Title: Systematic Literature Review of the Prevalence and Prognostic Value of Delta-Like Ligand 3 Protein Expression in Small Cell Lung Cancer

Journal: Targeted Oncology

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Additional file 1. Search Strategy.

Term	PubMed
Study population	
SCLC	carcinoma, small cell lung[MeSH Terms] OR small cell lung cancer OR SCLC
Exposure	
DLL3	DLL3 protein, human[MeSH Terms] OR delta-like ligand 3 OR DLL3 OR delta-like protein 3
Comparator	
N/A	
Outcome	
DLL3 Expression/Positivity	Express* OR positiv*
Prognostic Impact	Response OR survival OR progress* OR prognos*
Study type	
Observational studies, clinical trials, cases series with n≥20 patients	*
Inclusion criteria	
English language	Eng[la]

*Specific terms for study type not included to avoid accidental exclusion of studies not categorized under these terms.

Additional file 2. Conversion of Newcastle Ottawa Scale Scores to Agency for Healthcare Research and Quality (AHRQ) Standards.

Quality Rating	**Threshold**
Cohort and Case-Control Studies	
Good	3 or 4 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in outcome/exposure domain
Fair	2 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in outcome/exposure domain
Poor	0 or 1 points in selection domain OR 0 points in comparability domain OR 0 or 1 points in outcome/exposure domain
Cross-Sectional Studies	
Good	2 points in selection domain AND 1 or 2 points in comparability domain AND 2 points in outcome/exposure domain
Fair	1 point in selection domain AND 0 or 1 points in comparability domain AND 1 point in outcome/exposure domain
Poor	0 points in selection domain OR 0 points in outcome/exposure domain

Additional file 3. Study Characteristics of Included Studies, by SP347 Assays and Non-SP347 Assays (N=30 studies).

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
SP347 Assay Studies															
Ali, 2021[15]	Retrospective cohort	Italy (2007-2019)	32	78.1 %	NR	Never: 0% Current: 28.1% Former: 71.9%	NR	Limited: 100% I: 31.2% II: 34.4% III: 34.4% IV: 0%	NR	100% surgical resection; no neoadjuvant chemotherapy or radiation	NR	IHC (Ventana SP347, NR)	High: ≥50% Low: <50% H-Score: High: ≥150 Low: <150	Prevalence	Good
Brcic, 2019[16]	Cross-sectional	Germany (1996-2012)	24	NR	NR	NR	NR	NR	NR	Chemo-naive	Chemo-naive	IHC (Ventana, SP347, NR)	High: ≥50% Positive: : ≥25% Cut-offs at 25, 50, and 75%	Prevalence	Fair
Furuta, 2019[17]	Retrospective cohort	Japan (2003-2013)	95	77.9 %	NR	Never: 7.4% Current or former: 85.2% Unknown: 7.4%	0: 63.2% 1: 29.5% Unknown: 7.4%	I: 74.7% II: 13.7% III: 11.6%	NR	100% surgical resection Adjuvant chemotherapy: 63.2%	NR	IHC (Ventana, SP347, 4X)	High: ≥75% Low: <75%	Prevalence Survival	Poor

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
Huang, 2019b[24]	Cross-sectional	United States (NR)	1362	NR	NR	NR	NR	NR	NR	NR	NR	IHC (Ventana SP347, NR)	NR	Prevalence	Fair
Johnson, 2021[18]	Randomized controlled trial, Phase III (MERU; NCT03033511)	Multi-country (2017-2019)	748 (372 intervention; 376 placebo)	Overall: 66.4 Intervention: 69.4 % Placebo: 63.6 %	Overall: White: 82.2% Black or African American: 1.2% Asian: 16.2% American Indian or Alaska Native: 0.3% Multiple races: 0.1%	NR	Status: Intervention/Placebo 0: 39.0/40.0 % 1: 60.0/60.0 % Missing: 1.0/1.0%	Stage: Intervention/Placebo IA: 0.0%/0.3% IIB: 0.3/0.0 % IIIA: 1.0/1.0 % IIIB: 7.0/4.0 % IV: 77.0/78.0% Missing: 16.0/16.0%	History of brain metastases- Intervention: 15.0% Placebo: 15.0%	4 cycles of first-line platinum-based chemotherapy	Maintenance post 1L therapy	IHC (Ventana SP347, NR)	High: ≥75% Low: <75%	Prevalence Response Survival	High risk

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
Kuempers, 2021[10]	Retrospective cohort	Germany (NR)	42	64.3 %	NR	NR	NR	NR	NR	Platin-based chemotherapy	NR	IHC (Ventana SP347, NR)	High (≥50%) Low (<50%) Positive: ≥1% Cut-offs included 0, 1-49, and 50+% H-Score: High: ≥150 Low: <150	Prevalence Survival	Poor
Messaritakis, 2019[19]	Prospective cohort	Greece (NR)	108	84.3 %	NR	NR	NR	Limited: 34.3% Extensive: 65.7%	Liver metastases: 37.0% CNS metastases: 11.1% Bone metastases: 29.6%	NR	1	IHC (Ventana SP347, 20x and 4x)	High: ≥50% Low: <50%	Prevalence	Good

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
Morgenszt ern, 2019[20]	Single-arm clinical trial, Phase II (TRINITY; NCT02674568)	Multi-country (2016-2017)	339	50%	NR	NR	0: 22.0% 1: 77.0% 2: 1.0%	IA: 2.0% IB: 1.0% IIA: 2.0% IIB: 1.0% IIIA: 11.0% IIIB: 13.0% IV: 66.0% Missing: 1.0%	Brain metastases: 40.0% Pleural effusions: 25.0%	Prior therapies (#)- 2: 77.0% 3: 15.0% >3: 8.0% Prior therapies - Platinum - containing: 100.0% Topotecan: 39.0% PD-1 inhibitor: 17.0% Other: 44.0%	3+	IHC (Ventana SP347, NR)	High: ≥75% Low: <75% Positive: ≥25%	Prevalence Response Survival	Some concerns
Odashiro, 2020[21]	Cross-sectional	Canada (NR)	39	NR	NR	NR	NR	NR	NR	NR	NR	IHC (Ventana SP347, NR)	Cut-offs were <1, 1-49, 50-74, and >75%	Prevalence	Fair
Rojo, 2020[6]	Retrospective cohort	Multi-country (2008-2017)	1073	64.0 %	NR	Never: 7.0% Current: 57.0% Former: 32.0%	0: 25.0% 1: 37.0% 2: 15.0% 3: 7.0% 4: 1.0%	Limited: 32.0% Extensive: 63.0%	64.0%	Highest line received- None: 22.0% 1: 42.0%	1+	IHC (Ventana SP347, 4x)	High positive: ≥75% Non-high positive: 25-74%	Prevalence Survival	Good

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
						Unknown: 4.0%	Missing: 16.0%	Missing: 6.0%		2: 23.0% 2+: 14.0%			Positive: ≥25% Negative: 0-24%		
Tendler, 2020[25]	Cross-sectional	Sweden (2008-2015)	46	43%	NR	NR	0: 28.0% 1: 35.0% 2: 28.0% 3: 7.0%	NR	Brain metastases: 60.9%	1st line-Chemotherapy alone: 82.0%	NR	IHC (Ventana SP347, 20x or 40x)	Unclear text	Prevalence Survival	Good
Udagawa, 2019[22]	Single-arm clinical trial, phase I (NCT03086239)	Japan (2017-2018)	29	76%	NR	NR	0: 35.0% 1: 65.0%	NR	CNS metastases: 24.0%	Amrubicin: 100.0% Cisplatin: 72.0% Carboplatin: 52.2% Etoposide: 76.0% Irinotecan: 59.0% Topotecan: 14.0% PD-1 inhibitor: 3.0% Other: 45.0%	3+	IHC (Ventana SP347, NR)	High: ≥75% Low: <75% Positive: ≥25% Negative: <25%	Prevalence Response Survival	Low risk

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
Xie, 2019[23]	Retrospective cohort	United States (1995-2017)	44	43.2 %	NR	NR	NR	NR	32.0%	NR	NR	IHC (Ventana-Roche SP347, 40x)	High: ≥50% Low: <50%	Prevalence Survival	Good
Non-SP347 Assay Studies															
An, 2018[26]	Cross-sectional	Korea (NR)	88	NR	NR	NR	NR	NR	NR	NR	NR	NR (NR, NR)	NR	Prevalence	Fair
Calvo, 2021[27]	Single-arm clinical trial, Phase I (NCT03000257l)	Multi-country (2018-2019)	31	41.9 %	NR	NR	0: 32.3% 1: 67.7%	NR	71.0%	Prior therapies - Cisplatin: 58.1% Carboplatin: 51.6% Etoposide: 80.6% Etoposide + cisplatin: 9.7% Etoposide + carboplatin: 3.2%	2+	IHC (Ventana, NR)	High: ≥75% Low: <75%	Prevalence Response	Low risk
Fu, 2020[28]	Retrospective cohort	China (2011-2018)	43	81.4 %	NR	Current or former: 62.8%	NR	Limited; 100% I: 32.6%	NR	100% surgical resection	NR	IHC (bs-7860R, Bioss, China, NR)	Positive: NR	Prevalence Survival	Poor

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
								II: 53.5% III: 14.0%							
Goldman, 2021[29]	Single-arm clinical trial, Phase I (NCT02874664)	United States & Canada (2016-2018)	46	39%	NR	Never: 4.0% Current: 17.0% Former: 78.0%	0: 26.0% 1: 70.0% 2: 4.0%	NR	NR	Platinum-containing therapy: 100.0% Topotecan: 15.0% Immunotherapy: 52.0%	2+	NR (NR, NR)	High: ≥75% Low: <75% Positive: ≥25%	Prevalence	Low risk
Hu, 2022[41]	Retrospective cohort	China (2005-2016)	247	70.9 %	NR	History of smoking: 64.0%	NR	I: 31.6% II: 27.5% III: 40.9%	NR	NR	NR	IHC (E3J5R, Cell Signal Technology, NR)	NR	Prevalence Survival	Poor
Huang, 2019a[36]	Retrospective cohort	China (2010-2017)	72	NR	NR	NR	NR	NR	NR	Chemo-naive	1	IHC (ab103102, Abcam, USA, NR)	NR	Prevalence Response Survival	Poor
Li, 2022[30]	Prospective cohort	China (2012-2016)	134	85.1 %	NR	Heavy smoking: 66.4% Moderate	NR	IA: 21.6% IB: 11.9% IIA: 8.2%	NR	NR	NR	IHC (ab103102, Abcam, USA, NR)	Positive (≥1%) Negative (<1%)	Prevalence Survival	Poor

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
						smoking: 6.7% Light smoking: 3.0% Non-smoking: 23.9%		IIB: 14.9% IIIA: 35.8% IIIB: 3.7% IV: 3.7%					Cut-offs were <1, 1-60, and >60%		
Lim, 2019[37]	Retrospective cohort	Korea (NR)	56	89.1 %	NR	NR	NR	NR	NR	Etoposide and cisplatin: 90.9%	NR	IHC (AbbVie Stemcentrx, NR)	High: ≥50% Low: <50%	Prevalence Survival	Poor
Malhotra, 2021[31]	Non-randomized clinical trial, Phase I-II (NCT02874664)	Multi-country (2017-2019)	42 (30 group 1; 12 group 2)	Group 1: 53.3 % Group 2: 58.3 %	White: 92.9% Black: 4.8% Hispanic or Latino: 4.8% Not Hispanic or Latino: 92.9% NR: 2.4%	NR	0: 26.2% 1: 73.7%	NR	69.0%	Previous therapies - 1: 57.1% 2: 31.0% 3: 7.1% >3: 4.8%	2+	IHC (NR, NR)	High: ≥75% Low: <75%	Prevalence	Some concerns
Obermayr, 2019[42]	Retrospective cohort	Austria (NR)	48	62.5 %	NR	Never: 2.1% Current: 27.1%	NR	III: 11.4% IV: 88.6%	NR	NR	NR	RT-PCR (TaqMan)	NR	Prevalence Survival	Poor

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
						Former: 54.2% Unknown: 16.7%		Unknown: 27.1%							
Prieto, 2021[38]	Cross-sectional	Brazil (NR)	22	63.6 %	NR	Smoker: 90.9% Unknown: 9.1%	NR	I: 8.7% II: 4.3% III: 8.7% IV: 52.2%	NR	NR	NR	NR (NR, NR)	NR	Prevalence	Fair
Regzedma, 2019[32]	Retrospective cohort	China (2009-2014)	38	68.4 %	NR	Never: 31.6% Ever: 68.4%	NR	I-II: 42.1% III-IV: 57.9%	60.5%	Chemo-naive	1	IHC (SAB1302862, Sigma-Aldrich, China, NR)	High: ≥13.5% Low: <13.5%	Prevalence Survival	Good
Roy, 2017[43]	Single-arm clinical trial, Phase I	NR (NR)	58	NR	NR	NR	NR	NR	NR	NR	NR	RT-PCR (NR, NR)	NR	Prevalence	High risk
Rudin, 2017[33]	Non-randomized clinical trial	United States (2013-2015)	74	57%	NR	NR	0: 28.0% 1: 68.0% 2: 4.0%	NR	28.0%	Platinum + etoposide: 96.0% Platinum + another drug: 7.0%	2: 53.0% 3: 47.0%	IHC (Stemcentrx, USA, NR)	High: ≥50% Low: <50%	Prevalence Response Survival	Some concerns

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
										Platinum + etoposide + another drug: 9.0% Topotecan: 11.0% Temozolomide: 14.0% ABT-888: 11.0% Radiation: 82.0% Other: 22.0%					
Saito, 2018[34]	Cross-sectional	Japan (1991-2013)	20	100%	NR	Never: 5.0% Current or former: 95.0%	NR	I: 30.0% II: 5.0% III: 40.0% IV: 25.0%	10.0%	1st treatment - Surgery: 45.0% Chemotherapy only: 25.0% Radiation only: 5.0% Chemotherapy +	2+	IHC (ab103102, Abcam, USA, NR)	High: ≥50% Low: <50%	Prevalence	Fair

Author, Year	Study design (Cohort name or NCT number, if applicable)	Geographic Location (Dates)	N patients	Male sex (%)	Race/ Ethnicity	Smoking Status	ECOG Performance Status	Tumor stage at Diagnosis	% With metastases	Treatment History	Line of Therapy for Current Treatment	DLL3 testing method (assay type, magnification used)	DLL3 positivity threshold (% of tumor cell positivity and/or staining intensity and/or H-score)	Outcomes Reported	AHRQ Quality Score (Observational) or Cochrane RoB (RCT)
										radiation: 20.0% 2nd treatment - Surgery: 5.0% None: 95.0%					
Tanaka, 2018[35]	Cross-sectional	Japan (2012-2016)	63	82.5 %	NR	Never: 4.8% Current or former: 95.2%	NR	Limited: 41.3% Extensive: 58.7%	22.2%	Chemo-naive	NR	IHC (AbbVie Stemcentrx, 20x or 40x)	High: ≥50% Low: <50% Positive: ≥1% Negative: <1%	Prevalence Survival	Good
Yan, 2019[39]	Retrospective cohort	China (2006-2015)	335	91.3 %	NR	Non-smokers (<100 smokers in lifetime): 27.8% Smokers: 72.2%	NR	I: 3.6% II: 5.1% III: 40.6% IV: 50.7%	Distant metastasis: 50.7%	Chemo-naive	NR	IHC (ab103102, Abcam, UK, NR)	H-Score: High: ≥150 Low: <150	Prevalence Survival	Good

ECOG: Eastern Cooperative Oncology Group; IHC: Immunohistochemistry; NR: not reported; RT-PCR: real-time polymerase chain reaction.

Additional file 4. Prevalence of Delta-Like Ligand 3 (DLL3) Expression in Small Cell Lung Cancer (SCLC) Patient Tissue Using Non-SP347 Assays (N=15 studies).*

Author, Year	Study Design (Cohort name or NCT number, if applicable); population inclusion details	Geographic Location (Year)	N Patients (Assay Used)	DLL3 positivity threshold (proportion of positive cells), N (%)		DLL3 Expression (definition), N (%)		H-Score threshold, N (%)
				Positive	Negative	High	Low	
An, 2018[26]	Cross-sectional; SCLC tumor samples	Korea (NR)	88 (NR)	Undefined: 38 (43.2%)	Undefined: 50 (56.8)	NR	NR	NR
Calvo, 2021[27]	Single-arm clinical trial, Phase I (NCT03000257l); progressive SCLC	Multi-country (2018-2019)	24[a] (NR)	≥1%: 22 (91.7)	0%: 2 (8.3)	≥75%: 19 (79.2)	<75%: 3 (12.5)	NR
Fu, 2020[28]	Retrospective cohort; SCLC surgical specimens	China (2011-2018)	43 (bs-7860R, Bioss, China)	Undefined: 28 (65.1)	Undefined: 15 (34.9)	NR	NR	NR
Goldman, 2021[29]	Single-arm clinical trial, Phase I (NCT02874664); previously-treated ES-SCLC patients	United States & Canada (2016-2018)	37[b] (NR)	≥25%: 28 (75.7)	(0-24%): 9 (24.3)	≥75%: 21 (56.8)	<75%: 16 (43.2)	NR
Hu, 2022[41]	Retrospective cohort; SCLC surgical specimens	China (2005-2016)	247 (E3J5R, Cell Signal Technology)	NR	NR	NR	NR	High (undefined): 188 (72.8) Low (undefined): 59 (23.9)
Huang, 2019a[36]	Retrospective cohort; chemo-naïve surgical specimens	China (2010-2017)	72 (ab103102, Abcam, USA)	NR	NR	Undefined [c]: 23 (31.9)	Undefined [c]: 49 (68.1)	NR
Li, 2022[30]	Prospective cohort; SCLC surgical specimens	China (2012-2016)	101[d] (ab103102, Abcam, USA)	≥1%: 87 (86.1)	<1%: 14 (13.9)	>60%: 54 (53.5)	1-60%: 33 (32.7)	NR

Author, Year	Study Design (Cohort name or NCT number, if applicable); population inclusion details	Geographic Location (Year)	N Patients (Assay Used)	DLL3 positivity threshold (proportion of positive cells), N (%)		DLL3 Expression (definition), N (%)		H-Score threshold, N (%)
				Positive	Negative	High	Low	
Lim, 2019[37]	Retrospective cohort; ES-SCLC tumor samples	Korea (NR)	56 (AbbVie Stemcentrx)	NR	NR	≥50%: 50 (89.3)	<50%: 6 (10.7)	NR
Malhotra, 2021[31]	Non-randomized clinical trial, Phase I-II (NCT02874664); previously-treated ES-SCLC	NR (NR-2019)	41 (29 group 1; 12 group 2)[e] (NR)	≥25%: 39 (95.1)	<25%: 2 (4.9)	≥75%: 23 (56.1)	<75%: 18 (43.9)	NR
Prieto, 2021[38]	Cross-sectional; SCLC surgical specimens	Brazil (NR)	22 (NR)	NR	NR	Undefined: 12 (54.5)	Undefined: 10 (45.5)	NR
Regzedmaa, 2019[32]	Retrospective cohort; SCLC surgical resections	China (2009-2014)	38 (SAB1302862, Sigma-Aldrich, China)	Undefined: 38 (100.0)	Undefined: 0 (0.0)	≥13.5%: 20 (52.6)	<13.5%: 18 (47.4)	NR
Rudin, 2017[33]	Non-randomized clinical trial; SCLC progressed after 1 or 2 chemotherapy treatments	United States (2013-2015)	48[f] (Stemcentrx, USA)	≥1%: 42 (87.5)	<1%: 6 (12.5)	≥50%: 32 (66.7)	<50%: 16 (33.3)	NR
Saito, 2018[34]	Cross-sectional; SCLC samples from surgery or autopsy	Japan (1991-2013)	20 (ab103102, Abcam, USA)	≥1%: 18 (90.0)	<1%: 2 (10.0)	≥50%: 14 (70.0)	<50%: 6 (30.0)	NR
Tanaka, 2018[35]	Cross-sectional; SCLC tissue specimens	Japan (2012-2016)	63 (AbbVie Stemcentrx)	≥1%: 52 (82.5)	<1%: 11 (17.5)	≥50%: 20 (31.7)	<50%: 43 (68.3)	NR
Yan, 2019[39]	Retrospective cohort; *de novo* SCLC samples	China (2006-2015)	335 (ab103102, Abcam, UK)	NR	NR	NR	NR	High (≥150): 209 (62.4) Low (<150): 126 (37.6)

ES-SCLC: extensive-stage small cell lung cancer; NR: not reported.

*Roy et al. 2017 and Obermayr et al. 2019 not included in this table as DLL3 expression was evaluated in circulating tumor cells rather than primary tumor tissue.

[a] Calvo et al. 2021 included 31 patients but DLL3 expression was evaluated in 24 patients.

[b] Goldman et al. 2021 included 46 patients but DLL3 expression was evaluated in 37 patients.

[c] Huang 2019a categorized DLL3 expression as high or low based on the immune-reactive product score which is the product of proportion positive cells and staining intensity.
[d] Li et al. 2022 included 134 patients but DLL3 expression was evaluated in 101 patients.
[e] Malhotra et al. 2021 included 42 patients but DLL3 expression was evaluated in 41 patients.
[f] Rudin et al. 2017 included 74 patients but DLL3 expression was evaluated in 48 patients.

Additional file 5. Stratification of Delta-Like Ligand 3 (DLL3) Expression in Small Cell Lung Cancer (SCLC) by Demographic and Clinical Factors, in Non-SP347 Assay Studies (N=8 studies).

Author, Year	**DLL3 Expression (Definition)**	**N Patients**	**Age**	**Sex**	**Smoking Status**	**Stage**
Fu, 2020[28]	Positive (undefined)	28	<60: 46.4% ≥60: 53.6%	Male: 82.1% Female:17.9%	Current/former: 39.3% Never: 60.7%	TNM Stage I: 39.3% II: 46.4% III: 14.3%
	Negative (undefined)	15	<60: 46.7% ≥60: 53.3%	Male: 80.0% Female: 20.0%	Current/former: 33.3% Never: 66.7%	TNM Stage I: 20.0% II: 66.7% III: 13.3%
	p-value (univariate; positive vs. negative)		*0.988*	*0.863*	*0.700*	*0.393*
Hu, 2022[41]	High (undefined)	188	≤65: 81.9% >65: 18.1%	Male: 69.7% Female:30.3%	Yes: 62.2% No: 37.8%	AJCC Stage I: 30.3% II: 26.1% III: 43.6%
	Low (undefined)	59	≤65: 81.4% >65: 18.6%	Male: 74.6% Female: 25.4%	Yes: 69.5% No: 30.5%	AJCC Stage I: 35.6% II: 32.2% III: 32.2%
	p-value (univariate; high vs. low)		*1.00*	*0.52*	*0.35*	*0.28*
Li, 2022[30]	≥60%	54	NR	NR	NR	NR
	1-60%	33	NR	NR	NR	NR
	<1%	14	NR	NR	NR	NR
	p-value (univariate; group difference)		*>0.05*	*>0.05*	*>0.05*	*>0.05*
Lim, 2019[37]	High (≥50%)	50	NR	NR	NR	NR
	Low (<50%)	6	NR	NR	NR	NR
	p-value (univariate; high vs. low)		*>0.05*	*>0.05*	*>0.05*	*NR*
Regzedmaa, 2019[32]	High (≥13.5%)	20	<58:45.0% >58: 55.0%	Male: 75.0% Female: 25.0%	Ever: 55.0% Never: 45.0%	AJCC Stage I-II: 30.0% III-IV: 70.0%
	Low (<13.5%)	18	<58:50.0% >58: 50.0%	Male: 61.1% Female: 38.9%	Ever: 83.3% Never: 16.7%	AJCC Stage I-II: 55.6% III-IV: 44.4%
	p-value (univariate; high vs. low)		*1.00*	*0.489*	*0.086*	*0.188*
Saito, 2018[34]	High (≥50%)	14	Median (IQR): 68 (59.8-77.5)	Male: 100% Female: 0%	Median (IQR) pack-years: 50 (36.3-67.5)	pStage: I: 33.3%

Author, Year	DLL3 Expression (Definition)	N Patients	Age	Sex	Smoking Status	Stage
						II: 0% III: 66.7% IV: 0%
	Low (<50%)	6	Median (IQR): 69.5 (61.3-77.5)	Male: 100% Female: 0%	Median (IQR) pack-years: 53 (30.3-80.3)	pStage: I: 28.6% II: 7.1% III: 28.6% IV: 35.7%
	p-value (univariate; high vs. low)		*>0.05*	*>0.05*	*>0.05*	*>0.05*
Tanaka, 2018[35]	high (≥50%)	20	≥70: 50% <70: 50%	Male: 90% Female: 10%	Brinkman Index: ≥1200: 40% <1200: 60%	Limited: 35% Extensive: 65%
	low (<50%)	43	≥70: 51.2% <70: 48.8%	Male: 79.1% Female: 20.9%	Brinkman Index: ≥1200: 44.2% <1200: 55.8%	Limited: 44.2% Extensive: 55.8%
	p-value (multivariate; high vs. low)		*0.8015*	*0.2269*	*0.6042*	*0.4927*
Yan, 2019[39]	High (H-score ≥ 150)	209	≤60: 44.0% >60: 56.0%	Male: 93.8% Female: 6.2%	Smokers: 76.6% Non-smokers: 23.4%	TNM Stage I: 3.3% II:4.8% III: 37.8% IV: 54.1%
	Low (H-score <150)	126	≤60: 40.5% >60: 59.5%	Male: 87.3% Female: 12.7%	Smokers: 65.1% Non-smokers: 34.9%	TNM Stage I: 4.0% II: 5.6% III: 45.2% IV: 45.2%
	p-value (univariate; high vs. low)		*0.525*	***0.041***	***0.023***	*0.661*

NR: not reported. **Bold** values indicate statistical significance (p<0.05).

Additional file 6. Small Cell Lung Cancer (SCLC) Treatment Response and Survival by Delta-Like Ligand 3 (DLL3) Expression Level in Tumor Tissue, in Non-SP347 Assay Studies (N= 11 studies) [a].

Author, Year	**Geographic Location (Dates)**	**DLL3 Expression (Definition)**	**N patients**	**Response**	**Overall Survival**	**Progression-Free Survival or Disease-Free Survival**
				Response Measure: % or median (95% CI)	**Median (95% CI) or % by Milestone**	**Median (95% CI) or % by Milestone**
Calvo, 2021[27]	Multi-country (2018-2019)	High (≥75%)	19	ORR: 21.1% (90% CI: 7.5, 41.9) CR (confirmed): 5.3% PR (confirmed): 15.8%	NR	NR
		Low (<75%)	3	NR	NR	NR
		HR (95% CI), p-value		*NR*	*NR*	*NR*
Fu, 2020[28]	China (2011-2018)	Positive (undefined)	28	NR	21 months	DFS: 21 months
		Negative (undefined)	15	NR	37 months	DFS: 36 months
		p-value (univariate)		*NR*	*p=0.277*	*DFS: p=0.635*
Hu, 2022[41]	China (2005-2016)	High (undefined)	188	NR	NR	NR
		Low (undefined)	59	NR	NR	NR
		p-value (multivariate)		*NR*	*p>0.05*	*DFS: p>0.05*
Huang, 2019a[36]	China (2010-2017)	High (undefined)	23	ORR: 34.8% DCR: 56.5%	NR	NR
		Low (undefined)	49	ORR: 63.3% DCR: 77.6%	NR	NR
		p-value (univariate)		*ORR:* ***p=0.041*** *DCR: p=0.095*	***p<0.01***	*PFS:* ***p<0.01***
Li, 2022[30]	China (2012-2016)	≥60%	54	NR	NR	NR
		1-60%	33	NR	NR	NR
		<1%	14	NR	NR	NR
		p-value (univariate)		*NR*	*p=0.886*	*DFS: p=0.873*
Lim, 2019[37]	Korea (NR)	High (≥50%)	50	NR	5.3 months	PFS: 8.1 months
		Low (<50%)	6	NR	8.3 months	PFS: 5.5 months
		p-value (univariate)		*NR*	*p=0.975*	*PFS: p=0.90*
	China	High (≥13.5%)	20	NR	12 months	NR

Author, Year	**Geographic Location (Dates)**	**DLL3 Expression (Definition)**	**N patients**	**Response**	**Overall Survival**	**Progression-Free Survival or Disease-Free Survival**
				Response Measure: % or median (95% CI)	**Median (95% CI) or % by Milestone**	**Median (95% CI) or % by Milestone**
Regzedmaa, 2019[32]	(2009-2014)	Low (<13.5%)	18	NR	23 months	NR
		HR (95% CI), p-value (multivariate)		*NR*	***3.12 (0.99, 9.82), p=0.000[b]***	*NR*
Rudin, 2017[33]	United States (2013-2015)	High (≥50%)	29[c]	ORR: 35.0% DCR: 89.7% DOR: 4.3 months (2.2-15.0)	5.8 months (4.4, 11.6) 1-year OS: Refractory/ resistant: 29% Chemotherapy-sensitive: 33%	PFS: 4.3 months (2.8, 5.6)
		Low (<50%)	10[c]	ORR: 0.0% DCR: 60% DOR: 0 months	2.7 months (1.2, 10.0) 1-year OS: Refractory/ resistant: 0% Chemotherapy-sensitive: 23%	PFS: 2.2 months (1.3, 2.5)
		HR (95% CI), p-value		*NR*	*NR*	*NR*
Tanaka, 2018[35]	Japan (2012-2016)	High (≥50%)	20	NR	12.5 months	NR
		Low (<50%)	43	NR	15.7 months	NR
		HR (95% CI), p-value (univariate)		*NR*	*Overall: 0.975 (0.48-1.98), p=0.943* *LD: 0.75 (0.174, 3.23), p=0.699* *ED: 1.08 (0.473, 2.48), p=0.851*	*NR*
Yan, 2019[39]	China (2006-2015)	High (H-score ≥150)	209	NR	NR	NR
		Low (H-score <150)	126	NR	NR	NR
		p-value (multivariate)		*NR*	*p>0.05*	*NR*

CBR: Clinical benefit rate; CI: Confidence Interval; CR: Complete response; DCR: Disease control rate; DFS: Disease-Free Survival; DOR: Duration of objective response; ED: Extensive disease; HR: Hazard Ratio; LD: Limited disease; NR: Not reported; ORR: Overall response rate; PR: Partial response. **Bold** values indicate statistical significance (p<0.05).

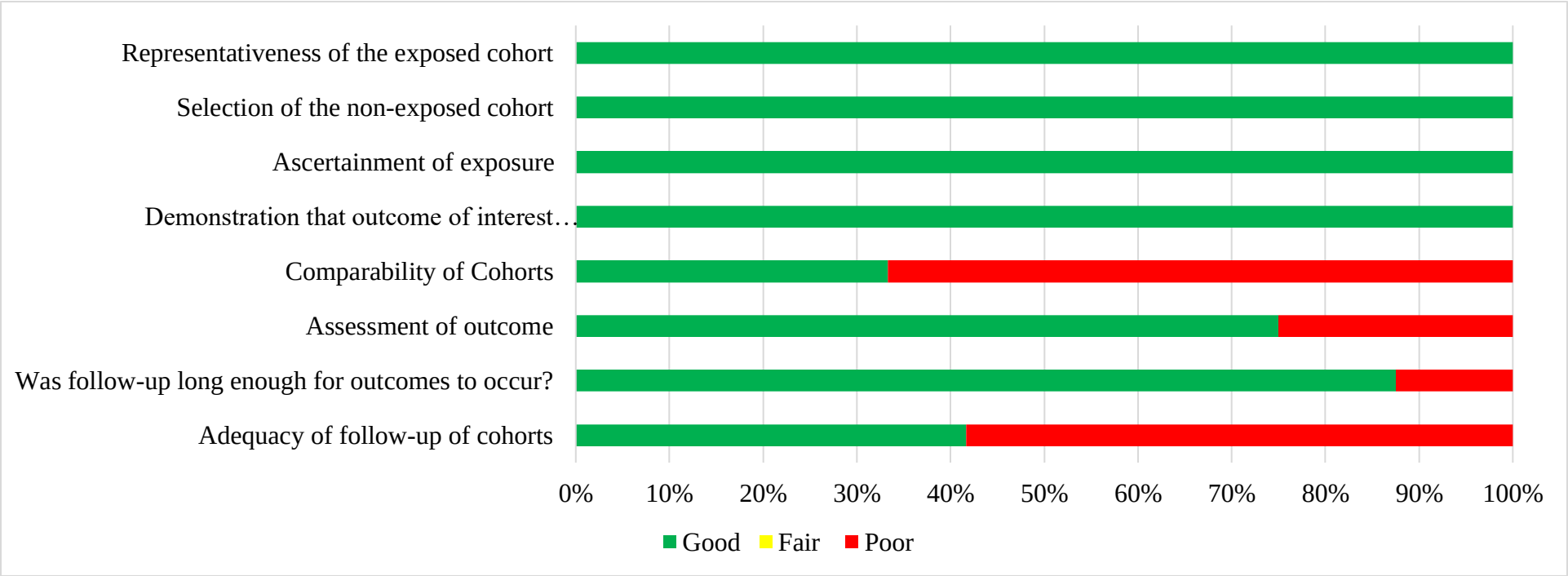
[a] If multiple values are reported for an outcome, the most adjusted is presented here. Some papers indicated there were no significant associations (p>0.05) between DLL3 expression subgroups but did not report the actual numbers.

[b] Regzedmaa et al. 2019 reported this HR as statistically significant (p=0.000), but the 95% CI includes 1.

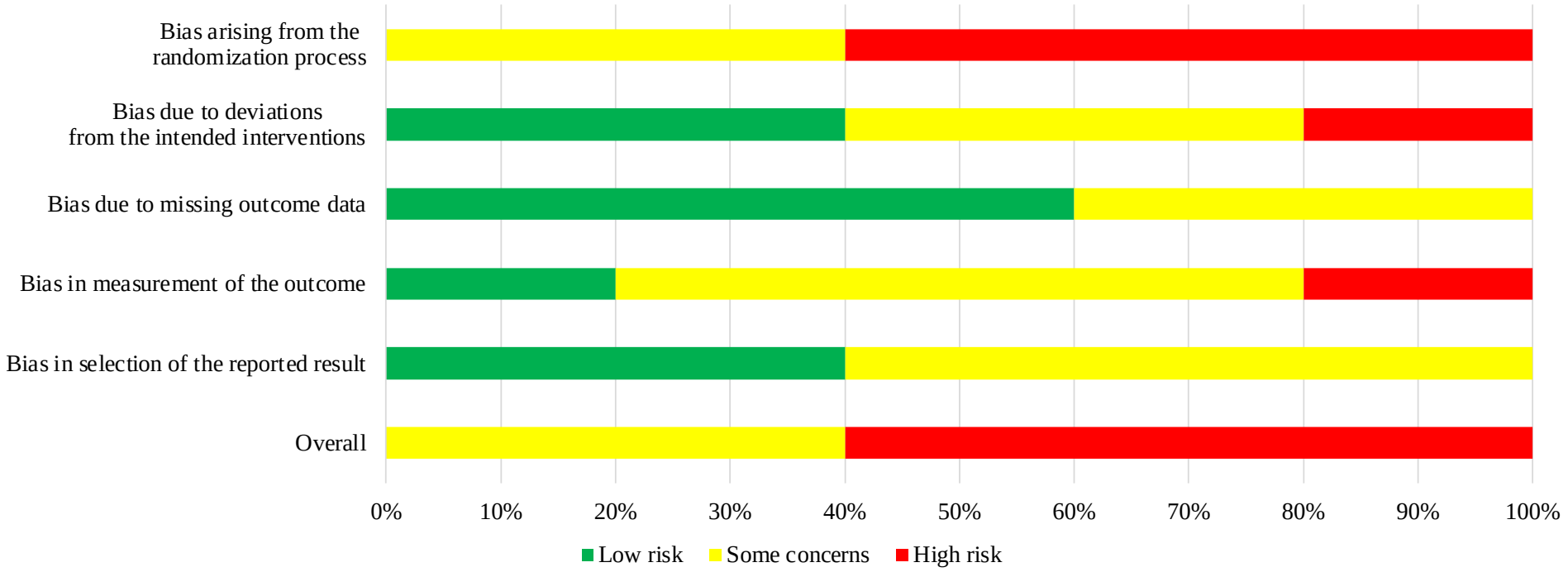
[c] Rudin et al. 2017 evaluated DLL3 expression in 48 patients but reported response and OS for 39 patients (29 high; 10 low) and PFS for 38 patients (29 high; 9 low).

Additional file 7. Summary of risk of bias scores in A) Observational studies (Newcastle-Ottawa Scale) and B) Clinical trials (Cochrane Risk of Bias Tool) among non-SP347 assay studies (N=17)

1A. Risk of Bias in Observational Studies (Newcastle-Ottawa Scale) Using Non-SP347 Assays (N=12 studies).



1B. Risk of Bias in Clinical Trials (Cochrane Risk of Bias Tool) Using SP347 Assays (N=5 studies).



Additional file 8. Supplemental Text

Study Characteristics: non-SP347

Among the 17 studies that used methods other than the Ventana SP347 IHC assay to evaluate DLL3 expression, most were observational in design, including 7 retrospective cohorts [28, 32, 36, 37, 39, 41, 42], 4 cross-sectional studies[26, 34, 35, 38], and one prospective cohort study [30] (Additional File 3). There were 5 clinical trials including 2 non-randomized [31, 33] and 3 single-arm trials [27, 29, 43]. Most (N=14) studies had less than 100 participants. Studies were conducted in China (N=6) [28, 30, 32, 36, 39, 41], Japan (N=2) [34, 35], Korea (N=2) [26, 37], the US (N=1) [33], multiple countries (N=3) [27, 29, 31], Austria (N=1) [42], Brazil (N=1) [38], and one study did not report the location[43].

Risk of Bias: non-SP347

The NOS scores of 12 observational studies that used methods other than the SP347 assay ranged from 3-9 with a mean of 5.75 and median of 5.5. When converted to the AHRQ standards, 4 studies were scored as good quality [23, 32, 35, 39], 3 were fair quality [26, 34, 38], and 5 were poor quality [28, 30, 36, 37, 41]. When evaluating bias by domain, risk was most apparent in the comparability and adequacy of follow-up (Additional File 7). In the Cochrane RoB scores of the 5 clinical trials that did not use SP347 assays, 3 studies were scored as high risk [31, 33, 43] and 2 had some concerns [27, 29]. Risk was most apparent in the randomization process (Additional File 7).

Patients and study characteristics: non-SP347

Patient and treatment characteristics varied across studies (Additional File 3). Sex was reported in 14 studies. The proportion of males ranged from 39% [29] in a Phase I trial of Rova-T in the US and Canada to 100% in a cross-sectional study of 20 patients with SCLC from Akita University, Japan (1991-2013) [34]. Only the Phase I-II trial of Rova-T reported race and/or ethnicity, with 93% of the study population being White [31]. Ten studies reported smoking status, of which most patients were current/former smokers (range: 62.8% in a retrospective cohort of 43 Chinese patients with SCLC from 2011-2018 [29] to 95.2% in a Japanese study of 63 patients with SCLC [35]). ECOG performance status was reported in 4 studies [27, 29, 31, 33], with the majority of patients having an ECOG performance status of ≥1 (range 67.7% [28, 35]-74.0% [28, 30, 32, 34, 38, 39, 41, 42]). Nine studies reported tumor stage at diagnosis as limited or extensive [28, 35] and/or by TNM stage [28]. The proportion of patients with extensive disease at diagnosis ranged from 0% in a retrospective cohort of 43 Chinese patients with SCLC from 2011-2018 [28] to 58.7% in a Japanese study of 63 patients with SCLC [35]; the proportion with TNM Stage III-IV disease at diagnosis ranged from 14% in the same Chinese cohort [28] to 100% in the Austrian SCLC cohort [42].

DLL3 positivity was determined by percentage of primary tumor cell positivity in 13 studies [26-38] and/or H-score in 2 studies [39, 41]. Tumor cell positivity threshold ranged from 1-25% and was often classified as "high" or "low" with cut-offs at 50 or 75%. The threshold for "high" DLL3 expression using the H-score was 150 in one study [39] and not reported in the other [41]. One study classified DLL3 positivity as "high" or "low" based on the immuno-reactive product [36]. This score, between 0-12, was the product of the maximum staining intensity score (0=no staining, 1=weak, 2=moderate, 3=strong) and the percentage of positive cells score (0=no staining, 1=1-9%, 2=10-49%, 3=50-79%, 4= ≥80%). In this study, all patients were ultimately assigned into DLL3-high group (scores ≥6) or DLL3-low group (scores<6). Two studies investigated DLL3 expression in circulating tumor cells (CTC) of patients with SCLC rather than primary tumor tissue [42, 43]. Messaritakis et al. (2019) also evaluated DLL3 expression in CTC in addition to primary tumor tissue [19].

DLL3 testing methods varied across studies with three studies not reporting the DLL3 testing method. All 17 studies reported prevalence as an outcome, though 2 studies were based on DLL3 expression in CTC [42, 43]. Other endpoints assessed in the studies included stratification of DLL3 expression by demographic or clinical factors (n=8), overall survival (n=10), progression-free survival or disease-free survival (n=6), and treatment response (n=3).

DLL3 Prevalence and Associated Factors – non-SP347

Among the 15 studies that reported DLL3 expression prevalence in patient tumor tissue using assays other than SP347 (Additional File 4), the most commonly used methods to assess DLL3 expression were ab103102 (Abcam, USA) (N = 4; 26.7% [30, 34, 36, 39]) and Stemcentryx (N = 3; 20% [33, 35, 37]). Three (20%) other studies described additional methods (bs-7860R [28] [Bioss, China], E3J5R [41] [Cell Signaling Technology, USA], SAB1302862 [32] [Sigma-Aldrich, China]) and 5 (33.3%) other studies did not report the method used to test DLL3 expression [26, 27, 29, 31, 38].

DLL3 positivity was defined as ≥1% of tumor cells in 5 studies [27, 30, 33-35]. The proportion of DLL3 positive patients ranged from 82.5% in a Japanese cohort of 63 patients with SCLC (2012-2016) [35] to 91.7% in a multi-country phase I trial of budigalimab and Rova-T in 24 patients with SCLC that had progressed on first-line platinum chemotherapy (2018-2019) [27]. Two studies defined positive DLL3 expression as ≥25% of tumor cells; a multicenter trial of Rova-T in the US and Canada (2016-2018) [29] reported 75.7% of

patients with SCLC were DLL3-positive while a Phase 1-2 trial of Rova-T + nivolumab reported 95.1% of patients were positive for DLL3 [31]. DLL3 positivity threshold was undefined in 3 studies [26, 28, 32]; the prevalence of DLL3 positivity ranged from 43.2% in a conference abstract of a Korean cohort of 88 patients with SCLC [26] to 100.0% in a cohort of patients with primary resected SCLC from the Tianjin Medical University General Hospital, China, from 2009-2014 [32].

DLL3 expression was categorized as high (vs. low) in 11 studies [27, 29-38]. High DLL3 expression was defined as ≥50% in 4 studies [33-35, 37]; prevalence ranged from 31.7% in a Japanese cohort of 63 patients with SCLC (2012-2016) [35] to 89.3% in a conference abstract of a Korean cohort of 56 patients with extensive stage SCLC [37]. High DLL3 expression was defined as ≥75% in 3 studies [27, 29, 31] with the prevalence of high expression ranging from 56.1% in a Phase 1-2 trial of Rova-T + nivolumab [31] to 79.2% in a multi-country phase I trial of budigalimab and Rova-T in 24 patients with SCLC that had progressed on first-line platinum chemotherapy (2018-2019) [27]. DLL3 expression was also defined as high using cutoffs of 13.5% [32] and 60% [30] and was undefined in 2 other studies [36, 38].

Two studies defined high and low DLL3 expression using the H-score [39, 41]. One study of surgically resected samples with limited stage disease conducted in China from 2005-2016 classified “high” and “low” expression level according to the best cut-off value determined by Xtile software but the cut-off was not specified in the paper; this study reported DLL3-high prevalence of 72.8% [41]. Another cohort of 335 patients with *de novo* SCLC at the Guangdong Provincial People’s Hospital (Guangzhou, China) from 2006-2015 used an H-score threshold of 150 to determine high vs. low DLL3 and reported 62.4% of patients as high [39].

The association between DLL3 expression and clinical or demographic factors was evaluated in 8 studies[28, 30, 32, 34, 35, 37, 39, 41], with all 8 studies investigating associations with patient age, sex, and smoking status/history, and 7 studies investigating an association with tumor stage (Additional File 5). All comparisons were univariate with the exception of the Japanese cohort of 63 patients with SCLC (2012-2016)[35], which conducted multivariate analyses adjusting for patient sex, age, disease stage, and smoking history. No statistically significant associations were reported between DLL3 expression and age or disease stage in any study. The association between DLL3 expression and sex or smoking status/history was null in 7 studies[28, 30, 32, 34, 35, 37, 41]. The cohort study of 335 patients with *de novo* SCLC at the Guangdong Provincial People’s Hospital (Guangzhou, China) from 2006-2015, which defined high vs. low DLL3 expression using an H-score of 150, reported in univariate analysis that patients with high DLL3 expression had significantly higher proportion of male patients (vs. female, p=0.041) and smokers (vs. non-smokers, p=0.023)[39].

Hu et al. reported a significant univariate relationship between DLL3 expression and vascular invasion, with more DLL3-high patients (undefined) having vascular invasion than DLL3-low patients (p=0.045) in the cohort of patients with SCLC from the Chinese Academy of Medical Sciences Cancer Hospital from 2005-2016[41]. Yan et al. reported in univariate analyses that the DLL3-high group (H-score ≥150) had a higher proportion of TTF-1-positive patients than the DLL3-low group in the cohort of Chinese patients with *de novo* SCLC from 2006-2015[39].

Circulating Tumor Cells (CTC) Studies

Among the 3 studies that evaluated DLL3 expression in CTC, cells were collected from patient blood samples and assessed for DLL3 expression using either RT-PCR[42, 43] or triple immunofluorescence assay[19]. The proportion of CTC that expressed DLL3 varied widely, from (7.8%) of samples in an Austrian cohort of patients with SCLC[42] to 63.8% at baseline in a Rova-T Phase 1 trial[43] and 74.1% of treatment-naïve Greek patients with SCLC[19]. The Greek cohort reported statistically significant univariate associations between baseline CTC expression of DLL3 and ECOG status, disease stage, LDH levels, and the presence of liver and bone metastases[19].

Survival and Response – non-SP347

Among the 15 studies that reported DLL3 expression in patient tumor tissue using assays other than SP347, there were 9 studies reporting the prognostic impact on overall survival (OS), 3 on progression-free survival (PFS), 3 on disease-free survival (DFS), and 3 on treatment response (Additional File 6).

OS was examined in 9 studies, 6 of which did not demonstrate any significant differences in survival by DLL3 expression in univariate[28, 30, 35, 37, 41] or multivariate[32, 36, 39] analysis. The cohort of *de novo* Chinese patients with SCLC from 2006-2015 reported significantly poorer survival among patients with DLL3-high (H-score ≥150) patients compared with DLL3-low in univariate analysis, but the significance disappeared in multivariate models[33]. Significantly poorer survival was reported among DLL3-high (undefined) patients in univariate analysis of a Chinese cohort of patients with SCLC from 2010-2017[36]. While multivariate models in another Chinese cohort from 2009-2014 also reported significantly poorer OS among DLL3-high (≥13.5% of tumor cells) patients (p=0.000), the lower limit of the 95% confidence interval included 1, and it is unclear

whether the estimate was actually statistically significant (HR=3.12; 95% CI: 0.99-9.82)[32]. One study reported longer OS among DLL3-high (≥50% of tumor cells) patients than low (median OS 5.8 vs. 2.7 months, respectively) but statistical significance (i.e., a p-value) was not reported[33].

Three studies evaluated the prognostic impact of DLL3 expression on PFS with inconsistent results. A study of Chinese patients with SCLC reported a significant difference in PFS across DLL3 groups ($p<0.01$)[36] but another study of Korean patients with SCLC did not observe significant differences ($p=0.90$)[37]. One study reported longer PFS among DLL3-high (≥50% of tumor cells) patients than low (median PFS 4.3 vs. 2.2 months, respectively) but the study did not report a test for statistical significance[33]. DFS was examined in 3 studies; no statistically significant differences were reported between DLL3-high and DLL3-low groups in any study ($p>0.05$)[28, 30, 41].

The impact of DLL3 expression on treatment response was assessed in 3 non-SP347 assay studies. One study of Chinese patients with SCLC reported a significantly lower ORR among DLL3-high (undefined) patients compared to DLL3-low (34.8% vs. 63.3%, $p=0.041$)[36]. One study reported overall response rate (ORR) by DLL3 group (ORR for DLL3-high vs. DLL3-low: 35% vs. 0%) but the study did not report statistical significance[33]. The third study only reported ORR and partial response for the DLL3-high (≥75% of tumor cells) group; no comparisons were made with the DLL3-low group[27].

CTC Studies

The association between DLL3 expression in CTC and clinical outcome was evaluated within two studies. Within the Greek SCLC cohort, multivariate analyses adjusting for performance status, disease stage, LDH level, liver metastases, bone metastases, and treatment response demonstrated significantly poorer PFS among patients with DLL3+ CTC at baseline (HR=10.8, 95% CI: 2.1-56.4), but not OS (HR=1.8, 95% CI: 0.1-25.5). When evaluating DLL3 expression among CTC after the first cycle of frontline chemotherapy, no significant difference was observed for PFS but survival was significantly worse among patients with DLL3+ CTC (HR=28.2, 95% CI: 2.0-39.1)[19]. In samples from an Austrian cohort of patients with SCLC, OS was significantly lower among those with DLL3+ CTC in univariate Cox regression analyses (HR 3.79, 95% CI: 2.80-115.60; $p=0.003$)[42].