	6.67
Scrotal pain	.	.	1	6.67	.	.	.	.	.	.	1	6.67
Sepsis	.	.	.	.	.	.	.	.	1	6.67	1	6.67
Skin and subcutaneous tissue disorders - Other, specify	2	13.33	.	.	.	.	.	.	.	.	2	13.33
Skin hypopigmentation	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Skin ulceration	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Syncope	.	.	.	.	1	6.67	.	.	.	.	1	6.67
Tumor pain	1	6.67	.	.	1	6.67	.	.	.	.	2	13.33
Urinary frequency	.	.	1	6.67	.	.	.	.	.	.	1	6.67
Urticaria	1	6.67	.	.	.	.	.	.	.	.	1	6.67
Vomiting	2	13.33	.	.	.	.	.	.	.	.	2	13.33
Patients with AE	.	.	.	.	.	.	.	.	.	.	15	100.00

Regarding the outcome of the adverse events, 61 adverse events (45.5%) were recovered and 8 adverse events (6.0%) were still ongoing at the end of the study with change in severity. 62 adverse events (46.3%) were still ongoing at the end of the study / death. 3 adverse events (sepsis; neoplasms –tumorprogression- in 2 cases) had a fatal outcome.

Only for a low number of AEs no relation to study medication was documented (n=15 (11.2%) for ipilimumab; n=19 (14.2%) for IL-2). For the other AEs an at least unlikely relationship to study medication was documented (Table 13), but mostly no action was taken regarding study medication. Ipilimumab therapy was interrupted due to an AE in 3 cases and was withdrawn due to 1 AE. IL-2 therapy was interrupted due to an AE only in one case.

11 of the 134 AEs (8.21%) were documented to be immune-related to ipilimumab. For 32 of the 134 AEs (23.9%) a therapy was required.

Table 13 Adverse event - Relation to study medication -

(Data source: Table 36 of the final statistical report)

AE related to study medication		N	%
Ipilimumab	**None**	15	11.19
	Unlikely	51	38.06
	Possibly	44	32.84
	Probably	22	16.42
	Certainly	2	1.49
	Total	134	100.00
Interleukin-2	**None**	19	14.18
	Unlikely	32	23.88
	Possibly	41	30.60
	Probably	32	23.88
	Certainly	10	7.46
	Total	134	100.00

9.2.4 Listing of Adverse Events by Patient

A complete listing showing all AEs is given in Listing 5 (section 13.2.3).

9.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

9.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

9.3.1.1 Deaths

10 of 15 patients (66.7%) died during study participation. 9 of them died because of disease progression. 1 patient died because of sepsis (causal relationship Ipilimumab: unlikely; causal relationship IL-2: unlikely). 5 patients were alive after the end of study.

9.3.1.2 Other SAEs

A total of 7 serious adverse events occurred in 4 of the 15 patients (26.7%). Colitis, malaise, sepsis, fracture and acute kidney injury was documented as SAE once. Neoplasm progression was documented as SAE in two cases. Hospitalization was the most frequent reported reason for seriousness (5 cases) followed by death (3 cases) (Table 14. At time of event onset, all patients received study medication. A possible relationship to iplimumab was documented for 1 SAE (colitis). None or an unlikely relationship to IL-2 or ipilimumab was documented for the other SAEs. One SAE (colitis) resulted in an interruption of ipilimumab therapy, an in one case (fracture) both study drugs were interrupted. Further details concerning the documented SAEs on an event based manner are shown in Table 14. Details concerning the SAEs on a patient based manner can be found in Listing 6 in section 13.2.3.

Table 14 Serious adverse events according to medDRA-SOC (event based)

(Data source: tables 42, 44, 45, 46, 48, and 49 of the final statistical report; [a]: multiple answers possible, n.a.: not applicable)

Serious adverse events (event based)		Intensity	Reason for Seriousness[a]	Outcome	Relation to IL-2	Action taken concerning IL-2	Relation to Ipilimumab	Action taken concerning Ipilimumab
Gastrointestinal disorders	**Colitis**	Grade III	hospitalization	recovered	unlikely	none	possibly	interrupted
General disorders and administration site conditions	**Malaise**	Grade II	hospitalization	unknown	unlikely	none	unlikely	none
Infections and infestations	**Sepsis**	Grade V	hospitalization life-threatening death	exitus	unlikely	n.a.	unlikely	n.a.
Injury, poisoning and procedural complications	**Fracture**	Grade III	hospitalization	unknown	unlikely	interrupted	unlikely	interrupted
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm progression**	Grade V	death	exitus	none	n.a.	none	n.a.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm progression**	Grade V	death	exitus	None	none	none	none
Renal and urinary disorders	**Acute kidney injury**	Grade III	hospitalization	recovered	unlikely	none	unlikely	none