

al., *Current Opinion in Immunology*, 22(2): 251-257 (2010); Rosenberg et al., *Nature Reviews Cancer*, 8(4): 299-308 (2008)). Immune cells can be genetically modified to express chimeric antigen receptors (CARs), fusion proteins comprised of a DLL3 antigen recognition moiety and T cell activation domains (see, e.g., Eshhar et al., *Proc. Natl. Acad. Sci. USA*, 90(2): 720-724 (1993), and Sadelain et al., *Curr. Opin. Immunol.*, 21(2): 215-223 (2009)). Immune cells that contain CARs, e.g., CAR-T cells (CAR-Ts), are engineered to endow them with antigen specificity while retaining or enhancing their ability to recognize and kill a target cell.

[006] DLL3 is a non-canonical Notch ligand, functioning in a cell autonomous manner to inhibit Notch signaling, thus blocking cell to cell interactions and internalization of Notch in the target cell. Delta-like ligand 3 (DLL3) is an SCLC tumor marker and has been found to be associated with cancer stem cells. Other indications that implicate DLL3 include melanoma, low grade gliomas, glioblastoma, medullary thyroid cancer, carcinoids, dispersed neuroendocrine tumors in the pancreas, bladder and prostate, testicular cancer, and lung adenocarcinomas with neuroendocrine features. There is a need for treatments for cancer and in particular malignancies involving aberrant expression of DLL3. Provided herein are methods and compositions addressing this need.

SUMMARY

[007] Provided herein are chimeric antigen receptors (CARs) comprising a DLL3 antigen binding domain that specifically binds to DLL3; and immune cells comprising these DLL3-specific CARs, e.g., CAR-T cells. Also provided are methods of making and using these DLL3-specific CARs, and immune cells comprising these DLL3-specific CARs. The DLL-3 targeting CAR T cells described herein demonstrate good transduction efficiency, in vitro phenotype and potent in vitro and in vivo anti-tumor activity.

[008] In one example, the present disclosure provides a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises at least one of: (a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 109, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460; (b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 110, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 254, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695; (c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the

group consisting of SEQ ID NOs 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 111, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 255, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462; (d) a variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 112, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 256, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696; (e) a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 113, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 257, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and (f) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 114, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 258, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

[008a] In one aspect, the present disclosure refers to a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises at least one of:

(a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 109, 253, 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460;

(b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 110, 254, 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695;

(c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 111, 255, 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462;

(d) a variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 112, 256, 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696;

(e) a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 113, 257, 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and

(f) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 258, 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

[009] In another example, the present disclosure provides a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises: (a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 109, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 253, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460; (b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 110, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 254, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, , and 695461; and (c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 111, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 255, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462.

[009a] In another aspect, the present disclosure refers to a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises:

(a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 109, 253, 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460;

5 (b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 110, 254, 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695; and

10 (c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 111, 255, 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462.

[010] In one example, the present disclosure provides a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the
15 extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises: (a) a variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 112, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 256,

265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696; (b) a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 113, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 257, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and (c) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 114, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 258, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

[010a] In another aspect, the present disclosure refers to a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises:

(a) a variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 112, 256, 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696;

(b) a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 113, 257, 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and

(c) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 258, 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

[011] In another example, the present disclosure provides a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises at least one of: (a) a variable heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 16, 25, 34, 43, 52, 61, 70, 79, 88, 97, 106, 115, 124, 133, 142, 151, 160, 169, 178, 187, 196, 205, 214, 223,

232, 241, 250, 259, 268, 277, 286, 295, 304, 313, 322, 331, 340, 349, 358, 367, 376, 385, 394, 403, 412, 421, 430, 439, 448, 457, 466; and (b) a variable light chain comprising an amino acid sequence selected from the group consisting of SEQ NOs: 8, 17, 26, 35, 44, 53, 62, 71, 80, 89, 98, 107, 116, 125, 134, 143, 152, 161, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, 287, 296, 305, 314, 323, 332, 341, 350, 359, 368, 377, 386, 395, 404, 413, 422, 431, 440, 449, 458, and 467, wherein the variable heavy chain and the variable light chain is linked by at least one linker.

[011a] In another aspect, the present disclosure refers to a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises at least one of:

(a) a variable heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 259, 7, 16, 25, 34, 43, 52, 61, 70, 79, 88, 97, 106, 124, 133, 142, 151, 160, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 268, 277, 286, 295, 304, 313, 322, 331, 340, 349, 358, 367, 376, 385, 394, 403, 412, 421, 430, 439, 448, 457, 466; and

(b) a variable light chain comprising an amino acid sequence selected from the group consisting of SEQ NOs: 116, 260, 8, 17, 26, 35, 44, 53, 62, 71, 80, 89, 98, 107, 125, 134, 143, 152, 161, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 269, 278, 287, 296, 305, 314, 323, 332, 341, 350, 359, 368, 377, 386, 395, 404, 413, 422, 431, 440, 449, 458, and 467,

wherein the variable heavy chain and the variable light chain is linked by at least one linker.

[012] In a further example, the present disclosure provides a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises: (a) a variable heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 16, 25, 34, 43, 52, 61, 70, 79, 88, 97, 106, 115, 124, 133, 142, 151, 160, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 259, 268, 277, 286, 295, 304, 313, 322, 331, 340, 349, 358, 367, 376, 385, 394, 403, 412, 421, 430, 439, 448, 457, and 466; and (b) a variable light chain comprising an amino acid sequence selected from the group consisting of SEQ NOs: 8, 17, 26, 35, 44, 53, 62, 71, 80, 89, 98, 107, 116, 125, 134, 143, 152, 161, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 260, 269, 278, 287, 296, 305, 314, 323, 332, 341, 350, 359, 368, 377, 386, 395, 404, 413, 422, 431, 440, 449, 458, and 467, wherein the variable heavy chain and the variable light chain is linked by at least one linker.

[012a] In another aspect, the present disclosure refers to a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises:

- 5 (a) a variable heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 259, 7, 16, 25, 34, 43, 52, 61, 70, 79, 88, 97, 106, 124, 133, 142, 151, 160, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 268, 277, 286, 295, 304, 313, 322, 331, 340, 349, 358, 367, 376, 385, 394, 403, 412, 421, 430, 439, 448, 457, and 466; and
- 10 (b) a variable light chain comprising an amino acid sequence selected from the group consisting of SEQ NOs: 116, 260, 8, 17, 26, 35, 44, 53, 62, 71, 80, 89, 98, 107, 125, 134, 143, 152, 161, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 269, 278, 287, 296, 305, 314, 323, 332, 341, 350, 359, 368, 377, 386, 395, 404, 413, 422, 431, 440, 449, 458, and 467,
- 15 wherein the variable heavy chain and the variable light chain is linked by at least one linker.

[013] In another aspect, the present disclosure refers to a chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and

wherein the antigen binding domain comprises a sequence selected from the group consisting of those scFvs presented in Table 1d.

[014] In another aspect, the present disclosure refers to a chimeric antigen receptor that specifically binds to DLL3, wherein the chimeric antigen receptor comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 482 to 533 and 632-683. In some examples, the chimeric antigen receptor comprises an amino acid sequence of any one of SEQ ID NOs: 482 to 533 and 632-683.

[015] In some examples, the present disclosure provides, a chimeric antigen receptor that specifically binds to DLL3, wherein the chimeric antigen receptor comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 482 to 533 and 632-683, with or without a signal sequence. In some examples, the chimeric antigen receptor comprises an amino acid sequence of any one of SEQ ID NOs: 482 to 533 and 632-683, with or without a signal sequence.

[016] In some examples, the intracellular domain of the chimeric antigen receptor comprises at least one costimulatory domain.

[017] In some examples, the costimulatory domain of the chimeric antigen receptor is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CD1 1a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptors, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFRR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRP1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha., CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD1 1d, ITGAE, CD103, ITGAL, CD1 1a, LFA-1, ITGAM, CD1 1b, ITGAX, CD1 1c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAMI (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

[018] In some examples, the costimulatory domain comprises a signaling region of CD28.

[019] In some examples, the CD28 costimulatory domain comprises SEQ ID NO: 550.

[020] In some examples, the costimulatory domain comprises a signaling region of 4-

1BB/CD137.

[021] In some examples, the 4-1BB/CD137 costimulatory domain comprises SEQ ID NO: 480.

[022] In some examples, the intracellular domain comprises at least one activating domain.

[023] In some examples, the activating domain comprises CD3.

[024] In some examples, the CD3 comprises CD3 zeta.

[025] In some examples, the CD3 zeta comprises SEQ ID NO: 481.

[026] In some examples, the chimeric antigen receptor is encoded by the polynucleotide sequence of any one of SEQ ID NOs: 571-621 and 631.

[027] In some examples, the chimeric antigen receptor further comprises a safety switch.

[028] In some examples, the safety switch comprises a CD20 mimotope or a QBEND-10 epitope.

[029] In some examples, the safety switch comprises one or more CD20 mimotopes or one or more QBEND-10 epitopes, or combinations thereof.

[030] In some examples, the chimeric antigen receptor comprises one or more safety switch in the format of QR3, SR2, RSR, or R2S.

[031] In some examples, the chimeric antigen receptor comprises the amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 622-628, 474-476, 565, and 684-694.

[032] In some examples, the chimeric antigen receptor comprises the amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 622-628, 474-476, 565, and 684-694, with or without a signal sequence.

[033] In another aspect, the present disclosure refers to an isolated polynucleotide encoding any one of the chimeric antigen receptors described herein.

[034] In another example, the present disclosure provides a vector comprising the polynucleotide encoding any one of the chimeric antigen receptors described herein.

[034a] In another aspect, the present disclosure refers to a vector comprising the polynucleotide as disclosed herein.

[035] In some examples, the vector is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.

[036] In another example, the present disclosure provides an engineered immune cell expressing a chimeric antigen receptors described herein.

[036a] In another aspect, the present disclosure refers to an engineered immune cell expressing any one of the chimeric antigen receptors as disclosed herein.

[037] In some examples, the present disclosure provides an engineered immune cell expressing the polynucleotide or vector encoding any one of the chimeric antigen receptors described herein.

[037a] In another aspect, the present disclosure refers to an engineered immune cell expressing the polynucleotide as disclosed herein or vector as disclosed herein.

[038] In some examples, the engineered immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

[039] In some examples, the engineered immune cell is an autologous T cell.

[040] In some examples, the engineered immune cell is an allogeneic T cell.

[041] In some examples, the engineered immune cell is TCR (e.g., TCRa, TCRb) knocked out.

[042] In one example, the present disclosure provides a pharmaceutical composition comprising the engineered immune cell expressing a chimeric antigen receptors described herein.

[042a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the engineered immune cell as disclosed herein.

[043] In some examples, the present disclosure provides a method of treating a disease or disorder in a subject in need thereof comprising administering to the subject the engineered immune cell or the pharmaceutical composition comprising the engineered immune cell expressing a chimeric antigen receptors described herein.

[043a] In another aspect, the present disclosure refers to use of the engineered immune cell as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[044] In some examples, the disease or disorder is cancer.

[045] In some examples, the disease or disorder is small cell lung cancer.

[046] In some examples, the present disclosure provides an article of manufacture comprising the engineered immune cell or the pharmaceutical composition comprising the engineered immune cell expressing a chimeric antigen receptors described herein.

[046a] In another aspect, the present disclosure refers to an article of manufacture comprising the engineered immune cell as disclosed herein, or the pharmaceutical composition as disclosed herein.

[047] In some examples, the present disclosure provides an anti-DLL3 binding agent disclosed herein.

[047a] In another aspect, the present disclosure refers to an anti-DLL3 binding agent comprising

(a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 109, 253, 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460;

(b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 110, 254, 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695;

(c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 111, 255, 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462;

(d) a variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 112, 256, 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 121, 130, 139, 148,

157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696;

(e) a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 113, 257, 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104,
5 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 266, 275, 284,
293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446,
455, and 464; and

(f) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 258, 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 123, 132, 141,
10 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 267, 276, 285, 294, 303, 312, 321, 330,
339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

[048] In some examples, the anti-DLL3 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof, optionally, a F(ab')₂ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, or a dAb fragment.

15 **[049]** In some examples, the binding agent is a monoclonal antibody comprising an IgG constant region.

[050] In some examples, the anti-DLL3 binding agent comprises a variable heavy (VH) chain sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to a VH sequence provided in Table 1b.

20 **[051]** In some examples, the anti-DLL3 binding agent comprises a variable light (VL) chain sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to a VL sequence provided in Table 1c.

[052] In some examples, the anti-DLL3 binding agent comprises a sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to an scFv sequence presented in
25 Table 1d.

[053] In some examples, the anti-DLL3 binding agent is a fusion protein comprising a scFv fragment fused to an Fc constant region.

[054] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the anti-DLL3 binding agent disclosed herein and a pharmaceutically acceptable
30 excipient.

[055] In some examples, the present disclosure provides a method of treating a disease or disorder in a subject in need thereof comprising administering to the subject an anti-DLL3 binding agent, or a pharmaceutical composition comprising the anti-DLL3 binding agent, as disclosed herein.

[055a] In another aspect, the present disclosure refers to use of anti-DLL3 binding agent as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[056] In some examples, the disease or disorder is cancer.

[057] In some examples, the disease or disorder is small cell lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[058] FIGS. 1A-1B are a series of plots showing that purified anti-DLL3 antibodies described herein bind to three DLL3-expressing small cell lung cancer cell lines (SHP-77, DMS 273 and DMS 454). The solid line and dashed line represent staining with anti-DLL3 antibodies or mouse IgG2A isotype control antibody, respectively.

[059] FIGS. 2A-2D show the results of epitope mapping experiments. FIG. 2A is a schematic representation of full length and truncated human DLL3 proteins expressed on CHO cells for epitope mapping, and all the proteins were fused at N-terminus with an HA tag for easy detection. FIGS. 2B and 2C show the amino acid sequences of full length and truncated human DLL3 proteins shown in FIG. 2A. FIG. 2D is a series of plots showing the results of epitope mapping of anti-DLL3 antibodies, and examples of anti-DLL3 antibodies recognizing DSL, EGF1 and EGF3 domain, respectively; the x-axis depicts signals from PE channel and the y-axis depicts counts.

[060] FIGS. 3A-3C are a series of plots and tables showing the structure, transduction efficiency of cells from two different donors and the cytotoxic activity of anti-DLL3 CARs. FIG. 3A is a schematic of a construct encoding an anti-DLL3 CAR comprising, from the N-terminus to the C-terminus: anti-DLL3 scFv, the hinge and transmembrane regions from human CD8 α , the cytoplasmic region from human 41BB and the cytoplasmic region from human CD3 ζ . FIG. 3B depicts experimental data showing that anti-DLL3 CARs are expressed on the surface of primary T-cells and can recognize recombinant DLL3; the plots are gated on live CD3 $^{+}$ cells and the numbers on the plots are the percentage of cells expressing each anti-DLL3 CAR. FIGS. 3C and 3D show the transduction efficiency of anti-DLL3 CARs comprising the scFv sequences described herein.

[061] FIGS. 4A-4C are a series of plots showing killing data for some anti-DLL3 CARs. FIG. 4A depicts experimental data showing that anti-DLL3 CAR-T cells specifically killed HEK-293T cells expressing human DLL3 but not parental HEK-293T cells in a 3-day cytotoxicity assay at the indicated effector:target (E:T) ratios. T cells that did not express anti-DLL3 CARs (labelled "empty vector") were used as negative control. FIG. 4B depicts experimental data showing that anti-DLL3 CAR-T cells killed SHP-77 and WM266.4 cells that express endogenous DLL3 in a 3-day cytotoxicity assay at indicated effector:target ratios. FIG. 4C depicts experimental data showing that anti-DLL3 CAR-T cells killed DMS 454 and DMS 273 small cell lung cancer cells that express

WHAT IS CLAIMED IS

1. A chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises at least one of:

(a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 109, 253, 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460;

(b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 110, 254, 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695;

(c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 111, 255, 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462;

(d) a variable light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 112, 256, 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696;

(e) a variable light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 113, 257, 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and

(f) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 258, 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

2. A chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises:

(a) a variable heavy chain CDR1 comprising an amino acid sequence

5 selected from the group consisting of SEQ ID NOs: 109, 253, 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460;

(b) a variable heavy chain CDR2 comprising an amino acid sequence

10 selected from the group consisting of SEQ NOs: 110, 254, 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695; and

(c) a variable heavy chain CDR3 comprising an amino acid sequence

15 selected from the group consisting of SEQ ID NOs: 111, 255, 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462.

3. A chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises:

(a) a variable light chain CDR1 comprising an amino acid sequence

selected from the group consisting of SEQ ID NOs: 112, 256, 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 25 238, 247, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696;

(b) a variable light chain CDR2 comprising an amino acid sequence

selected from the group consisting of SEQ NOs: 113, 257, 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 30 239, 248, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and

(c) a variable light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 114, 258, 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

4. A chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises at least one of:

(a) a variable heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 259, 7, 16, 25, 34, 43, 52, 61, 70, 79, 88, 97, 106, 124, 133, 142, 151, 160, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 268, 277, 286, 295, 304, 313, 322, 331, 340, 349, 358, 367, 376, 385, 394, 403, 412, 421, 430, 439, 448, 457, 466; and

(b) a variable light chain comprising an amino acid sequence selected from the group consisting of SEQ NOs: 116, 260, 8, 17, 26, 35, 44, 53, 62, 71, 80, 89, 98, 107, 125, 134, 143, 152, 161, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 269, 278, 287, 296, 305, 314, 323, 332, 341, 350, 359, 368, 377, 386, 395, 404, 413, 422, 431, 440, 449, 458, and 467,

wherein the variable heavy chain and the variable light chain is linked by at least one linker.

5. A chimeric antigen receptor comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding domain that specifically binds to DLL3, and wherein the antigen binding domain comprises:

(a) a variable heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 115, 259, 7, 16, 25, 34, 43, 52, 61, 70, 79, 88, 97, 106, 124, 133, 142, 151, 160, 169, 178, 187, 196, 205, 214, 223, 232, 241, 250, 268, 277, 286, 295, 304, 313, 322, 331, 340, 349, 358, 367, 376, 385, 394, 403, 412, 421, 430, 439, 448, 457, and 466; and

(b) a variable light chain comprising an amino acid sequence selected from the group consisting of SEQ NOs: 116, 260, 8, 17, 26, 35, 44, 53, 62, 71, 80, 89, 98, 107, 125,

134, 143, 152, 161, 170, 179, 188, 197, 206, 215, 224, 233, 242, 251, 269, 278, 287,
296, 305, 314, 323, 332, 341, 350, 359, 368, 377, 386, 395, 404, 413, 422, 431, 440,
449, 458, and 467,

wherein the variable heavy chain and the variable light chain is linked by at
5 least one linker.

6. A chimeric antigen receptor comprising an extracellular domain, a transmembrane domain,
and an intracellular domain, wherein the extracellular domain comprises a DLL3 antigen binding
domain that specifically binds to DLL3, and wherein the antigen binding domain comprises a
sequence selected from the group consisting of those scFvs presented in Table 1d.

10 **7.** A chimeric antigen receptor that specifically binds to DLL3, wherein the chimeric antigen
receptor comprises an amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%,
99% or 100% identical to any one of SEQ ID NOs: 482 to 533 and SEQ ID NOs: 632-683.

8. The chimeric antigen receptor of any one of claims 1 to 7, wherein the intracellular domain
comprises at least one costimulatory domain.

15 **9.** The chimeric antigen receptor of claim 8, wherein the costimulatory domain is a signaling
region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-
1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CD1
1a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14),
NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor
20 proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic
Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand
receptors, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2,
SLAMF7, Nkp80 (KLRF1), Nkp44, Nkp30, Nkp46, CD19, CD4, CD8alpha., CD8beta, IL-2R
beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, CD49D, ITGA6, VLA-6, CD49f,
25 ITGAD, CD1 1d, ITGAE, CD103, ITGAL, CD1 1a, LFA-1, ITGAM, CD1 1b, ITGAX, CD1 1c,
ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAMI
(CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229),
CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1,
CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp,
30 CD19a, a ligand that specifically binds with CD83, or any combination thereof.

10. The chimeric antigen receptor of claim 9, wherein the costimulatory domain comprises a
signaling region of 4-1BB/CD137.

- 11.** The chimeric antigen receptor of claim 10, wherein the 4-1BB/CD137costimulatory domain comprises SEQ ID NO: 480 or a fragment thereof.
- 12.** The chimeric antigen receptor of any one of claims 1 to 11, wherein the intracellular domain comprises at least one activating domain.
- 5 **13.** The chimeric antigen receptor of claim 12, wherein the activating domain comprises CD3.
- 14.** The chimeric antigen receptor of claim 13, wherein the CD3 comprises CD3 zeta.
- 15.** The chimeric antigen receptor of claim 14, wherein the CD3 zeta comprises SEQ ID NO: 481 or a fragment thereof.
- 16.** The chimeric antigen receptor of any one of claims 1-15, wherein the chimeric antigen
10 receptor is encoded by the polynucleotide sequence of any one of SEQ ID NOs: 570-621 and 631.
- 17.** The chimeric antigen receptor of any one of claims 1-16, further comprising a safety switch.
- 18.** The chimeric antigen receptor of claim 17, wherein the safety switch comprises a CD20 mimotope or a QBEND-10 epitope.
- 19.** The chimeric antigen receptor of claim 18, wherein the safety switch comprises one or more
15 CD20 mimotopes or one or more QBEND-10 epitopes, or combinations thereof.
- 20.** The chimeric antigen receptor of any one of claims 17-19, wherein the chimeric antigen receptor comprises one or more safety switch in the format of QR3, SR2, RSR, or R2S.
- 21.** The chimeric antigen receptor of any one of claims 17-20, wherein the chimeric antigen receptor comprises the amino acid sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%,
20 99% or 100% identical to any one of SEQ ID NOs: 686, 690, 622-628, 474-476, 565, and 684-685, 687-689, and 691-694.
- 22.** An isolated polynucleotide encoding any one of the chimeric antigen receptors of claims 1 to 21.
- 23.** A vector comprising the polynucleotide of claim 22.

24. The vector of claim 23, wherein the vector is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.

25. An engineered immune cell expressing any one of the chimeric antigen receptors of claims 1 to 21.

26. An engineered immune cell expressing the polynucleotide of claim 22 or vector of claim 23 or 24.

27. The engineered immune cell of claim 25 or 26, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

28. The engineered immune cell of claim 27, wherein the cell is an autologous T cell.

29. The engineered immune cell of claim 27, wherein the cell is an allogeneic T cell.

30. A pharmaceutical composition comprising the engineered immune cell of any one of claims 25-29.

31. Use of the engineered immune cell of any one of claims 25-29, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

32. The use of claim 31, wherein the disease or disorder is cancer.

33. The use of claim 31 or 32, wherein the disease or disorder is small cell lung cancer.

34. An article of manufacture comprising the engineered immune cell of any one of claims 26-29, or the pharmaceutical composition of claim 30.

35. An anti-DLL3 binding agent comprising

(a) a variable heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 109, 253, 1, 10, 19, 28, 37, 46, 55, 64, 73, 82, 91, 100, 118, 127, 136, 145, 154, 163, 172, 181, 190, 199, 208, 217, 226, 235, 244, 262, 271, 280, 289, 298, 307, 316, 325, 334, 343, 352, 361, 370, 379, 388, 397, 406, 415, 424, 433, 442, 451, and 460;

(b) a variable heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ NOs: 110, 254, 2, 11, 20, 38, 47, 56, 65, 74, 83, 92, 101, 119, 128, 137, 146, 155, 164, 173, 182, 191, 200, 209, 218, 227, 236, 245, 263, 272, 281, 290, 299, 308, 317, 326, 335, 344, 353, 362, 371, 380, 389, 398, 407, 416, 425, 434, 443, 452, 461, and 695;

5 (c) a variable heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs 111, 255, 3, 12, 21, 30, 39, 48, 57, 66, 75, 84, 93, 102, 120, 129, 138, 147, 156, 165, 174, 183, 192, 201, 210, 219, 228, 237, 246, 264, 273, 282, 291, 300, 309, 318, 327, 336, 345, 354, 363, 372, 381, 390, 399, 408, 417, 426, 435, 444, 453, and 462;

(d) a variable light chain CDR1 comprising an amino acid sequence selected from the group
10 consisting of SEQ ID NOs: 112, 256, 4, 13, 22, 31, 40, 49, 58, 67, 85, 94, 103, 121, 130, 139, 148, 157, 166, 175, 184, 193, 202, 211, 220, 229, 238, 247, 265, 274, 283, 292, 301, 310, 319, 328, 337, 346, 355, 364, 373, 382, 391, 400, 409, 418, 427, 436, 445, 454, 463, and 696;

(e) a variable light chain CDR2 comprising an amino acid sequence selected from the group
15 consisting of SEQ ID NOs: 113, 257, 5, 14, 23, 32, 41, 50, 59, 68, 77, 86, 95, 104, 122, 131, 140, 149, 158, 167, 176, 185, 194, 203, 212, 221, 230, 239, 248, 266, 275, 284, 293, 302, 311, 320, 329, 338, 347, 356, 365, 374, 383, 392, 401, 410, 419, 428, 437, 446, 455, and 464; and

(f) a variable light chain CDR3 comprising an amino acid sequence selected from the group
20 consisting of SEQ ID NOs: 114, 258, 6, 15, 24, 33, 42, 51, 60, 69, 78, 87, 96, 105, 123, 132, 141, 150, 159, 168, 177, 186, 195, 204, 213, 222, 231, 240, 249, 267, 276, 285, 294, 303, 312, 321, 330, 339, 348, 357, 366, 375, 384, 393, 402, 411, 420, 429, 438, 447, 456, and 465.

36. The DLL3 binding agent of claim 35, wherein the binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof, optionally, a F(ab')₂ fragment, a Fab' fragment, a Fab fragment, a Fv fragment, a scFv fragment, a dsFv fragment, or a dAb fragment.

37. The anti-DLL3 binding agent of claim 36, wherein the binding agent is a monoclonal
25 antibody comprising an IgG constant region.

38. The anti-DLL3 binding agent of any one of claims 35-37, comprising a variable heavy (VH) chain sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to a VH sequence provided in Table 1b.

39. The anti-DLL3 binding agent of any one of claims 35-38, comprising a variable light (VL) chain sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to a VL sequence provided in Table 1c.

40. The anti-DLL3 binding agent of any one of claims 35-39, wherein the binding agent
5 comprises a sequence that is at least about 80%, 85%, 90%, 95%, 96%, 98%, 99% or 100% identical to an scFv sequence presented in Table 1d.

41. The anti-DLL3 binding agent of any one of claims 35-40, wherein the binding agent is a fusion protein comprising a scFv fragment fused to an Fc constant region.

42. A pharmaceutical composition comprising the anti-DLL3 binding agent of any one of
10 claims 35-41 and a pharmaceutically acceptable excipient.

43. Use of anti-DLL3 binding agent of any one of claims 35-41, or the pharmaceutical composition of claim 42 in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

44. The use of claim 43, wherein the disease or disorder is cancer.

45. The use of claim 43 or 44, wherein the disease or disorder is small cell lung cancer.
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