Safety and Efficacy Profile of CDK 4/6 Inhibitor Palbociclib in Cancer Therapy: A Meta-Analysis of Clinical Trials

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Figure legend

Supplementary Figure S1a. All grade adverse events in single arm groups (Fixed model). Supplementary Figure S1b. All grade adverse events in single arm groups (Random model). Supplementary Figure S2a. Grade≥3 adverse events in single arm groups (Fixed model). Supplementary Figure S2b. Grade≥3 adverse events in single arm groups (Random model). Supplementary Figure S3a. All grade adverse events in controlled groups (Fixed model). Supplementary Figure S3b. All grade adverse events in controlled groups (Random model). Supplementary Figure S4a. Grade≥3 adverse events in controlled groups (Fixed model). Supplementary Figure S4a. Grade≥3 adverse events in controlled groups (Fixed model).

Supplementary Figure	S1a. All grade adverse	events in single arm gro	ups (Fixed model).

Group by	Study name	Subgroup within study		Statistic	cs for ea	ch study		Event rate and 95% Cl
Subgroup within study			Event rate	Lower limit	Upper	Z-Value	n-Value	
	0.1 1.01/0014							
sthenia sthenia	Schwartz GK 2011 Finn RS 2016	Asthenia Asthenia	0.061	0.015		-3.757 -12.579	0.000	
sthenia	Finn RS 2015	Asthenia	0.133	0.075	0.207	-5.804	0.000	
sthenia	1 111110 2010	Addrenia	0 160	0 132		-14 251	0.000	
Constipation	DeMichele A 2014	Constipation	0.081	0.026	0.223	-4.031	0.000	
Constipation	Schwartz GK 2011	Constipation	0.212	0.105	0.383	-3.082	0.002	
Constipation	Cristofanilli M 2016	Constipation	0.191	0.153	0.236	-10.532	0.000	
Constipation	Finn RS 2016	Constipation	0.194	0.160		-11.876	0.000	
Constipation	Finn RS 2015	Constipation	0.120	0.066	0.210	-5.895	0.000	
Constipation			0.185	0.161		-17.529	0.000	
ecreased appetite	Cristofanilli M 2016	Decreased appetite	0.151	0.117		-11.490	0.000	
ecreased appetite	Finn RS 2016	Decreased appetite	0.149	0.119		-13.082	0.000	
ecreased appetite	Finn RS 2015	Decreased appetite	0.157	0.093	0.251	-5.575	0.000	
ecreased appetite	0.116.7814.0040	D	0.150	0.128		-18.281	0.000	
)izziness)izziness	Cristofanilli M 2016 Finn RS 2016	Dizziness	0.119	0.089		-12.042	0.000	
Jizziness Jizziness	Finn RS 2016	Dizziness	0.142	0.112		-13.232	0.000	
	Finn RS 2015	Dizziness	0.096	0.049		-6.017	0.000	
)izziness)ysgeusia	DeMichele A 2014	Dysguesia	0.129	0.108	0.153	-18.830	0.000	
)ysgeusia	Finn RS 2016	Dysguesia	0.081	0.026		-4.031	0.000	
lysgeusia	1 111113 2010	Dy Syuesia	0.100	0.076		-14.446	0.000	
)ysphasia	Flaherty KT 2012	Dysphasia	0.024	0.070	0.150	-3 644	0.000	
)ysphasia	Finn RS 2016	Dysphasia	0.024	0.069		-13.941	0.000	
Dysphasia		o yapriuaiu	0.089	0.067		-14.345	0.000	
Dyspnea	Flaherty KT 2012	Dyspnea	0.049	0.012	0.175	-4.097	0.000	
)yspnea	Schwartz GK 2011	Dyspnea	0.121	0.046	0.282	-3.714	0.000	
)yspnea	Cristofanilli M 2016	Dyspnea	0.116	0.086		-12.080	0.000	
Dyspnea	Finn RS 2016	Dyspnea	0.149	0.119		-13.082	0.000	
Dyspnea	Finn RS 2015	Dyspnea	0.157	0.093	0.251	-5.575	0.000	
Dyspnea			0.134	0.114	0.158	-19.345	0.000	
pistaxis	Schwartz GK 2011	Epistaxis	0.121	0.046	0.282	-3.714	0.000	
pistaxis	Finn RS 2015	Epistaxis	0.108	0.057	0.195	-5.968	0.000	
pistaxis			0.112	0.066	0.184	-7.027	0.000	
leadache	Cristofanilli M 2016	Headache	0.232	0.190	0.279	-9.389	0.000	
leadache	Finn RS 2016	Headache	0.214	0.178	0.255	-11.244	0.000	
leadache	Finn RS 2015	Headache	0.145	0.084	0.238	-5.696	0.000	
leadache			0.216	0.190		-15.622	0.000	
Aucositis	DeMichele A 2014	Mucositis	0.189	0.093	0.347	-3.467	0.001	
lucositis	Schwartz GK 2011	Mucositis	0.091	0.030	0.247	-3.803	0.000	
lucositis	Vaughn DJ 2015	Mucositis	0.034	0.005	0.208	-3.274	0.001	
lucositis	Cristofanilli M 2016	Mucositis	0.125	0.094		-11.959	0.000	
lucositis	Finn RS 2016	Mucositis	0.153	0.123		-12.977	0.000	
lucositis	Finn RS 2015	Mucositis	0.120	0.066	0.210	-5.895	0.000	
/ucositis /valgia	D-Mi-h-l- A 0044	Mustele	0.139	0.118		-19.448	0.000	
	DeMichele A 2014 Finn RS 2016	Myalgia	0.135	0.057	0.286 0.153	-3.860 -13.653	0.000	
fyalgia fvalgia	Finn RS 2016	Myalgia	0.119	0.092	0.153	-13.053	0.000	
	Finn RS 2015	Myalgia	0.108	0.057		-5.968	0.000	
lyalgia ?ain in extremity	Cristofanilli M 2016	Pain in extremity	0.119	0.095		-15.380	0.000	
ain in extremity	Finn RS 2016	Pain in extremity	0.153	0.123		-12.977	0.000	
ain in extremity	Finn RS 2015	Pain in extremity	0.096	0.049	0.180	-6.017	0.000	
ain in extremity	1 111110 2010	7 diff in CAUCIFILITY	0.098	0.049		-18.576	0.000	
eripheral neuropathy	Flaherty KT 2012	Peripheral neuropathy	0.024	0.003	0.152	-3.644	0.000	
eripheral neuropathy	Finn RS 2015	Peripheral neuropathy	0.024	0.003	0.181	-6.017	0.000	
Peripheral neuropathy		. engine ar near opatity	0.082	0.043	0.151	-6.905	0.000	≩
leural effusion	Flaherty KT 2012	Pleural effusion	0.024	0.003	0.154	-3.644	0.000	
leural effusion	Cristofanilli M 2016	Pleural effusion	0.017	0.008	0.038	-9.796	0.000	
Pleural effusion			0.018	0.009		-10.446	0.000	
yrexia	Schwartz GK 2011	Pyrexia	0.091	0.030	0.247	-3.803	0.000	
yrexia	Cristofanilli M 2016	Pyrexia	0.110	0.081		-12.149	0.000	+
yrexia	Finn RS 2016	Pyrexia	0.124	0.096	0.158	-13.580	0.000	
yrexia		-	0.117	0.097		-18.598	0.000	
Rash	DeMichele A 2014	Rash	0.027	0.004	0.168	-3.535	0.000	
lash	Schwartz GK 2011	Rash	0.182	0.084	0.350	-3.333	0.001	
lash	Cristofanilli M 2016	Rash	0.151	0.117		-11.490	0.000	=
Rash	Finn RS 2016	Rash	0.178	0.145		-12.334	0.000	
Rash			0.165	0.141		-17.403	0.000	
'omiting	DeMichele A 2014	Vomiting	0.054	0.014	0.192	-3.937	0.000	
omiting	Schwartz GK 2011	Vomiting	0.091	0.030	0.247	-3.803	0.000	
omiting	Cristofanilli M 2016	Vomiting	0.168	0.132		-11.107	0.000	
/omiting	Finn RS 2016	Vomiting	0.155	0.125		-12.923	0.000	
omiting	Finn RS 2015	Vomiting	0.145	0.084	0.238	-5.696	0.000	
omiting			0.155	0.133		-18.673	0.000	
	DeMichele A 2014	Weight loss	0.027	0.004	0.168	-3.535	0.000	
		Weight loss	0.034	0.005	0.208	-3.274	0.001	
Veight loss Veight loss	Vaughn DJ 2015	Weight loss						
	vaugnn DJ 2015	Weight loss	0.031	0.008	0.114	-4.815	0.000	
/eight loss	Vaugnn DJ 2015	Weight loss		0.008	0.114	-4.815	0.000	-1.00 -0.50 0.00 0.50 1.0

Supplementary Figure S1b, All	rade adverse events in single arm gr	oups (Random model).
Supplementary Figure 515. An	and adverse events in single arm gr	oups (nanuom mouel).

	iroup by	Study name			Statistic	s for ea	ch study		Event rate and 95% CI
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	lopecia	Schwartz GK 2011	Alopecia	0.061	0.015	0.212	-3.757	0.000	
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pper respiratory infection Finn RS 2016 Upper respiratory infection 0.133 0.104 0.168 - 13.416 0.000 pper respiratory infection Finn RS 2015 Upper respiratory infection 0.108 0.057 0.195 5.5968 0.0000	pper respiratory infection	Cristofanilli M 2016	Upper respiratory infection	0.078					
oper respiratory infection 0.101 0.069 0.146 -10.175 0.000	pper respiratory infection		Upper respiratory infection	0.133					
		Finn RS 2015	Upper respiratory infection	0.108	0.057				_ I _ I =

Supplementary Figure S2a. Grade≥3 adverse events in single arm grou	

Sroup by	Study name	Adverse events		Statisti	cs for ea	ich study		Event rate and 95% CI
ubgroup within study					Upper			
			rate	limit		Z-Value		
Nopecia	Cristofanilli M 2016	Alopecia	0.001	0.000	0.023	-4.620	0.000	
Nopecia	Finn RS 2016	Alopecia	0.001	0.000	0.018	-4.799	0.000	
Nopecia			0.001	0.000	0.009	-6.660	0.000	
Inemia	DeMichele A 2014	Anemia	0.054	0.014	0.192	-3.937	0.000	
Inemia	Dickson MA 2013	Anemia	0.172	0.074	0.353	-3.191	0.001	
nemia	Flaherty KT 2012	Anemia	0.098	0.037	0.233	-4.227	0.000	
nemia	Schwartz GK 2011	Anemia	0.030	0.004	0.186	-3.413	0.001	
nemia	Vaughn DJ 2015	Anemia	0.069	0.017	0.238	-3.552	0.000	
nemia	Cristofanilli M 2016	Anemia	0.029	0.016	0.053	-10.942	0.000	
nemia	Finn RS 2016	Anemia	0.054	0.036	0.079	-13.638	0.000	
nemia	Finn RS 2015	Anemia	0.060	0.025	0.137	-5.955	0.000	
nemia			0.056	0.043	0.073	-19.900	0.000	
rthralgia	Cristofanilli M 2016	Arthralgia	0.003	0.000	0.020	-5.832	0.000	
rthralgia	Finn RS 2016	Arthralgia	0.007	0.002	0.021	-8.614	0.000	
rthralgia	Finn RS 2015	Arthralgia	0.012	0.002	0.081	-4.380	0.000	
rthralgia			0.006	0.003	0.015		0.000	
sthenia	Finn RS 2016	Asthenia	0.023	0.012	0.041	-11.788	0.000	
sthenia	Finn RS 2015	Asthenia	0.024	0.006	0.091	-5.171	0.000	
sthenia			0.023	0.013	0.040	-12.872	0.000	
ack pain	Cristofanilli M 2016	Back pain	0.012	0.004	0.030	-8.839	0.000	
ack pain	Finn RS 2016	Back pain	0.014	0.006	0.030	-10.438	0.000	
ack pain	Finn RS 2015	Back pain	0.012	0.002	0.081	-4.380	0.000	
ack pain			0.012	0.002	0.023	-14.360	0.000	
Couch	Cristofanilli M 2016	Couch	0.001	0.000	0.023	-4 620	0.000	
Cough	Finn RS 2016	Cough	0.001	0.000	0.023	-4.799	0.000	
ough	1 111110 2010	oougn	0.001	0.000	0.009	-4.799	0.000	
ougn ecreased appetite	Cristofanilli M 2016	Decreased appetite	0.001	0.000	0.009	-6.660	0.000	
ecreased appetite	Finn RS 2016	Decreased appetite	0.009	0.003	0.027	-8.108	0.000	
	Finn RS 2015		0.007	0.002	0.021	-8.614	0.000	
ecreased appetite	FIIN RS 2015	Decreased appetite	0.012	0.002	0.081		0.000	
ecreased appetite						-12.642		
liarrhea	Tamura K 2016	Diarrhea	0.038	0.002	0.403	-2.232	0.026	
iarrhea	Cristofanilli M 2016	Diarrhea	0.001	0.000	0.023	-4.620	0.000	
Jiarrhea	Finn RS 2016	Diarrhea	0.014	0.006	0.030	-10.438	0.000	
iarrhea	Finn RS 2015	Diarrhea	0.036	0.012	0.106	-5.583	0.000	
Diarrhea			0.017	0.009	0.031	-12.688	0.000	
lizziness	Cristofanilli M 2016	Dizziness	0.003	0.000	0.020	-5.832	0.000	
lizziness	Finn RS 2016	Dizziness	0.005	0.001	0.018	-7.617	0.000	
izziness			0.004	0.001	0.012	-9.587	0.000	
atique	Dickson MA 2013	Fatique	0.069	0.017	0.238	-3.552	0.000	
atigue	Flaherty KT 2012	Fatigue	0.073	0.024	0.204	-4.234	0.000	
atigue	Schwartz GK 2011	Fatigue	0.030	0.004	0.186	-3.413	0.001	
atigue	Tamura K 2016	Fatigue	0.038	0.002	0.403	-2.232	0.026	
atique	Cristofanilli M 2016	Fatique	0.023	0.012	0.046	-10.457	0.000	
atigue	Finn RS 2016	Fatigue	0.018	0.009	0.036	-11.206	0.000	
atique	Finn RS 2015	Fatigue	0.048	0.018	0.121	-5.821	0.000	
atigue		, angao	0.030	0.021	0.044	-17.563	0.000	
eadache	Cristofanilli M 2016	Headache	0.006	0.001	0.023	-7.254	0.000	
eadache	Finn RS 2016	Headache	0.000	0.000	0.025	-6.087	0.000	
eadache	1 111110 2010	ricadaciie	0.002	0.000	0.010	-9.438	0.000	
ot flushes	Cristofanilli M 2016	Hot flushes	0.004	0.001	0.013	-9.438	0.000	
ot flushes	Finn RS 2016	Hot flushes	0.001	0.000	0.023	-4.620 -4.799	0.000	
	Fill R5 2010	not nusnes		0.000				
ot flushes	0.117.10.0040		0.001		0.009	-6.660	0.000	
isomnia	Cristofanilli M 2016	Insomnia	0.003	0.000	0.020	-5.832	0.000	
Isomnia	Finn RS 2016	Insomnia	0.001	0.000	0.018	-4.799	0.000	
somnia			0.002	0.000	0.010	-7.533	0.000	
lucositis	Cristofanilli M 2016	Mucositis	0.006	0.001	0.023	-7.254	0.000	
ucositis	Finn RS 2016	Mucositis	0.002	0.000	0.016	-6.087	0.000	
lucositis			0.004	0.001	0.013	-9.438	0.000	
lusculoskeletal pain	Cristofanilli M 2016	Musculoskeletal pain	0.003	0.000	0.020	-5.832	0.000	
lusculoskeletal pain	Finn RS 2015	Musculoskeletal pain	0.012	0.002	0.081	-4.380	0.000	
lusculoskeletal pain			0.006	0.001	0.023	-7.224	0.000	
ain in extremity	Cristofanilli M 2016	Pain in extremity	0.001	0.000	0.023	-4.620	0.000	
ain in extremity	Finn RS 2016	Pain in extremity	0.002	0.000	0.016	-6.087	0.000	
ain in extremity			0.002	0.000	0.010	-7.637	0.000	
vrexia	Cristofanilli M 2016	Pyrexia	0.003	0.000	0.020	-5.832	0.000	
yrexia	Finn RS 2016	Pyrexia	0.001	0.000	0.018	-4.799	0.000	
yrexia	1 11110 2010	i yronia	0.001	0.000	0.010	-7.533	0.000	
ash	Cristofanilli M 2016	Rash	0.002	0.000	0.010	-7.254	0.000	
tash				0.001	0.023	-7.254		
	Finn RS 2016	Rash	0.009				0.000	
Rash	Oshursta Olf Oot t	Manakina	0.008	0.003	0.017	-11.830	0.000	
/omiting	Schwartz GK 2011	Vomiting	0.030	0.004	0.186	-3.413	0.001	
/omiting	Cristofanilli M 2016	Vomiting	0.003	0.000	0.020	-5.832	0.000	
/omiting	Finn RS 2016	Vomiting	0.005	0.001	0.018	-7.617	0.000	
/omiting	Finn RS 2015	Vomiting	0.006	0.000	0.088	-3.608	0.000	
/omiting			0.006	0.003	0.016	-10.649	0.000	
								-1.00 -0.50 0.00 0.50 1.00
								Favours A Favours B

Supplementary	/ Figure S2b.	Grade≥3 adverse	e events in single ar	n groups (Random model).

Group by	Study name	Adverse events		Statisti	cs for ea	ach study		Event rate and 95% CI
Subgroup within study				Lower				
			rate	limit	limit	Z-Value	p-Value	
Abdominal pain	Flaherty KT 2012	Abdominal pain	0.049		0.175		0.000	
Abdominal pain	Cristofanilli M 2016	Abdominal pain	0.006		0.023		0.000	
Abdominal pain	Finn RS 2016	Abdominal pain	0.009		0.024		0.000	
Abdominal pain			0.013		0.042		0.000	
Bone pain	Cristofanilli M 2016	Bone pain	0.006		0.023		0.000	
Bone pain	Finn RS 2015	Bone pain	0.024	0.006	0.091		0.000	
Bone pain	Distant MA 0012	Constinution	0.012		0.047		0.000 0.001	
Constipation Constipation	Dickson MA 2013 Cristofanilli M 2016	Constipation Constipation	0.034 0.001	0.005	0.208		0.001	
Constipation	Finn RS 2016	Constipation	0.001		0.023		0.000	
Constipation	1 1111 133 2010	Consupation	0.007	0.001	0.035		0.000	
Dyspnea	Flaherty KT 2012	Dyspnea	0.049		0.175		0.000	
Dyspnea	Cristofanilli M 2016	Dyspnea	0.003		0.020		0.000	
Dyspnea	Finn RS 2016	Dyspnea	0.011	0.005	0.027		0.000	
Dyspnea	Finn RS 2015	Dyspnea	0.024	0.006	0.091		0.000	
Dyspnea		-,	0.016		0.041	-8.223	0.000	
Leukopenia	DeMichele A 2014	Leukopenia	0.514	0.356	0.668	0.164	0.869	
Leukopenia	Dickson MA 2013	Leukopenia	0.483	0.311	0.659	-0.186	0.853	
Leukopenia	Flaherty KT 2012	Leukopenia	0.122	0.052	0.261	-4.136	0.000	
Leukopenia	Schwartz GK 2011	Leukopenia	0.212	0.105	0.383	-3.082	0.002	
Leukopenia	Vaughn DJ 2015	Leukopenia	0.379		0.564		0.198	
Leukopenia	Tamura K 2016	Leukopenia	0.417		0.692		0.566	
Leukopenia	Cristofanilli M 2016	Leukopenia	0.275		0.325		0.000	
Leukopenia	Finn RS 2016	Leukopenia	0.248		0.290		0.000	
Leukopenia	Finn RS 2015	Leukopenia	0.193		0.292		0.000	
Leukopenia		Marria	0.294	0.232	0.366		0.000	
Nausea Nausea	Flaherty KT 2012 Schwartz GK 2011	Nausea Nausea	0.049		0.175		0.000	
Nausea	Cristofanilli M 2016	Nausea	0.000	0.004	0.023		0.001	
Nausea	Finn RS 2016	Nausea	0.001		0.025		0.000	
Nausea	Finn RS 2015	Nausea	0.024	0.006	0.091	-5.171	0.000	
Nausea	1 1111110 2013	Nausea	0.024		0.046		0.000	
Neutropenia	DeMichele A 2014	Neutropenia	0.541	0.381	0.692		0.622	
Neutropenia	Dickson MA 2013	Neutropenia	0.517		0.689		0.853	
Neutropenia	Flaherty KT 2012	Neutropenia	0.317	0,194	0.473	-2.286	0.022	
Neutropenia	Schwartz GK 2011	Neutropenia	0.242	0.126	0.415	-2.805	0.005	
Neutropenia	Vaughn DJ 2015	Neutropenia	0.448	0.281	0.628	-0.556	0.578	
Neutropenia	Tamura K 2016	Neutropenia	0.583	0.308	0.815	0.575	0.566	
Neutropenia	Cristofanilli M 2016	Neutropenia	0.646	0.594	0.695	5.356	0.000	
Neutropenia	Finn RS 2016	Neutropenia	0.664	0.619	0.707		0.000	
Neutropenia	Finn RS 2015	Neutropenia	0.542		0.646		0.443	
Neutropenia			0.516		0.603		0.729	
Thrombocytopenia	DeMichele A 2014	Thrombocytopenia	0.189		0.347		0.001	
Thrombocytopenia	Dickson MA 2013	Thrombocytopenia	0.310		0.497		0.047	
Thrombocytopenia	Schwartz GK 2011	Thrombocytopenia	0.091	0.030	0.247		0.000	
Thrombocytopenia Thrombocytopenia	Vaughn DJ 2015 Tamura K 2016	Thrombocytopenia Thrombocytopenia	0.172		0.353		0.001	
	Cristofanilli M 2016		0.083		0.413		0.022	
Thrombocytopenia	Finn RS 2016	Thrombocytopenia						
Thrombocytopenia Thrombocytopenia	Finn RS 2016 Finn RS 2015	Thrombocytopenia Thrombocytopenia	0.016	0.008	0.033		0.000	
Thrombocytopenia	1 IIII NO 2013	птопьосуюренна	0.024		0.091		0.000	
Upper respiratory infection	Dickson MA 2013	Upper respiratory infection		0.029	0.208		0.000	
Upper respiratory infection	Cristofanilli M 2016	Upper respiratory infection		0.001	0.023		0.000	
Upper respiratory infection	Finn RS 2016	Upper respiratory infection		0.000	0.018		0.000	
Upper respiratory infection			0.007	0.001	0.037	-5.772	0.000	
						-		-1.00 -0.50 0.00 0.50 1.00
								Favours A Favours B

Supplementary Figure S3a.	All grade adverse events in controlled groups (Fixed model).

roup by ubgroup within study	Study name	Adverse events				ach study		Odds ratio and 95% Cl
ubgroup within study			Odds ratio	Lower limit		Z-Value		
bdominal pain	Cristofanilli M 2016	Abdominal pain	1.375	0.650	2.911	0.833	0.405	
bdominal pain	Finn RS 2016	Abdominal pain	2.221	1.157	4.262	2.399	0.016	
bdominal pain			1.807	1.105	2.955	2.357	0.018	
lopecia	Cristofanilli M 2016	Alopecia	2.958	1.509	5.797	3.159	0.002	
lopecia	Finn RS 2016	Alopecia	2.618	1.734	3.951	4.581	0.000	
lopecia lopecia	Finn RS 2015	Alopecia	10.385 2.903	2.321 2.062	46.455 4.086	3.062 6.108	0.002	
nemia	Cristofanilli M 2016	Anemia	3.105	1.824	5.284	4.176	0.000	
nemia	Finn RS 2016	Anemia	3.207	1.929	5.331	4.493	0.000	
nemia	Finn RS 2015	Anemia	7.733	2.809		3.960	0.000	
nemia			3.504	2.481	4.950	7.116	0.000	
thralgia	Cristofanilli M 2016	Arthralgia	0.889	0.534	1.481	-0.452	0.651	
thralgia	Finn RS 2016	Arthralgia	0.980	0.697	1.378	-0.116	0.908	+
thralgia	Finn RS 2015	Arthralgia	1.608	0.722	3.582	1.163	0.245	
thralgia	Finn RS 2016	Asthenia	1.008 1.532	0.772	1.317 2.472	0.060	0.952	
thenia thenia	Finn RS 2015	Asthenia	3.769	1.010		1.740	0.081	
thenia	1 111110 2013	Astronia	1.702	1.085	2.668	2.317	0.021	
ack pain	Cristofanilli M 2016	Back pain	0.855	0.520	1.407	-0.615	0.538	
ick pain	Finn RS 2016	Back pain	1.000	0.676	1.479	0.000	1.000	+
ck pain	Finn RS 2015	Back pain	0.915	0.384	2.181	-0.199	0.842	
ck pain			0.939	0.703	1.255	-0.425	0.671	
nstipation	Cristofanilli M 2016	Constipation	1.270	0.778	2.075	0.956	0.339	
nstipation	Finn RS 2016	Constipation	1.328	0.860	2.051	1.281	0.200	
nstipation	Finn RS 2015	Constipation	1.370	0.494	3.799	0.605	0.545	
nstipation ugh	Cristofanilli M 2016	Cough	1.309 1.183	0.960 0.691	1.784 2.024	1.701 0.612	0.089 0.540	
bugh	Finn RS 2016	Cough	1.429	0.959	2.024	1.753	0.080	
bugh	Finn RS 2015	Cough	1.182	0.441	3.168	0.331	0.740	
ugh		a	1.320	0.974	1.790	1.789	0.074	
creased appetite	Cristofanilli M 2016	Decreased appetite	2.003	1.076	3.727	2.192	0.028	
creased appetite	Finn RS 2016	Decreased appetite	1.763	1.039	2.992	2.103	0.035	
creased appetite	Finn RS 2015	Decreased appetite	2.674	0.906	7.895	1.781	0.075	
creased appetite			1.944	1.333	2.835	3.454	0.001	
arrhea	Cristofanilli M 2016	Diarrhea	1.195	0.753	1.896	0.754	0.451	
arrhea arrhea	Finn RS 2016 Finn RS 2015	Diarrhea Diarrhea	1.472 2.222	0.992		1.922 1.728	0.055 0.084	
arrhea	FINITIKO 2015	Diarmea	1.416	1.065	1.883	2 396	0.004	
zziness	Cristofanilli M 2016	Dizziness	1.315	0.715	2.418	0.881	0.378	
zziness	Finn RS 2016	Dizziness	0.947	0.600	1.494	-0.234	0.815	
zziness	Finn RS 2015	Dizziness	2.631	0.672	10.305	1.389	0.165	
zziness			1.132	0.795	1.610	0.688	0.492	
/spnea	Cristofanilli M 2016	Dyspnea	1.480	0.782	2.802	1.204	0.229	
rspnea	Finn RS 2016	Dyspnea	1.117	0.702	1.779	0.468	0.640	
spnea	Finn RS 2015	Dyspnea	2.198	0.791	6.107	1.510	0.131	
spnea	Cristofanilli M 2016	Fatigue	1.320 1.614	0.927	1.878 2.396	1.542 2.372	0.123 0.018	
tigue tigue	Finn RS 2016	Fatigue	1.576	1.109	2.350	2.572	0.018	
itigue	Finn RS 2015	Fatigue	2.274	1.146	4.514	2.349	0.019	
tigue		. engee	1.667	1.304	2.131	4.081	0.000	
adache	Cristofanilli M 2016	Headache	1.272	0.807	2.003	1.036	0.300	
adache	Finn RS 2016	Headache	0.770	0.529	1.121	-1.366	0.172	=+
adache	Finn RS 2015	Headache	1.458	0.562	3.784	0.774	0.439	
adache	0.1 + 6 - 10 + 4 0040		0.979	0.742	1.291	-0.151	0.880	
omnia	Cristofanilli M 2016	Insomnia	1.410	0.709	2.805	0.980	0.327	
omnia omnia	Finn RS 2016	Insomnia	1.316 1.347	0.810	2.139 2.002	1.109 1.471	0.267 0.141	
ukopenia	Cristofanilli M 2016	Leukopenia	23.165	10.563		7.844	0.000	
ukopenia	Finn RS 2016	Leukopenia	27.706	11.187		7.179	0.000	
Ikopenia	Finn RS 2015	Leukopenia	28.723	6.605	124.903	4.477	0.000	
Ikopenia			25.502	14.707	44.220	11.533	0.000	
cositis	Cristofanilli M 2016	Mucositis	5.980	2.110		3.365	0.001	│ │ │ <u></u> +
cositis	Finn RS 2016	Mucositis	2.908	1.569	5.388	3.391	0.001	
cositis	Finn RS 2015	Mucositis	5.137	1.088		2.067	0.039	
icositis ralgia	Finn RS 2016	Myalgia	3.649 1.369	2.208 0.796	6.030 2.353	5.052 1.137	0.000 0.256	
/algia /algia	Finn RS 2016 Finn RS 2015	Myalgia	1.369	0.796	2.353	0.963	0.256	
/algia	1 100 100 2010	myaigid	1.433	0.878	2.337	1.440	0.335	
usea	Cristofanilli M 2016	Nausea	1.278	0.853	1.915	1.192	0.233	
usea	Finn RS 2016	Nausea	1.532	1.072	2.189	2.339	0.019	
usea	Finn RS 2015	Nausea	2.269	0.991	5.196	1.939	0.053	
usea			1.479	1.147		3.014	0.003	
utropenia	Cristofanilli M 2016	Neutropenia		49.613		10.884	0.000	
utropenia	Finn RS 2016	Neutropenia	57.633			13.509	0.000	
utropenia in in extremity	Cristofanilli M 2016	Dain in automati		44.499		17.297 0.083	0.000 0.934	
in in extremity in in extremity	Finn RS 2016	Pain in extremity Pain in extremity	1.024 0.849	0.586 0.551	1.787 1.306	-0.746	0.934	
in in extremity	Finn RS 2015	Pain in extremity	1.262	0.551		0.412	0.456	
in in extremity	1 111110 2010	. and in overenity	0.937	0.676		-0.394	0.694	
rexia	Cristofanilli M 2016	Pyrexia	2.242			2.107	0.035	
rexia	Finn RS 2016	Pyrexia	1.511	0.873		1.474	0.140	
vrexia			1.733	1.113	2.699	2.433	0.015	
rombocytopenia	Cristofanilli M 2016	Thrombocytopenia	93.055	5.728	511.626	3.187	0.001	
rombocytopenia	Finn RS 2016	Thrombocytopenia	13.432		43.186	4.359	0.000	
rombocytopenia	Finn RS 2015	Thrombocytopenia	15.420		120.356	2.609	0.009	
rombocytopenia			17.359		45.065	5.863	0.000	
oper respiratory infection	Cristofanilli M 2016		1.132	0.559	2.294	0.344	0.731	
pper respiratory infection pper respiratory infection	Finn RS 2016 Finn RS 2015		1.208 1.561	0.734	1.987 21.823	0.742	0.458 0.057	
oper respiratory infection	1 100 143 2015		1.287	0.953	1.909	1.900	0.057	

Supplementary Figure S3b. All grade adverse events in controlled groups (Random model).

roup by	Study name	Adverse events	_	Statisti	cs for ea	nch study			Odd	ls ratio and 95	% CI	
Subgroup within study			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value					
ot flushes	Cristofanilli M 2016	Hot flushes	0.895	0.546	1.468	-0.439	0.661		1		1	
t flushes	Finn RS 2016	Hot flushes	0.600	0.416	0.865	-2.738	0.006					
t flushes	Finn RS 2015	Hot flushes	1.946	0.810	4.674	1.490	0.136				_	
t flushes			0.904	0.516	1.584	-0.353	0.724					
sh	Cristofanilli M 2016	Rash	3.214	1.544	6.690	3.122	0.002			1 —	-	
sh	Finn RS 2016	Rash	1.632	1.014	2.626	2.016	0.044					
sh			2.157	1.122	4.149	2.304	0.021					
miting	Cristofanilli M 2016	Vomiting	1.188	0.714	1.978	0.664	0.507			_ 		
miting	Finn RS 2016	Vomiting	0.920	0.595	1.423	-0.374	0.708					
miting	Finn RS 2015	Vomiting	4.169	1.129	15.395	2.142	0.032					
miting			1.267	0.722	2.224	0.824	0.410			-		
								0.01	0.1	1	10	10
									Favours A		Favours B	

Supplementary Figure S4a	Grade≥3 adverse eve	ents in controlled c	roups (Fi	ixed model).

Group by Subgroup within study	Study name	Adverse event				ach stud	Y
angroup within study			Odds ratio	Lower limit	Upper	Z-Value	n-Value
odominal pain odominal pain	Cristofanilli M 2016 Finn RS 2016	Abdominal pain Abdominal pain	0.997 4.546	0.090	11.073 84.811	-0.002 1.014	0.998 0.310
Abdominal pain	FINIT KS 2010	Abdominal pain	1.839	0.244	11.806	0.643	0.521
nemia	Cristofanilli M 2016	Anemia	1.682	0.457	6.191	0.782	0.321
nemia	Finn RS 2016	Anemia	3 1 1 4	1 067	9.089		0.038
iemia	Finn RS 2015	Anemia	4.872	0.556	42 675	1.430	0 153
iemia			2.654	1.225	5.750		0.013
thralgia	Cristofanilli M 2016	Arthralgia	1.502	0.061	37.067	0.249	0.804
thralgia	Finn RS 2016	Arthralgia	1.503	0.155	14.536	0.352	0.725
rthralgia	Finn RS 2015	Arthralgia	0.457	0.041	5.147	-0.633	0.526
rthralgia			0.969	0.223	4.217	-0.042	0.966
sthenia	Finn RS 2016	Asthenia	10.754		184.359		0.101
sthenia	Finn RS 2015	Asthenia	4.755		100.621	1.001	0.317
thenia			7.362	0.920		1.881	0.060
one pain	Cristofanilli M 2016	Bone pain	0.496	0.069	3.549		0.485
one pain	Finn RS 2015	Bone pain	4.755	0.225	100.621	1.001 -0.045	0.317
one pain	Cristofanilli M 2016	Decreased appetit	0.963	0.184	5.036 14.528		0.964
creased appetite	Finn RS 2016	Decreased appetit		0.155	14.528	0.350	0.726
ecreased appetite	Finn RS 2015	Decreased appetit		0.113	70.223		0.528
ecreased appetite	Fillin K3 2013	Decreased append	2.218	0.460	10.691	0.032	0.328
arrhea	Cristofanilli M 2016	Diarrhea	0.165	0.007	4.083		0.271
arrhea	Finn RS 2016	Diarrhea	1.000	0 248	4.036		1.000
arrhea	Finn RS 2015	Diarrhea	6.739		132.620		0.209
arrhea			1.057	0.326	3.424		0.927
zziness	Cristofanilli M 2016	Dizziness	1.502	0.061	37.067	0.249	0.804
izziness	Finn RS 2016	Dizziness	2.514	0.120	52.592	0.594	0.552
zziness			1.970	0.217	17.889	0.602	0.547
yspnea	Cristofanilli M 2016	Dyspnea	0.247	0.022	2.744		0.255
yspnea	Finn RS 2016	Dyspnea	0.831	0.197	3.511	-0.251	0.802
rspnea	Finn RS 2015	Dyspnea	1.877	0.167	21.120		0.610
yspnea			0.763	0.254	2.295		0.631
atigue	Cristofanilli M 2016	Fatigue	2.018	0.424	9.606		0.378
atigue	Finn RS 2016	Fatigue	4.055	0.504	32.626		0.188
tigue	Finn RS 2015	Fatigue	3.848	0.421	35.212		0.233
itigue	Cristofanilli M 2016	Leukopenia	2.852 32.300	0.961	8.466 132.817	1.888 4.817	0.059
ukopenia	Finn RS 2016		47.003		2377.23		0.000
ukopenia ukopenia	Finn RS 2016 Finn RS 2015		37.889		2377.23 643.556		0.000
ukopenia	FIIII R3 2015	Leukopenia	42.988		043.550 135.989		0.012
ucositis	Cristofanilli M 2016	Mucositis	2.511	0.120	52.589		0.553
ucositis	Finn RS 2016	Mucositis	1.505	0.061	37.096		0.803
ucositis	1 111110 2010	Macosias	1 970	0.217	17.891	0.602	0.547
usculoskeletal pain	Cristofanilli M 2016	Musculoskeletal pai		0.031	7 996	-0.493	0.622
usculoskeletal pain	Finn RS 2015	Musculoskeletal pai		0.113	70.223		0.528
sculoskeletal pain			1.043	0.128	8.539	0.040	0.968
usea	Cristofanilli M 2016	Nausea	0.165	0.007	4.083		0.271
usea	Finn RS 2016	Nausea	0.123	0.014	1,107	-1.869	0.062
usea	Finn RS 2015	Nausea	1.877	0.167	21.120	0.510	0.610
sea			0.348	0.082	1.484	-1.426	0.154
Itropenia	Cristofanilli M 2016	Neutropenia 3	12.566	43.240	2259.39	6 5.692	0.000
utropenia	Finn RS 2016	Neutropenia	44.530	45.480	459.299	8.431	0.000
utropenia	Finn RS 2015	Neutropenia	90.000	11.945	678.124		0.000
eutropenia			54.215				0.000
ain in extremity	Cristofanilli M 2016	Pain in extremity		0.004	1.365		0.079
ain in extremity	Finn RS 2016	Pain in extremity		0.017	1.593		0.119
ain in extremity			0.120	0.020	0.729		0.021
lash	Cristofanilli M 2016	Rash	2.511	0.120	52.589		0.553
ash	Finn RS 2016	Rash	2.009	0.223	18.082		0.534
ash	Cristofenelli M 0010	Thromboouteraai	2.169	0.365	12.875		0.394
hrombocytopenia	Cristofanilli M 2016 Finn RS 2016	Thrombocytopenia Thrombocytopenia			151.427 134.177	1.483 1.389	0.138 0.165
irombocytopenia irombocytopenia	Finn RS 2016 Finn RS 2015	Thrombocytopenia			134.177	1.389	0.165
nrombocytopenia hrombocytopenia	FIIII NO 2010	mombocytopenia	4.755	0.225	37.329		0.317
nrombocytopenia omiting	Cristofanilli M 2016	Vomiting	0.497	0.031	7.996		0.025
miting	Finn RS 2016	Vorniting	0.330	0.031	1.990	-0.493	0.822
omiting	Finn RS 2016	Vorniting	0.330	0.055	7 610	-0.723	0.227
'omiting	1 111110 2010	vorniung	0.359	0.012	1.409		0.142
			0.000	0.002	1.400	1.400	0.172

Supplementary Figure S4b. Grade≥3 adverse events in controlled groups (Random model).

