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Review

Translational Gap in Lung Cancer Research

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Abstract

Lung tumors display intratumoral heterogeneity and contain "cancer stem-like cells" (CS-LCs) that drive chemoresistance and tumor relapse. Cancer relapse occurs when treatment does not target all types of cell subpopulations. Clinical trials often test only one drug, which will likely not be effective on heterogeneous tumors. Studies testing two or more drugs seldom incorporate cancer stem cell- targeting drugs. This translational gap, defined as a delay in the clinical applications of scientific discoveries, may be present in other cancers. In this study, we reviewed 50 Phase I/II and II lung cancer clinical trials (PI/IICT) published in 2015 and 50 studies published in 2004. We compared the number of anticancer drugs used in each CT, the drugs' ability to target CS-LCs, and the use of radiotherapy. Between 2015 and 2014, the use of radiotherapy (10% and 12%, respectively) and the percentage of studies using drugs known to target CS-LCs (32% and 26%, respectively) were similar. There was an increase in the percentage of PI/IICT testing three drugs when comparing 2015 to 2004 (34% vs 16%). We conclude that a translational gap exists in lung cancer research.

Keywords: Lung cancer, translational gap, stem cells, chemotherapy, clinical trial.

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Lung cancer is the leading cause of cancer-related deaths in Western countries.[1] Even though vast amounts of resources have been allocated for both basic and clinical research to find a cure for this disease, the prognosis for lung cancer is still poor.[1] For instance, the 5-year relative survival rate for patients diagnosed the 1970s was about 12% and increased only to 18% for those diagnosed between 2003 and 2009.[2] During those decades, important advances in the understanding of lung cancer biology have been accomplished. One of the breakthrough discovery in cancer research has been the isolation in 2005 of putative lung cancer stem-like cells (CS-LCs)[3] and their association with chemoresistance.[4] Lung CSCs (LCSCs) constitute a subpopulation of cancer cells (accounting for 0.03-6.1% of the cell population) that can regenerate a heterogeneous tumor. This discovery has led to the assumption that if CSCs were eliminated, the cancer would be cured. It is then expected that clinical trials performed after 2005 will focus in eliminating LCSCs.

The poor advance in the treatment of lung cancer is somehow similar to what have been described for other tumors. For instance, glioma patients' prognosis has remained the same during the last four decades. In this type of tumor, we have previously described a translational gap, defined as a delay in the application of rudimentary cancer cell biological concepts in the design of clinical trials.[6] In particular, we found that key concepts, such as the importance of the blood brain barrier and the existence of glioma stem cells, are seldom incorporated in Phase I/II clinical trials. These explain, at least in part, the failure of most clinical trials and why the prognosis of glioma patients remains similar to decades ago.

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To accomplish this objective, the number of drugs used in each clinical trial, their ability to target LCSCs, and the use of concomitant radiotherapy were compared in a set of 50 Phase I/II clinical trials published in 2004 (a year before the isolation of LCSCs) with 50 Phase I/II clinical trials published in 2015, around a decade later. These parameters are indicative of how basic findings in lung cancer biology can be translated into clinical trials.

Methods

Phase I/II clinical trials for lung cancer were retrieved from PubMed (https://pubmed.ncbi.nlm.nih.gov/), with some references from https://www.clinicaltrials.gov, using the search phrases "phase II lung cancer 2015" and "phase II lung cancer 2004". The search was restricted using the filters "Clinical Trial" and "Free Full Text." 100 unique articles reporting results of phase I/II and phase II clinical trials were selected. Table 1 displays the information of 50 phase II clinical trials published in 2015, and Table 2 shows information of 50 clinical trials published in 2004. This information includes type of lung cancer, number of patients (as well as the male/female ratio), drugs for treatment (and other interventions, such as radiation therapy), endpoints of the studies, and the study start and end dates (along with duration of the trial). In order to characterize the drugs utilized in the clinical trials, as well as to determine their effectiveness at targeting LCSCs, a Google search was first used to find any alternate drug names, as well as the drug type. Then, information regarding whether a particular drug is known to target LCSCs was derived from Pubmed and Google Scholar using the search terms "(drug name) cancer stem cells" and "(drug name) lung cancer stem cells". This information is recorded in Table 3.

Results and Discussion

From PubMed, using the search criteria described in Methods, we have retrieved a set of 50 Phase I/II clinical trials (PI/IICT) published in 2015 to compare with another set of 50 PI/IICT published in 2004 to evaluate if there is a translational gap in lung cancer research, as we have described for gliomas.[6] The rationale for selecting these two groups (2004 vs 2015) is that the isolation of cancer stem-like cells from lung tumors was reported in 2005;[3] therefore, it is expected that PI/IICT published before 2005 did not consider these cells. However, one would expect that after about a decade, an increasing number of PI/IICT will be designed with the specific goal to eliminate LCSCs and other factors known to affect clinical outcomes, such as intratumoral heterogeneity and concomitant use of radiotherapy. With this aim, we evaluated the number of drugs used in each PI/IICT, the concomitant use of radiotherapy, and their ability to target lung CS-LCs.

Number of Drugs Included in Clinical Trials

Lung cancers display high intratumoral heterogeneity, a factor that has been associated with chemoresistance and tumor relapse.[7] Therefore, for a more successful outcome, it is expected that PI/IICT are designed to test at least 2 drugs. This rationale is supported by clinical evidence that when treating cancer, utilizing multiple chemotherapeutic agents and/or combining radiation therapy with chemotherapy is, overall, a more effective treatment compared to monotherapy.[8,9] A meta-analysis completed by Delbaldo et al.[10] determined that the addition of a second drug to advanced NSCLC treatment significantly improved tumor response and patient survival.

Our data show that the number of PI/IICT published in 2015 (Table 1) that used 1, 2, 3 or >3 drugs were 14 (28%), 19 (38%), 17 (34%) and 0 (0%), respectively. The number of PI/IICT published in 2004 (Table 2) that used 1, 2, 3 or >3 drugs were 7 (14%), 35 (70%), 8 (16%) and 0 (0%) (Fig. 1). Overall, these results are unexpected. The percentage of studies that incorporated two drugs decreased by approximately one-half when comparing 2004 to 2015. Conversely, the percentage of studies in 2015 that tested only one drug is double that of the 2004 clinical trials. However, the number of PI/IICT that tested three drugs doubled. None of the studies tested >3 drugs, but this appears to be a common finding; our previous studies in gliomas showed that only a small percentage of PI/IICT tested >3 drugs,[6] even in ongoing but not published clinical trials.[13] Despite the rise in the number of

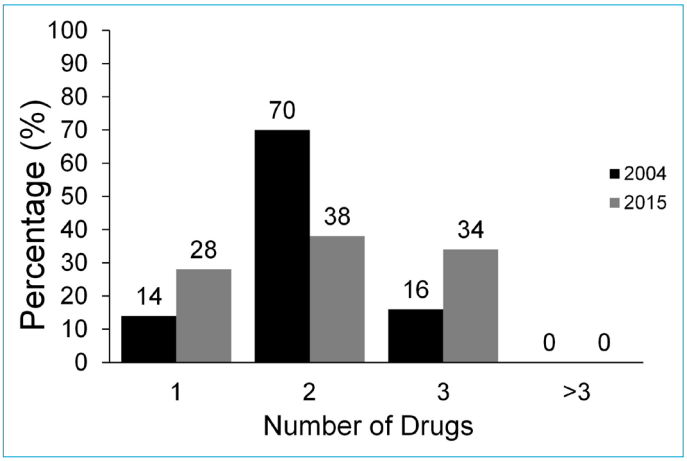

Figure 1. Percentage of chemotherapeutic agents administered in each clinical trial (n=100). For 2004 (n=50), 7 trials tested one drug (14%), 35 trials tested two drugs (70%), and 8 trials tested three drugs (16%). As for 2015 (n=50), 14 clinical trials tested one drug (28%), 19 trials tested two drugs (38%), and 17 trials tested 3 drugs (34%). None of the clinical trials tested more than three drugs at once.

PI/IICT using 3 drugs, an important fraction of studies (28%) published in 2015 were designed to test only one drug and only four out of 14 (28.5%) of such studies used drugs with proven ability to target LCSCs. From this observation we can predict that at least 10 studies out of 50 (20%) will likely be of no more benefit than current treatments.

Use of Concomitant Radiation

Like in other tumors the use of concomitant radiation improves patient survival and response rates of lung cancer patients compared to patients that receive chemotherapy alone.[11, 12] Applying this reasoning, we evaluated the number of studies that added radiotherapy to the tested drugs. Our analysis showed that in both sets of clinical trials published in 2004 and 2015 only ~10% of the studies evaluated the use of concomitant radiotherapy (Fig. 2). This result is also surprising, but it can be explained by either the necessity to first evaluate the effect of chemotherapy alone and, if effective, add radiotherapy in future clinical trials, or to simplify the design and analysis of P2CTs.

Use of Drugs Targeting LCSC

Since their isolation in 2005, putative lung cancer stem-like cells have been extensively associated with chemoresistance and tumor relapse (see above). We anticipated that recently published PI/IICTs will employ drugs with known activities against this particular cell fraction. Our data (Fig. 3) shows that contrary to this expectation, only 16 out of 50 studies (32%) published in 2015 used drugs that were known to target LCSCs. This is only a small improvement, considering that in the set of P2CTs published in 2004, 13 out of 50 studies (26%) used known LCSC-targeting drugs.

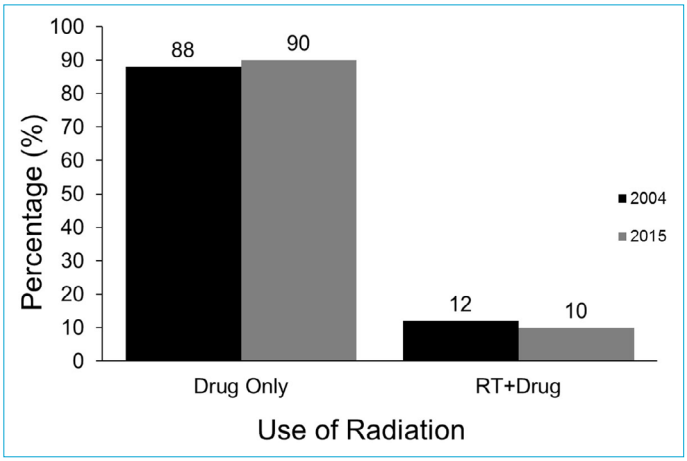

Figure 2. Chemotherapy and radiotherapy versus chemotherapy alone in 2004 and 2015 phase II clinical trials (n=100). Of the 2004 clinical trials (n=50), 44 did not use radiation therapy, and instead tested chemotherapy only (88%), while 6 trials did use radiation therapy (12%). For 2015 (n=50), 45 clinical trials utilized chemotherapy only (90%), while 5 studies used a combination of chemotherapy and radiation therapy (10%).

Impact of the Translational Gap in Lung Cancer Research

Our results clearly show about 70% of recently published (in 2015) clinical trials do not test drugs known to target LCSCs (see above). A similar result was observed in gliomas,[6] and even ongoing (but still not published) clinical trials are failing to incorporate glioma stem cell targeting drugs.[13] Currently there are 174 ongoing (Recruiting: 102; Active, not recruiting: 50; not yet recruiting: 21; enrolling by invitation; 1) interventional phase II clinical trials for lung cancer (www.clinicaltrials.gov, retrieved in June, 2021) and it would be logical to assume that a translational gap is still present and that most of these studies will not be successful. This gap represents a challenge when searching to participate in new experimental treatments. Our study may provide a valuable reference to educate both patients and physicians and help them to decide to participate in clinical trials that will likely have more chances to improve the prognosis of this disease. This goal can be achieved by selecting those studies that test multiple drugs with at least one of them with known ability to target LCSCs.

Conclusion

We have analyzed three parameters of PI/IICTs that indicate how basic findings in lung cancer biology can be translated into clinical trials to improve study outcomes and ultimately lead to better prognoses for lung cancer patients. Overall, our data provide evidence that little advances have been made during the last decade in incorporating

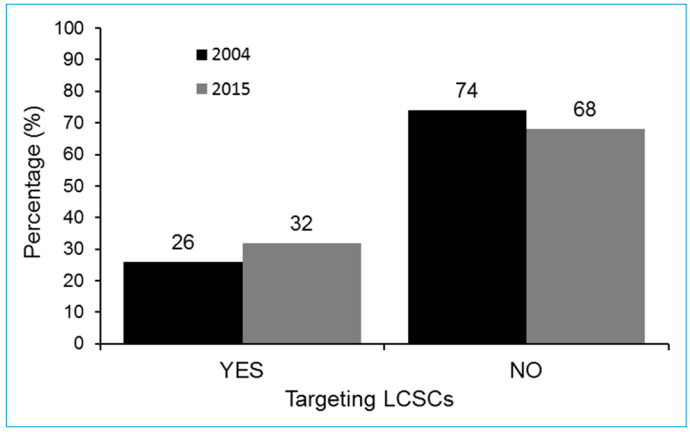

Figure 3. Targeting LCSCs in clinical trials. Studies in which at least one drug administered was known to target LCSCs were considered attempts at targeting LCSCs. Studies in which at least one drug administered was known to not target LCSCs, or those in which drugs tested were of unknown status regarding the targeting of LCSCs, were considered to have not targeted LCSCs.

potential breakthroughs obtained from basic research into clinical practice. This constitutes a translational gap in lung cancer research. Our group previously reported a similar finding for gliomas. Since lung cancer is one of the leading causes of cancer-related deaths, it is possible that this translational gap may also occur in other types of common cancers (e.g., breast, prostate). Future research in this area is necessary to determine whether the translational gap is a widespread phenomenon in translational oncology that needs to be fixed by engaging preferentially in PI/IICT with higher chances of improving patient prognosis while reducing the cost of clinical cancer research.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Table 1. Initial data collection for phase II lung cancer studies published in 2015. Each study was given a number for reference in the discussion (column 1).The second column lists the phase at which the clinical trial was completed (mostly phase II, but occasionally researchers will complete multiple phases at once). The patient "PT m/f ratio" column signifies the ratio of male to female patients who participated in the clinical trials. Column four denotes the type or stage of small cell lung cancer. Column five contains a list of the anticancer drugs evaluated in the clinical trial. Columns six and seven identify whether radiation therapy or another type of intervention was utilized to treat the patients' cancer, respectively. The "Endpoints" columns serve to identify what clinical outcomes were measured in the study (MOS, OS-6, etc., see abbreviations), the "LCSCs" column identifies whether the study considered the presence of lung cancer stem cells in its methodology and determination of drug therapy. The final columns, "Start Date,""End Date,""Duration (in months)" and "Reference or Clinical Trials ID," are self-explanatory.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference or ClinicalTrials ID
1	II	25/9 (34)	Refractory/Sensitive	Amrubicin	NO	NO	RR (PR, CR)		NK	June 2003	Jan. 2005	19	(14)
2	II	(138)	Relapse SCLC Extensive Stage SCLC	Cisplatin, carboplatin, or etoposide followed by sunitinib or placebo	NO	NO	PFS	CR, PR, SD	Cisplatin: NK Carboplatin: NK Etoposide: NK Sunitinib: NK	March 2007	Dec.2011	57	(15)
3	II	18/9 (27)	Extensive Stage SCLC	Carboplatin+paclitaxel	NO	NO	RR	PFS, OS	Carboplatin: NK Paclitaxel: NK	(No dates given)		(16)	
4	II	125/54 (179)	Progressive SCLC	Cabazitaxel versus Topotecan	NO	NO	PFS	CR,PR, OS	Cabazitaxel:NK Topotecan: NO	March 2012	April 2014	25	(17)
5	II	38/20 (58)	Refractory/ Relapse SCLC	Doxorubicin + vindesine + cyclophosphamide (VAC)	NO	Valproic acid	PFS	RR	Doxorubicin:NK Vindesine: NK VAC: NK Valproic Acid: NK	Nov 2008	Dec 2013	61	(18)
6	II	(57)	Sensitive/Relapse SCLC	Amrubicin+ Platinum-doublet regimen	NO	NO	RR	PFS, OS	NK	Feb 2008	June 2013	64	(19)
7	II	30/3 (33)	Metastatic/Recurrent SCLC	Paclitaxel + gemcitabine	NO	NO	RR	TTP, OS	Paclitaxel: NK Gemcitabine: NO	Dec 2004	Feb 2009	50	(20)
8	II	113/25 (138)	Extensive Stage SCLC	Endostatin + carboplatin/ etoposide regimen	NO	NO	PFS	OS, ORR, QoL	Endostatin: YES Carboplatin: NK Etoposide: NK	July 2009	Aug 2011	25	(21)
9	II	13/25 (38)	Stage IIB/IV NSCLC	Carboplatin + Pemetrexed + Bevacizumab	NO	NO	PFS	RR (CR, PR), SD, DCR, OS	Carboplatin: NK Pemetrexed: YES Bevacizumab NK	Mar 2010	Nov 2013	26	(22)
10	II	51/8 (59)	Limited Stage SCLC	Etoposide/cisplatin regimen	YES;HypoTRT	NO	2YR PFS	MST, OS	Etoposide: NK Cisplatin: NK	July 2007	Feb 2012	55	(23)
11	II	(22)	Extensive Stage SCLC	Cisplatin + Etoposide + Bevacizumab followed by maintenance Etoposide/ Bevacizumab regimen	NO	NO	TTP, DCR	OS, PFS, RR	Cisplatin: NK Etoposide: NK Bevacizumab NK	(No dates given)			(24)
12	II	100/31 (131)	Progressive SCLC	Lomustine+ cyclophosphamide+ etoposide versus cyclophosphamide+ doxorubicin+ vincristine	NO	NO	OS	PFS, RR, TT	Lomustine: NK VAC: NK Etoposide: NK Doxorubicin: NK Vincristine: NK	(No dates given)		(25)	

Table 1. CONT.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference or ClinicalTrials ID
13	II	90/99 (189)	Extensive Stage SCLC	Topotecan with or without Aflibercept	NO	NO	PFS	OS, RR (PR,CR)	Topotecan: NO Aflibercept: NK	May 2009	June 2012	37	(26)
14	II	36/44 (80)	Extensive Stage SCLC	Amrubicin + Carboplatin+ pegfilgrastim	NO	NO	IYRSR	RR (CR, PR), TTP, OS	Amrubicin: NK Pegfilgrastim NK Carboplatin: NK	Dec 2009	March 2012	27	NCT01076504 (Clinical Trials.gov)
15	II	19/25 (44)	Relapse SCLC	Linsitinib + Topotecan	NO	NO	PFS	DCR, OS, RR	Linsitinib: NK Topotecan: NO	Feb 2012	Nov 2014	33	NCT01533181 (Clinical Trials.gov)
16	II	41/32 (73)	Extensive Stage SCLC	Cisplatin + Etoposide with or without Vandetanib	NO	NO	TTP	RR (CR, PR), DCR, OS	Cisplatin: NK Etoposide: NK Vandetanib: NK	June 2008	Aug 2015	86	NCT00613626 (Clinical Trials.gov)
17	II	18/15 (33)	Refractory/Relapse SCLC	Pazopanib	NO	NO	PFS, SD	OS, RR	NK	June 2010	Dec 2014	54	NCT01253369 (Clinical Trials.gov)
18	II	39/53 (92)	Refractory/ Sensitive SCLC	Temozolomide (TMZ)	NO	NO	RR (CR, PR), PD, SD	OS	NK	Aug 2008	Feb 2013	54	NCT00740636 (Clinical Trials.gov)
19	II	239/146 (385)	NSCLC	Docetaxel+ Ganetespib	NO	NO	PFS, OS		Docetaxel: NO Ganetespib: NK	July 2011	May 2013	22	(27)
20	I/II	17/10 (27)	Nonmetastatic Stage III NSCLC	Bortezomib+ Paclitaxel/ Carboplatin regimen	YES; TRT	NO	MTD (Phase I), 12MS (Phase II)	PFS, OS, RR (PR,CR), TT	Bortezomib: NK Paclitaxel: NK Carboplatin: NK	July 2008	Jan. 2011	30	(28)
21	II	50/57 (107)	Stage IIIB/IV NSCLC	Erlotinib+Celecoxib	NO	NO	PFS	RR, OS, DCR	Erlotinib: YES Celecoxib: NK	Nov 2007	May 2011	42	(29)
22	II	36/7 (43)	Stage III/IV NSCLC	Vinorelbine	NO	NO	RR, CB>12	HRQoL, OS, TTP	YES	March 2010	July 2013	40	(30)
23	II	65/49 (114)	Stage IV NSCLC	Imetelstat+bevacizumab, or bevacizumab alone, or neither drug	NO	NO	PFS	ORR, OS	Imetelstat: NK Bevacizumab NK	July 2010	April 2012	21	(31)
24	I/II	28/24 (52)	Stage IV NSCLC	Gefitinib+vorinostat	NO	NO	PFS	RR	Gefitinib: NO Vorinostat: YES	July 2010	June 2013	35	(32)
25	II	10/6 (16)	EGFR-wt Stage IIIB/IV NSCLC	Erlotinib	NO	NO	RR (PR,CR)	DCR, PFS, OS	YES	April 2010	May 2013	37	(33)
26	II	40/13 (53)	Stage IV NSCLC	Disulfiram + cisplatin/ vinorelbine regimen	NO	NO	PFS	OS, TTP, QoL	Disulfiram: YES Cisplatin: NK Vinorelbine: YES	March 2006	Dec 2009	45	(34)
27	II	69/63 (132)	KRAS-Mutant Advanced NSCLC	Trametinib, compared to docetaxel	NO	NO	PFS	RR, OS, TT, DOR	Trametinib: NK Docetaxel: NO	Sept 2011	July 2012	17	(35)
28	I/II	30/100 (130)	EGFR mutant NSCLC	Rociletinib	NO	NO	RR, DCR, PFS		NK	March 2012	April 2014	25	(36)
29	II	15/31 (46)	Stage IIIB and Stage IV NSCLC	Erlotinib	NO	NO	PFS	RR, OS	YES	(No month) 2008	Feb 2013		(37)
30	II	149/48 (197)	Stage II and Stage IIIA NSCLC	S-1, compared to Cisplatin + S-1	NO	NO	RFS	OS	S-1: NK Cisplatin: NK	Sept 2007	Dec 2009	27	(38)
31	II	35/34 (69)	EGFR FISH-positive NSCLC	Afatinib	NO	NO	RR	OS, DCR, PFS, PR, CR, SD	NO	Dec 2008	Sept 2011	33	(39)

Table 1. CONT.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference or ClinicalTrials ID
32	II	25/6 (31)	Advanced NSCLC	S-1 + irinotecan	NO	NO	RR	PFS, OS	S-1: NK Irinotecan: NK	Jan 2008	May 2011	40	(40)
33	II	51/39 (90)	Stage III NSCLC	Pemetrexed + cisplatin	YES; TRT	NO	PFS	RR, OS, TT	Pemetrexed: YES Cisplatin: NK	Oct 2009	July 2011	21	(41)
34	II	112/111 (223)	Stage IV NSCLC	Paclitaxel+carboplatin + bevacizumab	NO	Nitroglycerin patches (with or without)	PFS	OS, RR, DCR, DOR	Paclitaxel: NK Carboplatin: NK Bevacizumab NK NTG: NK	Jan 2011	Jan 2013	24	(42)
35	II	44/31 (75)	Stage III NSCLC	Paclitaxel+ carboplatin, followed by TRT + erlotinib	YES; TRT	NO	12MS	RR, PFS	Paclitaxel: NK Carboplatin: NK Erlotinib: YES	March 2008	Oct 2011	43	(43)
36	II	108/61 (169)	Advanced NSCLC	Cilengitide+Cetuximab + platinum-based, chemotherapy or Cetuximab + platinum-based chemotherapy alone	NO	NO	PFS	OS	Cilengitide: NK Cetuximab: NK	Feb 2010(No end date given)			(44)
37	II	9/1 (10)	Stage III NSCLC	Paclitaxel + carboplatin	YES, TRT	NO	RR (PR)	PFS	Paclitaxel: NK Carboplatin: NK	Sept 2013	Jan 2014	4	(45)
38	II	17/25 (42)	EGFR mutant, Stage IIIB/IV NSCLC	Gefitinib+ bevacizumab	NO	NO	PFS	OS, RR	Gefitinib: NO Bevacizumab NK	Oct 2010	April 2012	18	(46)
39	II	46/21 (67)	Metastatic Stage IV NSCLC	Bevacizumab + + carboplatin paclitaxel, + or bevacizumab erlotinib	NO	NO	6MPFS	OS, RR	Bevacizumab NK Carboplatin: NK Paclitaxel: NK Erlotinib: YES	April 2009	April 2011	24	(47)
40	II	29/21 (50)	Recurrent/Metastatic NSCLC	Patupilone	NO	NO	3MPFS	PD, OS	NK	Nov 2005	July 2009	44	(48)
41	II	43/57 (100)	Stage IIIB/IV NSCLC	Pemetrexed + gemcitabine versus carboplatin +gemcitabine	NO	NO	OS	DOR, TTP	Pemetrexed: YES Gemcitabine: NO Carboplatin: NK	(No dates given)			(49)
42	I/II	10/27 (37)	EGFR-mutant, Stage IV LC	Luminespib + Erlotinib	NO	NO	MTD (Phase 1) OR (CR, PR) (Phase 2)	PFS	Luminespib: NK Erlotinib: YES	(No dates given)			(50)
43	II	38/10 (48)	Stage III NSCLC	Endostar + Docetaxel or Cisplatin	NO	NO	PFS	OS, RR	Endostar: YES Docetaxel: NO Cisplatin: NK	May 2009	Dec 2013	54	(51)
44	II	77/13 (90)	EGFR-wt Stage IIIB/IV NSCLC	Paclitaxel/carboplatin + gefitinib versus paclitaxel/carboplatin alone	NO	NO	RR (CR,PR)	PFS, OS	Paclitaxel: NK Carboplatin: NK Gefitinib: NO	April 2010	Dec 2011	20	(52)
45	II	40/ 23 (63)	PI3K Pathway-Activated NSCLC	Buparlisib	NO	NO	PFS	OS, RR (PR), DCR, TTR, DOR	NK	Sept 2013	June 2014	9	(53)

Table 1. CONT.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference or ClinicalTrials ID
46	II	40/32 (72)	Stage IIIB/ IV NSCLC	Apricoxib + either docetaxel or pemetrexed	NO	NO	PFS	OS, RR, DOR	Apricoxib: NK Docetaxel: NO Pemetrexed: YES	Nov 2008	Dec 2014	73	(54)
47	II	18/21 (39)	Stage IV NSCLC	Erlotinib	NO	Fluorodeoxyglucose-/ Fluorothymidine-Positron Emission Tomograph (FDG-/FLT-PET)	-	-	YES	Oct 2007	Dec 2009	26	(55)
48	II	126/98 (224)	Stage IIIB/IV NSCLC	Erlotinib +bevacizumab versus cisplatin + gemcitabine + bevacizumab	NO	NO	PFS	OS, RR	Erlotinib: YES Bevacizumab NK Cisplatin: NK Gemcitabine: NO	Nov 2007	Aug 2009	21	(56)
49	II	41/42 (83)	KRAS-mutant Stage III/IV NSCLC	Docetaxel+ Selumetinib	NO	NO	OS, PFS, RR		Selumetinib:NK Docetaxel: NO	April 2009	May 2011	25	(57)
50	II	34/4 (38)	Stage IIIB/IV NSCLC	Axitinib + cisplatin/ gemcitabine regimen	NO	NO	RR (CR,PR)	PFS, OS, DOR	Axitinib: YES Cisplatin: NK Gemcitabine: NO	Dec 2008	Nov 2011	35	(58)
												Average duration: 35.5 months	

Type of Cancer: SCLC=Small Cell Lung Cancer; NSCLC=Non-Small Cell Lung Cancer; LC=Lung Cancer; Endpoints: PFS=Progression Free Survival; OS=Median Overall Survival; RR=Objective Response Rate; CR=Complete Response; PR=Partial Response; 12MS=12-Month Overall Survival; 2YR PFS= Two Year Progression Free Survival; 6/3MPFS= Six Month/ Three Month Progression Free Survival; MTD=Maximum Tolerated Dose; TT=Treatment Tolerability; DCR=Disease Control Rate; CB>12=Clinical Benefit (Disease response and disease stabilization >12 weeks); MST=Median Survival Time; HRQoL=Health-Related Quality of Life; QoL= Quality of Life; TTP=Time to Progression; SD=Stable Disease; DOR=Duration of Response; RFS=Relapse Free Survival; ORR= Objective Remission Rate; 1YRSR=1-Year Survival Rate; PD=Progressive Disease; TTR= Time to Response; PF12=Disease Progression-Free Rate at 12 weeks; Other abbreviations: PT=Patient; RT=Radiation Therapy; LCSC=Lung Cancer Stem Cell; NK=Not Known; EGFR-wt= epidermal growth factor receptor wild-type; KRAS=V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; EGFR FISH= epidermal growth factor receptor Fluorescence In-Situ Hybridization; RT: HypoTRT= Hypofractionated Thoracic Radiation Therapy; TRT=Thoracic Radiation Therapy.

Table 2. Initial data collection for phase II lung cancer studies published in 2004. Each study was given a number (column 1). The second column lists the phase at which the clinical trial was completed (mostly phase II, but occasionally researchers will complete multiple phases at once). The patient "PT m/f ratio" column signifies the ratio of male to female patients who participated in the clinical trials. Column four denotes the type or stage of small cell lung cancer. Columns five and six identify whether radiation therapy or another type of intervention was utilized to treat the patients' cancer. The "Endpoints" column serves to identify what the study measured (MOS, OS-6, etc. (see abbreviations)), the "LSCS" column identifies whether the study considered the presence of lung cancer stem cells in its methodology, and the final columns, "Start Date," "End Date," "Duration (in months)" and "Reference," are self-explanatory.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference
1	II	24/16 (40)	Advanced Stage SCLC	Docetaxel + gemcitabine	NO	NO	RR (PR)	OS, SD	Docetaxel: NO Gemcitabine: NO	July 2000	June 2002	23	(59)
2	II	29/11 (40)	Sensitive Relapsed SCLC	Irinotecan + Cisplatin/ Etoposide regimen	NO	NO	RR (CR, PR)	PD	Irinotecan: NK Cisplatin: NK Etoposide: NK	Oct 1998	March 2001	29	(60)
3	II	11/11 (22)	Relapsed SCLC	tipifarnib	NO	NO	RR	TTP, OS	NK	Jun 1999	Nov 2000	17	(61)
4	II	(32)	Extensive Stage SCLC	Topotecan+ Paclitaxel	NO	Prophylactic granulocyte colony-stimulating factor	PR, CR	SD, PD	Topotecan: NO Paclitaxel: NK	Jan 1995	Aug 1999	55	(62)
5	II	(42)	Extensive Stage SCLC	Topotecan+ cyclophosphamide	NO	NO	OTR, TTP, OS	SD	Topotecan: NO VAC: NK	(No dates given)			(63)
6	II	39/48 (87)	Limited Stage SCLC	Cisplatin + etoposide	YES	NO	RR (CR,PR), OS, PFS		Cisplatin: NK Etoposide: NK	July 1998	Aug 1999	13	(64)
7	II	39/38 (77)	Extensive Stage SCLC	Paclitaxel+ carboplatin	NO	NO	1YRSR	OS, RR, DOR, TTP	Paclitaxel: NK Carboplatin: NK	July 2000	Dec 2001	17	(65)
8	II	34/35 (69)	Extensive Stage SCLC	Carboplatin + gemcitabine	NO	NO	RR	SD, PD, TTP, DOR, 1YRSR	Carboplatin: NK Gemcitabine: NO	Aug 2000	Feb 2002	18	(66)
9	II	(31)	Limited or Extensive Stage SCLC	Irinotecan + gemcitabine	NO	NO	RR (PR)	TTP, DOR	Irinotecan: NK Gemcitabine: NO	(No dates given)			(67)
10	I/II	18/2 (20)	Stage IIIA/IIIB NSCLC	Paclitaxel + nedaplatin	YES, TRT	NO	MTD	CR, PR, SD, PD, OS, PFS	Paclitaxel: NK Nedaplatin: NK				
11	II	134/ 13 (147)	Advanced NSCLC	Irinotecan + gemcitabine versus Irinotecan alone	NO	NO	OS	RR, OTR, DOR, TTP, TT, QoL	Irinotecan: NK Gemcitabine: NO	Aug. 1999	April 2002	32	(69)
12	II	41/14 (55)	Stage IIIB/ IV NSCLC	S-1 + cisplatin	NO	NO	RR (CR, PR)	OS	S-1: NK Cisplatin: NK	Sept. 2000	Nov. 2001	14	(70)
13	I/II	Phase I: 10/8 (18) Phase II: 16/4 (20)	Stage IIB/IV NSCLC	Cisplatin + paclitaxel	NO	NO	MTD, RD	RR (CR, PR), PFS, OS, 1YRSR	Cisplatin: NK Paclitaxel: NK	Phase I: July 2000 Phase II: April 2001	Phase I: Feb. 2001 Phase II: Dec. 2001	Phase I: 7 Phase II: 8	(71)
14	II	57/13 (70)	Stage III NSCLC	Uracil/tegafur + cisplatin	NO	NO	RR	OS	Uracil/Tegafur: NK Cisplatin: NK	May 1999	March 2001	22	(72)

Table 2. CONT.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference
15	I/II	25/19 (44)	Stage IIIB/IV NSCLC	Affinitak + gemcitabine/ cisplatin regimen	NO	NO	RR (CR, PR)	ST, DOR, TTP, OS	Affinitak: NK Gemcitabine: NO Cisplatin: NK	(No dates given)			(73)
16	II	(140)	Stage IIIB/IV	Paclitaxel or Vinorelbine +Cisplatin	NO	NO	RR, OS, TTP, ST		Paclitaxel: NK Vinorelbine: YES Cisplatin: NK	Oct 2000	May 2002	19	(74)
17	II	75/33 (108)	Stage IIIB/IV NSCLC	Docetaxel/Cisplatin versus Docetaxel/ Irinotecan	NO	NO	CR, PR, PD, DOR	OS, PFS	Docetaxel: NO Cisplatin: NK Irinotecan: NK	Oct 1998	Aug 1999	10	(75)
18	II	114/64 (178)	Stage IIIB/IV NSCLC	Carboplatin/ Gemcitabine followed by paclitaxel, or Cisplatin/ Vinorelbine followed by docetaxel	NO	NO	PFS	RR (CR, PR), SD, PD, TTP	Carboplatin: NK Gemcitabine: NO Paclitaxel: NK Cisplatin: NK Vinorelbine: YES Docetaxel: NO	(No dates given)			(76)
19	II	26/10 (36)	Stage IIIB/IV NSCLC	Docetaxel	NO	NO	PFS	RR	NO	Jan 1999	April 2000	15	(77)
20	I/II	34/10 (44)	Stage IIIB/IV NSCLC	Cisplatin + Vinorelbine	NO	NO	TTP, OS	IYRSR, 2YRSR, OS, RR	Cisplatin: NK Vinorelbine: YES	July 1996	June 1998	22	15456520 (78)
21	II	(50)	Stage IIIA/IIIB NSCLC	Gemcitabine + Cisplatin	NO	NO	PR, SD, PD		Gemcitabine: NO Cisplatin: NK	(No dates given)			(79)
22	II	31/3 (34)	Advanced/ Metastatic NSCLC	Paclitaxel + Gemcitabine	NO	NO	PR, SD, PD	TTP, OS, 1YRSR	Paclitaxel: NK Gemcitabine: NO	June 1999	June 2002	36	(80)
23	II	(33)	Advanced NSCLC	Cisplatin + Docetaxel	NO	NO	RR (CR, PR)	1YRSR	Cisplatin: NK Docetaxel: NO	Feb 2000	March 2002	25	(81)
24	II	38/22 (60)	Stage III/IV NSCLC	Pemetrexed + Gemcitabine	NO	NO	RR	SD, OS, PFS, DOR, 1YRSR, 2YRSR	Pemetrexed: YES Gemcitabine: NO	Aug 1999	May 2001	17	(82)
25	II	16/9 (25)	Stage IIIB/IV NSCLC	Docetaxel + Carboplatin	NO	NO	PR, CR, SD, PD	OS	Docetaxel: NO Carboplatin: NK	July 1997	July 1999	24	(83)
26	II	(75)	Stage IIIB/IV NSCLC	BMS-275291 + paclitaxel/ carboplatin regimen	NO	NO	RR		BMS-275291: NK Paclitaxel: NK Carboplatin: NK	(No dates given)		(84)	
27	II	32/13 (45)	Stage IIIB/IV	Tirapazamine +	NO	NO	RR, PFS, OS	1YRSR	Tirapazamine: YES	April 2002	July 2002	3	(85)

Table 2. CONT.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference
			NSCLC	cisplatin + gemcitabine					Cisplatin: NK Gemcitabine: NO				
28	I/II	(30)	Limited Stage SCLC	Tirapazamine + Cisplatin/Etoposide	YES; TRT	NO	RR (CR, PR), SD, PD		Tirapazamine: YES Cisplatin: NK Etoposide: NK	Dec 2000	Sept 2001	9	(86)
29	I/II	17/3 (20)	Advanced/ Metastatic NSCLC	Nedaplatin + Gemcitabine	NO	NO	MTD	RD	Nedaplatin: NK Gemcitabine: NO	Aug 2001	Feb 2003	18	(87)
30	II	30/10 (40)	Stage IIIB/IV NSCLC	Docetaxel + Ifosfamide	NO	NO	DOR, TTP, PD	OS, RR	Docetaxel: NO Ifosfamide: NK	July 2000	July 2004	48	(88)
31	II	(18)	Stage IIIB/IV NSCLC	Endostar + Vinorelbine/ Cisplatin regimen	NO	NO	OS, TTP, QoL	SD	Endostatin: YES Vinorelbine: YES Cisplatin: NK	Sept 2002	April 2003	7	(89)
32	II	18/2 (20)	Stage III NSCLC	Paclitaxel+ Cisplatin	YES; TRT	NO	RR, TTP	OS, DOR	Paclitaxel: NK Cisplatin: NK	Feb 2000	Dec 2002	34	(90)
33	II	30/14 (44)	Stage IIIB/IV NSCLC	Gemcitabine + Cisplatin	NO	NO	RR, TTP, OS	SD	Gemcitabine: NO Cisplatin: NK	Feb 2001	Oct 2002	32	(91)
34	I/II	7/18 (25)	Metastatic LC	9-nitrocamptothecin	NO	NO	SD, PR	RD	NK	(No dates given)		(92)	
35	II	53/7 (60)	Stage IIIB/IV NSCLC	Gemcitabine + Cisplatin	NO	NO	RR (CR,PR)	TTP, OS, IYRSR	Gemcitabine: NO Cisplatin: NK	Aug 1997	Aug 2001	48	(93)
36	II	20/4 (24)	Stage IIIB/IV NSCLC	Gemcitabine + Epirubicin	NO	Amifostine			Gemcitabine: NO Epirubicin: NK Amifostine:NO	Dec 2000	April 2002	16	(94)
37	II	22/2 (24)	Stage III NSCLC	Vinorelbine + Cisplatin	YES; RT	NO	PF, OS, 1YRSR, 2YRSR	RR (CR,PR), SD, PD	Vinorelbine: YES Cisplatin: NK	Oct 2000	Sept 2002	23	(95)
38	II	(56)	Localized/ Metastatic NSCLC	Vinorelbine + Cisplatin followed by Vinorelbine	NO	NO	RR	PFS, OS	Vinorelbine: YES Cisplatin: NK	April 2001	April 2002	12	(96)
39	II	(56)	Stage III NSCLC	Cisplatin	YES; TRT	NO	2YRSR, 3YRSR		NK	April 1995	March 2002	83	(97)
40	II	21/6 (27)	Stage IIIB/IV NSCLC	Paclitaxel + Gemcitabine	NO	NO	SD, PD	OS, PFS	Paclitaxel: NK Gemcitabine: NO	Oct 2001	Aug 2002	10	(98)
41	II	60/39 (99)	Stage IIIB/IV NSCLC	Bevacizumab + carboplatin + paclitaxel, or carboplatin + paclitaxel alone	NO	NO	TTP, RR	OS, DOR	Carboplatin: NK Paclitaxel: NK Bevacizumab: NK	(No dates given)		(99)	
42	II	183/37 (220)	Stage IIIB/IV	Docetaxel	NO	NO	QoL	OS	NO	Dec 2000	Aug 2002	20	(100)

Table 2. CONT.

Study #	Phase	PT m/f ratio (Total)	Type of Cancer	Drug(s)	RT	Other Intervention	Primary Endpoints	Secondary Endpoints (if applicable)	LCSC	Start Date	End Date	Duration (months)	Reference
43	II	236/28 (264)	NSCLC Stage IIIB/IV NSCLC	Gemcitabine + Paclitaxel or Vinorelbine, versus Paclitaxel or gemcitabine alone	NO	NO	1YRSR	RR (PR)	Gemcitabine: NO Paclitaxel: NK Vinorelbine: YES	May 1999	March 2003	46	(101)
44	II	33/7 (40)	Stage III/IV NSCLC	Gefitinib	NO	NO	RR (CR,PR)	SD, DOR, DCR, TTP	NO	Aug 2001	May 2003	33	(102)
45	II	68/16 (84)	Limited and Extensive Stage SCLC	Cyclophosphamide + epirubicin + vincristine	NO	Low-molecular weight heparin (w/ or w/o)	CR, PR, SD, PD	PFS, OS	VAC: NK Vincristine: NK Epirubicin: NK LMWH: YES	Dec 1998	Sept 2001	33	(103)
46	II	65/10 (75)	Stage III/IV NSCLC	Cisplatin + Vinorelbine	NO	NO	QoL	CR, PR, SD, PD, TTP, OS	Vinorelbine: YES Cisplatin: NK	Jan 1994	Oct 2001	81	(104)
47	II	18/13 (31)	Metastatic NSCLC	Gefitinib	NO	NO	QoL	CR,PR,SD, PD,PFS,OS	NO	Oct 2002	Oct 2003	1	(105)
48	II	16/9 (25)	Stage IIIB/IV NSCLC	Paclitaxel + Carboplatin	NO	NO	RR, PR, SD, PD		Paclitaxel: NK Carboplatin: NK	(No dates given)			(106)
49	II	(37)	Stage IIIB/IV NSCLC	Irinotecan + Carboplatin	NO	NO	RR (PR), PD, SD	1YRSR	Irinotecan: NK Carboplatin: NK	(No dates given)			(107)
50	II	30/20 (50)	Stage III/IV NSCLC	Vinorelbine + Gemcitabine	NO	NO	PR, CR, SD, PD	TTP, OS, IYRSR	Gemcitabine: NO Vinorelbine: YES	April 2000	Sept 2000	5	(108)
												Average Duration: 25 months	

Type of Cancer: SCLC=Small Cell Lung Cancer; NSCLC=Non-Small Cell Lung Cancer; LC=Lung Cancer; Endpoints: PFS=Progression Free Survival; OS= Median Overall Survival; RR=Objective Response Rate; CR=Complete Response; PR=Partial Response; 6MOPFS= 6-Month Progression Free Survival MTD=Maximum Tolerated Dose; TT=Treatment Tolerability; DCR=Disease Control Rate; QoL= Quality of Life; TTP=Time to Progression; SD=Stable Disease; DOR=Duration of Response; PD=Progressive Disease; OTR=Objective Tumor Response; 1(2)(3)YRSR=1(2)(3)-Year Survival Rate: RD= Recommended dose; ST= Survival Time; Other abbreviations: PT=Patient; RT=Radiation Therapy; LCSC=Lung Cancer Stem Cell; HypTRT= Hyperfractionated Thoracic Radiation Therapy.

Table 3. Drug Characterization. Any alternative names for each drug were identified and recorded. The type of drug was recorded in the second column. Whether the drug targets LCSCs was recorded in column three.. References are included in order to elaborate on the answers placed in the "Targets LCSC" column.

Drug	Drug Type	Targets LCSC	Reference/ Pubmed ID
Docetaxel (Taxotere, Docecad)	mitotic inhibitor	NO	(109), (110)
Ganetespib (STA-9090)	HSP90 inhibitor	NK, Targets TNBC	(111)
Amrubicin (SM-5887)	Anthracycline antibiotic	NK	(No relevant articles)
Bortezomib(VELCADE®, PS-341)	proteasome inhibitor	NK, Targets AML Stem Cells	(112)
Paclitaxel (Taxol, Onxal, Abraxane)	Vinca (plant) alkaloid	NK, Used to target BCSC	(113)
Carboplatin (Paraplatin)	platinum-based antineoplastic	NK, Used to target OCSC	(114)
Erlotinib (Tarceva)	Tyrosine kinase inhibitor (acts on epidermal growth factor receptor)	YES	(115), (116)
Celecoxib (Celebrex)	COX-2 selective nonsteroidal anti-inflammatory drug (NSAID)	NK, Targets BCSC	(117)
Vinorelbine (NVB, Navelbine)	Vinca (plant) alkaloid	YES	(118)
Imetelstat (GRN163L)	Telomerase inhibitor	NK, Targets BCSC, PrCSC and PCSC	(119), (120)
Bevacizumab (Avastin)	Recombinant umanoid antibody (specifically, an angiogenesis inhibitor)	NK, Targets MCSC	(121)
Sunitinib (Sutent, SU11248)	Tyrosine Kinase Inhibitor	NK, Targets RCSC and PrCSC	(122), (123)
Gefitinib (Iressa®)	Tyrosine kinase inhibitor (acts on epidermal growth factor receptor)	NO	(124), (125)
Vorinostat (IVORI, SAHA)	HDI--HDAC Inhibitor (Histone Deacetylase Inhibitor),	YES	(126)
Disulfiram (Antabuse)	Acetaldehyde Dehydrogenase Inhibitor	YES	(127)
Cisplatin (Platinol)	platinum-based alkylating antineoplastic	NK, Targets PrCSC	(128)
Trametinib (GSK1120212)	selective allosteric inhibitor of MEK1/MEK2	NK	(No relevant articles)
Rociletinib (CO-1686, AVL-CO1)	Mutant-selective tyrosine kinase inhibitor (acts on epidermal growth factor receptor)	NK	(No relevant articles)
S-1 (Teysuno) *Combination of Tegafur/gimeracil/oteracil)	Fluorouracil antitumor drug	NK	(No relevant articles)
Afatinib (Gilotrif)	Tyrosine kinase inhibitor (acts on epidermal growth factor receptor)	NO	(129)
Irinotecan (Campto, CPT-11)	DNA topoisomerase I inhibitor	NK, targets CRC-SCs	(130)
Pemetrexed (Alimta, LY231514)	Folate Antagonist (Folate Analog Metabolic Inhibitor)	YES	(131), (132)
Nitroglycerin (NTG)	hypoxia-inducible-factor (HIF)-1 inhibitor	NK	(No relevant articles)
Cilengitide (EMD 121974)	cyclic RGD pentapeptide, and αvβ3 and αvβ5 integrin inhibitor	NK, Targets PCSCs	(133)
Cetuximab (Erbitux)	epidermal growth factor receptor inhibitor	NK, Targets TNBC-SCs and Glioblastoma SCs	(134), (135)
Topotecan (Hycamtin)	DNA topoisomerase I inhibitor	NO, Targets GSCs	(136), (137)
Cabazitaxel (Jetvana)	Anti-microtubule agent (mitotic inhibitor)	NK	(No relevant articles)
Doxorubicin (Adriamycin, Rubex)	Anthracycline antibiotic	NK, may be used to target BCSCs when encapsulated in chitosan-decorated nanoparticles	(138)
Vindesine (Eldisine)	Vinca (plant) alkaloid	NK	(No relevant articles)
Cyclophosphamide (Cytoxan, Endoxan, Neosar, Procytox, Revimmune, Cycloblastin)	Alkylating agent	NK, may be used to target BCSCs when used in combination therapy	(139)
Valproic Acid	Anticonvulsant	NK, Targets HNSCC CSCs	(140)
Gemcitabine (Gemzar)	Antimetabolite	NO, Targets PCSCs	(141), (142)
Etoposide (Toposar, VePesid, Etopophos, VP-16)	Vinca (plant) alkaloid, topoisomerase II inhibitor	NK, Targets MCSCs	(121)
Endostar (Endostatin, YH-16)	recombinant human endostatin (anti-angiogenic agent)	YES	(143)

Table 3. CONT.

Drug	Drug Type	Targets LCSC	Reference/Pubmed ID
Tipifarnib (Zarnestra, R115777)	farnesyl transferase inhibitor	NK, may be used to target CD34+ /CD38- subset of AML cells when used in combination with Gemtuzumab ozogamicin (Mylotarg)	(144)
Lomustine (CeeNU®, CCNU)	Alkylating agent	NK	(No relevant articles)
Vincristine (leurocristine, Oncovin)	Vinca (plant) alkaloid, Antileukemic drug	NK	(No relevant articles)
Prophylactic granulocyte colony-stimulating factor	Glycoprotein	NK; has been used in a vaccine against bladder cancer, but may also contribute to the development of glioma	(145), (146)
Pegfilgrastim (Neulesta)	granulocyte colony-stimulating factor	NK	(No relevant studies)
Linsitinib (OSI-906, ASP7487)	Small molecule inhibitor of insulin receptor and IGF-1 receptor kinases	NK, treats Osteosarcoma	(147)
Vandetanib (ZD6474, Caprelsa)	Tyrosine kinase inhibitor (acts on epidermal growth factor receptor)	NK, increased number of CSCs in salivary gland cancer cell line; vandetanib is not restricted by ABCG2, an element characteristically augmented in CSCs	(148), (149)
Pazopanib (Votrient)	Multi-target tyrosine kinase inhibitor	NK, has negligible effects on Sarcoma CSCs	(150)
Temozolomide	Alkylating agent	NK	(151)
Patupilone (EPO906)	epothilone B	NK, produces growth inhibition and/or tumor regression in lung, breast, colon, and prostate cancers	(152)
Luminespib (AUY-922, INN, NVP-AUY922)	HSP90 inhibitor	NK	(No relevant articles)
Buparlisib (NVP-BKM120)	PI3K inhibitor	NK, Inhibits LC growth when used in combination with RAD001 (a protein kinase inhibitor), and targets BCSCs	(153), (154)
Apricoxib (CS-706)	COX-2 Inhibitor	NK	(No relevant articles)
Axitinib (Inlyta®)	Tyrosine kinase inhibitor (acts on epidermal growth factor receptor)	YES	(155)
Nedaplatin (Aqupla, Latoplatin, 254-S)	platinum-based antineoplastic	NK, exhibits antitumor effects against LC	(156), (157)
Tegafur/Uracil (UFT, Uftoral)	fluorouracil prodrug	NK; metformin synergizes tegafur/uracil in combination with other drugs to target BCSC	(Soo et al., 2015)
Aflibercept (Zaltrap, Eylea)	vascular endothelial growth factor (VEGF) inhibitor	NK	(No relevant articles)
Affinitak (LY900003, ISIS 3521)	Antisense Inhibitor of Protein Kinase C-α -	NK	(No relevant articles)
BMS-275291	matrix metalloproteina1se (MMP) inhibitor2	NK	(No relevant articles)
Tirapazamine (SR-4233, Tirazone)	hypoxia-selective 1cytotoxin	YES	(158)
Ifosfamide (Mitoxana)	Alkylating agent1	NK	(No relevant articles)
9-nitrocamptothecin (RFS-2000)	Topoisomerase I i-nhibitor	NK, enhances the effects of radiation in H460	(159)
Amifostine (WR-1065, Ethyol)	cytoprotective adjuvant	NO; not used to treat cancer, but to reduce toxicity of chemotherapeutic agents	(160)
Epirubicin	Anthracycline drug	NK; metformin synergizes tegafur/uracil in combination with other drugs to target BCSC	(Soo et al., 2015)
Low-molecular weight heparin	Anticoagulant	YES	(161)
Selumetinib	Mitogen-activated protein kinase inhibitor	NK, treats TNBC	(162)

LCSC=Lung Cancer Stem Cell; NK=Not Known; TNBC (-SCs)=Triple Negative Breast Cancer (-Stem Cells); AML= acute myeloid leukemia; BCSCs=Breast Cancer Stem Cells; OCSC= Ovarian Cancer Stem Cells; PrCSC=Prostate Cancer Stem Cells; PCSC= Pancreatic Cancer Stem Cells; MCSC= Melanoma Cancer Stem Cells; RCSC=Renal Cancer Stem Cells; CRC-SCs=Colorectal Cancer Stem Cells, GSC=Glioma Stem Cells; HNSCC CSCs= Head and Neck Squamous Cell Carcinoma Cancer Stem Cells.